

## Summary



- 2**      **Dossier**  
Safety in external radiotherapy  
treatments: the French point of view



- 50**      **International conference on modern  
radiotherapy:  
advances and challenges in radiation  
protection of patients**



The safety of radiotherapy treatments is a major issue for ASN in its role as regulator, just as it is for other players in the health and safety sector, organised around the national radiotherapy action plan executed by the Minister for Health and supervised by the French National Cancer Institute (INCa).

Since 2007, ASN has conducted annual inspections of all radiotherapy centres, with results presented in regional and national inspection reports. ASN has also reinforced regulations by publishing a technical decision on quality management, along with methodology guidelines on quality assurance and risk analysis in radiotherapy. A severity scale, established in cooperation with the French Society of Radiation Oncology (SFRO), can now be used to classify reported events or incidents, providing clearer information for the public.

Three years after the most recent issue of *Contrôle* magazine to be devoted to radiation protection for patients<sup>1</sup>, ASN decided to organize an international conference on “Advances and Challenges in Radiation Protection of Patients” to review the state of measures taken in France (Part I in this issue of *Contrôle*), to analyse current knowledge on radiotherapy-related risks and to present feedback on risk reduction obtained through various experiences from around the world (Part II).

The various articles presented in this issue of *Contrôle* magazine, as well as the speeches and oral presentations to be made at the conference and the debates to be held during the two round-table discussions on challenges in radiotherapy and informing patients, will contribute to advances in medical knowledge and help ASN to refine its doctrine and adapt its approach in order to improve the safety of radiotherapy treatments.

I thank you for your interest in ASN's activities.

Jean-Christophe Niel  
ASN Director-General  
Paris, October 29, 2009

1. La radioprotection des patients : pour une meilleure prise en compte de la radioprotection des patients dans la pratique médicale, [Radioprotection for patients: giving greater consideration to patient radiation protection in medical practices] in *Contrôle* no. 172, September 2006.



## **Safety in external radiotherapy treatments**



## A FRENCH POINT OF VIEW

■ ■	<b>Mesures taken by the French Health Minister to ensure safety in radiotherapy treatments</b>	5
	by Roselyne Bachelot-Narquin, French Health Minister	
	<b>Radiotherapy: meeting the challenge of radiation protection for patients</b>	7
	by Michel Bourguignon – ASN	
	<b>Lessons from expert assessments of radiotherapy and interventional radiology accidents</b>	12
	by Jacques Repussard and Pr Patrick Gourmelon – IRSN	
	<b>The actions of the national radiotherapy plan</b>	15
	by Dominique Maraninchi and Evelyne Fournié – INCa	
	<b>AFSSAPS contribution to the enhancement of the safety and the quality of radiotherapy procedures</b>	19
	by Dr Gérard Berthier and Nathalie Marliac – AFSAPS	
	<b>Certification of health establishments, assessment of professional practices and external radiotherapy</b>	22
	by Nafissa Abdelmoumene and Raymond Le Moign – HAS	
	<b>Quality in radiotherapy: the actions of the French society for radiation oncology (SFRO)</b>	26
	by Jean-Jacques Mazon, Françoise Mornex, François Eschwège and Éric Lartigau	
	<b>Medical physics in France – current situation and the changes required (reflections on safety improvements in radiotherapy)</b>	30
	by Thierry Sarrazin – SFPM	
	<b>The role of X-ray technologist in the safety of radiotherapy treatments</b>	34
	by Roger Husson – AFPPE	
	<b>Safety of radiotherapy treatments and future prospects</b>	36
	by Claude Évin – FFH	
	<b>Quality control and risk management: specific characteristics of the French health care system</b>	38
	by Denis Franck, Bernard Couderc and Gérard Parmentier – SNRO/UNHPC	
	<b>What information should patients be given before radiotherapy?</b>	44
	by Philippe Bergerot – LNCC	
	<b>My objective: zero contempt, not zero risk</b>	47
	by Jean-Paul Delevoye – Mediator of the French Republic	

## INTERNATIONAL CONFERENCE ON MODERN RADIOTHERAPY: ADVANCES AND CHALLENGES IN RADIATION PROTECTION OF PATIENTS

### OPENING SESSION: WELCOME ADDRESS AT THE INTERNATIONAL CONFERENCE ON MODERN RADIOTHERAPY

■ ■	<b>by André-Claude Lacoste (ASN), Eliana Amaral (IAEA), Dr Maria Neira (WHO), Dominique Ristori (EC) and Jean-Marc Cosset (Curie Institute)</b>	51
-----	---	----

### SESSION I. PARADIGMS OF EXTERNAL RADIOTHERAPY AND BRACHYTHERAPY: “NEW TECHNIQUES, NEW BENEFITS AND NEW RISKS”

■ ■	<b>Advances in external beam radiotherapy</b>	60
	by Michael Brada – ICR, Royal Marsden Hospital – United Kingdom	
	<b>Advances in brachytherapy</b>	62
	by Didier Peiffert – Alexis Vautrin Center – Nancy (France)	
	<b>The impact of new technologies on the risk of accident</b>	65
	by René Amalberti – HAS – France	
	<b>Highlights of the IAEA International Conference on Advances in Radiation Oncology (ICARO)</b>	67
	by Rethy K. Chhem – IAEA	

### SESSION II. CHALLENGES IN RADIOTHERAPY – PART 1: “INDIVIDUAL RADIOSENSITIVITY”

■ ■	<b>The range of radiosensitivity in the human population: hyper- and hypo-sensitivity</b>	69
	by Simon Bouffler – HPA – United Kingdom	
	<b>Radiation-induced sequelae and predictive tests: toward an individual profile</b>	71
	by David Azria – CRLC Val d'Aurelle – Montpellier (France)	
	<b>Human radiosensitivity: new concepts and new tools to predict over-acute reactions after radiotherapy</b>	74
	by Nicolas Foray – INSERM, Neurosciences Institute – Grenoble (France)	

### SESSION III. CHALLENGES IN RADIOTHERAPY – PART 2: “RISK/BENEFIT ISSUE”

■ ■	<b>Evaluation and management of secondary cancer risk in modern radiotherapy: elaboration of an ICRP/ICRU publication</b>	78
	by Jean-Marc Cosset – Curie Institute – ICRP member – France	
	<b>Risk acceptability in radiotherapy</b>	79
	by Klauss Rüdiger Trott – University College London Institute – United Kingdom	

### ROUND TABLE: CHALLENGES IN RADIOTHERAPY

■ ■	<b>Round table on “Challenges in radiotherapy”</b>	81
	by Michel Bourguignon – ASN – France	
	<b>“Ethical justification: an urgent challenge for radiotherapy</b>	81
	by Santiago Sia – Milltown Institute – Ireland	



## SESSION IV. ACCIDENTS – PART 1: “LESSONS OF THE PAST”

- ■ **Lessons learned from accidents in conventional external radiotherapy** 82  
by Ola Holmberg – IAEA
- Lessons from accidental exposure in modern external radiotherapy** 83  
by Pedro Ortiz López – ICRP
- Accidents, Lessons of the Past. Lessons learned from accidents in Brachytherapy** 85  
by Luis Pinillos – National Cancer Institute – Lima (Peru)

## SESSION V. ACCIDENTS – PART 2: “EVENTS RECORDING, REPORTING AND EVALUATION”

- ■ **WHO Radiotherapy risk profile** 88  
by Michael Barton – University of New South Wales – Australia
- Methods of risk analysis applied to radiotherapy** 90  
by María Luisa Ramírez Vera – FORO/CSN – Spain
- Radiation safety issues linked to the omnipresence of computers** 93  
by Jean-Claude Rosenwald – SFPF – France
- Quality and safety in radiotherapy: precursor events and feedback from experience** 95  
by Pr Eric Lartigau – INCa – France
- Accident reporting system: the ROSIS experience** 98  
by Mary Coffey – ROSIS – Ireland

## SESSION VI. TREATMENT OF COMPLICATIONS AND LATE MORBIDITY

- ■ **Use of adult stem cells in the treatment of radiation-induced skin burns** 99  
by Pr Jean-Jacques Lataillade – Percy Military Hospital – Clamart (France)

## SESSION VII. EQUIPMENT SAFETY, STAFFING, EDUCATION AND TRAINING

- ■ **Radiation therapy equipment: safety, commissioning, calibration; the medical physicist’s point of view** 101  
by Albert Lisbona – Centre A. Gauducheau – Nantes (France)
- The Radiation Therapist profession: a challenge and an opportunity to improve the safety and the patient care in Radiation Oncology** 103  
by Gianfranco Brusadin – EFRS – Italy
- EFOMP approach to reducing errors in Radiotherapy** 106  
by Herman Van Kleffens – EFOMP – Netherlands
- Education and training: the IAEA experience** 107  
by Ola Holmberg – IAEA

## SESSION VIII. CONTROLS/QUALITY/ASSURANCE/AUDITS

- ■ **The IAEA quality audits in radiotherapy** 109  
by Joanna Izewska – IAEA
- Equal-Estro: a dosimetry laboratory keeping pace with modernisation in radiotherapy** 111  
by Attila Veres – EQUAL-ESTRO – France
- The Norwegian Program on Quality Assurance in Radiotherapy (KVIST) – Organisation, Benefits and Experiences of this initiative for stakeholder’s involvement** 115  
by Hilde Merete Olerud – NRPA – Norway
- Clinical? Audits: who should control what? – european guidelines** 118  
by Hannu Järvinen – STUK – Finland

## SESSION IX. NATIONAL STRATEGIES AND REGULATIONS

- ■ **The ICRP take-home message** 121  
by Pedro Ortiz López – ICRP
- Radiation protection in modern radiotherapy: a regulator’s point of view** 123  
by Jürgen Griebel – BFS – Germany
- UK initiatives to improve patient safety in radiotherapy – the role of the Health Protection Agency** 125  
by Úna O’Doherty – HPA – United Kingdom
- The system of radiological events evaluation in radiotherapy in the Czech Republic** 128  
by Karla Petrová – Czech Republic
- Inspecting radiotherapy treatment safety: a priority for ASN for several years to come** 129  
by Jean-Luc Godet – ASN – France

## SESSION X. ROUND TABLE: PATIENT INFORMATION

- ■ **Informed consent process: a patient centred approach of the therapeutic decision** 133  
by Dr Marie-Charlotte Bouësseau – WHO – Swiss

A FRENCH POINT OF VIEW

# Mesures taken by the French Health Minister to ensure safety in radiotherapy treatments

by Roselyne Bachelot-Narquin, French Health Minister

The international conference organised by ASN, the French Nuclear Safety Authority, on safety in radiotherapy will provide an opportunity to take stock of challenges and advances in radiation protection for patients. As Minister of Health, I would like to take this opportunity, in consideration of the contributions made by the various stakeholders, to express my unshakable commitment to guaranteeing the safety to which patients and professionals are entitled.

In this respect, I would like to go over the measures of the cancer plan that has just come to an end and those of the forthcoming plan and underline how they help and support radiotherapy practices.

The 2003-2007 cancer plan was devised as a response to the expectations expressed by patients and their families during the convention organised by the *Ligue nationale contre le cancer* in 1998 and those expressed by doctors, nurses and researchers during the first World Summit Against Cancer in 2000.

The plan set out to improve the quality of patient care in terms of equal access, coordination between the parties involved and professional practices.

Eight of the plan's seventy measures were related to radiotherapy.

They addressed the following issues: licensing procedures for cancer treatment at public- and private-sector health centres, renovating equipment, identifying new specialist fields in the profession, training and supervision of professionals, fees for service and, lastly, research and innovation.

I had barely arrived at the Ministry of Health and Sport in May 2007, when I was confronted with the radiotherapy accident in Toulouse which, though quite different from the Epinal accident, nonetheless represented in some ways an unfortunate repeat incident.

Both accidents had dramatic consequences for the patients and their loved ones and triggered a health crisis.

The first priority was to take action on the spot to ensure that the patients received urgent medical treatment as well as the necessary subsequent health and social care.

It struck me immediately that we were faced with a systemic crisis in radiotherapy and that the next urgent step



Roselyne Bachelot visiting the new facilities at the Radiotherapy and Oncology Unit at Jean Monnet Hospital in Epinal (France) – April 2008

was to complete the work of the radiotherapy working group set up after the Epinal accident.

This major task involved all categories concerned with radiotherapy (Government departments and agencies, professional unions and learned societies) and was completed in six months. It was this work that finalised the nation-wide measures for radiotherapy which I presented on 29 November 2007.

The purpose of these measures is to rebuild the trust of both patients and professionals in a tool that is vital for cancer treatment and constantly progressing. Every year, seventy per cent of cancer patients benefit from curative or palliative radiation therapy, representing 180,000 new cases treated per year. With the growing number of cancer cases and the fact that the screening strategies now implemented allow increasingly early diagnosis of certain tumours, which thus become curable, these figures could rise.

The national radiotherapy measures are aimed at making practices safer, improving quality of care and keeping a closer watch to prevent unwanted events.

I have set up a follow-up committee, chaired by Professor Dominique Maraninchi, to see that the measures are implemented. A number of organisations are associated with the committee including the French National Cancer Institute, the General Directorate for Health, the Directorate for Hospitalisation and Health Care, the Nuclear Safety Authority, the Agency for the Safety of Health Products, the National Authority for Health, the French Society of Radiation Oncology, the French Society



of Medical Physics, the CISS (the inter-association collective on health) and, whenever necessary, representative federations of public- and private-sector hospitals with a radiation oncology department and any other persons with special expertise in the field.

I would like to pay tribute to the commitment and tenacity of the committee, which is not simply another control body. It keeps me informed of the progress made in the implementation of the measures on the ground and suggests ways of overcoming any problems encountered.

Eighty per cent of the 33 measures had been implemented at the time of the first progress report in May 2009. The remaining measures will come into effect gradually between late 2009 and late 2011, depending, for example, on the time allowed hospitals and medical centres to meet licensing requirements or the duration of professional training schemes.

I would now like to focus particularly on two measures included in the first cancer plan and which the national radiotherapy measures have backed up.

Regional health care provision schemes are currently being revised under the decrees of March 2007. All radiotherapy centres will now need a special licence to treat cancer patients and, to this end, will be required to meet the seventeen approval criteria published by the National Cancer Institute in December 2007.

Mandatory use of *in vivo* dosimetry is among these criteria. Had this technique been used in Epinal, the overexposure accident could have been mitigated or even completely avoided.

Radiophysicists were given official recognition in the public sector under a decree in May 2005, while the principle of payment for trainee radiophysicists was established by a circular in December 2008.

I would now like to take things further by doubling the number of radiophysicists in five years, from 300 in 2007 to 600 in 2012. The number of trainees in this speciality rose from 42 in 2007 to 81 in 2009 and 105 places are available to successful candidates for 2010, which goes to show that our target could well be within reach.

A few weeks ago, the President of France introduced the second cancer plan.

A number of measures have been integrated to support radiotherapy, based on proposals put forward by the national radiotherapy monitoring committee and Professor Jean-Pierre Grünfeld's recommendation and drawing on the resources made available under the "Hospitals - Patients - Healthcare - Regions" Act of 21 July 2009.

We shall all have to work together to implement these measures which are designed to guarantee standardised safe, high quality treatment throughout the country and equal access for all to a full range of care and treatment, including the latest technical innovations, in radiotherapy.

The first cancer plan led to significant advances in cancer treatment. By reorganising radiotherapy centres in particular and supporting progress in practices, the second cancer plan aims to provide professionals in the field with highly specific resources to offer cancer patients the very best in treatment and care. ■



A FRENCH POINT OF VIEW

# Radiotherapy: meeting the challenge of radiation protection for patients

by Michel Bourguignon, Commissioner at the French Nuclear Safety Authority (ASN) – Paris (France)

ASN, the French Nuclear Safety Authority, is tasked with regulating nuclear safety and radiation protection on behalf of the State and keeping the public informed in these matters. Its control and regulation tasks are particularly concerned with the medical field as the highest doses of artificial radiation are given to patients, especially in radiotherapy.

The serious radiotherapy accidents that occurred at Epinal Hospital (2004-2005) and Rangueil Hospital in Toulouse (2006-2007), together with other radiotherapy-related events reported to ASN after 2005, highlight the significant role played by human and organisational factors in such incidents.

In the light of these events, ASN has drawn on its experience in regulating basic nuclear installations to set up a new regulation strategy aimed at promoting safety culture at all radiotherapy centres, together with an information initiative targeting patients and the general public. Since 2007, yearly inspections have been carried out at 178 radiotherapy centres (see ASN article, page 129).

The considerable efforts made by all the personnel and institutions concerned have brought about some improvements. At certain centres, however, the situation remains delicate owing to persistent organisational and human shortcomings for which provisional measures have been taken. Progress must still be made to prevent the occurrence of radiotherapy accidents.

The radiotherapy profession must also consider and overcome risks relating to side effects and complications. In its capacity as observer and regulator, it is ASN's duty to bring all parties together to discuss the issues at stake and find ways to address the challenge that radiotherapy represents for all parties involved in radiation protection.

Radiotherapy accidents, side effects and complications are observed all over the world. The protection of radiotherapy patients is a challenge that must be considered from an international perspective.

## Radiotherapy

Radiotherapy is a powerful tool in the local treatment of cancer and is based on the use of a beam of ionising radiation. The energy absorbed by the cancer cells helps to kill them by preventing them from multiplying. The purpose of irradiation is to destroy all the cells of the tumour, while minimising damage to the healthy tissue surrounding it, which has a greater ability to recover.



An illustration of early radiotherapy treatment in Copenhagen, published in "L'illustration" – March 23, 1901

Radiotherapy must strike the best balance between delivering the highest possible dose to the tumour while ensuring that the dose remains acceptable to the healthy tissues and organs at risk nearby. This means that it is not an option in the treatment of some types of cancer.

In the developed countries, cancers are the cause of 25% of deaths among women and 30% of deaths among men. Radiotherapy is used to treat about 60% of cancers. Around 80% of cancers treated by radiotherapy are cured. Radiotherapy can be used on its own or in combination with surgery and chemotherapy. The decision as to whether or not radiotherapy should be prescribed is based on the type of tumour, its location, the stage it is at and the patient's general state of health.

External radiotherapy is particularly useful because the source of radiation, located outside the body, can reach tumours in a non invasive manner, which is something surgery cannot do. The radiation beams delivered by the accelerators can also get to tumours in areas that are difficult for a surgeon to reach. The latest accelerators are equipped with multileaf collimators that are used to change the radiation beam size in real time. It is used in what is known as conformal radiotherapy. This type of therapy has two advantages: 1) the beam targets the region of interest more precisely, whatever the angle of attack, allowing a higher dose to be delivered straight to the tumour and 2) by targeting the tumour more effectively, the healthy surrounding tissue receives less radiation and the patient is better protected. Multiplying irradiation angles, however, means that the radiation



beam passes through a relatively larger volume of healthy tissue farther away from the tumour, even though the dose to this tissue is lower. The change in healthy tissue exposure does not seem to have any significant effect. The cost of radiotherapy is relatively low compared with the overall cost of cancer treatment, especially chemotherapy. This is another of the advantages radiotherapy offers for cancer treatment.

Every year, some 320 000 new cases of cancer are reported in France. Most cancers occur in the elderly as the cancerisation phenomenon is caused by cell ageing due to the loss of certain cell and tissue control functions. As the population grows older, the incidence of cancer rises, leading to a growing number of patients in radiotherapy.

### **Reinforced regulations for more reliable internal procedures**

Quality assurance in services using ionising radiation for medical purposes became compulsory under French law in 2003 (Article R.1333-59 of the French Public Health Code) in application of Euratom Directive 97/43<sup>1</sup>. Its content, however, was left to the initiative of professionals and was never formally documented. Only quality control regarding medical devices was brought within a regulatory framework and supervised by organisations approved by the AFSSAPS, the French Agency for the Safety of Health Products.

On 1 July 2008, ASN adopted a technical decision (ASN-2008-DC-103) laying down the main requirements relating to quality management in external radiotherapy and brachytherapy and defining the implementation schedule until 2012. The decision was approved in January 2009 by the Minister of Health and Sport and has been enforceable since March 2009. A guide, produced with the help of professionals and distributed by ASN in March 2009, includes a proposal for a specific management baseline concerning safety and quality of care. A second document, also produced with the assistance of professionals, focuses on methodology and risk analysis in external radiotherapy. Risk analysis must be completed by March 2011 and the quality management system set up by September of the same year.

This decision shall be implemented gradually and coordinated with action by INCa, the French National Cancer Institute, to ensure that quality criteria are met before authorising radiotherapy activities.

### **Strengthening human resources at radiotherapy centres**

Care needs to be made safer at many radiotherapy centres. This cannot be achieved, however, without a significant increase in human resources, which means not only more medical radiation physicists and dosimetrists, but also more radiation oncologists and radiation therapy technicians.

ASN already drew attention to the shortage of medical radiation physicists in France in 2007. Representing around 410 full time jobs, the number per million inhabitants is two to three times lower there than in the country's main European neighbours. This shortage can be explained by the fact that the profession does not have the benefit of a proper status in France. Considering training schemes, ASN estimates that it will take between five and ten years for numbers to rise sufficiently.

Many accelerators (>50) were renewed as part of Cancer Plan I (2004 – 2009). As a consequence of this and improved performance, operating these machines has become a more complex task, making the shortage of medical radiation physicists even more sorely felt.

The measures introduced by the Ministry of Health to increase the number of people training as medical radiation physicists are steps in the right direction but it will be some time before their effects are felt. In 2009, the continuing acute shortage of medical radiation physicists has destabilised the work force in the medical physics field and remains a critical organisational problem at about 20% of centres. ASN has had to temporarily suspend accelerator operating licences at three centres owing to a total lack of medical radiation physicists (now hired by other centres).

Efforts to build up human resources in the radiotherapy field must therefore be sustained over the next few years. It should also be pointed out that medical radiation physicists in France do not benefit from anywhere near the same status as their counterparts in other major neighbouring countries.

### **Reporting events to ASN with a view to organising feedback and keeping the public informed**

In order to encourage and share feedback, ASN has endeavoured to set up an event reporting system in the medical field, as some events can lead to serious incidents. Such events should be first recorded at the radiotherapy centre and the causes analysed by the doctor in charge and his/her personnel. This would help to guarantee safe care and set up and implement corrective action where necessary. As of March 2010, it will be mandatory for all radiotherapy centres to have an internal system for recording and analysing malfunctions.

Within this context, ASN published an experimental guide for reporting significant radiation protection events in July 2007, including events relating to patients exposed to ionising radiation during radiotherapy. Events that are not expected to have any impact on health are also to be reported. Once the guide has been evaluated, ASN will make a technical decision, subject to approval by the Minister of Health, to make compliance with the guide mandatory in 2009.

ASN has also produced an experimental severity scale in association with a number of learned societies. Distributed in July 2007, the scale aims to provide the public with clear and simple details of radiation protection events concerning patients during external

1. Euratom Directive 97/43 of 30 June 1997 on health protection of individuals against the dangers of ionizing radiation in relation to medical exposure.



radiotherapy procedures. After one year of practical use, the scale was updated and published in July 2008 ([www.asn.fr](http://www.asn.fr)).

### ASN – a stakeholder in the national radiotherapy action plan

In response to the radiotherapy accidents in Epinal and Toulouse, the Ministry of Health launched a national action plan for radiotherapy, to which ASN has made a significant contribution. It works alongside other players in the health and safety sector on the national monitoring committee of the plan, headed by the Chairman of the INCa (see INCa article), where it plays a major role.

At the national level, ASN has signed collaboration agreements with HAS (the French National Authority for Health, December 2008), the French Agency for the Safety of Health Products (AFSSAPS, July 2009) and the French Institute for Public Health Surveillance (InVS, September 2009) and will soon be signing an agreement with INCa, the French National Cancer Institute. These collaboration initiatives are aimed in particular at setting up or consolidating information sharing procedures between ASN inspections, the healthcare organisation accreditation system supervised by HAS, the medical device monitoring activities carried out by AFSSAPS, as well as InVS surveillance of serious events and the monitoring of the most at-risk radiotherapy centres across the country by INCa.

### Individual radiosensitivity

Cancer is a serious disease. Effective treatment calls for the use of high-dose radiotherapy, with the attendant risk of the healthy tissue surrounding the tumour being overexposed to radiation. Radiotherapy is not without side effects or even complications.

The radiotherapist has no choice but to offer patients a treatment that involves striking a delicate balance. On the one hand, doses need to be reduced to significantly reduce side effects, although doing so would increase the risk of relapse. On the other hand, if the tumour is to be destroyed once and for all, doses must be increased, which leads to the risk of healthy tissue overexposure and other complications. What is the solution?

More needs to be known about the biological mechanisms at play in radiation, especially on the subject of individual radiosensitivity. This is because patients do not all exhibit the same degree of sensitivity to ionising radiation. Although radiobiologists and radiotherapists are aware of this phenomenon, it is not taken into account at the clinical level. This will have to change.

Radiotherapists first described individual hypersensitivity to high doses of ionising radiation many years ago. The pathologies related to severe hypersensitivity to radiation are documented and concern homozygous genetic disorders in DNA repair and cell signalling (both chromosomes are affected). According to the international literature, individual hypersensitivity to radiation also exists, but to a lesser extent, in patients who would appear to be

**A comprehensive quarterly report of level 1 events (on the ASN/SFRO scale) declared to ASN can be consulted on the ASN website ([www.asn.fr](http://www.asn.fr)). Note that:**

- As at 1 October 2009, 50% of centres (of a total 178) had declared at least one event to ASN.
- As at 1 October 2009, 73 events were declared whose five events were classified as level 2 on the ASN-SFRO scale and described in an incident report on the ASN website. Level 2 events are those resulting in or likely to result in moderate alteration of an organ or function.

heterozygous (a single chromosome affected) for the same genes. It is thought that this concerns about 5% of the population.

Radiotherapists also report that about 5% of the patients they treat present varying degrees of overdose-related complications, even though no errors have been made in the dose delivered or in the volumes exposed. The number of complications of this type seems to be rising with the current upward trend in radiotherapy doses.

Are the patients concerned by complications during radiotherapy the same as those exhibiting individual hypersensitivity? If, as seems likely, this is so, then radiotherapy complications are the world's most serious radiation protection problem. In France, these deterministic effects could affect 10,000 patients every year. Yet we have no reliable statistics on this topic at present. This must be remedied.

Conversely, 5% of patients could be considered less sensitive to radiation than average, based on a normal distribution (bell curve) assumption. In such cases, the radiotherapy dose given might be too low to sterilise the tumour. How can the dose be increased to guarantee effective treatment here? This is a tremendous challenge for radiotherapists and cancer specialists alike.

Individual sensitivity to ionising radiation is therefore a central issue in radiotherapy. It is also a matter of great concern for radiation protection; in fact, it is probably the single most important question in this area.

It is not known whether individual radiosensitivity exists at low doses. As the hyper-radiosensitivity phenomenon is related among other things to a DNA repair deficiency, cell signalling defects and abnormal genes, all of which play a role in cancerisation, we cannot rule out the possibility of a stochastic risk, in other words, a risk of radiotherapy-related secondary cancer. This assumption takes on a particular significance if we consider that some people have genes that make them especially fragile with regard to DNA repair deficiencies (for example, in families where the women have breast cancer and carry genes from the BRAC family). Is the risk of developing secondary cancer after radiotherapy higher for these people? Until now, no radiological signature for a cancer has been observed, meaning that no characteristic cell





Prostate brachytherapy: preparing the wires that will contain the radioactive seeds

lesion has been found to indicate that the cancer is due to ionising radiation. Recent research indicates that this problem could be overcome with the development of DNA chips designed to analyse thousands of genes - if not all the genes in a cell - simultaneously.

Lastly, individual radiosensitivity is variable and could encompass several different situations:

- is individual radiosensitivity with deterministic effects at high doses any different from that with possible stochastic effects at low doses?
- is radiosensitivity identical in normal cells and in cancer cells in the same patient?
- what are the mechanisms behind different degrees of radiosensitivity in tissues and organs and why are children and women more radiosensitive than adult men?

We have no answers to these questions as yet.

### **Is it possible to test for individual hyper-radiosensitivity?**

A great deal of research is concerned with screening for individual hyper-radiosensitivity. For patients who have presented complications during radiotherapy, the possible existence of individual hypersensitivity can be demonstrated by testing for DNA fragility and repair mechanisms and the presence of abnormal genes. Other work focuses on ways to carry out this screening before treatment begins. A scientific monitoring effort is therefore required in this area and research activities should be supported to find simple methods for detecting individual hyper-radiosensitivity. Detecting radiosensitivity

prior to radiotherapy would allow the radiotherapist to "customise" the dose for each patient and, hopefully, reduce risks to a minimum.

Predictive tools would open the way to molecular epidemiology: how many people are hypersensitive? how hypersensitive are they? how is hypersensitivity connected with deterministic or stochastic risks? what is the risk of hypersensitivity at low doses? what effect does the dose rate have? This would be extremely useful, although the ethical issues would have to be discussed beforehand.

### **Treating lesions**

Deterministic lesions due to the overexposure of tissue to radiation are highly inflammatory. They are also painful and particularly resistant to pain killers. Once a dose threshold is overrun, tissue necrosis seems unavoidable. New treatments for damage caused by overexposure must therefore be developed.

Since 2006, specialist teams at Percy Military Hospital in Clamart and IRSN have demonstrated that mesenchymal stem cell grafts can produce outstanding and previously un hoped-for results. Although it is true that the lesions in question have concerned young people suffering from the effects of accidental overexposure from sealed sources, they do not differ fundamentally from the more severe lesions observed in more elderly patients in radiotherapy.

Here, too, research into MSC grafting should be promoted because, even if the occurrence of severe, lasting complications may never be completely eradicated, an effective treatment must nevertheless be found.

### Conclusions and prospects

Radiotherapy is an effective tool in cancer treatment. It has more than proved its worth and, on the whole, radiotherapy available in France is of high quality.

The regular occurrence of incidents can be explained by human error and defective organisational procedures. A constant effort must be made to minimise the number and consequences of these incidents. ASN inspections continue to maintain a high level of risk awareness in the profession. The Ministry of Health, however, should also press on with its efforts to remedy the problem of understaffing at radiotherapy centres in France. This problem is particularly sensitive among medical radiation physicists and makes it difficult to meet the stringent safety requirements in this area.

About 5% of radiotherapy patients present side effects and complications, which represent the most serious problem in radiation protection. Research into individual radiosensitivity is doing a great deal to improve our

understanding of the mechanisms behind lesions. Screening for individual radiosensitivity would make it possible to "fine tune" the doses given to patients and minimise side effects and complications outside accident situations. Mesenchymal stem cells show great promise for treating any lesions that do occur.

In the same way that improved radiation protection for patients drives progress in radiotherapy, radiotherapy drives progress in radiation protection.

Lastly, patient radiation protection does not only serve a purpose in radiotherapy. Interventional radiology allows high-quality, diagnostic and therapeutic procedures, with real-time image guidance. It involves the use of high doses of radiation leading to significant side effects and even complications and has been the focus of close attention from ASN since 2009.

This is ASN's road map regarding patient radiation protection. ■



## A FRENCH POINT OF VIEW

# Lessons from expert assessments of radiotherapy and interventional radiology accidents

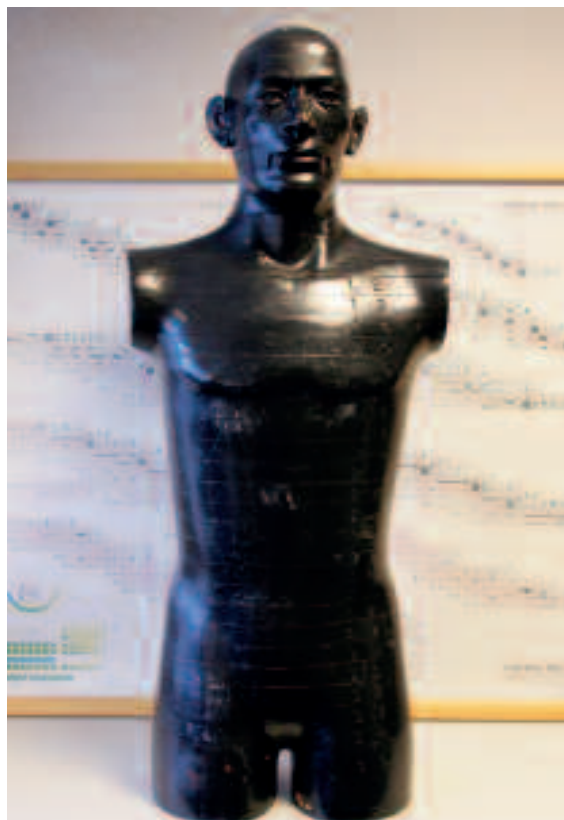
by Jacques Repussard, Director-general, and Pr Patrick Gourmelon, Director of human radiation protection – French Institute for Radiation Protection and Nuclear Safety (IRSN) – Fontenay-aux-Roses (France)

Since 2005 some twenty radiotherapy or interventional radiology accidents involving almost 600 patients have been declared in France. At the request of the minister for health or of ASN, the French nuclear safety authority, the French institute for radiation protection and nuclear safety (IRSN) has conducted an in-depth expert assessment of the causes and the consequences of nine of these accidents, the most serious in terms of clinical complications for the patients<sup>1</sup>. For the most dramatic, in Épinal, the minister for health also asked IRSN to apply its know-how in radiopathology to propose innovative therapy for volunteer patients. In relation to the number of radiotherapy or radiosurgery procedures in France (more than 180,000 patients treated each year, with constantly improving results), these accidents, gradually becoming better known thanks to the obligation to declare them, in no way cast doubt on the use of ionising radiation for therapeutic purposes.

Nevertheless, through its expert reports, the most significant of which are available on its website [www.irsn.fr](http://www.irsn.fr)<sup>2</sup>, IRSN has drawn the attention of the public authorities to a number of fundamental causes on which it is possible and necessary to take action by means of appropriate measures. The most important recommendations put forward by the have now been incorporated by the public authorities in the “radiotherapy road map” which the national cancer institute, INCa, was tasked with drawing up in cooperation with the bodies concerned and with the professions.

Moreover, the complications inherent in overdoses to organs at risk justify not only more detailed knowledge of the risks associated with the implemented protocols but also the development of innovative therapeutic strategies. IRSN has undertaken new research programmes in these two areas.

The principal recommendations on improvements to practices and the research priorities that IRSN has identified from the accident assessments with which it has been tasked are described in the following paragraphs.



“Rando” anthropomorphic phantom for patient dosimetry

## In radiotherapy, IRSN has identified four priorities for improvement

### • Better knowledge of the doses effectively delivered

The evolution of techniques towards more individualised radiotherapy delivering a high dose to a complex volume necessitates the most detailed possible knowledge of the doses effectively delivered. This demands improved knowledge of the doses delivered by the cutting-edge techniques. In addition, the growing complexity of techniques increases the risk of errors. Only the introduction of *in vivo* dosimetry provides a reliable way of detecting serious anomalies potentially leading to substantial overdoses or underdoses. Although possible at present for conventional radiotherapies, *in vivo* dosimetry suitable for innovative radiotherapy techniques such as intensity-modulated radiotherapy, tomotherapy or the *CyberKnife* has yet to be

1. Seven radiotherapy accidents were included in the study: Lyon (2004); Epinal, with three phases corresponding to different situations (2004-2005, 2001-2006 and 1987-2000); Tours (2006) and Toulouse (2006-2007). Two interventional radiology accidents were assessed: Lyon (2007) and Strasbourg (2009).

2. In the section “Avis et rapports” (opinions and reports).



developed. The increasing use of imaging for treatment monitoring also necessitates better knowledge of the associated doses, so that, if necessary, they can be taken into account in the calculation of the therapeutic dose.

Lastly, studies and research must be undertaken to define the most suitable detectors and/or the protocols to be followed in order to characterise the beams, particularly in the case of innovative techniques. In particular, improvement of techniques and protocols for dosimetry of narrow beams is one of the priorities necessitating the most urgent efforts. In the longer term, the development of 2D, 3D and dynamic *in vivo* dosimetry, taking account of patient morphology and potentially going as far as real-time control of the delivered dose, will considerably improve the dosimetric management of the most complex radiotherapy protocols.

### • Enhanced monitoring of practices

Complex techniques must be restricted to establishments that have the appropriate skills and the necessary human and equipment resources. Checks when systems are commissioned and quality controls during their use must be appropriate for the types of beam actually used for treatments. The number of professional personnel, in particular medical physicists, must be sufficient in relation to the number of patients treated and the treatment techniques used. Lastly, the organisation of medical physics in the establishment must guarantee the indispensable separation of authority between the person responsible for prescribing the treatment and the person responsible for its implementation.

### • Better personnel training

The rapid development of techniques and protocols and their increasing complexity necessitate regular updating of the knowledge and maintenance of the skills of the personnel. As soon as possible, professional training in medical physics must be brought into line with best European practices, based on a two-year curriculum, rather than one year at present. This requires the introduction of university status for medical physics.

### • Development of a safety culture

The increased complexity of techniques, software and systems makes it indispensable to design high-performance human-machine interfaces enabling the user to maintain control of the physical process implemented. Industrial firms in the sector (hardware and software), users and human and organisational factors specialists must work together to develop a safety culture, similar to that introduced in the nuclear industry.

### In interventional radiology, the IRSN has identified three priorities for improvement

#### • Better information on the delivered dose

Dosimetric information must be available in real time to the operating doctor on all systems and a warning device must be activated whenever the skin dose exceeds 2 Gy. For each interventional radiography procedure, a detailed



Homepage of the IRSN website: [www.irsn.fr](http://www.irsn.fr)

dosimetric record must be included in the patient file. Studies must be conducted to develop *in vivo* dosimetry, at least for long procedures likely to generate deterministic effects. Reference dose levels must be established at national level for diagnostic procedures and at local (establishment) level for therapeutic procedures.

### • Enhanced monitoring of practices

Before a system is put into service, the planned procedures must be optimised. A medical physicist must always be involved in this process. For long and complex procedures, the operating doctor must be assisted by an operator tasked solely with selection of exposure parameters, given the difficulty of optimising these parameters while carrying out a diagnostic or therapeutic procedure. The procedure guide drafted by the professional personnel must be revised to give better definitions of the procedures and to take better account of the technical means of dose optimisation. Industrial firms must ensure that the ergonomics of their systems facilitate access to the adjustment of the various factors influencing the dose and that the dosimetric information supplied to the users is standardised.

### • Better personnel training

Each operating doctor must be trained in the use of the displayed dosimetric information so that it can be easily interpreted and compared with a reference value specific to the system and to the procedure. Given the increasing complexity of the systems, the manufacturers must provide training for the operators on the use of their system, giving details of all the means of dose optimisation.

### IRSN has also issued several recommendations concerning research priorities

#### • Better understanding of clinical data relating to the side effects of the use of ionising radiation in medical practice

In the course of its expert assessments, IRSN has noted a deficiency of knowledge on the assessment and





quantification of the risk of complications that appear not only during innovative radiotherapies but also in conventional radiotherapy. Conventional and molecular epidemiology studies should be conducted to obtain a better understanding of radiotherapy complication rates, based on data obtained from the medical follow-up of patients. In the area of interventional radiology, use of which has been shown by European studies to be increasing by 10% to 20% per year, little work has been done on the thresholds of appearance of radiation-induced adverse effects. Epidemiological studies coordinated both by radiologists and by doctors in the various medical specialties concerned by the different types of complication encountered would contribute to better assessment and thus prevention of this risk of adverse effects.

IRSN has now undertaken studies on these lines by participating in clinical and scientific follow-up studies on targeted cohorts of patients who have developed radiotherapy complications (EPOPA study on patients involved in the Épinal radiotherapy accident) and epidemiological studies on cohorts of patients and of medical personnel exposed in radiology (O'clock study, study on the cancer risk of paediatric CT scanners, feasibility study on the cataract risk of paediatric CT scanners).

### • Increased research on the side effects of irradiations

The technical facilities for radiotherapy have become substantially more complex in recent years, with the introduction of new technologies derived from particle accelerators, capable of delivering sophisticated irradiations based on complex ballistics or beam intensity modulations. The use of these new technologies in patients must be accompanied by mastery of the knowledge of biological effects on each of the organs at risk from this type of treatment. However, there remain a number of unknowns concerning the definition of tissues and organs at risk and their clinical radiosensitivity, for example with regard to the central nervous system, as shown by feedback from the Toulouse stereotactic radiotherapy accident.

With regard to better understanding of side effects, IRSN has joined forces with the *Institut national de la santé et de la recherche médicale* (INSERM – French national institute for health and medical research) to develop a research programme (ROSIRIS) on the assessment of risks related to treatments using ionising radiation for medical purposes. This research programme is based on the combination of new concepts in the modelling of radiation-matter interactions and the radiobiology of integrated systems. In the longer term, the objective is the development of tools for estimating the risk of complications after radiotherapy and of predictive biomarkers for better screening of at-risk patients. This programme should eventually lead to improvement of the dosimetric models used routinely at present in human clinical medicine. The IRSN is also participating in the European research programme Cardiorisk on the non-cancer

effects of irradiation. This programme aims to demonstrate the biological reality underlying epidemiological studies revealing an excess risk of the development of cardiovascular pathologies for doses greater than 1 Gy.

### • Increased research on treatment of the side effects of radiotherapy

The complications of radiotherapies in the most severe cases are today still beyond the reach of conventional therapeutic regimens. IRSN considers that the development of translational research programmes with the objective of validating the use of cell therapy in the treatment of severe radiotherapy complications and ensuring its safe clinical transfer is necessary in order to provide the best possible care to the patients in these critical situations.

In the area of medical management of the side effects of radiotherapy, IRSN has taken this path by setting up an ambitious research programme on the application of cell therapy to the treatment of severe radiation-induced damage. The objective of this programme is to describe the modes of action of the adult stem cells responsible for accelerating the healing of such damage and to demonstrate the therapeutic efficacy of the grafting of autologous adult stem cells in appropriate experimental models.

In the very rapid development of radiotherapy in France in recent years, boosted by the cancer plan and technological innovations, risk management has clearly been the poor relation of progress. This has resulted in serious medical accidents, which have drawn the attention of opinion, patient associations, the public authorities and professional personnel to the urgent necessity of taking better account of the associated risks. The road map adopted by the public authorities proposes a raft of appropriate measures, some regulatory, for improving practices. But the essential may lie elsewhere: in the minds of the professional personnel, who should place at the same level of their preoccupations their concern to accomplish the optimum medical procedure for the benefit of their patient and their concern to master the risk associated with that procedure, which may be detrimental to the same patient. This is the fundamental meaning of the principles of justification and optimisation that guide radiation protection. On their own, along with the determination to apply them resolutely, these two principles, which have proven their worth in the nuclear industry, can generate considerable progress for the safety and the trust of patients and guide the pursuit of technical and therapeutic progress.

The IRSN experts and researchers in radiobiology, dosimetry and radiopathology have invested considerably in these topics following the accidents mentioned in this article. In cooperation with INSERM and hospital teams, IRSN will continue its research work to advance knowledge of the risks related to the use of ionising radiation for medical purposes and the techniques and professional practices that will reduce their scope and potential consequences. ■

## A FRENCH POINT OF VIEW

# The actions of the national radiotherapy plan

by **Dominique Maraninchi**, President and **Evelyne Fournié**, radiotherapy task force manager, French national Cancer Institute (INCa) – Paris (France)

Radiotherapy is a major discipline in cancer treatment in France, but it must adapt to the change in the profile of the disease in our country. Cancers are diagnosed earlier, and early diagnosis is a major factor in recovery.

With nearly 180,000 patients treated per year in 176 centres, radiotherapy is a curative treatment, contributing to the recovery of many cancer locations; it provides access to non-mutilating treatments, which is a major advance.

These advances are amplified by the growing use of high-precision techniques. Their aim is to optimise the dose over the entire volume of the tumour target while reducing the doses received by adjacent healthy tissues.

Moreover, the quantitative and qualitative upgrading of the installed base of radiotherapy systems has been rapid and substantial in recent years, with almost 50% of systems less than five years old. It is also marked by the disappearance of cobalt sources in favour of linear accelerators.

After the Epinal and Toulouse tragedies, in November 2007 the French Minister for Health and Sport announced national measures intended to ensure the safety and the quality of radiotherapy procedures.

A genuine emergency plan, these measures resolved a health crisis and initiated a calmer transition period (2009-2010) leading up to the deadline for bringing all the radiotherapy centres into compliance (2011).

## An emergency plan: 2007-2009

These measures, implemented in 33 actions, were included in a ministerial road map which also defined the timetable and the responsibilities of the various institutional and professional partners.

Produced by institutions concerned (learned societies, ministry with responsibility for health, French Nuclear Safety Authority and agencies), the national measures were divided into seven areas of action<sup>1</sup>: quality and safety of practices (7 measures), radiation protection monitoring (4 measures), human resources and training (7 measures), safety of systems (5 measures), relations with patients and the public (4 measures), reinforcement of inspections (1 measure) and knowledge of the discipline (4 measures).

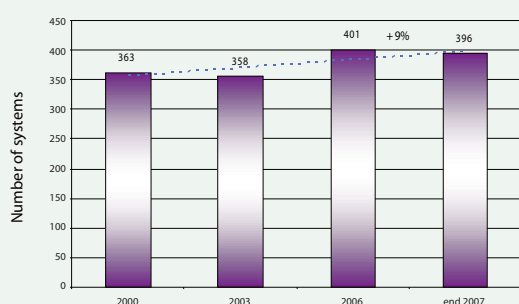
By March 2009 more than 80% of these measures were fully implemented<sup>2</sup>. The remaining actions were being finalised.

All the measures set out down in the ministerial road map concerning the safety of practices were fully implemented. ASN inspections conducted systematically since the emergency plan have been one of the factors of knowledge of organisations; they have generated input for discussions on the functioning of radiotherapy departments, in particular in the organisation of medical radiation physics.

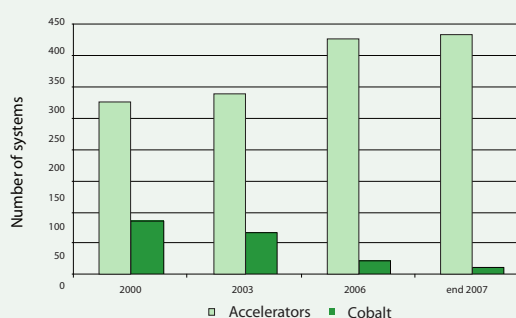
## The national radiotherapy monitoring committee

Following the emergency plan, a national committee<sup>3</sup> was set up in December 2008, chaired by INCa. This committee followed on naturally from the working group

French installed base of radiotherapy systems from 2000 to end-2007



Composition of the French radiotherapy installed base



1. For further information, refer to the first report of the national radiotherapy monitoring committee, available at [www.e-cancer.fr](http://www.e-cancer.fr)

2. Table of implementation of the 33 national measures.

3. Orders of 8 July 2008 on the establishment of a national radiotherapy measures monitoring committee.



coordinating the implementation of the national radiotherapy measures.

It is tasked with guiding and coordinating the introduction of new measures, in particular for providing guidance to the centres between now and 2011. It will also be involved in the implementation and monitoring of the next cancer plan.

This monitoring committee is organised in 5 topic groups<sup>4</sup>:

- radiotherapy professions, group coordinated by the *Société Française de Radiothérapie Oncologique* (SFRO – French society for oncological radiotherapy) and the *Société Française de Physique Médicale* (SFPM – French society for medical physics);
- radiation protection monitoring and quality, coordinated by the *Direction Générale de la Santé* (health directorate-general);
- cooperation between centres, coordinated by the *Direction de l'Hospitalisation et de l'Organisation des soins* (DHOS – hospital admission and healthcare organisation directorate);
- national support group, coordinated by the *Institut National du Cancer* (INCa – French national cancer institute);
- research and development group, coordinated by INCa, the CEA (French atomic energy commission) and INSERM (French national institute for health and medical research).

These working groups have already implemented very practical actions, in particular for guidance during the transition period.

## An interim period: 2009-2010

Initially, regulatory actions were shown to be indispensable for managing medical radiation physics practices up to 2011: interim measures have thus been proposed pending the application of the 2007 decrees on the establishment conditions and approval criteria:

– the decree of 29 July 2009 on certain technical operating conditions applicable to the cancer treatment care activity introduces the concept of the radiation physics team;

– the order of 29 July 2009 amending the order of 19 November 2004 on the training, tasks and working conditions of persons specialised in medical radiation physics incorporates these new provisions.

But the priority remains the improvement of the recruitment of the necessary human resources, particularly in radiation physics:

- the order of 29 July 2009 amending the order of 19 November 2004 on the training, tasks and working conditions of persons specialised in medical radiation physics broadens the conditions of access to the diploma;
- the DHOS circular of 17 June 2009 on the hosting of trainees within the framework of initial training requires that the CHRU (regional university hospitals) and CLCCs (cancer treatment centres) accept at least two trainees. A grant of € 5000 is paid to the establishments for the purchase of technical equipment for trainee supervision.

The objective, announced by the minister in 2007, is to attain the figure of 600 physicists in radiotherapy in 2011. The figure below illustrates the increase in the number of radiation physicists.

This increase is driven by the increase in the number of physicists in training since 2007, which has doubled, from 42 students in 2007 to 85 for the start of the 2009-10 academic year.

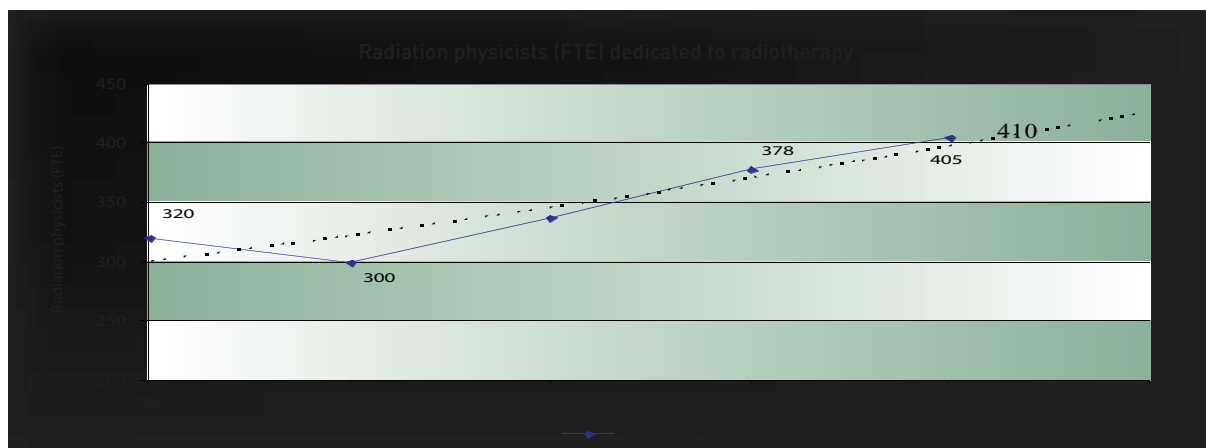
Other actions are under discussion to recognise the teaching activity of radiation physicists; university recognition of this activity is being considered.

The other key posts in radiotherapy also have the full attention of the national committee:

- a new post of dosimetry technician is to be established;
- skills in the area of quality need to be organised;
- the increase in the number of radiology technicians must be sustained in order to meet the needs in radiotherapy.

Other subjects are covered concerning radiation protection monitoring, cooperation between radiotherapy centres, organisation of healthcare activities during the

4. First report of the national radiotherapy monitoring committee, available at: [www.e-cancer.fr](http://www.e-cancer.fr)





Direction de la Qualité des soins

## Status of radiotherapy road map actions

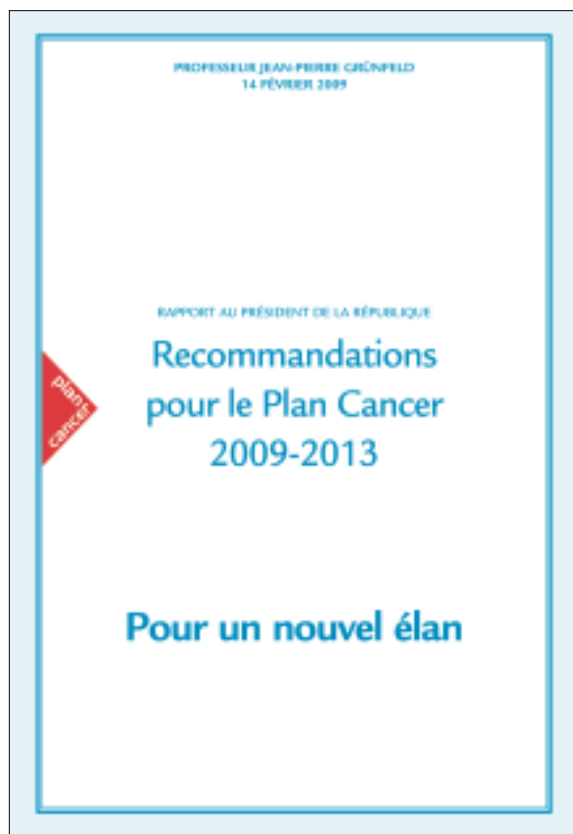
Actions	Status	april 08	may 08	June 08	July 08	aug. 08	sept. 08	oct. 08	nov. 08	dec. 08	Jan. 09	feb. 09	March 09
PART 1 : QUALITY AND SAFETY OF PRACTICES – QUALITY ASSURANCE													
1.1 Publish an ISO 9000 type quality assurance baseline for radiotherapy	C												
1.2 Define, circulate and assess the implementation of approval criteria in radiotherapy, including <i>in vivo</i> dosimetry	C												
1.3 Draw up clinical cancerology recommendations incorporating radiotherapy indications and their place in patient management strategies	C												
1.4 Draw up an external radiotherapy procedures guide	C												
1.5 Include criteria on the radiotherapy quality approach in the certification of establishments	C												
1.6 Provide support for radiotherapy centres in the integration of the quality and safety approach	C												
1.7 Draw up a guide to good practice in medical physics	IP												
PART 2 : SET UP A RADIOOTHERAPY MONITORING SYSTEM													
2.1 Draw up procedures ensuring the consistency of all radiation protection monitoring procedures in radiotherapy and draw up a guide to statutory declaration obligations	IP												
2.2 Issue a guide for use by professional personnel on the notification of radiation protection events	C												
2.3 Draw up an incident classification scale for use in communication with the public	C												
2.4 Pilot notification of healthcare-related severe adverse events involving all medical specialties, including a section on radiotherapy	IP												
PART 3 : HUMAN RESOURCES/TRAINING													
3.1 Conduct a study on the demographics of radiotherapy professionals (radiotherapists, radiation physicists and technicians)	C												
3.2 Establish the recognition of private radiotherapy practices with a status similar to that of health establishments	IP												
3.3 Publish a decree and an order intended to ensure better recognition of radiation physicists in public-sector establishments	C												
3.4 Increase the number of radiation physicists in training (year of the qualifying diploma in radiological and medical physics)	C												
3.5 Improve the place granted to radiology technicians in radiotherapy	NS												
3.6 Draw up a continuing training programme and a module for risk analysis and management in radiotherapy for health professionals	C												
3.7 Update the initial training baseline for radiation physicists and reinforce continuing training	IP												
PART 4 : SYSTEM SAFETY													
4.1 Improve the safety of software	C												
4.2 Reinforce the checks on irradiating devices placed on the market (systems and software), and in particular reinforce the checks on the language of the software and the manuals	C												
4.3 Reinforce external quality control	C												
4.4 Extend internal control to multileaf collimators, portal imaging, treatment planning systems and data verification and recording systems	C												
4.5 Improve the acceptance conditions for radiotherapy systems	C												
PART 5 : RELATIONS WITH PATIENTS AND THE PUBLIC													
5.1 Inform the public: prepare an information document intended for the general public	C												
5.2 Inform general practice doctors	C												
5.3 Draw up recommendations on communication by the establishment and the authorities to the patients concerned and the public – crisis management communication (IGAS/ASN recommendations)	C												
5.4 Set up a working group on the answers to give patients, families and associations on the consequences of radiotherapy treatments	IP												
PART 6 : INSPECTIONS AND CONTROLS													
6.1 Reinforce the ASN inspection programme	C												
PART 7 : KNOWLEDGE OF THE DISCIPLINE: ANNUAL REPORT DOCUMENTED FROM VARIOUS SOURCES													
7.1 Report on ASN inspections	C												
7.2 Radiotherapy monitoring unit	C												
7.3 Survey of radiotherapy practices	C												
7.4 Report on radiation protection monitoring declarations	C												

Action in progress IP

Action completed C

No started NS





Report by Professor Jean-Pierre Grünfeld to the French President for the National Cancer Plan 2009-2013

transitional period in relation with the DHOS/INCa circular of 14 April sent by the minister to the regional hospital agencies (ARH), which reviews the importance of the authorisation procedure for radiotherapy activities, the timetable and the requirements of this transitional regulatory process, while confirming the maintenance of the 2011 deadlines.

### Cancer plan 2

The Grünfeld report<sup>5</sup> outlined the major priorities of the future cancer plan<sup>6</sup>. For, as the minister stated, the fight against cancer must be pursued rigorously, as it is still the leading cause of mortality in France and the disease most feared by the French.

Radiotherapy will be the subject of specific actions in the plan, which will be monitored by the national committee. ■

5. Available at [www.e-cancer.fr](http://www.e-cancer.fr)

6. This plan has been announced by the French President, November 2nd, 2009



## A FRENCH POINT OF VIEW

# AFSSAPS contribution to the enhancement of the safety and the quality of radiotherapy procedures

by Dr Gérard Berthier, AFSSAPS deputy medical devices assessment director, and Nathalie Marliac, head of the medical equipment monitoring unit, AFSSAPS – Paris (France)

Radiotherapy is one of the medical specialties that is most dependent on the use of medical devices. It calls upon devices emitting ionising radiation and software for optimising the delivery of radiation, with a marked tendency for interconnection of the various links in the chain of devices by means of computer networks. This sector, characterised by its technological complexity necessitating continuous support for radiotherapists by specialist scientific personnel, is also experiencing hectic innovation.

In 2006 and 2007 French radiotherapy was confronted with two major accidents which revealed the difficulties linked with this complexity, leading the public authorities to undertake unprecedented efforts to reinforce the safety and effectiveness of radiotherapy procedures. As a consequence, in Spring 2007 all the professionals and institutions concerned started working together to implement the actions set out in the 'road map' drawn up by the minister for health.

AFSSAPS, the authority responsible for the health and safety of health products, has been heavily involved in this road map with regard to the aspects related to the safety and quality of medical devices used in radiotherapy. All stages of the life cycle of the medical devices concerned have benefited from this commitment. The work has also been an opportunity to establish close links between AFSSAPS and ASN (French nuclear safety authority), given concrete form in July 2009 by the signature of a framework agreement between the two institutions with a view to extending to other sectors a cooperation until then mainly focused on radiotherapy.

## Design of medical devices used in radiotherapy

The marketing of medical devices used in radiotherapy is governed by Directive 93/42/EEC, the so-called 'new approach' directive: free movement within the European Union of devices marked CE by their manufacturers, the CE marking indicating conformity with basic health and safety requirements stipulated by the directive. Conformity with the basic requirements is assessed by independent bodies approved by the competent authorities. The application by the manufacturers of harmonized European standards for the design of devices entails presumption of conformity with the basic requirements.



Report on the notifications received by AFSSAPS and ASN within the framework of increased vigilance in radiotherapy (external radiotherapy) – July 2007 to June 2008

The authorities do not take an active role in placing medical devices on the market, this being under the responsibility of the manufacturers. However, the authorities can influence the level of safety imparted by the harmonised standards by participating in their drafting.

As part of the road map, in July 2007 AFSSAPS conducted a survey of manufacturers to determine the use made of harmonised European standards to design the safety and ergonomics of their devices: linear accelerators (13 devices on the market, 14 standards concerned), treatment planning systems (14 devices, 8 standards) and radiotherapy recording and verification systems (4 devices, 7 standards). In parallel, a second survey was conducted on the availability of a manual in French, the language of the human-machine interface, the operator profile recommended by the manufacturer and the user

training materials. This dual survey led in August 2007 to a notice to the manufacturers reminding them of the measures that had to be implemented to cover the basic requirements of the directive for medical devices used in radiotherapy.

During the same period, AFSSAPS also examined the potential weak link represented by the use by radiotherapy centres of 'in-house' calculation software. Such software, developed by the centres themselves and so not placed on the market, does not benefit from the conformity assessment provisions stipulated by CE marking. It was revealed that 55% of the 180 radiotherapy centres were using 'in-house' software, which led AFSSAPS in July 2008 to draw the attention of the centres to the safety problems raised specifically by such software.

### **Acceptance of medical devices used in radiotherapy**

The acceptance of radiotherapy systems newly acquired by the radiotherapy centres or after their modification is an eminently critical operation, a potential source of accidents in routine use of such systems. For this reason the issue of acceptance was also highlighted by the road map as needing to be covered by specific recommendations.

Technically difficult, acceptance also involves a number of participants, who must be coordinated, each having to be clearly aware of the task they have to accomplish during the various steps, including procurement of the device, installation, acceptance testing, technical acceptance, device commissioning, user training, and statutory quality control before putting into service. Some of the operations are under the responsibility of the supplier, others that of the radiotherapy centre.

With the collaboration of an ad hoc working group including representatives of the professions concerned, in March 2008 AFSSAPS published recommendations intended to offer suppliers and centres a method for formal implementation of each step of acceptance and clarification of the responsibility of each of the protagonists involved in these steps.

This document, general in scope, was supplemented in July 2009 by joint publication with ASN of recommendations concerning the conduct of dosimetric measurements for calibration of 'minibeams' used in stereotactic radiotherapy, based on the conclusions of a report produced by IRSN (French institute for radiation protection and nuclear safety) at the request of AFSSAPS and ASN.

### **Market monitoring and incident monitoring**

Although they are not involved directly in the process of placing medical devices on the market, the authorities nevertheless have two a posteriori levers for ensuring the safety of devices placed on the market from the health point of view.

Market monitoring consists in verifying that devices are placed on the market in accordance with the regulatory provisions in force. If necessary, it may lead to the issue

of conformity requests to the manufacturers. Since 2002, France has introduced statutory provisions requiring manufacturers to communicate to AFSSAPS all information on devices newly placed on the market, including those in class IIb to which devices used in radiotherapy belong. In this area the number of communications has increased from an average of 6 per year during the period 2003-2006 to an average of 23 per year for the period 2007-2008. Since 2007 AFSSAPS has monitored these devices closely, particularly with regard to the standards referred to by the manufacturers, the human-machine interface and the instruction manual.

Incident monitoring is based on incident reports submitted to the authorities by health professionals. Two incident monitoring systems cohabit in radiotherapy: equipment monitoring, which is an AFSSAPS responsibility, concerns incidents or risks of incidents involving medical devices during their use. In addition, persons responsible for nuclear activities must declare to ASN any incident or accident likely to harm the health of persons exposed to ionising radiation.

In radiotherapy, the number of reports received by AFSSAPS increased five-fold between 2006 (18 reports) and 2008 (89 reports), while the total number of equipment monitoring reports remained stable (about 8,000 per year). From July 2007 to June 2008, corresponding to the experimental period for introduction of the ASN notification system, 87 reports concerning serious incidents or risks of serious incidents were communicated to AFSSAPS.

Half of these 87 reports came from industrial firms and half from radiotherapy centres: over this period, 23 radiotherapy centres declared directly to AFSSAPS 31 incidents involving radiotherapy devices. The large proportion of reports from industrial firms, which is not observed in other medical device categories, can be at least partly explained by AFSSAPS work on raising awareness among industrial firms in this area.

Of the 87 declared reports, 82 have now been assessed and 58 reports have led to one or more safety actions on the device: modification of the device design (software updates), modification of manufacture, mailing of information and/or recommendations for use of the devices concerned to the users by the manufacturer or by AFSSAPS, AFSSAPS user survey, etc. Only 7 of these 87 reports included evidence of established inappropriate treatment, with or without clinical consequences.

The substantial increase in the number of equipment monitoring reports concerning radiotherapy devices and the potential seriousness of such incidents led AFSSAPS to set up a group of specialist experts in radiotherapy (radiotherapists, radiation physicists, biomedical engineers, dosimetrists) and radiologists, tasked with issuing opinions on the causes of incidents and the measures to be taken. AFSSAPS has also introduced a file of radiotherapy centres enabling very rapid (within an hour) distribution by fax of safety-related information or surveys to all the

radiotherapy centres potentially concerned. Lastly, exchange of information relating to equipment monitoring incidents between European competent authorities has been increased.

When reports also concern a radiation protection problem, joint AFSSAPS/ASN actions are implemented. This collaboration began in 2005 following an accident at the Grenoble university hospital, resulting in the issue of a joint AFSSAPS/ASN circular and the introduction of an information exchange procedure. Over the period June 2007 – July 2008, 11 mixed radiation protection monitoring events in external radiotherapy, falling within the definitions of a significant radiation protection event and an equipment monitoring incident or risk of incident, were subject to coordinated investigations of industrial firms and users by AFSSAPS and ASN. Five of the 11 mixed events necessitated investigations by the authorities in order to identify the centres potentially concerned and/or the consequences for the patients. In this context, 6 inquiries were conducted by AFSSAPS and ASN, including two joint inquiries.

This collaboration between AFSSAPS and ASN resulted in the preparation of a joint statement for the period June 2007 - July 2008, as stipulated by the road map.

### **Quality control of external radiotherapy systems in use**

Quality control of medical devices was introduced by a provision of the 1998 act on the reinforcement of health monitoring and control of the safety of products intended for humans and its implementation decree published in December 2001. The order of March 2003 initially limited the list of medical devices subject to quality control to devices emitting ionising radiation. This control is both internal, carried out under the responsibility of medical device operators, and external, carried out by inspection bodies approved by AFSSAPS, according to procedures defined by AFSSAPS decisions in both cases.

In March 2004, AFSSAPS issued two decisions defining the internal and external quality control procedures for external radiotherapy systems, undertaking to review these decisions after an initial three-year control cycle.

The review work on this programme, undertaken in 2006, was finalized within the framework of the road map. As a result, three further decisions were issued by AFSSAPS in July 2007, in consultation with the professions concerned, in order to reinforce the quality control of external

radiotherapy systems: extension of internal controls to multileaf collimators, portal imaging systems, treatment planning systems and data verification and recording systems; introduction of an additional external control — for any modification of any component of the radiotherapy chain, the operator must now have a new external quality check carried out; and lastly, introduction of an annual internal control audit.

### **Current and future work**

On 15 December 2008 the minister of health and sport inaugurated the national committee for monitoring of national radiotherapy measures, chaired by Professor Dominique Maraninchi, president of INCa (French national cancer institute), tasked with monitoring the implementation of road map actions and also with preparing for 2011, date of application of the radiotherapy centre approval criteria. Radiation protection monitoring is one of the working priorities of this committee.

In addition ASN and AFSSAPS, both members of the national monitoring committee, have signed a framework agreement to strengthen the synergies between the two institutions in the area of health products emitting ionising radiation. The 2009-2010 work programme includes the establishment of a joint portal for online notification of mixed radiation protection monitoring events, a critical analysis of the basic health and safety requirements of Directive 93/42/EEC with regard to radiation protection, and reinforcement of the monitoring of quality control implementation.

### **Conclusion**

In November 2007, 33 national measures intended to reinforce the safety and the quality of radiotherapy procedures were set out in a road map intended for the health professionals and institutions concerned. An unprecedented mobilisation resulted in the implementation of 80% of the planned measures by December 2008, and even 100% of those coordinated by AFSSAPS. The establishment of the national radiotherapy monitoring committee consolidates these achievements.

A substantial part of the road has been travelled, but much remains to be done between now and 2011, date on which French radiotherapy will have accomplished its transformation. In this perspective, as in the past and in accordance with its mission, AFSSAPS will continue to make its contribution to reinforcing the safety and the quality of French radiotherapy. ■



## A FRENCH POINT OF VIEW

# Certification of health establishments, assessment of professional practices and external radiotherapy

by **Nafissa Abdelmoumene**, project leader, and **Raymond Le Moign**, Director of healthcare quality and safety improvement – French National Health Authority (HAS) – Paris (France)

The tasks of the *Haute Autorité de Santé* (HAS – French national health authority) include the improvement of the quality of care in healthcare establishments and medical practices, based on the following procedures:

- certification of healthcare establishments as a mandatory procedure, applicable every four years to all establishments: this represents an appraisal of the quality of an establishment and, from the second procedure (ANAES, 2004), incorporates a section on assessment of professional practices (APP);
- assessment of professional practices, mandatory, every five years for doctors: it requires clinical practice based on recommendations and its analysis with regard to these recommendations. This system is being revised as part of the definition of the new obligation of continuing professional development;
- drafting of recommendations on good professional practices and definition of protocols for care pathways for patients with long-term diseases (ALD) such as ALD30 “Malignant tumour, malignant disease of the lymphatic or haematopoietic tissue”;
- implementation of quality indicators.

## Certification of healthcare establishments and external radiotherapy (ERT)

The procedure for certification of healthcare establishments appraises the quality and the safety of the care according to a generalist and cross-functional approach at establishment level: general baseline, non-exhaustive inspection, generalist experts-inspectors. It is not a specific certification of each of the sectors of activity accommodated in the establishment.

### V2007 certification procedure for healthcare establishments and external radiotherapy

Following the Epinal radiotherapy accident (*Inspection générale des affaires sociales* (General inspectorate of social affairs), 2006) and in accordance with the national external radiotherapy road map (Ministry for Health, 2007), the HAS introduced into the 2007 certification manual (HAS, 2007), which will be operational until 2010, a criterion (33a) for the introduction of quality assurance in external radiotherapy (ERT), in consultation with the *Autorité de Sureté Nucléaire* (ASN – French nuclear safety authority) (HAS – ASN agreement, 2008), the Institut National du Cancer (INCa – French national

cancer institute) (HAS – INCa agreement, 2007), the *Mission Nationale d’Expertise et d’Audit Hospitaliers* (MEAH – French national hospital expert assessment and audit task force) and the *Société Française de Radiothérapie Oncologique* (SFRO – French oncological radiotherapy society).

To assess the extent to which the ERT sector satisfies this criterion, the expert-inspectors, as well as taking into account the opinions and recommendations of the monitoring and inspection agencies, examine the quality documentation and the application of national baselines, verify the adequacy of the human resources and the plan for personnel training on new equipment and techniques, the management of equipment resources and their maintenance logs, the organisation of patient management (from initial appointment to post-treatment follow-up) and the interfaces with the other sectors of activity, prevention of healthcare-related risks and management of dysfunctions, including their analysis and feedback from experience in order to avoid their repetition, and the introduction of improvement actions.

### Changes in the V2010 healthcare establishment certification procedure

In the V2010 procedure, the HAS has revised its information sharing with ARH (regional hospital agencies) and ARS (regional health agencies), both upstream and downstream of inspections. Upstream, this involves reception by the HAS, five months before the inspection, of the HAS – ARH/ARS interface document which reviews the specific features of the establishment and its situation with regard to statutory health safety and conformity of healthcare activities subject to authorisation.

### ERT among the major risk activities in V2010 (criterion 26b)

The expert inspectors are not competent to appraise the safety of equipment, treatment preparation and execution steps and treatment validation, systematic controls and, in particular, in vivo dosimetry, falling within the scope of ASN inspections. The HAS expectations with regard to patient management quality are:

- in terms of coordination, organisation (E1):
  - the production of an inventory of the risks related to the activity (ASN, 2009) and the prioritisation of these risks, with a view to defining a quality policy with



precise objectives and implementing a programme of preventive actions and monitoring. The documents made available might include, for example, the project of the sector and the partnership agreements, the personnel continuing training plan [training on equipment and techniques, in particular when they are new, and on the notification of adverse events (refer to criteria 3a, 3b, 8f)], the patient booklet providing information about ERT, the quality manual/written procedures, protocols, updated as required, the thesaurus of good practices and, if appropriate, the ISO 9001 (quality management system) certificate of the declared sector(s) of activity;

- a reliable system of information exchange with the other sectors, ideally integrated into the hospital information system, and taking account of the radiotherapy system maintenance programme in patient scheduling.

– in terms of implementation (E2):

- effective operation of the quality approach under the responsibility of the person tasked with quality assurance;
- application by the professional personnel of the procedures and standard protocols derived from INCa, SFRO and HAS good practice recommendations throughout patient management and follow-up;
- recording of the decisions of the multidisciplinary discussion meeting, and of the procedures and verifications carried out, in the patient file/individual care programme;

– in terms of assessment-analysis-improvement (E3):

- activity report with any deviations from the defined objectives, their analysis and proposed solutions;
- existence of an adverse event log, adverse event analysis documentation, internal communication on improvement actions in the context of feedback from experience (refer to criteria 8f, 8i, 28a);
- internal audit report, tracking of quantitative (volume of activity with respect to resources) and qualitative (ERT waiting times according to pathology, morbidity, survival time, patient satisfaction, etc.) indicators (refer to criterion 28c);
- implementation of improvement actions and assessment of their effectiveness.

### Upstream data for establishments treating cancer by ERT

The observations on safety formulated by the MRIICE (regional and interdepartmental inspection, control and assessment office) and the ARH/ARS may lead the HAS to postpone the certification inspection, and this decision is made public on the HAS website. In the absence of statutory controls in a critical health safety area, the HAS asks the establishment and the competent supervisory authority to take all necessary measures to implement the control actions rapidly and to inform the ARH/ARS of this.



HAS headquarters building at Saint-Denis La-Plaine (France)

### Statutory equipment and radiation protection monitoring in V2010 (criterion 8i).

The newly-introduced radiation protection monitoring organisation (Art L.1333-3 of the French public health code, ASN 2007) is designed to enable professional personnel to notify any significant event likely to harm the health of a patient, a user or a third party by exposure to ionising radiation.

### The APP approaches in cancerology in V2010 (criterion 28a)

are incorporated into the relevant section.

A number of generic criteria, often in the form of priority required practices<sup>1</sup> (PRP), are also applicable to the ERT activity (refer to box 3).

### Assessment of professional practices in the health establishment certification procedure

APP consists of “analysis of professional practice with reference to recommendations and according to a method developed or validated by the HAS and includes the implementation and follow-up of practice improvement actions” (decree of 14 April 2005).

### APP in the V2/V2007 procedure

Starting with the second establishment certification procedure (V2) (ANAES, 2004), implemented between 2005 and mid-2008, HAS set itself the objective of appraising the therapeutic value to the patient by APP. The topic of external radiotherapy was not included in V2. The V2 manual was revised and entitled V2007. V2007 includes a criterion concerning ERT, and its APP section was improved compared with V2 by the definition of appraisal points for any APP approach and of the number of actions to be completed according to the characteristics of the establishment, but without fundamental modification of the references.

In the V2/V2007 procedures APP is the subject of three approaches:

- relevance of practices (reference 44 in V2, 40 in V2007);
- care-related risk (reference 45 in V2, 41 in V2007);
- medical management of the main pathologies or health problems (reference 46 in V2, 42 in V2007).

1. PRPs are criteria subject to systematic standardised examination by the expert-inspectors and to a more stringent scoring scheme than that of the other criteria.





The appraisal points applicable to the three approaches are set out as follows:

- choice of a topic with potential for improvement;
- analysis of the organisation and practices according to a method appropriate for the objective (ANAES, 2003, 2004, HAS 2005, 2006, 2006, 2006, 2008);
- positioning with respect to references (recommendations, baselines, etc.);
- definition of improvement objectives;
- implementation of improvement actions;
- measurement of the results of the improvements (indicators or other follow-up method).

### Overview of V2/2007 APPs “assessment of the relevance of practices” in ERT

Assessment of the relevance of practices consists in analysing the match between the diagnostic or therapeutic procedures and the needs of the patient against a validated grid. This approach has been very rarely (and not at all in V2) chosen by the ERT sectors. Examples:

- assessment of the relevance of palliative radiotherapy by case file audit in 2004 and 2006, using a grid constructed on the basis of literature data and previous experience at the centre: the nature of the defined improvement actions was not specified, but they were implemented and assessment of their effectiveness was planned;
- audit of multidisciplinary discussion meetings for bronchial cancer set up since 2001, approved by a cancerology network: in fact, only the completeness of these meetings with regard to all new files and the effective application of the decisions taken at the meetings were analysed, with no assessment of the relevance of the therapeutic decision with regard to the cited good practices.

### Overview of V2/2007 APPs “assessment of care-related risk” in ERT

In V2, the rareness of choice of ERT-related topics is confirmed. Two establishments assessed the risks related to patient management in radiotherapy with regard to the regulations. Failure mode, effects and criticality analysis (FMECA) was used. In one case, the following improvement actions were identified: “use the electric hoist whenever possible, replace the machines, generalise radiographic controls for curative treatments, control patient positioning by infrared detection”. In the second case, organisational changes were made (new procedures), while measures necessitating investment in equipment were postponed.

In V2007 a significant increase in APP on this topic is observed, as a result of the media coverage of the Epinal accident, the establishment of experience feedback committees (CREX) in the radiotherapy sectors (MEAH, summary report 2009) and the availability to professional personnel of reference guides, including those relating to external radiotherapy procedures 2007 (SFRO 2008) and to the notification of significant events (ASN, 2007): organisational improvement, formal procedures for parameter controls, development of task protocols, verifications of patient identity (inclusion of the patient's

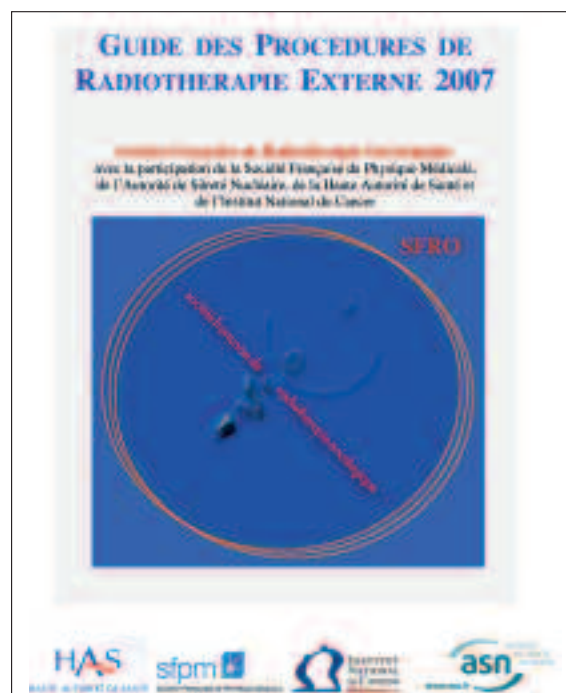
photograph in the file) and the side to be treated are reported, along with sector computerisation to facilitate data recording, follow-up and feedback to the professional personnel. Benchmarking is initiated with other centres and the assessment is reported as continuous.

### Overview of V2/2007 APPs “assessment of management of the main pathologies and health problems” in ERT

The topics of general, medical or surgical oncology are more frequent than those of ERT. The choice by the establishment of the management to be assessed is motivated:

- most often, by the frequency of the pathology (breast cancer, colon cancer) or by its seriousness: for example, aiming for conformity of radiotherapy waiting times for patients with breast cancer, with guidance from MEAH;
- by aiming for improvement of multidisciplinary management through better organisation, traceability and exhaustiveness of multidisciplinary discussion meetings or better coordination of the participants in complex management cases (example of ENT cancer with concomitant radiochemotherapy and supportive care indication);
- sometimes by management cost;
- by the status of the establishment as reference centre for the management of a rare cancer (example of sarcomas);
- by the complexity of the management and the existence of poorly-coded data (example of medulloblastomas in children).

The initial informing of the patient was also the topic of an APP with actions to improve the announcement system (conditions and content of the information, announcement training for professional personnel, traceability of the delivered information).



Guide to external radiotherapy procedures, 2007

In summary, whereas APPs related to ERT were rare in V2 (2005 to mid-2008), with the choice of the establishments, including the cancer treatment centres, more oriented towards general practice topics relating to supportive care, in V2007 a cultural change is perceptible, probably a consequence of the MEAH work and the national radiotherapy road map measures. The majority of the pathology management improvement actions are at the definition stage and their implementation is scheduled. The V2010 certification reports should throw some light on their results.

## APP changes in the V2010 procedure

APP changes essentially concern:

- the PRP status of the criterion on APP policy and organisation (1e): the establishment must demonstrate continuity of the assessment culture and rollout of APP to all sectors of activity by monitoring its APP management chart, produced in a format defined by the HAS which includes the results of improvement actions (HAS 2009);
- the obligation of APP approaches in cancerology (28a) concerning respectively:

- holding and assessment of multidisciplinary discussion meetings (HAS 2006, Institut National du Cancer 2007) with regard to their exhaustiveness and the quality of the therapeutic decision based on good practice baselines, and

- analysis of morbidity and mortality according to the HAS methodology (HAS 2009), similar to the experience feedback committees, recommended by the MEAH (MEAH 2009), which the establishments started to report on in the V2007 procedure;
- the use of indicators for monitoring the quality of management of pathologies (28c).

In addition, the assessment of the relevance of practices (28b) is maintained.

APP approaches, individual or collective (medical care and/or multidisciplinary), on freely-chosen topics are possible, subject to their consistency with the quality improvement programme of the establishment and their methodology conforming to that recommended by the HAS.

## Conclusion

The health establishment certification procedure and its APP section based on day-to-day application of good practices and, in V2010, generalised to all activities, contributes through a generalist approach to improving the quality and the safety of care and probably the results of patient management. However, the procedure has not been designed to assess complex multidisciplinary specialties such as ERT. ■

## References

1. Agence nationale pour l'accréditation et l'évaluation en santé. Manuel d'accréditation des établissements de santé. Deuxième procédure. Septembre 2004. Direction de l'accréditation et de l'évaluation des pratiques. ([www.has-sante.fr](http://www.has-sante.fr)).
2. Agence nationale d'accréditation et d'évaluation en santé. Chemin clinique 2004.
3. Agence nationale d'accréditation et d'évaluation en santé. Revue de pertinence des soins. Guide méthodologique. 2004.
4. Agence nationale pour l'accréditation et l'évaluation en santé. Réussir un audit clinique et son plan d'amélioration. Guide méthodologique. 2003.
5. Arrêté du 22 janvier 2009 homologuant la décision ASN N° 2008 DC 103 du 1<sup>er</sup> juillet 2008, fixant les obligations d'assurance de qualité en radiothérapie définies à l'article R.1333-59 du Code de la santé publique.
6. ASN. Guide de management de la sécurité et de la qualité des soins de radiothérapie. 2009. ([www.asn.fr](http://www.asn.fr)).
7. ASN. Guide d'auto-évaluation des risques encourus par les patients en radiothérapie externe. 2009.
8. ASN. Guide ASN/DEU/03 relatif aux modalités de déclaration et à la codification des critères relatifs aux événements significatifs dans le domaine de la radioprotection hors installations nucléaires de base et transports de matières radioactives ; 2007.
9. Code de la santé publique. Articles R.1333-59 à R.1333-66 relatifs à l'application du principe d'optimisation lors d'exposition aux rayonnements ionisants.
10. Code de la santé publique. Article L.1333-3 relatif à la déclaration de tout incident ou accident susceptible de porter atteinte à la santé des personnes par exposition aux rayonnements ionisants.
11. Code de la santé publique. Articles R.6124-131 à R.6124-134. (introduit par décret n° 2007-389 du 21 mars 2007 relatif aux conditions techniques de fonctionnement applicables à l'activité de soins du traitement des cancers).
12. Directive Européenne 97/43 du 30 juin 1997 relative à la protection sanitaire des personnes contre les dangers des rayonnements ionisants lors d'expositions à des fins médicales.
13. European Commission guideline on clinical audit for medical radiological practices (diagnostic radiology, nuclear medicine and radiotherapy). Final draft of 1st December 2008.
14. HAS. Manuel de certification des établissements de santé V2010. Direction de l'amélioration de la qualité et de la sécurité des soins. Juin 2009.
15. HAS. Guide préparer et conduire votre démarche de certification V2010. Guide pratique. Juin 2009.
16. HAS. Tableau de bord EPP V2010. 2009. ([www.has-sante.fr](http://www.has-sante.fr)).
17. HAS. Guide de revue de mortalité et de morbidité (RMM). Evaluation et amélioration des pratiques. Juin 2009.

18. HAS. Registres, observatoires, bases de données et évaluation des pratiques professionnelles. Méthodes d'amélioration des pratiques. 2008.
19. HAS. Accord cadre HAS- ASN pour améliorer la sécurité des pratiques professionnelles dans le domaine des soins médicaux utilisant les rayonnements ionisants. Communiqué de presse. 16 décembre 2008.
20. HAS. Accord de coopération HAS-INCA sur l'harmonisation des documents pour les professionnels de santé et sur l'accès aux soins des patients atteints de cancer. Dossier de presse 3 juillet 2007.
21. HAS. Manuel de certification des établissements de santé V2007. Direction de l'amélioration de la qualité et de la sécurité des soins. ([www.has-sante.fr](http://www.has-sante.fr)).
22. HAS. Le staff EPP des équipes hospitalières. Méthodes d'amélioration des pratiques. 2006.
23. HAS. Réunion de concertation pluridisciplinaire en cancérologie. Méthodes d'amélioration des pratiques. 2006.
24. HAS. Réseaux de santé : guide d'évaluation. Méthodes d'amélioration des pratiques. 2006.
25. HAS. Maîtrise statistique des processus en santé. Méthodes d'amélioration des pratiques. 2005.
26. HAS. Radiothérapie extra-crânienne en conditions stéréotaxiques, 2006.
27. HAS. Radiothérapie conformationnelle avec modulation d'intensité, 2006.
28. HAS. Guides médecin affection de longue durée. ALD 30 - Tumeur maligne, affection maligne du tissu lymphatique ou hématopoïétique. 2008 à 2009.
29. Inspection générale des affaires sociales. Résumé du rapport ASN n° 2006 ENSTR 019 - IGAS n° RM 2007-015P sur l'accident de radiothérapie d'Epinal, présenté par Guillaume WACK (ASN), et le docteur Françoise Lalande, membre de l'Inspection générale des affaires sociales, avec le concours de Marc David Selingman. Février 2007 ([www.asn.fr](http://www.asn.fr)).
30. INCa. Guide pour la pratique quotidienne de la dosimétrie in vivo en radiothérapie externe, INCA, SFPM, ASN, 2008. ([www.e-cancer.fr](http://www.e-cancer.fr))
31. INCa. Critères d'agrément pour la pratique de la chirurgie des cancers, de la chimiothérapie et de la radiothérapie externe, adoptés par délibération du conseil d'administration de l'Institut national du cancer le 20 décembre 2007 ([www.e-cancer.fr](http://www.e-cancer.fr)).
32. Ministère de la santé. Mesures nationales pour la Radiothérapie, 29 nov 2007 ([www.sante-jeunesse-sports.gouv.fr](http://www.sante-jeunesse-sports.gouv.fr)).
33. Mission Nationale d'Expertise et d'Audit Hospitaliers. Organisation et sécurité des services de radiothérapie. Mise à jour mars 2009. ([www.meah.sante.gouv.fr](http://www.meah.sante.gouv.fr)).
34. Société Française de Radiothérapie Oncologique. Guide 2007 des procédures de radiothérapie externe. 2008. ([www.sfro.org](http://www.sfro.org)).



## A FRENCH POINT OF VIEW

# Quality in radiotherapy: the actions of the French society for radiation oncology (SFRO)

by Jean-Jacques Mazeron, President of SFRO, Radiation oncology department, Pitié-Salpêtrière – Paris, Françoise Mornex, Secretary-general of SFRO, Radiotherapy and Oncology Unit Lyon-Sud – Pierre-Bénite Hospital complex, François Eschwège, Administrative director of SFRO, Antoine Bécère Center – Paris, et Éric Lartigau, President of SFRO (2010–2011), Radiotherapy Department Oscar-Lambret Center – Lille (France)



20th National SFRO Congress on young radiation oncologists – Paris, 21 to 23 October 2009

Radiotherapy, introduced more than a century ago, has become one of the essential therapeutic means of cancer treatment. Over the last decade it has benefited from unprecedented technological development, in parallel with the increasing power of computers and the progress in three-dimensional imaging. The patient is offered treatment by techniques that would have been difficult to imagine possible at the end of the last century. As a corollary, professional personnel are confronted with the necessity of continuous and rapid updating of their knowledge. They are thus responsible for finding a compromise between two risks, that of not rapidly offering their patients technical developments with undisputable benefits, and that of making treatments available before all the safety conditions have been satisfied. Recent events, in

particular those in Épinal and Toulouse, remind us of this compromise [8]. It must be added that good practice of optimised techniques also requires that the various personnel involved devote more time to it, which, in a period when their number is not increasing, raises further problems.

Under these conditions it is easy to understand that reinforcing the quality and the safety of treatments has become more than ever the primary objective of radiation oncology. The ministry for health has clearly realised this and nearly three years ago proposed to both guide and help the professional personnel of the speciality within the framework of what is commonly referred to as the “road map”. This is a series of measures to be taken over a period of about five years which supplement those already implemented as part of the Cancer Plan and which cover investment in equipment, recruitment of personnel, equipment safety, treatment safety, improvement of practices, organisation of departments, declaration of serious adverse events, and other matters.

## Support for management of overexposed patients and resumption of activity at the Centre Jean-Monnet in Épinal

The external irradiation accident that occurred at the Centre Jean Monnet in Épinal led the authorities to halt all treatments completely [8]. The management of the medical activities of the centre, including the victims of the accident, was taken over, in collaboration with IRSN, by a group of seconded doctors and physicists, initially from the Centre Alexis-Vautrin in Nancy (D. Peiffert, A. Noël and coworkers), SFRO (F. Eschwège), the Pitié-Salpêtrière hospital group in Paris (J.-M. Simon), and the Centre G.-F. Leclerc in Dijon (P. Maingon). This enabled treatment activities to be resumed in March 2008 within the framework of a *Groupe de coopération sanitaire* (GCS – health cooperation group) with the Centre Alexis Vautrin.

## Main SFRO actions within the road map framework

The road map is a series of actions to be completed in order to improve the safety of practices, the quality of

healthcare, and monitoring in radiation oncology. It was drawn up by the ministry for health, and INCa was tasked with monitoring its implementation. It defines the timetable of the actions and the respective responsibilities of the various institutional and professional partners. It includes regular meetings attended by representatives of SFRO, SNRO (*Syndicat des radiothérapeutes oncologues* – association of radiation oncologists), SFPM (*Société française de physique médicale* – French society of medical physics), ASN (*Autorité de sûreté nucléaire*, the French nuclear safety authority), HAS (*Haute autorité de santé* – French national health authority), DHOS (*Direction de l'hospitalisation et de l'organisation des soins* – hospitalisation and healthcare organisation directorate), IRSN (*Institut de radioprotection et sûreté nucléaire* – institute for radiation protection and nuclear safety), AFSSAPS (*Agence française de sécurité sanitaire de produits de santé* – French health product safety agency), InVS (*Institut national de veille sanitaire* – national health monitoring institute), SFOM (*Syndicat national des oncologues médicaux* – national association of medical oncologists) and AFPPE (*Association française du personnel paramédical d'électroradiologie* – French association of paramedical radiology personnel). To date more than 70% of the tasks planned in the road map have been completed. Those in which SFRO is or has been involved are summarised below.

#### *Participation in the INCa working group tasked with proposing approval criteria for the practice of external radiotherapy*

Since 2005 INCa has organised a series of meetings with the objective of supplying the regional hospitalisation agencies with a list of approval criteria for the practice of external radiotherapy. The INCa board approved the final list of 18 criteria by a vote at the end of 2008. These criteria will come into effect in 2011 [6].

#### *Establishment of a national monitoring unit*

The introduction of measures decided as part of the cancer plan cannot be assessed unless there are reliable and above all regularly-updated statistical data on the installed base of radiotherapy equipment; the demography of radiation oncologists, practising or in training, hospital physicists, radiology technicians; the activity of radiation oncology centres; the introduction of new techniques, etc. The first survey was conducted in 2007, backed by INCa, ASN, SFPM, SNRO and CNAM (*Caisse nationale d'assurance maladie* – national health insurance fund) and in collaboration with ONDPS (*Observatoire national des professions de santé* – national health professions monitoring unit). The responses to the questionnaire sent to each radiation oncology centre were collected by INCa and analysed. The results of this first survey covering 161 centres were presented at the annual congress of SFRO in 2007 and published in *Cancer Radiothérapie*, issue 5, 2008. A new survey has been conducted recently [2] and it is planned to repeat the survey each year.

#### *Guide to external radiotherapy procedures*

A working group, in collaboration with INCa, ASN and HAS (which contributed its methodology), has produced a guide to “good practices” in radiation oncology [7]. The objective of the guide, which includes chapters of general information and others covering the cancers encountered most commonly, is to give recommendations for performing high-quality radiotherapy under optimum safety conditions. These recommendations naturally take account of the available equipment, and although 3D conformal radiotherapy has most often been considered as the “standard”, two-dimensional radiotherapy has by no means been sidelined where the group of experts judged that it was still applicable, and at the opposite end of the technological spectrum intensity-modulated conformal radiotherapy (IMRT) has been recommended where they considered that it contributed a benefit and could be performed under good safety conditions. The guide, which it should be remembered is not binding, was published in issue 3-4 of *Cancer Radiothérapie* (2008) [4]. Its principal objective is to achieve uniformity of practices throughout France. The guide is currently being updated.

#### *ASN-SFRO incident/accident scale*

The declaration of patient radiation protection events, i.e. differences between the dose (total or per fraction) delivered to the tissues as specified by the treatment plan signed jointly by the physicist and the radiation oncologist and the dose effectively delivered, whether such overdoses could be partially or completely “corrected” or not, defines, according to ASN, an incident or an accident (term employed when the overdose has caused or is likely to cause severe effects). The confusion that has arisen between major events and others that can be qualified as minimal or minor, for example when communicating to the public, has made it necessary to develop a scale of seriousness of such events. This work was done by a working group led by ASN in 2007, resulting in the ASN-SFRO scale, derived from the scale used for nuclear installations (INES, international nuclear event scale) [3]. The ASN-SFRO scale has eight levels (0 to 7), and has completed its one-year trial period. It has been assessed by means of a questionnaire addressed to the radiation oncology centres, and undergone minor revision after analysis of the responses.

#### *Monitoring of unexpected serious adverse events*

At the end of 2006 SFRO reached agreement in principle with InVS to institutionalise the declaration of serious adverse events, i.e. severe unexpected complications of radiotherapy, with the objective of monitoring such events, as must be done in the other medical specialities [5]. SFRO has nevertheless requested that these declarations to InVS exclude those already made to ASN for radiation protection events (these declarations would be transmitted to InVS by ASN). It also requested that all event declarations (including equipment monitoring declarations to AFSSAPS) be made through a single entry





point, to be defined, so as to simplify the procedures. With the same concern to facilitate procedures, a declaration guide is being drafted by INVS.

### *Ministerial mission conferred on SFRO*

Prepared by the then minister for health, solidarity and the family, Xavier Bertrand, with the help of his staff, mandated by his successor, Philippe Bas, and finally confirmed by the present minister, Roselyne Bachelot, a mission was conferred on SFRO to "make proposals so that the measures that will be implemented take into account the demographic situation of professional radiotherapy personnel and the high level of skill required (training pathways; career development; collaboration with medical oncologists, interns and assistants; delegation of tasks; pooling of human and equipment resources between the public and private sectors". Mr Bolla coordinated this mission, which involved representatives of the societies and professional associations concerned. The mission was completed early in 2008 by the submission of a report to the minister [1].

### *Support unit for radiation oncology centres in difficulty*

In 2007 ASN inspected all French radiation oncology centres and then wrote to the heads of establishment asking them, if necessary, to review a number of safety points, such as the physics organisation plan, equipment checking procedures and patient identification procedures. Following these inspections a number of centres were in difficulty, and a small number were even obliged to close down temporarily in the absence of immediate measures. INCa set up a support unit for these centres, in which SFRO, SFPM and the hospital federations participated. This led to several members of the support unit conducting on-site inspections in order to help identify solutions.

### *ASN quality management baseline*

At the request of the ministry for health, ASN has produced a quality management baseline derived from the ISO 9001 standard. SFRO, SFPM and SNRO participated in several meetings at which the text was adapted to the practice of radiation oncology. The application of the baseline in each establishment will require the assistance of a quality specialist, and financial aid has been requested from the ministry for health. The baseline will be applied in several stages according to the resources made available. The first obligation will concern the analysis of deviations, the second the analysis of risks. In parallel, a guide to risk assessment in radiotherapy, the fruit of multidisciplinary work coordinated by the Nantes division of the ASN with broad participation by the Centre René Gauducheau, has been issued.

Meanwhile, HAS is working on the inclusion of criteria on the radiotherapy quality approach in the certification of establishments.

### *Aid for the organisation of radiotherapy centres*

In recent years the *Mission nationale d'expertise et d'audits hospitaliers* (MEAH – national hospital assessment

and audit office) has audited several dozen centres with the objective of improving their organisation. Particular attention has been paid to patient management waiting times. Two reports on the results of these audits have now been published. It was decided to audit some forty centres in 2008, with aid from INCa. One of the main objectives of these audits is to inculcate a genuine culture of risk, particular attention being paid to raising the awareness of the personnel regarding the concept of a precursor event and feedback from experience. The methodology proposed by MEAH, based on the use of feedback from experience, comes from air transport [9], where it has proven its effectiveness since 1975. The consensus among experts is that without feedback and given the increase in the number of flights, there would be about four aircraft crashes per week world-wide (based on the 1975 accident rate). Feedback from experience seems to have been the vector of substantial improvements in terms of the safety of cancerology departments. Its transfer from air transport to radiotherapy has appeared satisfactory, and initial experience on a limited number of sites should improve the rate of implementation on a larger scale.

### *Informing the public and general medicine specialists*

SFRO and SJRO (*Société des jeunes radiothérapeutes oncologues* – society of young radiation oncologists) have participated in an INCa commission which prepared a patient information leaflet on radiotherapy techniques, the machines, the side effects, etc. Another leaflet has been drafted for general medicine specialists. These leaflets have been widely distributed and can also be viewed on the INCa and SFRO websites.

### *Radiotherapy indications*

SFRO participates in the INCa and HAS working groups on radiotherapy indications as part of therapeutic strategies for cancer of the breast, prostate, the ENT region and the rectum, and also lymphomas. These groups submitted their conclusions in 2008. Updating every five years is planned.

## Discussion

French oncological radiotherapy was and still is considered to be among the best in the world. Nevertheless, over the last two decades it has lagged behind some industrialised countries in terms of technology. To a large extent this gap can be attributed to administrative and financial difficulties in updating equipment and techniques rapidly. Much certainly remains to be done in order for patients to benefit rapidly and safely from the many technical advances of the past decade. This effort must include:

- an increase in staff numbers, primarily physicists and dosimetrists, but also radiation therapists, doctors and quality specialists;
- modernisation of the installed base of simulation (CT scanners) and treatment (linear accelerators) systems;
- development of new techniques: intensity-modulated conformal radiotherapy, image-guided radiotherapy, breathing adapted radiotherapy, etc.;



– development of leading-edge techniques: brachytherapy, proton therapy, stereotactic radiotherapy, etc.

The challenge in coming years will also be to manage new modes of organisation. The development of equipment and the shortage of medical and physics time are going to necessitate grouping of professional personnel in expanded technical facilities. This type of organisation should meet the needs of patients for innovative techniques while complying with stricter regulatory requirements. This reorganisation must be accomplished in a way that takes account of current and future practices. It will be implemented over about ten years, time essential for planning groupings of sites and facilities (in terms of system lifetimes and investment amounts). This policy must have political and financial support from the public authorities. It will involve firm political choices to guide patients towards treatment sites sometimes further away but providing them with all the guarantees of quality and safety of care in cancerology.

Lastly, it is clear that these objectives will not be achieved without revision of the financial envelope dedicated to radiation oncology. Unfortunately, to the incomprehension of the professional personnel from whom much has been demanded in recent years, the public authorities have reduced the reimbursement of procedures in the hospital sector, which obviously does not encourage hospital managers to invest. It is therefore indispensable to review the tariffs, introducing a schedule which fosters both innovation and quality in real time.

### Conclusion

The recent external irradiation accidents have led the ministry for health, SFRO and SFPM, in collaboration with the various institutes, authorities, agencies, trade unions, federations, societies and associations, to set up a work programme intended to drive our discipline, radiation oncology, into the third millennium. However, all the work accomplished in recent decades must not be forgotten, particularly in terms of safety and quality control. The unhappy occurrence of a series of accidents, due to a large extent to disparities between the practices of the establishments, has caused a sudden acceleration of the processes of modernisation and safety improvement made necessary by the formidable technological advances of recent years. The road map has been and remains its catalyst, but it would have had no effect without the day-to-day work of the professional personnel, in particular those of SFRO and SFPM, to make radiation oncology as rapidly as possible the discipline of excellence to which we aspire. Of course much remains to be done, but it is now certain that many innovative solutions imagined in the emergency situation in which SFRO and SFPM found themselves are going to be used as models for radiation oncologists in other countries and probably also for specialists in the medical and surgical disciplines with whom we are used to working. ■

### References

1. Bolla M., Mazeron J.-J., Mornex F., Eschwège F. Les actions de la Société française de radiothérapie oncologique (SFRO), dans le contexte du plan cancer et des événements récents de radioprotection. *Cancer Radiother* 2007; 11: 305-8.
2. Chauvet B., Bolla M., Alies-Patin A., Bara C., Bourguignon M., Chantôme G., et al. Observatoire national de la radiothérapie : rapport de l'enquête conduite en 2008 sur l'année 2007. *Cancer Radiother* 2009; 13.
3. Godet J.L. Les actions de l'Autorité de sûreté nucléaire (ASN) dans le domaine de la radiothérapie. *Cancer Radiother* 2007; 11: 313-5.
4. Guide des procédures de radiothérapie externe 2007. *Cancer Radiother* 2008; 12: 141-314.
5. Maingon P., Simmon-Tellier S. Déclaration des événements indésirables graves liés aux soins à l'Institut de veille sanitaire. *Cancer Radiother* 2007; 11: 317-20.
6. Mazeron J.J., Mornex F., Eschwège F., Lartigau E., Bolla M. Qualité en radiothérapie : les actions de la Société Française de Radiothérapie Oncologique (SFRO). *Cancer Radiother* 2008; 12: 601-5.
7. Ortholan C., Estivalet S., Barillot I., Costa A., Gérard J.P. Guide des procédures de radiothérapie externe 2007. *Cancer Radiother* 2007; 11: 329-30.
8. Peiffert D., Simon J.M., Eschwège F. L'accident d'Épinal : passé, présent, avenir. *Cancer Radiother* 2007; 11: 309-12.
9. Woynar S., Debouck F., Cellier, Bourhis J., Cauterman M., Lartigau E. Vers une "politique sécurité" en oncologie-radiothérapie. La mise en œuvre du retour d'expérience. *Cancer Radiother* 2007; 11: 320-8.



## A FRENCH POINT OF VIEW

# Medical physics in France – current situation and the changes required (reflections on safety improvements in radiotherapy)

by **Thierry Sarrazin**, president of the French Society for Medical Physics, Head of Medical Physics at the “Centre Oscar Lambret” – Lille (France)

Radiotherapy has seen a number of technological revolutions since the introduction of the first cancer treatments using X-rays at the very beginning of the 19th century. They have brought with them huge changes in practice and significant improvements in outcomes. The first of these developments was the arrival of what were too hastily called cobalt “bombs” towards the middle of the 1950s. The first linear particle accelerators appeared 10 years later in the late 1960s. The technical complexity of these devices that were nearly 8 metres long, required a treatment room with a retractable floor and offered a huge range of X-ray energy and electron treatments led the French Government to issue the Order of 23 April 1969. This Order required that medical physicists be on hand in radiotherapy centres equipped with what was then called a ‘Sagittaire’, a treatment device developed by Thomson CSF.

After about thirty years without any significant developments in these medical accelerators, multileaf collimators appeared during the 1990s and beam intensity modulation in the early 2000s. As we approach the end of this decade robot-assisted radiotherapy equipment or cyber-radiotherapy (CyberKnife) are joining the fray at the same time as what may be, for the moment, the peak of the technology – the Tomotherapy machine which brings together the scanner and the accelerator in one device.

Alongside all this, significant developments in medical imaging at the beginning of the 1990s improved the process of locating target tumours and at-risk organs from a simple 2-D snapshot to definition down to the nearest millimetre thanks to 3D Computed Tomography (CT), Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET). Now these different techniques can even be used together and include the time factor (4D imaging) to take into account the movement of internal organs or the breathing of the patient.

The third pillar of treatments which use ionising radiation is a computer system. This has developed from single-point calculations to computer-aided 2D calculations in the 1970s to what we have now, where each patient receives a 3D personal treatment calculation, including the time factor and soon the biological clock.

In fact, since the beginning of this decade we have been witnessing a sort of an exponential improvement in

radiotherapy technology, with dosimetric calculations that have increased from 10 min per patient (telecobalt therapy and two opposite fields) to several hours (robotic radiotherapy, Tomotherapy or Intensity-Modulated Radiation Therapy (IMRT)). This major and unprecedented development in high-tech medicine has taken place without any significant discussion of the changes it demands in user training, without a culture of risk management and without a proactive approach to the necessary advances in safety, organisational structures and staff.

A new Order was issued by the French government on 19th November 2004 which defined the role of the medical physicist. This came after 35 years of uncertainty about radiotherapy regulations (1969 – 2004) and failure to rigorously observe those that were in place, in particular with regard to the correct numbers of medical physicists who had to be present, an issue which had not been consistently monitored by the authorities and therefore not observed by all institutions.

This Order took us on from the ambiguous notion of the “presence” of medical physicists, and gave them responsibility for “guaranteeing the dose”. Subsequent legislation required them to co-validate the preparation of each treatment with a doctor certified in radiotherapeutic oncology or nuclear medicine (Article R.1333-60 of the French Public Health Code and Decree no. 2007-389 of 21 March 2007 relating to the technical operating conditions applicable to the operation of cancer treatments).

Major legislative and regulatory changes (radiation protection of staff and patients, risk management policy, French health service health and safety agency decisions) which have come about largely under the banner of Cancer Plan 1 initiated by the French President have strengthened this initial legislation, and encourage better quality and safety for medical treatments using ionising radiation. The result of all these developments is to increase the activities of the medical physics department. Medical physicists, who are the hospital specialists in ionising radiation, now get involved in radiotherapy, brachytherapy, nuclear medicine, radiodiagnostics, radiosurgery and radiation protection. In these contexts, they bring their specific knowledge of theoretical physics and practice to bear in the service of patients, workers and

the public. We have no doubt that Cancer Plan 2, initiated by President Nicolas Sarkozy and based on work carried out by Professor Jean-Pierre Grunfeld will continue to improve quality, safety and “dose awareness” for treatments using ionising radiation.

Medical physicists obtain an understanding of dosimetry and radiological risks through a two-year Masters course in specialised physics, often supplemented by a PhD in the field. This is followed by a year, soon to be two, of additional training in a hospital involved in care, screening, teaching and research (university hospitals or specialist cancer hospitals).

The need to guarantee the doses given by medical devices, to know how to operate all the tools needed to calculate those doses and ensure that they are correctly measured in all medical processes using ionising radiation means that medical physicists now have greater responsibility and require new organisational structures. Their roles are now precisely defined and they are having to rethink their activities and their ongoing professional development training and practices in terms of personal and/or shared responsibility with the other medical practitioners. These changes require a completely new way of thinking on the part of institutions or heads of functional care units who are not very used, or even very interested, in working with medical scientists. These changes in particular require that *“a medical physics department commensurate with the activities of the institution be defined and implemented in concert with the head of the institution”* (2004 regulations). They thus establish the basis for new medical physics departments in France and affirm that they are cross-organisational bodies.

Organisational and human factors are implicated in 94% of radiotherapy incidents or accidents. It is therefore extremely surprising that it has taken over five years for some very straightforward and sensible French legislation relating to the organisation of medical physics to be broadly accepted and implemented. The truth is that healthcare institutions and certain health groups which should have been leading the way have been inordinately slow, or have simply failed to implement this new policy ordered by the Government in the interests of patient safety.

### The role of medical physicists

Medical physicists have a role whenever physics is associated with the practice of medicine, and especially in areas which use ionising radiation in any way, whether as a therapy, for screening or imaging, as part of diagnostic imaging or nuclear medicine. They are highly trained individuals who are genuine project managers responsible for organising the technical and functional handling of standard and/or innovative radiological procedures, ensuring safety and guaranteeing dose levels and examination quality.

The role of medical physicists is therefore to understand and use the fundamental concepts and principles of physics and the recognised protocols of medical physics to



Particle accelerator for radiotherapy

ensure optimal dose delivery during medical procedures involving radiation exposure. They also provide a guarantee of quality and safety, and ensure that examination procedures are up to date. They offer training to ensure that routine treatments follow the standards and/or the regulations in force, but they also need to foster problem-solving skills by implementing a rigorous scientific approach in any new, atypical or emergency situation. In particular they:

- calibrate radiation beams and characterise them;
- manage equipment quality assurance;
- manage physics and technology procedures and risk management;
- write device and system specifications and commission equipment;
- assess and implement innovative techniques and equipment;
- assess image quality;
- optimise imaging systems and procedures;
- offer their expertise in radiation protection in order to limit the exposure of patients, their families and friends, the general public and any environmental damage;
- determine and optimise the doses integrated by patients and third parties through a diagnostic or therapeutic procedure;
- prepare treatments together with practitioners in order to assess the dose to be given.

Medical physicists are trained in research, often by doing research, and they are also scientists who develop the treatment and imaging techniques of the future. Together with other professionals they monitor the latest scientific, technological and safety advances.

However, there seems to be a real failure in our country in this field. As far as we know, France is the only country, or one of the only countries in the 27 European Union nations without a University Chair in medical physics, and thus without a research laboratory in this discipline. Without a clear political will, or desire on the part of teaching and research institutions to develop medical



physics departments, the research which is a driver for the creation, use and understanding of “radiation beams” simply will not take place here. All radiotherapy and brachytherapy equipment, all measurement systems (ionisation chambers), integrating dosimeters, two or three-dimensional beam explorers, all computerised control and management systems for radiotherapy equipment (R & V), and, with only one exception, all treatment planning systems (TPS) currently in use have been developed in American, English, German or Scandinavian universities and companies. The same applies to heavy imaging equipment and nuclear medicine.

### Training medical physicists

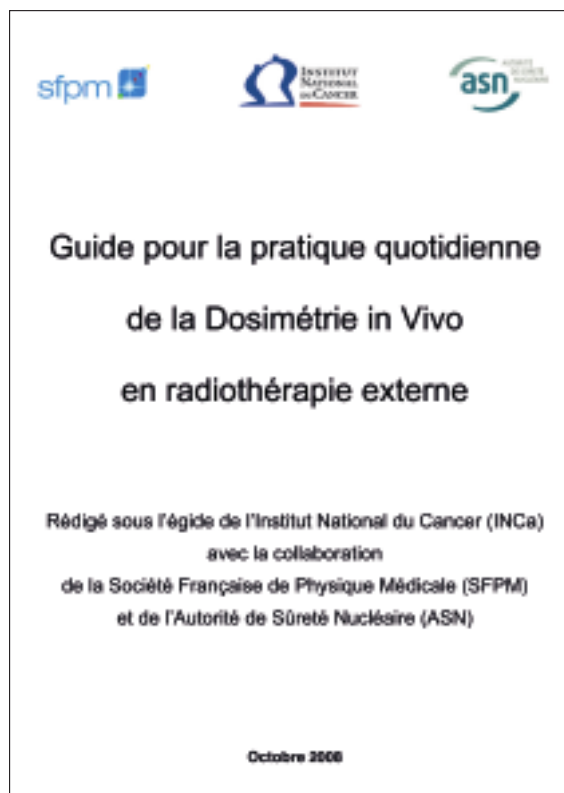
As explained in the introduction, students wishing to follow a career in medical physics must have a solid basic training in fundamental physics. A Masters in physics or a diploma in engineering from a specialist physics school is a pre-requisite. This basic training must be supplemented by specialised training via a two-year's Master course in medical physics. There are currently five such courses in France, and there seems to be no reason why in time there should not be a Masters course in every cancer centre or regional partnership. Finally, a training course in the clinical practice of medical physics, which is accessed via a competitive entrance exam, concludes the theoretical part of this training. This additional training in teaching and research healthcare institutions (CHU-CLCC) lasts 1 year in France, but 2 years in the UK, 3 years in Spain and Switzerland, and 4 years in Italy.

The training takes place in hospitals with “validating” medical physics departments that are managed by senior physicists in partnership with the French National Institute of Science and Nuclear Technologies (INSTN) and in association with the licensed radiotherapy, nuclear medicine and imaging departments of the relevant institution. This leads to the Diplôme de Qualification en Physique Radiologique et Médicale (DQPRM – Certifying Diploma in Radiological and Medical Physics) issued by the INSTN.

In order to fulfil their research and development roles in health institutions that participate in teaching and research, medical physicists can supplement their training with a doctoral thesis which then licenses them to lead research work (HDR certification). This profession is full of genuine scientific potential, but it is surprising that physics teaching on medical courses is never provided by medical physicists, when our country has some top quality physicists and medical physics dosimetry specialists.

### Professional ethics

Once they have finished their initial training, medical physicists can register on the professional register set up by the French Society for Medical Physics in line with the recommendations of the European Federation of Organisations for Medical Physics (EFOMP) arising from the European directives. They thereby undertake to follow the profession's rules of conduct and ethics and to maintain their level of competency throughout their career in



**Practical Guidelines on the implementation of daily *in vivo* dosimetry in external radiotherapy, October 2008**

order to guarantee high-quality services. This is a “rough and ready” approach which relies on medical physics professionals volunteering to maintain the professional development register, and the sense of duty of those who are registered. It is not a model that can be relied upon to sustain a culture of radiological risk management and the safety of ionising radiation treatments.

The technical advances in imaging and high-tech therapy demands the restructuring of a system which is starting to show signs of wear. A medical physicist can no longer be certified for the entirety of their professional life, and “re-certification” after a year without work in the hospital system must now be brought in. In the same way, certification must be reviewed by a national commission for medical physics after 5 years of professional practice, or there is no doubt that we will see more major accidents like those that we experienced in France in 2006 and 2007. We have seen too much suffering to be satisfied with a mere patch-up operation. We need an “intellectual revolution”, and in this area again, some of our neighbouring countries are ahead of us.

### Towards a delegation of certain tasks

A team of physicists must not be like General Alcazar's army in the Tintin story “The Broken Ear”. Just as the radiologist is assisted by radiographers, the surgeon by qualified theatre nurses, physicists who frequently have a PhD in physics and additional training in radiological or nuclear physics need to share their training and their work with dosimetry technicians, known in France as TDM (Techniciens de Dosimétrie Médicale). Patients end up at



the centre of a huddle of specialists including an organ specialist, an imaging specialist or radiologist, a cancer specialist or oncologist/radiotherapeutic oncologist, and a dosimetry specialist, or medical physicist. Each of these individuals is supported by highly trained assistants such as nurses, radiographers or dosimetry technicians. These comparisons with other professions bear more than simple organisational similarity. Just as mammograms are required to have a second opinion in the systematic screening of breast cancer and we are steadily moving towards a second opinion in anatomopathology, a second calculation is now required by the quality criteria of the French National Cancer Institute, which will come into effect in 2011.

A number of reports, inquiries or audits carried out by the institutional agencies on the radiotherapy accidents that have occurred in France have been insisting for years on the fact that it is essential to create functional medical physics units.

The goals of a new organisational structure for medical physics (delegation of tasks and functional medical physics units) should be specified in the plan for the organisation of medical physics and must be established in agreement with the executives and management of the relevant functional care and imaging units. The goals will obviously depend on the technical infrastructure, the type and number of examinations carried out, the treatment and imaging techniques used, and teaching and research tasks. This reference document, which is reviewed every three years and validated by the management committee and the medical commission of the establishment, thus allows the plan for the organisation of medical physics to become part of a driving force within an institution. It could then be included in the contract of goals and resources which is agreed with the regional agency for hospitalisation in order to identify and release the resources required for it to be achieved. Reasonable estimates of required staff numbers were published in Appendix 1 of a DHOS circular of 3 May 2002:

- for radiotherapy centres in health institutions involved in training, teaching and research (cancer centres and university hospitals), the medical physics team should include 1 full-time equivalent medical physicist for 300 to 400 external radiotherapy treatments per year, 1 full-time equivalent medical physicist for 250 brachytherapy treatments per year, and 1 dosimetry technician for 300 to 500 planned treatments per year;
- for other radiotherapy centres (other public centres, PSPHs (private institutions offering public healthcare services) other than cancer centres and private health

centres), the medical physics team should have one medical physicist for 350 to 500 treatments per year, with at least 1 full-time equivalent per centre, and at least 1 dosimetry technician.

These numbers recommended by professionals as part of the Cancer Plan correspond to the standards in many countries. They are, however, a long way from becoming reality in France, more than 7 years after they were published. We need to ask if the interests of patients and treatment safety have really been taken into account amidst the corporate battles and private interest groups, which have put France so far behind in medical physics in research, teaching, healthcare and imaging. Before the first Cancer Plan was launched we were among the poorest examples in the European Union. The Health Minister set a target of 600 medical physicists by 2012, and there should be 900 to 1000 in another ten years or so. This aggressive policy will do no more than bring us up to the average ratio in Europe.

Notwithstanding this major development, it is no longer reasonable to allow new equipment and treatment techniques to be taken on without an external Authority or Agency to verify if the medical physics team has sufficient numbers of licensed staff and sufficient equipment to ensure the safety of treatments. Is it right that nobody today can give a full list of the teams using IMRT techniques, or the number of patients receiving radiotherapy treatments or stereotactic radiosurgery every year?

### Conclusion

If we look at the development of radiotherapy in France over recent years, we have to acknowledge that we have fallen from our position of technological leader and innovator in brachytherapy and radiotherapy, to a position of user and importer of therapies, diagnostic systems and specialist software packages. This fact demonstrates that the lack of an established position for teaching and research in medical physics in the universities has left a gap that we must fill in order to take back the place that should be ours among the ranks of the great scientific nations.

For French radiotherapy get back to the top of the class, political decisions must be taken now because these affect the healthcare budget and also the quality of treatment using ionising radiation for patients. We can really only come to one conclusion – let us do everything we can to avoid a repeat of disasters like the Epinal tragedy in 2004-2005! We have the results of the audits and operating feedback. The solutions are out there. We just need to find the will to implement them. ■





## A FRENCH POINT OF VIEW

# The role of X-ray technologist in the safety of radiotherapy treatments

by Roger Husson, national president, French association of paramedical radiology personnel – AFPPE – Paris (France)

The two official programmes governing the studies leading to the State diploma and Higher Technician diploma for medical radiology technicians (MRT) date from 1990 and 1992 respectively. They already introduced the basic concepts of quality in the application of radiotherapy treatments, but without formalizing them precisely.

However, from 1995 the publication by the *European Radiotherapy Technologist* as part of the European Commission action plan “Europe against Cancer” has been taken into account by radiotherapy educators, particularly in the part relating to the general patient safety and quality assurance. The role of the MRT in the safety of radiotherapy treatments is undisputable and in fact growing in the scheme of current methods, so particular emphasis has been placed, in both theoretical and clinical training, on strict application of treatment procedures.

The planned re-engineering of the training is an opportunity to use activity and skills baselines to reinforce the involvement of technicians in the various phases of treatment setup, making use of their knowledge of imaging and anatomy.

The learning methodology centred on the individual approach, questioning, self-criticism and assessment will contribute to the development of genuine skills in this area.

In radiotherapy departments, technicians fulfil missions and tasks in the different sectors of the specialty, including reception, positioning-simulation-CT, dosimetry, triggering of the irradiation, and, for some technicians, in brachytherapy. In each of these sectors of activity, the presence of this professional contributes to treatment safety, as he or she plays an important role in the organisation and the management of these treatments.

This observation is confirmed in part in view of analyses of the causes of the radiotherapy incidents and accidents that have occurred over the last two years or more; organisational weaknesses and human factors are often precursor factors in the reported incidents or accidents (transmission of knowledge, consistency of practices, training on the equipment used, translation of user manuals, etc.).

Although technicians, as medical auxiliaries tasked with performing procedures “under the responsibility and the supervision of a physician capable of monitoring their execution and intervening immediately...” (Art R. 4351-2),



Measuring the parameters for radiotherapy

cannot be held directly responsible for errors (except intentional or repeated faults), it is nonetheless the case that their involvement in the various steps of the treatment process give them a substantial place in ensuring safe patient management.

This contribution to treatment safety takes different forms according to the sectors of activity mentioned above:

- on reception of the patient, at the beginning or during a step of the treatment, thorough verification of the patient's identity and the location of his or her pathology is a basis for safety; the information delivered in the case of a paramedical appointment for announcement of diagnosis also contributes to improving management quality and safety;
- on positioning or simulation, the technician is tasked with verification of identity and treated pathology, acquisition of anatomical data of the regions to be treated and application of procedures, in order to maintain a level of patient safety and radiation protection complying with recommendations and with the applicable regulations, whatever type of apparatus is used;
- in dosimetry, a position often occupied by technicians with specific training, the medical prescription is prepared and organised. The technician participates in treatment planning, performs the dosimetry and the dose calculations checked and confirmed by the radiotherapist and the medical physicist. This double validation is an essential step for high-quality management;
- during treatment, the technician is given responsibility, as the last link in the chain, for analysing, interpreting and understanding the treatment sheet parameters, and for setting and starting the irradiation complying in all respects with the medical prescription. In addition, reference

images are produced by the technician before and during treatment and subjected to medical validation, thus monitoring the conformity of the treatment to the prescription;

- in brachytherapy, the preparation and the handling of the radioactive sources are covered by procedures intended to ensure the safety of the actions of the technician, which have potentially serious consequences.

Other factors influence the maintenance of an optimum level of safety:

- technological and computing developments in the medical devices used (latest-generation accelerators with embedded imaging, tomotherapy, CyberKnife, etc.) necessitate regular individual refresher training;
- maintenance of the clinical knowledge of the technician for patient monitoring and for accomplishment of conservative procedures;
- assimilation by the technicians of changes in practices (treatment protocols, irradiation techniques, etc.).

Training on the management of radiotherapy risks is offered regularly to the various professional personnel:

radiotherapists, medical physicists, dosimetrists, radiology technicians. The latter participate in the rollout of the quality approach and safety in radiotherapy. A large number of radiotherapy departments are aware of risk management or even trained in risk analysis.

Involved in experience feedback committees, radiology technicians participate in the analysis of the identified precursors (a priori and a posteriori risk mapping), and propose and implement defence barriers, if appropriate. They also participate in follow-up and assessment of the actions undertaken.

Through their various actions within a radiotherapy department, radiology technicians have a multiple role in treatment safety. They are one of the links in a chain, having to use a language common to the specialty. Their knowledge of pathologies, therapeutic protocols and the equipment used enables them to deliver irradiations in accordance with medical prescriptions, while remaining vigilant.

As such they contribute to safety in radiotherapy. ■



## A FRENCH POINT OF VIEW

# Safety of radiotherapy treatments and future prospects

by Claude Évin, President, Hospital Federation of France – Paris (France)

Radiotherapy occupies a major place in cancer treatment, a place tending to expand under the impetus of several factors: constant progress of the techniques used, which provide new treatment options and now enable precision management of tumours with complex shapes; the development of conservative surgery with which it is combined; the ageing of the population, which should on its own lead to a 10% increase in treatments over the next few years.

At the beginning of the third millennium French radiotherapy has experienced a major crisis with the occurrence in 2006 and 2007 of accidents which have had very serious consequences on the health of the patients involved. This crisis led the public authorities to introduce a “national road map” to avoid the occurrence of further accidents in the future and to guarantee treatments of optimal quality to the patients. The mobilisation of all concerned has been at the level of the challenge, and the implementation of measures to ensure treatment safety is now well under way in the radiotherapy establishments and centres. In his report preparing the way for the drafting of the Second Cancer Plan 2009-2013, Professor Grunfeld<sup>1</sup> notes that “a major paradigm change in the discipline” has been initiated as a consequence. Our system of care in radiotherapy nevertheless still has a worrying weakness; it concerns the fragility of the human resources of the radiotherapy teams, which it is essential to consolidate rapidly.

Although the majority of the events declared to the *Autorité de sûreté nucléaire* (ASN, the French nuclear safety authority) in 2008 were without consequences on the health of the patients<sup>2</sup>, the specific characteristics of radiotherapy nevertheless demand a very high level of rigour in the management of risks. It uses high doses of radiation which are focused directly on the patients. Any significant error in positioning can thus have serious consequences for the patients. Complications, when they occur, become detectable a relatively long time after the treatment, and this delay contributes to a biased view of the risks, particularly in cancers with good prognosis.

For this reason the coordination and regulation system introduced by the national road map combines several



Homepage of the FHF website: [www.fhf.fr](http://www.fhf.fr)

approaches through the reinforcement of the regulations and inspections, but also the development of tools for sustained and continuous improvement of the quality of practices in the centres. The principal measures are:

- obligation for the radiotherapy centres to meet the approval criteria published by the *Institut national du cancer* (INCa – national cancer institute) in order to be authorised to treat patients suffering from cancer; the criteria include an obligation to implement *in vivo* dosimetry;
- reinforcement of the safety of equipment and systems by means of the measures implemented by the *Agence française de sécurité sanitaire des produits de santé* (AFSSAPS – French health product safety agency) to not only monitor the conformity of the equipment placed on the market but also guarantee this level of safety throughout its operating lifetime;
- inspection of all radiotherapy centres by the ASN in order to identify organisational weaknesses that might lead to events likely to affect the health of patients;
- a requirement for organisations to develop a quality assurance approach based on the baseline published by ASN, along with a risk management policy to identify incident precursor elements. Some fifty volunteer centres, with support from INCa and MEAH (hospital assessment and audit office), have rolled out a methodology based on

1. Report to the President of the French Republic, recommendations for the 2009-2013 Cancer Plan, for a new impetus, 14 February 2009, Professor J-P Grunfeld.

2. ASN 2008 annual report: in external radiotherapy, out of 208 declared events, 4 were classified at level 2 on the ASN-SFRO scale.

feedback from experience, drawing inspiration from the risk management model developed by the aircraft industry.

- new requirements for transparency with regard to the patients: declaration of incidents to the ASN on the basis of a scale drawn up for communicating with the general public;
- introduction of a radiation protection monitoring system.

What is the present balance sheet of the introduction of these measures?

Although it is still too early to appraise the overall effectiveness of this national system, which dates from November 2007, a number of advances are already perceptible:

- facilitated acceptance of the measures through a policy based on collaboration between the ministry, INCa, ASN, the *Institut de radioprotection et sûreté nucléaire* (IRSN – institute for radiation protection and nuclear safety), AFSSAPS, the *Institut de veille sanitaire* (InVS – institute for health monitoring), the *Haute Autorité de santé* (HAS – national health authority), learned societies and professional associations. The framework agreement signed in December 2008 between HAS and ASN is a good example of this. One of its aims is to develop synergies between the inspection of radiotherapy centres and the healthcare establishment certification procedure as part of the gradual introduction of quality assurance, but also in the areas of drawing up clinical practice recommendations and of assessment of professional practices (clinical audits);
- raised awareness of all involved of the importance of the organisation factor in risk prevention;
- more detailed understanding of the overall organisation of radiotherapy and its changes, through the setting-up of the radiotherapy monitoring unit by the *Société française de radiothérapie oncologique* (SFRO – French society of radiation oncology) and INCa;
- continuous monitoring of the operational effectiveness of the road map measures by a committee which also includes representatives of patients and of establishment federations. The role of this committee is to identify the difficulties encountered and propose suitable assistance measures to deal with them;

What are the remaining challenges to be met in order to achieve this objective of guaranteed safety of treatment everywhere and maintain it over time?

The major challenge concerns the fragility of the radiotherapy teams, and this will remain the case for several years, even though measures have been taken. At present the radiotherapy centres do not have the human resources that they need to meet the quality criteria required of them. This inadequacy at national level has led the FHF (French hospitals federation) to request the application of transitional measures, for example because of the fact that for one-third of the centres it is

impossible to ensure that a radiation physicist is on duty at all times. To accomplish this at least 600 would be required, while at present there are a little more than 400. Looking beyond the most sensitive issue at present, that of medical radiophysics staffing levels, the expansion of all radiotherapy disciplines, including radiation oncologists, dosimetrists and medical physics technicians and quality specialists, is necessary in order to achieve the defined objectives. Answers are expected within the framework of the Second Cancer Plan 2009-2013.

It will also be necessary to continue the effort to modernise the technical facilities in radiotherapy, because although the risk of overdose is well known, the risk of “underdose” related to equipment that is too old is at least as important, as it leads to relapses. The 2007 report of the national radiotherapy monitoring unit shows that the equipment upgrading effort still has some way to go: 13% of the accelerators in the centres at present are more than 15 years old and 36% are at least 10 years old.

It would also be necessary to achieve a better match between funding and technical and human resources. It is somewhat paradoxical at a time when requirements in terms of safety and quality are being raised that the tariffs applied to radiotherapy are being reduced. It is true that one-off funding has been granted to the centres, but it is insufficient. It is important that the radiotherapy funding system includes the quality aspects and provides greater incentive to replace equipment and introduce technical innovations, as is the case in other areas.

Lastly, the crisis that French radiotherapy has been through has shown the necessity of developing collaborations between centres. At present each centre still functions in a fairly isolated manner. Cooperation would foster mutual aid and the identification of solutions, for example to the staffing problems that a number of centres encounter each summer given the general shortage of radiation physicists. It would also ensure that care pathways were implemented and thus provide access to quality healthcare for all, including, where necessary, more sophisticated technical facilities.

### Conclusion

One of the most notable advances obtained through the national road map is improved transparency with regard to the patients, an essential factor in restoring complete patient trust in radiotherapy.

In the final analysis, the issues raised by the radiotherapy crisis and the response to them concern the choice of how the safety and the quality of treatments are regulated. What is the most effective system to ensure treatment safety? Is a system specific to each speciality needed? The answer is perhaps to develop a common certification model, based on that recently selected for laboratory medicine, which is then adapted according to each speciality. ■



## A FRENCH POINT OF VIEW

# Quality control and risk management: specific characteristics of the French health care system

by **Denis Franck**, Radiotherapy oncologist, President of the National Syndicate of Radiotherapy Oncologists (SNRO), Member of the board of the French Society of Radiation Oncology (SFRO), **Bernard Couderc**, Radiotherapy oncologist, President of the National Union of Private Cancer Treatment Hospitals (UNHPC), Administrator of the National Cancer Institute (INCa), Administrator of the National League Against Cancer and **G rard Parmentier**, National secretary of the UNHPC, former Vice-President of the National Accreditation Committee, Member of the National Public Health Council, author of the MediBrev medical abbreviations dictionary (available from AppleStore) – (France)

The techniques used in the field of radiotherapy are the same everywhere, but the organisation and scope of activities vary depending on the country, and sometimes depending on the specific region. The International Radiotherapy Conference held in Paris and devoted to the radiation protection of radiotherapy patients provides us with an opportunity to discuss some of the specific characteristics of the French health care system. These past years, the context of workforce shortage associated with strong government initiatives, the implementation of several successive National Cancer Plans, the transposition of European Directives into French law (Euratom 96/29 and 97/43) and the accident in Epinal have had a rapidly restructuring effect on the French radiotherapy sector.

## Radiotherapy and specific characteristics of the organisation of the French health care system

- In France, the conditions of admission of patients for radiotherapy treatment are no different from the general conditions of admission in hospitals. The principle is that of health care access for all. All French citizens are now covered by the National Health Insurance system. This does not mean that there are not a relatively significant number of individuals unable to exert their right to health care access, but such deficiencies do not contradict the existence of this right. Cancer patients are treated as long-term affliction (ALD) patients, with 100% coverage of treatment expenses.
- The majority of radiotherapy patients (over 53%) are treated by private practice doctors in private hospital structures. However, when explaining these issues to an international public, it is important to note the following: for a French patient, there is no financial difference between receiving treatment in a private or public hospital structure. This is based on the legal principle of "free choice". The patient is free to choose the doctor (private practice or staff) and therefore the hospital structure where treatment is to be received (public structure, or profit-making or non-profit-making private structure), with equivalent health coverage and patient-borne

expenses. The only condition is that the doctor be qualified and that the hospital structure be authorised. This does not mean that the actual cost and the cost borne by society will not differ depending on the legal status of the doctor and hospital structure. But the patient is protected from this. Overall, the private sector is significantly less expensive for society than the public sector.

For those familiar with the French health care system, it must be noted that these past years government and social security agencies have been tempted to develop a commercial medical system. This is in principle prohibited by the code of deontology, but in order to fight the social security deficit, government and social security agencies are currently allowing and encouraging the loosely structured development of "non-reimbursable expenses" (possibility of charging the patient more than what is reimbursed) in private practices and in the "private sector" of public hospitals. Fortunately, these deviations from the principle whereby "medical care is not a business" and from the principle of solidarity remain marginal and insignificant in the field of radiotherapy, but in the absence of rapid measures they could a significant modification of the French health care system.

- The third specific characteristic worth noting is that all medical activities within a hospital structure are subject to prior authorisation. This prior authorisation is considered as a right to exert a health care activity. It is granted by a government administrative authority after verification of compliance with minimum quality and safety requirements regarding personnel qualifications and technical infrastructures and procedures. Three main principles for the quality control of medical services in health care establishments dominate and structure the French health care system:

- minimal conditions for proper treatment: personnel qualifications, technical infrastructures and procedures (i.e. prior authorisation);
- compliance between the service provided and that stipulated and paid for: cost, quality, schedule (i.e. resource allocation control);



- development of good practices through increased compliance with baseline requirements and increased monitoring of result indicators (i.e. certification and accreditation procedures).

The logic behind this approach is clear and well founded, even though it should be considered in light of institutional practices, which are marked by a certain confusion and a more or less effective implementation. The fact that the French health care system has become a government-controlled system currently contributes to a certain confusion of roles, where all participants feel legitimately entitled to handle all aspects. This confusion often results in a certain loss of perspective and in bureaucratic inflation.

In France, the verification of compliance between the service provided and that stipulated and paid for is superficial. It is entrusted to the health insurance system, which is government-controlled but draws its legitimacy from social, employer and employee contributions. This duality has a paralysing effect, making the French health service purchaser a blind payer, particularly in the case of public hospitals.

What is interesting in France as compared to other countries is the existence of this prior authorisation framework based on minimum national criteria regarding infrastructures and procedures. This paves the way for the assessment of service quality, leaving French certification and accreditation authorities free to adopt an approach based exclusively on medical results. Many countries wish to adopt such an approach, and the literature on the subject is abundant, but most initiatives in that direction are slowed down or even stopped by the absence of this prior authorisation framework. Quality control ensures this role, focusing on the assessment of infrastructures and procedures. This is not the case in France: It is therefore all the more regrettable that France has not seized this historic opportunity to take a lead in the implementation of a result-based assessment approach. This leads us to question the mobilisation capacity of medical assessment professionals. We will discuss this point further below.

### **Institutional framework**

The institutional framework concerned with quality control and risk management within the French health care system is characterised by the following:

- major role played by the government. These past years, the government's presence within the health care system has grown considerably. It now effectively or legally controls all major organisations involved in planning, scheduling, regulation or funding within the health system. This control is centralised and plan-oriented. As a result, the French government is very vulnerable to patient safety issues. In order to alleviate this situation, particularly after the contaminated blood scandal that led the highest French officials to appear in court, it has created a multiplicity of "independent" agencies. These agencies are all dependent on the government (with the

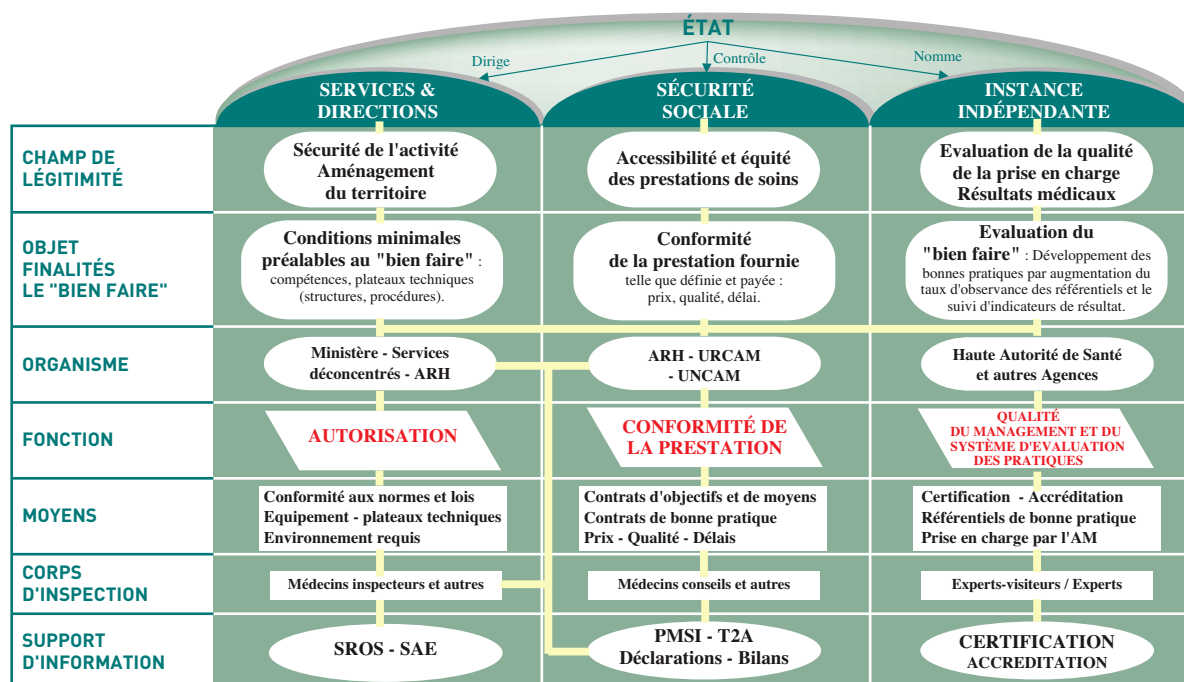
exception of the Nuclear Safety Authority), but their function is to create a protective framework reducing the government's exposure to media pressure and allowing issues and deadlines to be handled objectively;

- multiplicity of official participants. As mentioned earlier, recent years have witnessed the creation of a multiplicity of agencies. It should be noted that cancer issues are handled by a specialised agency, the National Cancer Institute (INCa). Initially intended as "an open house for patients, professionals and researchers", it is now a government agency under the supervision of the Ministry of Health and the Ministry of Research. Cancer patients therefore have the privilege of a specific agency entirely devoted to them, but this privileged status also weakens the institute, since it remains and will always remain an exception. As coordinator of the national radiotherapy programme, the National Cancer Institute legitimately participates in all aspects of the programme, with all relevant parties. France is fortunate to have an agency in charge of coordinating the radiotherapy and radiation protection sectors;

- weakness of professional organisations. Professional organisations are numerous and cover the entire range of participants. For example, the two main scientific societies, the French Society of Radiation Oncology (SFRO) and the French Society of Medical Physics (SFPMP), each encompass all the respective specialists, regardless of their status (public staff, private staff, private practice). Syndicates for doctors, physicians and specialised personnel and establishments (including training establishments) also exist. These organisations are, of course, highly specialised. But what is to be noted is the weakness of all of these organisations, both in terms of scope and budget. There is one exception, the National Federation of Cancer Treatment Centres (FNCLCC), which has considerable resources and a significant influence. As in other countries with specialised anticancer centres, the number of patients treated in these centres is relatively low, i.e. less than in each of the three other types of hospital structures (university hospitals, general hospitals and private clinics). The same applies to radiotherapy. Even though anticancer centres are traditionally very active in this field, the number of patients treated in private structures remains much higher. The influence of these centres stems from their high degree of specialisation, their ability to provide high-quality training (equivalent to that provided by university hospitals) and their often leading role in research and innovation. However, they have been unwilling or unable to play a leading role in terms of quality control and safety assessment in the field of cancerology in general or in that of radiotherapy in particular;

- failure of the National Health Care Accreditation and Evaluation Agency. The history of the French hospital system is very significant and stimulating in terms of challenges and progress regarding the institutional framework of quality control and safety assessment. The first national specialised institution was the National Agency for the Development of Medical Evaluation (ANDEM). It





enabled significant and rapid progress in the appropriation and/or development of specialised tools and methods. In 1996, it became the National Health Care Accreditation and Evaluation Agency (ANAES). This institution gathered all participants in a manner similar to the agricultural associations existing in numerous countries (such as France's National interprofessional association for seeds and plants). For example, for issues directly concerning evaluation and accreditation, government agencies, health insurance companies and extended health insurance companies had no vote in the Administration Council. Only private practice and staff doctors and public and private and public hospital structures had a right of vote. Moreover, in a manner also similar to existing agricultural associations, an "accreditation committee" was created, with strictly professional legitimacy but officially acknowledged by the government. The assessment of medical treatment quality and safety was therefore entirely entrusted to professionals benefiting from the support (and non-interference) of government and funding agencies. The code of deontology guarantees the independence of individual practice. The ANAES guaranteed the collective independence of our professions. This reform did not result from demands or struggles on the part of professionals. It institutionalised the societal acknowledgement of the fact that medical evaluation can only be performed by peers. Needless to say, what society expected in return was an accreditation system based on "medical results". Experience has shown that French professionals were not able to seize this opportunity. The particular circumstances and the political opportunism of

a French minister led to the replacement of the ANAES with the newly created National Health Authority (HAS). There is therefore no longer an institution devoted to collectively protecting the independence of our professions. On the contrary, they are now dependent on the political sphere. The legitimacy of the HAS for replacing the ANAES lies in the fact that it is also a very strong institution, but its source is exclusively political and no longer professional. In France, the recent history of the institutionalisation of quality control (and therefore of the collective protection of professional independence) reflects a paradigm shift much more pronounced than in other developed countries. At the collective level, medical legitimacy is no longer a question of professional independence. It is now a political issue. It is still too early to evaluate all the consequences. Articles unaware of these changes can still be found in the literature, but professional initiatives remain rare and with little impact on the organisation of the system. The same applies to the field of radiotherapy<sup>1</sup>. For example, the French Society of Radiation Oncology (SFRO) has decided to establish a national system to report and manage undesirable incidents, which will protect those reporting the incidents (therefore more efficient than the official system). To date, this initiative has not been implemented;

– recent creation of patient organisations. French culture tends to privilege a "patient-oriented" approach rather than a "client-oriented" approach. The role of "citizen" representation was normally entrusted to social security organisations. In their struggle against the government, these organisations have not developed this aspect of their responsibilities. As for the government, it has actively supported the creation and development of organisations representing patients. In the field cancerology, the dominant organisation is the League Against Cancer.

1. G. Parmentier, Qualité-sécurité en radiothérapie : pour une stratégie professionnelle (Quality & Safety in radiotherapy: Advocacy for a professional strategy), Cancer/Radiothérapie 12(2008) 584-600.

This is actually a charity collection organisation that was almost exclusively devoted to the funding of anticancer centres, particularly research centres. In the late 1990s, the League Against Cancer developed patient-oriented initiatives and organised information campaigns that succeeded in attracting the attention of political authorities. As a result, the government has now given it an important role. Similarly, the government has supported the creation and development of the Interassociative Committee of Health Care System Users (CISS), intended to federate all patient-representing organisations. These recent evolutions are very positive. However, the difficulty of finding patients that can receive training and assume a long-term commitment, together with the difficulties encountered with funding, make these organisations highly dependent on their relations with public authorities and professional opinion leaders. The fact that their managers are often practicing oncologists, their frequent indulgence towards public authorities, and the fact they sometimes continue to finance equipment already funded by tariffs (and therefore paid for twice) are all indicative of the lack of maturity of these patient organisations, which often still lack the capacity for genuine independence.

Due to this tendency to privilege a patient-oriented approach rather than a client-oriented approach, French consumer organisations show very little interest in safety and quality issues regarding the health care system. There is only one exception: "non-reimbursable expenses" resulting in an increase of fees "payable by patients". To date, consumer organisations are the only ones to freely address the matter, to question the principle itself (i.e. not just the sums not reimbursed) and to organise fully independent evaluation and information campaigns.

In addition, local accident victim associations are established after every accident or incident affecting patients, with a view to protecting their interests.

### **Impact of National Cancer Plans and recent accidents**

Two major events have had a significant impact on the French radiotherapy sector in recent years:

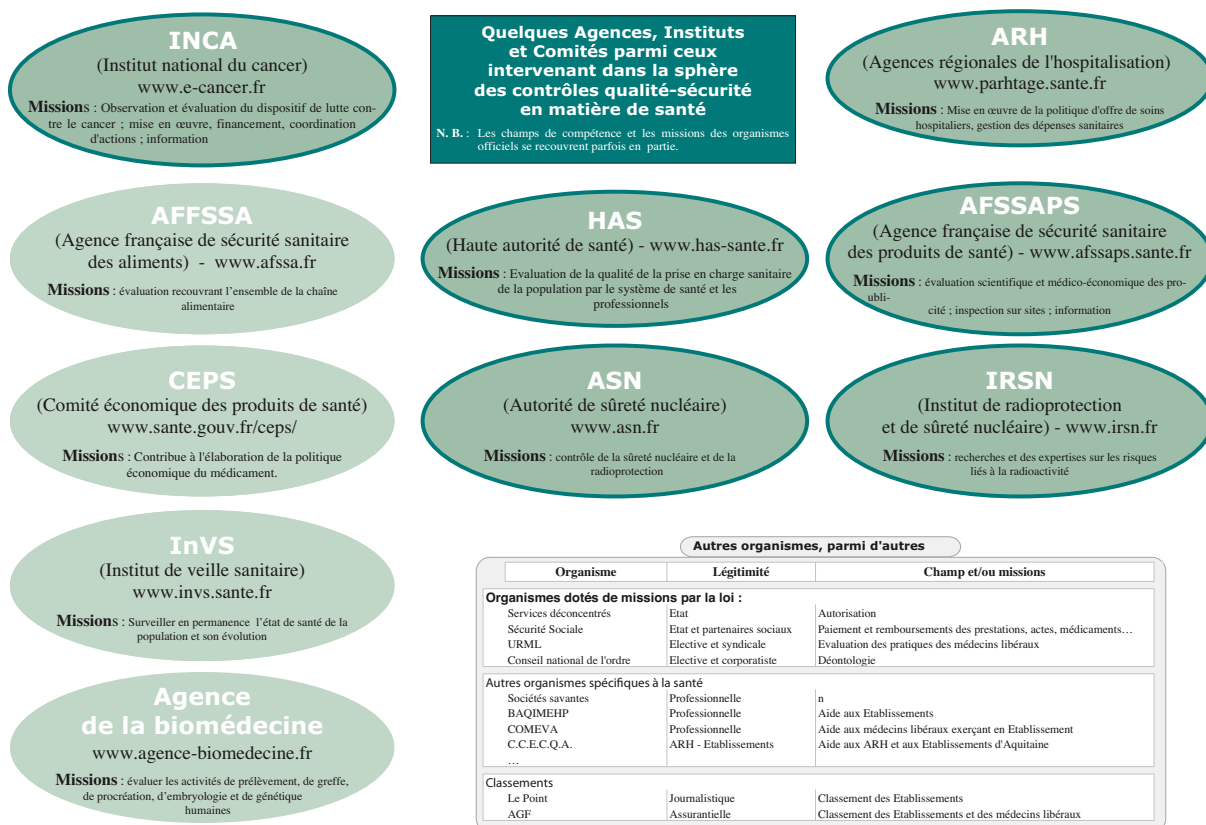
– National Cancer Plans, particularly the last one (2003-2007). A new National Cancer Plan (it will be the fourth) should follow shortly. These National Cancer Plans are marked by a strong initiative on the part of the highest government authorities, and by significant funding (particularly the last one). The National Cancer Plan of 2003-2007 had a significant impact on professionals by raising the minimum requirements for good practice. Emphasis was placed on the announcement of the disease and on the organisation of the pluridisciplinary concertation meeting. Significant progress was made in both of these areas. The quality and safety of patient treatment and the professionalism of participants were both reinforced. The same can be said of the "personalised treatment programme", which is being progressively implemented and whose content is evolving toward a genuine contract between the patient and the doctor responsible for

treatment. The implementation of funding assistance to upgrade the radiotherapy infrastructures of public or assimilated hospitals is also to be noted. This assistance was significant and presented multiple aspects. Curiously, the private sector did not benefit from it (effectively, not legally). This is partly due to the fact that private practice professions are under the supervision of the social security authority, which only feels concerned by the strictly public health aspects of government-backed public health plans, and which considers everything concerning private practice professionals as its specific domain not to be interfered with by the government. As for the government, it is very cautious when it comes to private practice doctors, which it is unfamiliar with and fears (whether rightly or wrongly).

On the whole, a plan such as the National Cancer Plan constitutes an advantage for the professionals and institutions targeted. Responses such as the politicalisation of technical issues and the struggle for power or to obtain public funding have severe adverse effects and develop strong iniquities. These plans are therefore very costly for the nation. Nevertheless, they do have positive effects. In France, they are still implemented without assessment. There is an inconsistency between the potential assessment schemes and the objectives sought. The National Public Health Council is now requesting that the government accompany each measure of a public health plan with a set of assessment criteria defined after verification of the availability of the necessary databases. There is nothing to suggest that this common sense recommendation will be quickly followed by an effect. Beyond the adverse effects mentioned earlier, we can nevertheless assume that these plans contribute to the implementation of requirements that are on the whole beneficial to everyone;

– accidents in Epinal and Toulouse. They are regrettably well known and will be largely commented (and rightly so) during the present international conference. It should be noted that the two accidents are not at all comparable. However, one of the lessons learned from them is precisely that the media coverage makes all accidents or incidents comparable regardless of the effective consequences for patients. In France, as elsewhere, the public authorities are far more sensitive (and therefore more attentive) to the safety of medical treatments than to their quality. This also applies to radiotherapy. Beyond the indispensable progress to be made (improvement of personnel training, development of quality and safety awareness, better consideration of organisational quality indicators, development of simple and robust assessment tools for comparison purposes and for use as alert systems), what are the lessons to be drawn? Progress has been achieved in each of these areas, e.g. systematisation of in vivo dosimetry, implementation of the ASN-SFRO indicator scale, renewal of training programmes to decrease the severe deficit of trained personnel (radiotherapists and radiation physicists in particular), preparation of procedure and certification manuals, etc. Two difficulties rather typical of the French context are to be noted in particular:





– as is well known, France is a country of written law, and the inclination to produce regulatory texts is stronger than anywhere else. What is less well known is the record-breaking number of health-related texts produced. The number of regulatory texts currently applicable in the health sector nearly doubles those available in other highly regulated sectors (legal, economic, etc.). The health sector amounts to 23% of the entire production of French regulatory texts (labour and employment: 6%, defence: 4%, education: 2.4%, etc.), and the growth rate is one of the highest (14% increase per year). This is far from consistent with the recommendations of the IOM "To Err is Human" report, which indicated that apart from minimum safety measures, regulations tend to be decreasingly effective. The field of radiotherapy is the caricature of this French defect. In addition to texts devoted to the general evolution of the system, this field includes the vast workload associated with the transposition of European directives into French law. The National Cancer Plans significantly accelerated the text-production machine, and the accidents in Epinal and Toulouse drove it crazy. With the implementation of National Cancer Plan measures currently in progress, an extensive roadmap document stipulating further measures has also been published. Each text may be justified in itself, but this avalanche can only have an adverse, discouraging and demotivating effect on professionals, thereby producing avoidance responses rather than facilitating the development of the quality and safety awareness needed to restructure organisations and behaviours. Even the administration has fallen into the trap. Through its management of student

training quotas, the administration has generated the workforce shortage, self-justifying itself with the theory of regulation based on supply, according to which fewer resources will cut down expenses. There is therefore a severe shortage of physicians. But recent accidents implicate them at the core of the process. Instead of consolidating this profession and assigning it a specific sphere of responsibility (which would lead to complaints from university students), we have opted for an approach unique in the world, but highly promising from a media perspective: we impose regulatory requirements according to which the physician must be present throughout the patient's treatment! Salaries skyrocket and savage competition creeps in. And it is not certain that the level of safety increases accordingly. The rigidity of the French legal system is partly responsible for the difficulties encountered in the necessary development of the incident report system. In France, it is difficult to implement protective measures such as those successfully implemented in Anglo-Saxon countries. In the absence of protection, professionals hesitate to issue reports;

– what is most important for political authorities (and therefore for government-controlled agencies) is the communication framework ensuring their protection. Until recently, the culture of the Nuclear Safety Authority (ASN), which is responsible for both nuclear safety and radiation protection, was civilian nuclear industry-oriented. In the event of an accident, the classification according to a severity scale allows for the implementation of a population protection and supervision plan, which can be indispensable for survival purposes. Communication

quality is one of the key factors determining the success of such a plan. This requires significant know-how. A radiotherapy accident involving one or more patients is very different from an accident in a nuclear power plant. The risk management culture and know-how implemented are very different. The patient needs to be contacted and provided with a satisfactory analysis, including compensation measures if applicable. The real catastrophe would occur if the patient were to find out about the accident through the press. That is what happened in Toulouse. The causes of this catastrophic information leak have never been fully determined. We are therefore dealing with two different risk management processes, incompatible in certain respects. In the case of civilian nuclear accident, the only issue is the excess dose. In the case of a radiotherapy accident, it is not clear whether insufficient doses are statistically more or less deadly than excess doses. In France, the development of a proper understanding and control of these two risk management processes is still in progress. The differentiation of communication systems will constitute one of the indicators of our progress in this respect;

– beyond these issues, what experience shows are the government's difficulties and contradictions regarding regulation based on supply. Earlier we mentioned the issue of contradictions between training policies and personnel qualification requirements. The same can be said of the "investments required to guarantee safety and quality" (expression used in official statements and documents). Since the abandonment of the overall budget for public hospitals, two resource allocation approaches prevail in France. The first approach is based on the justification of costs. All experiences (industrial experiences in particular) show that this approach is expensive for public funds and inefficient for professionals, creating guaranteed income and causing inefficiency and lack of productivity. Despite this, it is the prevailing approach in government spheres and among professionals. The second approach, consisting of price-based regulation, has been implemented up to now by health insurance companies with regard to private radiotherapists. It is far more efficient and shows that medical care need not be treated as an exception. Although there is no single explanation for it, private radiotherapy is indeed considerably more efficient than public radiotherapy. It requires a good mixture of competitiveness (which does not mean submitting to the "free market"), incentives and inspections. All the technical ministries of the French government are aware of this, but not the Ministry of Health. Planning, administration of production sectors, cost-based allocation, fear of inspections, "cooperation" (mostly consisting of the consolidation of public hospitals through the assimilation of activities handled by other structures), overevaluating the form as opposed to the content, absence of contractual culture, assisting those behind schedule instead of implementing performance-based incentives, etc. The fear of abandoning this paradigm or the lack of

knowledge of other operating modes are such that, to date, the government prefers to not subject private radiotherapy centres to the obligation of declaring their activities as per PMSI rules (French equivalent of a DRG-type system). Rather than dealing with the comparison of the two sectors (public and private), it prefers to ignore who does what and where for over half of French radiotherapy activities. This affects the capacity to control quality and safety factors, thereby perpetuating the recurrent problems associated with the monitoring and assessment of investment quantity and quality. Even though more efficient, the private practice sector remains the poor relation in National Cancer Plans and radiotherapy roadmaps. Moreover, the weakening effect of the disappearance of entrepreneurial culture in young doctors, combined with the lack of interest in this problem among supervisory authorities, poses a risk of collapse of the private sector and of increased costs for the nation.

It is always difficult to briefly summarise the characteristics of such a highly complex health care system, particularly for a foreign public, so as to identify its specific characteristics and thereby establish the grounds for a fruitful and mutually enriching discussion. These reflections therefore constitute a risky and necessarily biased attempt to identify the issues that are most relevant with regard to foreign experience. Privileging a challenge-based approach may give a negative impression. In France, the challenges and expected progress in the field of the radiation protection of radiotherapy patients remain numerous. The French radiotherapy sector is undergoing a period of rapid change and progress in terms of technical capacities, organisation and practices. In a context of workforce shortage and strong and growing bureaucratic pressure, it is characterised by the relatively weak involvement of professionals in the formalised implementation of quality and safety assessment functions, the relinquishment on the part of professionals in favour of government-controlled planning, scheduling and regulation, and the overevaluation of a safety approach mainly focusing on the prevention of media repercussions, in a manner not necessarily consistent with the requirements of patients. This safety approach is also reflected in terms of research funding, with larger budgets currently being devoted to the analysis of low-dose exposure risks than to the analysis of therapeutic dose effects and interactions with living matter. Apart from the fact that there is no waiting list and that access to treatment is guaranteed (which are points not to be neglected), there is still an absence of robust, systematised, national and public indicators for assessing the quality and safety of radiotherapy treatments in France. This by no means implies a qualitative judgement, but it confirms that even though the increase in requirements reflects a positive trend, the challenges and expected progress also remain significant and important in France. ■





## A FRENCH POINT OF VIEW

# What information should patients be given before radiotherapy?

by **Philippe Bergerot**, France's National Anti-Cancer League (LNCC) – Collective international voluntary health (CISS) – Paris (France)

Following a number of accidents at radiotherapy units, at Épinal and Toulouse hospitals in particular, and the problems encountered in the summer 2008, mainly caused by a shortage of radiation physicians and probably due to legislation that bears little relation to reality, a national radiotherapy monitoring committee was set up on 15 December 2008 in the presence of Roselyne Bachelot-Narquin, France's Minister for Health and Sport. A first progress report was submitted to the Minister in May 2009.

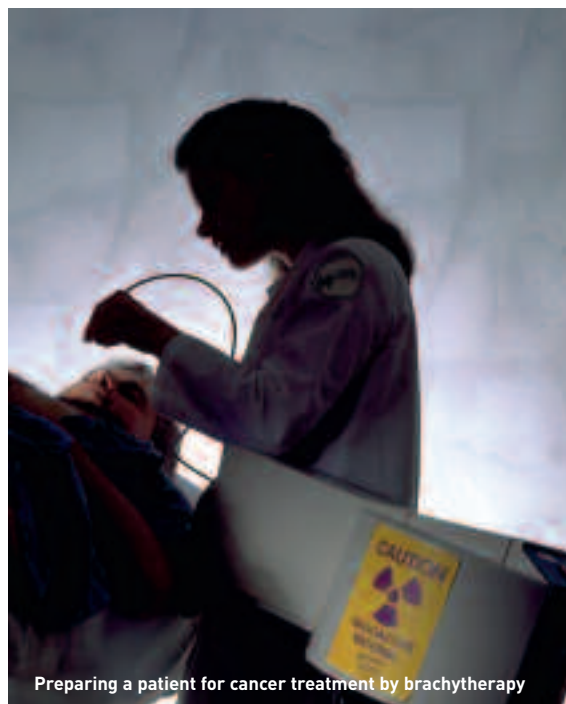
Twelve members sit on this national monitoring committee, including a CISS representative and a person that has received radiotherapy treatment. This demonstrates the seriousness and the commitment required of users on this issue.

Radiotherapy, one of the main treatments for cancer, is a loco-regional treatment that uses radiation capable of destroying cancer cells. It can be used on its own, or before, during or after another treatment method (surgery or a medical treatment such as chemotherapy, for example). The decision to treat a patient by means of radiotherapy is based on the opinions of healthcare professionals discussed at a multidisciplinary team meeting, the minutes of which are sent to the various doctors involved.

The radiotherapy treatment prescribed (the technique, total radiation dose, length of the treatment, number of sessions, etc.) is adapted to the individual situation of each patient. It is designed to be as effective as possible in light of the tumour pathology, while protecting neighbouring organs as far as is possible.

## What do patients and the people close to them want to know before starting radiotherapy treatment? They want to know that:

- a. they will be given the most suitable, cutting-edge, effective and least toxic treatment in the very safest conditions, i.e. in accordance with the regulatory and medical planning procedures;
- b. the treatment received by the patient takes account of them as a whole person, not just someone with cancer. Thus, objectively informed of the various treatment options, the possible benefits but also any likely risks, they can have a say in the proposed treatment and the care pathway;



Preparing a patient for cancer treatment by brachytherapy

c. if these 2 conditions are met:

- they can be treated close to home, wherever possible, so that the entire course of treatment (specific treatment and transportation) has the least negative impact on work and family life;
- and this, most often; regardless of who the healthcare provider is, while keeping the costs that the patient has to bear to the minimum.

## To this end, the patient wants to know that:

### 1. the radiotherapy unit

a. is not isolated, but, on the contrary, an integral part of a chain of care, through the intermediary of the structure in which it is based, which organises its cancer care activity within the framework of a "3C", a *Centre de Coordination en Cancérologie* (cancer coordination centre), within the local network that set it up in liaison with the regional cancer network, or even in direct liaison with the latter.

### b. complies

- with the INCa accreditation criteria relative to radiotherapy practice, including the requirement relative to in vivo dosimetry;

- with the enforceable requirements regarding quality assurance in radiotherapy (ASN reference framework) and the stepwise implementation schedule;
- c. applies the measures regarding vigilance in radiotherapy published by the ASN in a guide for healthcare professionals on notifying radiation protection events;
- d. is gradually developing records of notifications of serious adverse events related to treatment.

**2. patients are treated** by the healthcare professionals collectively, as part of an organisation, as recommended in Circular *DHOS/SDO/2005/101 of 22 February 2005* relative to care planning in oncology. This Circular sets out all the organisational measures. The first section focuses on the patient, with recommendations as to the various organisational procedures to be implemented at each establishment and site. The second section describes the links between structures and how the provision of care is organised and its accessibility at regional and local level, with an appendix on cancer coordination centres (intra- or inter- establishment), the responsibilities of which are clearly defined and include:

- providing doctors and carers with good practice reference guides (INCa, SFRO, ASN, HAS, IRSN, etc.)
- ensuring:
  1. that multidisciplinary teamwork functions effectively;
  2. that a procedure for announcing the disease and informing patients is implemented;
  3. that every patient receives his/her personalised care plan;
- being able to inform patients, and provide guidance within the care structures;
- producing information on cancer care, medical, surgical and pharmaceutical activities carried out at the establishment,

**3. the number of healthcare professionals** involved in providing the treatment is adequate and complies with the recommendations applicable and that they work as part of a team, including:

- The Radiation Oncologist, a doctor specialising in oncology, who, in addition to attending the multidisciplinary team meeting, is in charge of specifying, planning and ensuring smooth implementation of the radiotherapy treatment. It is s/he that:
  - draws up the irradiation plan;
  - defines the volume(s) to be irradiated and the organs and tissue that must be protected;
  - prescribes the total dose to be delivered and the number of sessions this will entail;
  - ensures monitoring throughout the treatment;
  - checks that everything goes according to plan and deals with any side effects;
  - together with the other doctors involved in the case, monitors and provides long-term follow-up of the patient following treatment.
- The Medical Physicist, who specialises in medical radiation physics:
  - ensures that the radiation dose received by tumour tissues is the dose prescribed by the Radiation

Oncologist and validates the treatment plan in conjunction with the Radiation Oncologist;

- is responsible for checking the different parameters of the equipment used in the treatment.

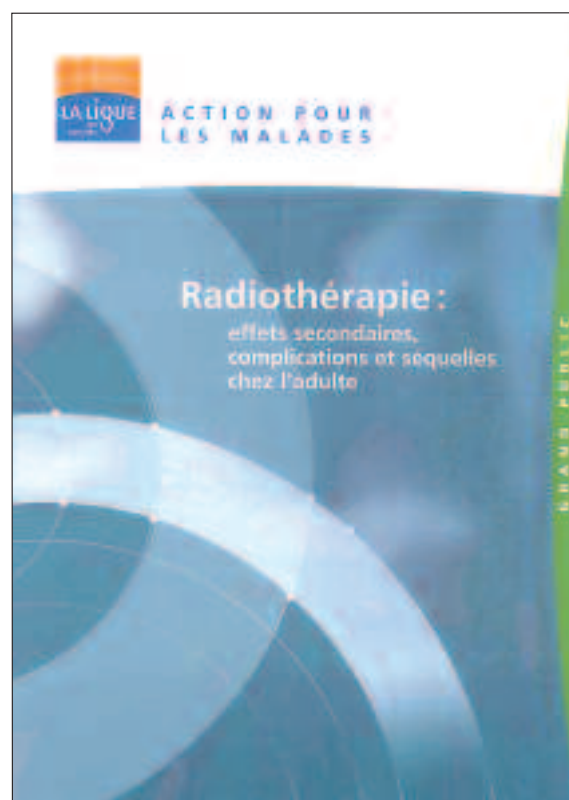
- The Dosimetrist, together with the Radiation Oncologist and the Medical Physicist, is involved in calculating the radiation dose required for the radiotherapy and in planning the treatment.

- The Radiation Therapist performs the irradiation according to the treatment plan defined and validated by the Radiation Oncologist and the Medical Physical.

**4. the radiotherapy treatment satisfies the quality criteria:**

- Following the consultation, the first major step prior to any treatment, since it is the first time that the patient and the Radiotherapist meet. The treatment is generally first announced during this consultation. The Radiotherapist explains the practical procedures involved in the treatment and is involved in drawing up the Personalised Care Plan. Time is usually allowed for discussion so that the doctor can answer any questions the patient or his/her family may have, especially with regard to side effects during treatment and the risk of sequelae and possible complications. In some units, this consultation may be followed by a second consultation, this time with the Radiology Operator, to go over any points the patient may not have fully understood. Other services may also be proposed as part of what is known as patient support.

- External radiotherapy is divided into four main stages:
  - imaging and locating, the first essential preparatory



French National Anti-Cancer League (LNCC) publication on radiotherapy



stage in the treatment, during which the patient is present. This is known as the imaging or simulation stage. The Radiation Oncologist, assisted by an Radiation Therapist, locates the target to which the radiation will be directed, as well as any high-risk organs that must be protected;

- dosimetry, consisting, for the Medical Physicist and the Dosimetrist, in carrying out a computer-assisted study of the dose distribution to be applied to the area being treated, and optimising the irradiation technique with the help of the Radiation Oncologist. The definitive treatment plan, which mainly defines the dose and delivery program (dose per session, number of sessions, interval between sessions, etc.) is jointly validated by the Radiation Oncologist and the Medical Physicist;

- daily treatment, since radiotherapy entails several sessions, usually once a day, for four or five days a week, over a period of several weeks. This program may be modified depending on the patient's general state and/or the area being treated. On the first day, the planned treatment is checked and the patient is positioned under the treatment device. By 2011, at all authorised radiotherapy centres, in vivo dose measurements will systematically be taken at the first or second session, and every time any change is made to the treatment. This in vivo dosimetry technique entails measuring the dose received directly on the patient during irradiation;

- monitoring during and after radiotherapy, entails monitoring in the short- and the long-term on a regular basis and adapted to the patient and his/her cancer, designed to check the effectiveness of the radiotherapy

treatment and to deal with any side effects that may occur;

- during radiotherapy treatment, progress is reviewed each week during a consultation with the Radiation Oncologist. S/he checks that the treatment is going as planned, checks for the onset of any side effects and, if necessary, proposes additional treatment;

- once the treatment is over, follow-up visits serve to regularly review the patient's state of health, thus monitoring the stages in improvement and detecting (and treating) any late onset side effects of the radiotherapy.

### Is this information available?

In order to monitor and know more about radiotherapy, four measures have been taken by the national monitoring committee:

- ASN publishes its report on inspections carried out at all the different radiotherapy departments;
- INCa/SFRO publish the "Observatoire de la radiothérapie" (Radiotherapy Observatory) annual report;
- an annual report on notifications within the framework of increased vigilance in radiotherapy is published;
- INCa survey on radiotherapy practices.

Some useful websites

- The French National Cancer Institute (INCa) [www.e-cancer.fr](http://www.e-cancer.fr)
- the French Nuclear Safety Authority (ASN) [www.asn.fr](http://www.asn.fr)
- The French National Anti-Cancer League (LNCC) [www.ligue-cancer.net](http://www.ligue-cancer.net) ■

## A FRENCH POINT OF VIEW

# My objective: zero contempt, not zero risk

by Jean-Paul Delevoye, mediator of the French Republic — Paris (France)

Medicine has achieved excellence by focusing its efforts on scientific research, dissemination of knowledge and development of technical resources. These choices have evidently turned out to be beneficial in view of the quality of our healthcare system and the competency proficiency of our professional staff. Isn't time now to consider the human dimension of medicine as offering new and genuine potential for improvement? That is the thought inspired by my first steps in the area of health and the safety of healthcare since the establishment of a Health Unit within the office of the Mediator of the French Republic in January 2009. Subsidiary we should wound if what the medical world has considered and secondary is not becoming the new priority.

There are obviously a number of scientific and medical issues in risk management. There are latent social and human issues in risk management; my role as Mediator is to let this voice be heard. I am not a doctor, but I have the weakness of believing that this lack of qualification is an advantage: it gives me a different outlook on these issues and allows me to focus on their human impact.

I distinguish two major issues in risk management, which I will discuss consecutively: the first is the organisational management of risk, the second is the human management of the relationship with the patient.

The organisational management of risks has three objectives:

- minimize the probability of accidents throughout patient management;
- manage accidents when they occur, limit their impact and their potential propagation;
- investigate the accident, analyse its causes, and if necessary implement appropriate measures.

The quality of a system depends as much to the individual quality of its members as to the quality of the processes and the organisation. What is true for an industrial enterprise is all the more so for a hospital. There is nothing new in this; nevertheless, it is useful to bear this precept in mind in view of the evolution of our societies. The increasing specialisation and technical complexity of systems requires allocation of tasks, circulation of information and constant improvement of the monitoring of the activity.

## How can the quality of the organisation be improved?

Each visit to a university hospital, each fact-finding trip in the field has been an opportunity for me to discover new



Jean-Paul Delevoye,  
Mediator of the French Republic

processes, new methods, new experiments. I think that awareness has come as a consequence of resounding dramas such as the contaminated blood scandal, or the Epinal scandal which concerned you, as radiotherapy professionals, directly and painfully. These shocks for the profession have led to the setting-up of effective monitoring and reporting processes. These approaches must be encouraged, good practices identified and disseminated. Today the work done on blood transfusion safety can be held up as an example to follow. I would also like to put forward the example of mortality and morbidity reviews: their introduction in each establishment seems to me to be a good thing. These reviews are intended to cast a critical eye over the way the patient has been managed, ask questions about the avoidable character of an event (morbid or fatal) and collectively seek the causes of any failure occurring during management, backed by expert assessments.

## How can the individual quality of practitioners be improved?

Obviously individual practitioner quality is not in question. In France we have medical personnel among the best trained in the world. But I think that we still have plenty of room for progress; the answer will require not only updating of knowledge but also a change of culture in medical circles, with the ultimate objective of enabling everyone to practise and develop their skills in a climate of trust or, perhaps one should say, thanks to this climate of confidence. I am effectively calling for a change of culture, and I formulate this wish: transition from a culture of fault to a culture of error. In France we have a strong Judaeo-Christian culture which condemns the person at fault, who has the need to punish. Like the scapegoat, loaded with all the sins and chased out of the city in times gone by, the person at fault takes full and sole responsibility for a collective failure. Take the recent





examples of the deaths of young children in hospital early this year which shook public opinion and medical circles: the investigation is not completed and consequently obliges us not to comment. But I can take a look at the media coverage of this story: it would appear that there was a sequence of adverse events that led to this tragic conclusion. Opinion only retained the connection of the wrong bottle by a nurse. This quasi-Pavlovian behaviour has a unfortunate consequence: the incident is closed when the guilty person is identified and punished. The desire for justice for the victims is assuaged, the profession is blamed through the condemnation of one of its members and not shaken to its foundations. Work on the analysis of the causes becomes anecdotal, whereas it is fundamental.

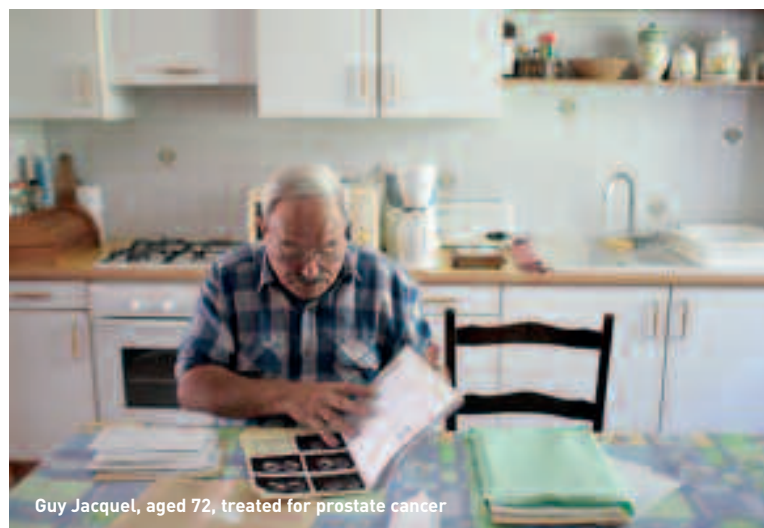
This transition from a culture of fault to a culture of error is based on different attitudes: a change from the clandestine nature of a person at fault, their isolation and their shame, to a discussion by all persons involved; a change from questioning the reliability of persons to investigation of the causes of the accident; a change from a repressive reflex to a preventive view; a change from secrecy to transparency; stop seeing a report as an accusation, an indiscretion or an act of denunciation; see an error or the discontent expressed by a user as an opportunity to learn and improve, not a new source of constraint.

The ultimate objective is to restore trust in an environment beset by doubt. This climate of mutual distrust between the parties leads to turning inwards and attitudes of self-protection. Shelter is taken behind a statute, the authority of a superior, knowledge. The principle of precaution is hijacked and used as a shelter to the point of maximum protection: inaction. In the end the comfort of the organisation and personal comfort is preferred to the comfort of the user and the patient.

This brings me to the second part of this contribution: how is risk management linked with the problem of the relationship with the patient? The relationship with the patient has changed profoundly. An accident often reveals latent discontents, buried frustrations, tensions in this relationship. Managing risks includes providing the human response to contribute to these extreme situations, where emotional stress reaches a peak; it means managing the relationship all the way.

Thought must be given to this relationship between health professional and patient. It seems to me that several parameters have modified the situation.

The figure of the doctor has lost its sacred character, it no longer has 'natural' authority. By natural authority I mean the spontaneous attitude of the patient to respect and listen to the doctor. In itself it has nothing natural, in the sense of innate, since this respectability came to the doctor through social status, the role of the doctor as a notable, and essentially through his or her knowledge. I think that today there is practically no longer any limit to questioning. We are in an environment of continuous questioning: the opinion of the doctor, the expert, the specialist is no longer accepted as authoritative.



Guy Jacquiel, aged 72, treated for prostate cancer

At the moment we are working on legal medical expert assessments, and we observe this phenomenon: for the victims, the good expert is first of all the one who agrees with them rather than the one who clarifies their situation. Anyone in a position of authority or possessing any decision-making power is today likely to be questioned. This questioning can take various forms. Consumer-like questioning when changing doctor until finding the one that gives the right diagnosis. Violent and litigious questioning when legal action is taken against a doctor; this judicialisation of disputes between patients and doctors, observed even though the number of medical accidents has not really increased in recent years, has increased the discontent. Fear of legal proceedings now hangs over the health professional before any medical procedure. Lastly, violent questioning, uncontrolled because outside the procedures established for this purpose and fed by very deep feelings of distress, is also observed. My personal fear is that this latter manifestation will increase.

A successful medical procedure is now the norm, and no longer a prowess. In a way medical practice has become commonplace, and the concepts of risk have been set aside. Success is what one has the right to expect from the doctor. Under these circumstances, the concept of the no-fault medical accident is difficult to grasp intellectually: a probable risk, incompressible and sometimes inexplicable. The same considerations apply for the concept of strict liability. Under these circumstances, a medical accident is a real shock. How can one not understand the incomprehension of the patient or the family in view of this shock? How can one not understand their anger? The doctor then plays the difficult role of interface and can expect to be the recipient of all this accumulated distress.

Everybody then manages the situation in their own way, according to their personality, and if there were a miracle recipe, no doubt it would be taught today in all the medical faculties. So I shall allow myself to give just one piece of advice: make sure not to add one pain to another, one incomprehension to another. I think that a person can understand a medical accident, even though it may take a long time, even if it is distressing. Conversely, a person will

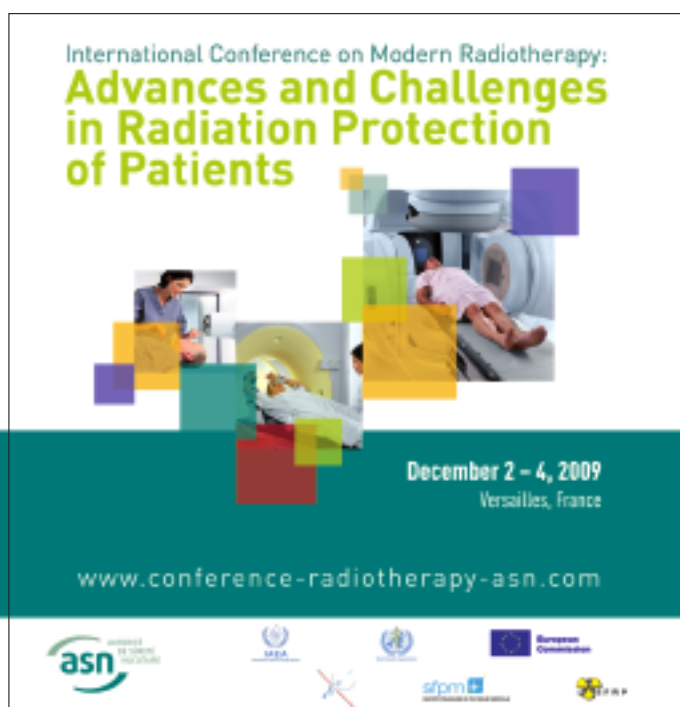


not understand why no-one explains to him or her what has happened. If the effort to explain is not made, the professional generates additional frustration and arouses suspicion. We see this at the health unit, in our organisation: 90% of the persons who request our services abandon their litigation proceedings after they have been given a detailed explanation. In general, in the Mediator's office, 50% of the 65,000 cases we handle each year are requests for information. This need for explanation is vital.

Obviously there is no such thing as zero risk. I am one of those who think that there is certainly such a thing as zero disdain.

Today we are condemned to excellence and transparency in our relations with the public. Our behavior can be governed by two attitudes: turning inward for protection, or openness in the quest for improvement and restoration of a relation of trust. Do I still need to specify which I choose and recommend? ■





## INTERNATIONAL CONFERENCE ON MODERN RADIOTHERAPY: ADVANCES AND CHALLENGES IN RADIATION PROTECTION OF PATIENTS

**Programme – Versailles (France) – December 2-4, 2009**

■ ■	Opening session: by A.C. Lacoste, ASN chairman of the conference and E. Amaral (IAEA), M. Neira (WHO), D. Ristori (EC), J.M. Cosset (Curie Institut)	51
	<b>SESSION I. Paradigms of external radiotherapy and brachytherapy: “New techniques, new benefits and new risks”</b>	60
	<b>SESSION II. Challenges in radiotherapy – Part 1: “Individual radiosensitivity”</b>	69
	<b>SESSION III. Challenges in radiotherapy – Part 2: “Risk/benefit issue”</b>	78
	<b>Round Table: Challenges in radiotherapy</b>	81
	<b>SESSION IV. Accidents – Part 1: “Lessons of the past”</b>	82
	<b>SESSION V. Accidents – Part 2: “Events recording, reporting and evaluation”</b>	88
	<b>SESSION VI. Treatment of complications and late morbidity</b>	99
	<b>SESSION VII. Equipment safety, Staffing, Education and Training</b>	101
	<b>SESSION VIII. Controls/Quality Assurance/Audits</b>	109
	<b>SESSION IX. National strategies and regulations</b>	121
	<b>SESSION X. Round table: Patient information</b>	133



French Nuclear Safety Authority (ASN)

## André-Claude Lacoste

President of ASN – Paris (France)

*It is both a great honour and a pleasure for me in my capacity as President of the French Nuclear Safety Authority to open this "International Conference on Modern Radiotherapy: Advances and Challenges in Radiation Protection of Patients".*

*Radiotherapy is a remarkable and fully proven method of treating cancer. It is used to treat more than half the total number of cancers, a family of diseases that affects or will affect 30% of men and 25% of women. It is also an effective method of treatment as it succeeds in curing some 80% of the patients treated.*

*The Nuclear Safety Authority has been in charge of regulating radiation protection in the medical field since 2002, when the French authorities responsible for nuclear safety and radiation protection were brought together. At that time, we immediately identified the radiation protection of patients as a major concern, for the doses delivered to radiotherapy patients are very high compared with those received by workers in the nuclear industry.*

*Unfortunately, the radiotherapy accidents that occurred in Epinal in 2004-2005 and in Toulouse in 2006-2007 justified this concern. These repeated accidents, as well as other isolated occurrences in France, have shown that incidents caused by organisational and human factors and equipment failures can still arise. The consequences for patients can be serious.*

*The ASN implements a rigorous and comprehensive policy for supervising radiation protection in the medical field:*

- all radiotherapy services in our country have been inspected on a yearly basis since 2007;*
- inspection reports highlighting good points and areas requiring improvement can be consulted on the ASN website: [www.asn.fr](http://www.asn.fr);*
- a quality assurance policy has been developed in coordination with professionals in the sector;*
- according to regulations, all incidents and unwanted events must be reported. A register exists for recording minor events which, though not serious in themselves, may be precursors of an accident;*

*– an event severity scale has been developed in association with radiotherapists to give the public and the media a clearer understanding of the situation. It is based on the International Nuclear Event Scale (INES) used for accidents at large nuclear facilities and during the transport of radioactive materials. Like the INES, the severity scale ASN/SFRO for radiotherapy has seven levels. It is currently used as the basis for work aimed at developing an international scale under the aegis of the IAEA.*

*According to available ASN statistics on reported events, few serious radiotherapy accidents have been reported. Only five level-2 events are reported each year, level 2 being the first level at which there may be clinical effects for the patient.*

*The new accelerators used at today's radiotherapy units are increasingly robotised. They are designed to increase the doses delivered to tumours and thus improve the chances of a cure. The increased dose is made possible by the use of multileaf collimators in conjunction with high-resolution imaging systems to target tumours more precisely. Any error, however, whether in the dose delivered to the tumour or in the irradiated volume, can have very serious consequences.*

*We are confident that radiotherapy professionals, radiotherapists, medical radiophysics specialists, dosimetrists and operators are suitably qualified. But their numbers must be increased to handle the heavy work load. This is a problem in France, for there is a shortage of physicists. The Ministry of Health has taken significant measures to address this problem but it will be some time before the effects are felt.*

*It should also be noted that in addition to accidents, complications and side effects can be observed, even when no error has been made in delivered dose or irradiated volume.*

*In the international literature, radiotherapists have reported that some 5% of patients presented serious side effects, although no error had been made concerning the delivered dose or irradiated volume. Radiobiologists believe that these side effects could be related to individual hypersensitivity to ionising radiation. These serious side effects must be taken into consideration as they could concern around 10,000 people in France. Improvements must be made in three areas regarding these side effects: documentation, prevention and treatment.*

*Modern radiotherapy is making significant advances. Radiation protection for patients must move forward at the same pace. A good way of achieving this is to assess each patient's radiosensitivity before radiotherapy begins.*

*As these issues do not concern France alone, we believe that all parties concerned - safety and radiation protection authorities, professionals and patients - should have an opportunity to share their experience on an international level.*

*This international conference was organised to that end.*

*I would like to thank all those who helped in this organisation work, and first of all the International Atomic*

*Energy Agency (IAEA), the World Health Organisation (WHO) and the European Commission. Secondly, I would like to thank all the professionals for their involvement on a personal level or in their capacity as members of a learned society or professional organisation. I am especially grateful to all the members of the Scientific Council who prepared the conference programme, in particular its Chairman, Professor Jean-Marc Cosset. Lastly, my thanks go to all the ASN staff members who have worked so hard to make this congress a success.*

*This international conference will address every aspect of modern radiotherapy, focusing on the advances and challenges in the radiation protection of patients. I hope your work will be both stimulating and profitable and wish you a very pleasant stay in Versailles and Paris.*



International Atomic Energy Agency (IAEA)

## Eliana Amaral

Director, Division of Radiation, Transport and Waste Safety (NSRW), IAEA – Vienna (Austria)

*The use of ionizing radiation in medicine has brought tremendous health benefits to the population globally, even though these benefits are not evenly distributed*

*around the world. It should not be forgotten, however, that the use of ionizing radiation has an associated risk. It is a statutory function of the International Atomic Energy Agency (IAEA) to establish standards of safety for protection of health and minimization of danger to life and to provide for their use. A core element of safety is setting and promoting the application of international safety standards for the management and regulation of activities involving nuclear and radioactive materials.*

*Radiation safety in radiotherapy means protecting patients against radiation risks as a consequence of incidents, as well as radiation risks under normal circumstances. We should also consider that when radiation is used for therapeutic purposes, there is also a risk for the patient when less radiation than intended is used, thereby compromising the tumour control. Two reports from 2008 showed examples of incidents involving systematic under dosage of 869 patients in Australia and 620 patients in Canada.*

### **Activities and challenges for the IAEA regarding safety in medical exposure**

*The key standards in this area are the International Basic Safety Standards for Protection against Ionizing Radiation and for the Safety of Radiation Sources, also known as the International BSS. These standards mark the culmination of efforts that have continued over the past several decades towards the harmonization of radiation protection and safety standards internationally. Sponsoring organizations of the International BSS, in addition to the IAEA, are the Food and Agriculture Organization of the United Nations, the International Labour Organisation, the Nuclear Energy Agency of the Organisation for Economic Co-operation and Development, the Pan American Health Organization and the World Health Organization. The Standards have been developed with specific objectives to establish requirements for*

*protection against the risks associated with exposure to ionizing radiation, and are presently being revised with participation from representatives of the sponsoring organizations and the IAEA Member States. In the Standards are mentioned what “shall” be done in relation to accidental medical exposures, e.g. what incidents to be promptly investigated and a “to-do”-list in relation to these required investigations.*

*There are many challenges in working towards safety in medical exposure on a world-wide scale. Medical exposure is a massive and increasing global activity. Every day, throughout the world, ionizing radiation is used in more than ten million diagnostic procedures and one hundred thousand nuclear medicine procedures, while more than twenty thousand radiotherapy courses are started. In order to coordinate international efforts and enable the provision of international guidance on radiation protection of patients, the International Action Plan (IAP) for the Radiological Protection of Patients has been in effect since 2002, forming a framework for the joint efforts of the IAEA with WHO, EC and other organizations. Under this framework, many challenges have been met, in relation to radiation protection of patients undergoing medical exposure using ionizing radiation, such as the development of the website dedicated to protection of patients. This web site can reach regulators, millions of health professionals and billions of patients, disseminating relevant information, standards, guidance and training material.*

*In the rapidly developing technology for anatomical imaging of patients, several safety reports have been published in the last couple of years to guide health professionals and regulatory authorities on radiation protection in newer medical imaging, such as cardiac CT and CT-colonography. Training course packages on issues such as these have also been compiled and made available to all interested parties. Also in functional/anatomical imaging using ionizing radiation, such as PET/CT, have there been safety guides and training material published, on radiation protection of patients. Interventional radiology is another rapidly expanding field, and one of the approaches made here under the IAP is the creation of an educational safety reporting system called “Safety in*





radiological procedures" (SAFRAD). This system is now starting a pilot-period through hospitals in several Member State through the Technical Cooperation activities of the IAEA.

Despite these efforts, there are many challenges remaining in the area of medical exposure. The global annual per caput effective dose is increasing rapidly, nearly exclusively due to the increasing medical exposure. Contrary to other exposures to ionizing radiation such as occupational exposure in nuclear installations, which have remained constant or decreased over the past decades, medical exposures have increased at a remarkable rate. Furthermore, occupational exposure of medical workers is becoming an increasingly challenging area, with more than half of all radiation exposed workers presently in the medical field, and with substantial occupational exposure arising from new and expanding techniques such as interventional radiology. While much of these increases reflect on positive issues, e.g. better access to medical procedures using ionizing radiation, there is also evidence that many diagnostic imaging procedures are unnecessary (sometimes several tens of percent), and many procedures are also lacking in optimization. This will require more work and more coordination of international efforts.

## **Efforts by the IAEA specific to safe radiotherapy**

Regarding radiotherapy, the IAEA is undertaking many activities. The Programme of Action for Cancer Therapy (PACT) was created within the IAEA in 2004 to build upon the experience in radiation medicine and technology, enabling developing countries to introduce, expand or improve their cancer care capacity and services in a sustainable manner by integrating radiotherapy into a comprehensive cancer control programme that maximizes its therapeutic effectiveness and impact. PACT was launched as an IAEA initiative but its vision is to build a global alliance and fund for cancer control. The IAEA recently signed an agreement with the World Health Organization on a Joint Programme on Cancer Control. It is envisioned that in the period leading to 2011, up to 12 new PACT Model Demonstration Sites (PMDS) will be established and plans are also underway for a regional cancer control training network in Africa and the creation of a Virtual University for Cancer Control.

The IAEA has a long history in the transfer of radiation medicine technology and skills, including the diagnosis and treatment of cancer, to low and middle income countries. The Human Health programme, which focuses on prevention, diagnosis and treatment of diseases, especially cancer using radiation and nuclear techniques, is playing a key-role in this.

Through its programme on radiation protection of patients, the IAEA is also addressing radiation protection of radiotherapy patients. Two specific training courses, on radiation protection in radiotherapy and on prevention of accidental exposure in radiotherapy, have been put together.

These training courses have been given on a regional and a national level many times over the last number of years. The accident prevention course uses a multi-disciplinary approach, to reflect the important part that teamwork plays in the provision of safe and effective radiotherapy.

An educational safety reporting system called "Safety in radiation oncology" (SAFRON) is being created by the IAEA. This system aims to enable reporting and learning from incidents and near incidents in radiotherapy; integrate retrospective reporting and prospective risk analysis; and integrate with existing systems so that it complements national and mandatory reporting systems.

There has also been much guidance and information published by the IAEA on specific radiotherapy safety issues over the last number of years, such as several booklets with information on lessons to learn from specific radiotherapy accidents, and safety reports on radiotherapy, all of which are freely available on the Internet.

With the continued appearance of reports on radiotherapy accidents, it is however clear that there remains many challenges to be addressed in this area. While 8 million full treatment courses are given annually in the world, this figure is expected to grow. It has been estimated that 50-60% of cancer patients could benefit from radiotherapy. Only few countries reach this level of treatment yet. In areas where radiotherapy is available, the fraction of cancer patients treated with this modality has, however, been shown to be increasing. In many cases, regulatory oversight of medical exposure is lacking, even in highly developed countries, and the sharing of experience among practitioners needs to be further developed. This technology is now increasingly reaching developing countries with less developed infrastructure, making these issues even more crucial. Therefore joint international and multidisciplinary actions are necessary to reach an improved and harmonised radiation safety in application of ionizing radiation for medical purposes, in particular in radiotherapy. Such actions should reflect the need to strengthen international efforts on ensuring learning from past accidental exposures, as well as prospectively assessing safety in radiotherapy and implementing appropriate measures based on these assessments. In this approach to safety, radiotherapy can learn from high-reliability activities, such as nuclear installations. Actions should also reflect the need for further strengthening of efforts in education and training for all groups of health professionals and engineers involved in the radiotherapy treatment chain. A chain is only as strong as its weakest link. As radiotherapy is a highly complex and rapidly developing activity, measures to ensure the safety of the patient in radiotherapy should be developing at the same pace, at least.

Therefore it is expected from this Conference a good exchange of lessons learned and good practices and enough input to develop a roadmap of integrated actions to be implemented by international organizations, regulators and health professionals in the direction towards a more effective and safe use of radiotherapy.



World Health Organization (WHO)

## Dr Maria Neira,

WHO Director, Department of Public Health and Environment – Geneva (Swiss)

*Ladies and Gentlemen,*

*It is a privilege to welcome you on behalf of WHO to this International Conference on Modern Radiotherapy- advances and challenges in radiation protection of patients.*

*I wish to congratulate the French Nuclear Safety Authority (ASN) for organizing this Conference on such an important topic. I wish to thank the other co-sponsoring organizations, the EC and the IAEA, for contributing to our joint effort for its concretion. I also congratulate the Scientific Committee for putting together the exciting programme you will develop during the next three days. Your joint presence here today demonstrates that radiation protection of patients established itself as an important topic not only for regulatory bodies and health authorities, but also for health care providers, scientists, medical devices manufacturers, patients, and general public.*

*Through the rapid development of diagnostic radiology, imaging-guided interventions, nuclear medicine and radiotherapy, ionizing radiation is today one of the most important diagnostic tools and a key component of cancer treatment. Medical research, technological advancements, the global burden of disease and a population that is living longer are all reasons that influence the greater demand of such technologies in terms of public health. Although the global resource base for health has been growing, the health sector remains under-resourced in many countries and considerable health inequalities still exist between and within countries. While on one hand, low and middle income countries lack adequate capacity and resources to provide these services, on the other hand high income countries are increasingly facing the risk of overuse of these technologies.*

*An area of special concern is the unnecessary use of radiation imaging when clinical evaluation or other imaging modalities could provide an accurate diagnosis. To optimize protection, methods for dose reduction should be applied, keeping the dose commensurate with the medical purpose. Justification and optimization are particularly critical in pediatric healthcare. Children are especially vulnerable to environmental threats and have*

*longer life-span to develop long-term radiation induced health effects like cancer.*

*While the development of modern technology is bringing new applications and medical equipment continues to become safer, inappropriate or incorrect handling can cause potential health hazards for patients and staff. A number of accidents have been reported in patients undergoing radiological medical procedures, some of them resulting in severe health consequences, even death. Improving radiation protection and safety in healthcare calls for a public health approach to control and minimize health risks, while maximizing the benefits.*

*The International Basic Safety Standards (BSS) for Protection against Ionizing Radiation and for the Safety of Radiation Sources embody the international benchmark for radiation safety requirements, with major implications for policy and decision making in the area of radiation and human health. Co-sponsored by six international organizations, the BSS represent the culmination of unprecedented international efforts towards global harmonization of standards for radiation protection. As a co-sponsor of the BSS, WHO is fully engaged in its current revision process and will continue supporting MS for the implementation of the BSS.*

*The involvement of health authorities in the implementation of BSS in the medical field is weak in many countries and this is still a matter of concern. Through its program on Radiation and Environmental Health WHO is conducting a Global Initiative on Radiation Safety in Health Care Settings to mobilize the health sector towards safer use of radiation in medicine. This initiative brings together health authorities, international organizations, professional bodies, scientific societies and academic institutions in concerted action to improve BSS implementation in healthcare settings. Addressing a number of activities in the areas of risk assessment, risk management and risk communication, this initiative seeks to complement the International Action Plan for the Radiological Protection of Patients established by the International Atomic Energy Agency (IAEA) in 2002.*

*The engagement in the promotion of radiation safety in healthcare has a long history within WHO. This has been reflected in several resolutions of the World Health*



Assembly (WHA), the governing body of the WHO. Following a request of the WHA to "study the optimum use of ionizing radiation in medicine and the risks to health of excessive or its improper use", a further WHA resolution (WHA 25.57) urged WHO to continue technical assistance to governments in the promotion of radiation medicine, .... and to cooperate with IAEA, UNSCEAR and other international organizations in evaluating the world situation as regards the medical use of ionizing radiation and the effects of radiation on populations".

The World Alliance for Patient Safety (WAPS) was launched by WHO in 2004 in response to a resolution of the WHA urging to establish and strengthen science-based systems, necessary for improving patients' safety and the quality of health care (WHA55.18). The Alliance facilitates the development of patient safety policies and practices in Member States (MS). Regarding risk reduction in radiotherapy WAPS established a Radiotherapy Safety Expert Consensus Group and produced the WHO Technical Manual on Radiotherapy Risk Profile, which will be presented during this conference.

WHO provides leadership to prevent and control cancer, among other major chronic diseases. The World Health Assembly resolution on cancer prevention and control (WHA58.22) called on MS to intensify action against cancer by developing and reinforcing cancer control programmes including the four basic components of cancer control: prevention, early detection, diagnosis and treatment, and palliative care. Through the Global Action Against Cancer WHO provides for better cooperation between MS as well as with other international organizations, including the IAEA's Programme of Action for Cancer Therapy (PACT). Through the International Agency for Research on Cancer (IARC) WHO coordinates and conducts experimental and epidemiological research on the causes of cancer and the mechanisms involved in carcinogenesis, and develops evidence-based strategies for cancer prevention and control.

In accordance with a later resolution of the WHA urging Member States (MS) to draw up guidelines to ensure the quality, safety and efficacy of medical devices (WHA 60.29), WHO assists MS in establishing and optimizing the use of health technologies, including diagnostic imaging services and equipment. The Diagnostic Imaging and Medical Devices program aims to make safe and reliable diagnostic imaging services available to as many

as possible and to provide advice, guidance and technical support for developing and maintaining diagnostic imaging services.

All of these WHA resolutions mention the need for a stronger WHO voice in this area and stress on the need for increased cooperation with other major actors. WHO has a unique role to bring together stakeholders and partners in the health sector and is determined to provide a platform to engage the health community to join the international efforts towards a safer and effective use of radiation in health care.

The main purpose of RT is to deliver the prescribed dose to the target volume while sparing healthy tissues, in order to maximize tumor control and minimize risks (i.e. radiation toxicity, second cancer). Advances in imaging technology improved not only cancer diagnosis but also RT planning. Modern RT allows today to deliver higher doses with a better target definition. But this also implies new challenges in terms of quality assurance, equipment safety, education, training and staffing and requires a stronger safety culture in healthcare providers. According to ICRP publication 86 annually worldwide more than 2,000 patients are being reported as accidentally overexposed during RT and many other accidental or unintended exposures not recognized or reported may occur. The consequences of RT accidents can be very severe and affect many patients. Since RT is increasingly used, unless effective preventive strategies are implemented, it may be expected that the frequency of accidental and unintended exposures in RT will also increase. Primary prevention being essential, error reporting systems can contribute to risk profile analysis and dissemination of lessons identified. This Conference will give you a unique opportunity to enhance international cooperation in this field.

During the next three days you will have the chance to influence the way to face these and other emerging challenges. Your deliberations and conclusions can substantially contribute to improve the capacity for responding to these public health problems and to ensure that the available tools are used in the most effective way. I wish you a productive and successful conference and an enjoyable stay in this wonderful place with such a long distinguished history.

Thank you very much.



European Commission

## Dominique Ristori

Deputy Director-General

Directorate-General for Energy and Transport – Brussels  
(Belgium)

*On behalf of the European Commission I am delighted and honoured to welcome all participants to the International Conference on Modern Radiotherapy: 'Advances*

*and Challenges in Radiation Protection of the Patients' organised by the French Nuclear Safety Authority in cooperation with the International Atomic Energy Agency, the World Health Organization and the European Commission.*

*Radiotherapy has been in use in the cancer treatment for more than hundred years, with its earliest roots traced to the discovery of X-rays. Nowadays, more than 40% of all cancer patients in the European Union are treated with this technique in more than 1000 radiotherapy centres, either alone or in combination with other types of treatment. While new equipment and techniques in radiotherapy bring new benefits for the patients, it also increases the risk of accidents due to the high complexity of these techniques and required involvement of many groups of professionals. Severe radiotherapy accidents occurred during the last years, which call for action to be taken, both at national and at international level.*

*Therefore the Directorate-General for Energy and Transport of the European Commission undertook a series of initiatives including proposals for legislative changes in the new draft of the EURATOM Basic Safety Standards. The development of European guidance materials, for example on Clinical Audit for Medical Radiological Practices, on Radiation Criteria for Acceptability of Radiotherapy Installations and on Medical Physics Expert will also contribute to improving radiation protection in medical applications. Radiation protection, in particular in the medical application of ionizing radiation, is one of the policy priorities of the Commission nuclear energy policy. In line with this commitment the European Commission plans for next year the adoption of a Communication defining our long-term policy in the medical area. Another important aspect I would like to mention here, is our cooperation with other international organisations like the IAEA and the WHO which also undertake many initiatives on radiation safety in radiotherapy practices.*

*I am convinced that this conference will allow reaching a consensus about further activities to be undertaken to strengthen existing international actions for prevention of accidents in radiotherapy. I am also sure that the conference will provide an excellent forum to exchange experience and provide a deep insight into specific aspects of radiotherapy such as risk acceptability and individual radiosensitivity.*

*I wish you a fruitful conference!*





Conference Scientific Committee

## Jean-Marc Cosset

Professor, M.D., Vice-Chairman, ICRP committee 3,  
Institut Curie – Paris (France)

*Historically, Radiotherapy, now more than one century old, stands as the second treatment of cancer, after Surgery (the only existing cancer therapy for centuries), before Chemotherapy (which only appeared in the sixties-seventies), and well before the newborn "targeted therapies", based on a better understanding of the molecular bases of carcinogenesis.*

*In spite of its age, Radiotherapy remains in 2009 one of the main weapons in the oncologist's armament.*

*In France, among the 320 000 patients who are diagnosed yearly with cancer, between 180 000 and 200 000 benefit from Radiotherapy. In the entire world, some data suggest that about 5 to 6 millions people receive radiotherapy each year.*

*How efficient is it? It is usually recognized that about half of the patients who are cured from their cancer benefited from Radiotherapy, either used alone or in combination with one or several other cancer therapies (So far, mostly Surgery and Chemotherapy).*

*Maybe surprisingly, the remarkable advances in Surgery and Chemotherapy, as well as the very recent emergence of the targeted therapies, did not lead to a decrease of the Radiotherapy's indications.*

*The explanation may be found in the known performances of Radiotherapy in terms of local control of the tumors, for which it often matches Surgery, while most of the more recently introduced cancer weapons are rather directed towards the systemic extensions of cancer (i.e., metastases).*

*Moreover, the oncologists have well understood since the very beginning of the last century that "United we stand, divided we fall"; more and more, Surgery, Radiotherapy and Chemotherapy (and very soon the targeted therapies) are used together in a logical way. The more obvious example is the widely used association of a local treatment (Surgery or/and Radiotherapy), aimed at eradicating the primary tumor, with systemic Chemotherapy, aimed at destroying the distant metastases.*

*But other examples of successful associations include the combined schedules allowing the so-called "conservative treatments". The now universally accepted association of limited breast surgery ("lumpectomy") and post-operative irradiation has allowed thousands of women to be cured from their cancer while conserving their breast. Other examples of such conservative treatments can be found in head and neck tumors, or rectal cancers, only to mention these ones.*

*In parallel, one should not forget the impressive efficacy of Radiotherapy for cancer pain, as well as its ability to recalcify bones destroyed by cancer; often – unrighteously – poorly considered, this "palliative" Radiotherapy still stands as one of the main available weapons to help patients with advanced non-curable tumors.*

*However, one of the main reasons why Radiotherapy, after more than a century, remains unavoidable is the huge recent advance of its technology and its biology.*

*Our 2009 Radiotherapy has very little to do with the radiation treatments given to the patients in the 70-80s... Conformal techniques, based on a three-dimensional reconstruction of the anatomical structures and irradiated volumes, are now almost universally used, while more sophisticated developments, such as intensity-modulated Radiotherapy (IMRT), tomotherapy and cyberknife, are expanding rapidly. Last but not least, some pioneer centers are proposing the unrivalled precision of protontherapy, while carbon ions are being evaluated by a few other groups.*

*Brachytherapy (known as "Curiethérapie" in french) found a second youth, with the arrival on the market of new small radioactive seeds (mainly for prostate cancer), while the use of more and more performant source "projectors" benefitted patients with gynecological tumors...*

*In parallel, a much better understanding of radiobiology has allowed the oncologists to increase the local cure rate while decreasing both the incidence and severity complications.*

*Unfortunately, the dark side of those technological developments has been the increase, in the past few years (real or apparent?), of the risks of accidents; new technologies, new risks...*



*Whether or not those accidents are more frequent and/or more severe today than a few years ago remains a matter of debate. It could be also the result of a better transparency towards the public and the authorities (a transparency which was far from being the rule some decades ago...). The sure thing is that, while technology has changed, the accidents have changed, and that they are now more often and more precisely reported.*

*Those "dark side" effects have to be reported, discussed, analyzed, because it is only the detailed analysis of those new types of accidents which will allow us to decrease both their frequency and their severity, with the hope of seeing them disappear totally.*

*Nevertheless, while doing that, we must not forget that Radiotherapy has cured and will cure thousands of cancer patients; the necessary transparency about Radiotherapy accidents must not occult the crude fact that they remain rare, and even very rare.*

*It would be a societal disaster if patients, frightened by an inaccurate information, decide to turn down a radiation treatment which would have saved their life!*

*In conclusion, the communication to the public and patients should remain well balanced, recognizing the problems arising from an increased technological sophistication (The present meeting has been organized for that reason), but also insisting on the quality and on the efficacy of the work performed by a large majority of radiation oncologists all over the world.*



## Advances in external beam radiotherapy

by **Michael Brada**, BSc, MB ChB, FRCP, FRCR, Professor of Clinical Oncology, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London and Sutton (United Kingdom)

### Current practice of external beam radiotherapy

External beam radiotherapy (RT), as an effective curative and palliative treatment for localised malignant disease is generally delivered as photons (X-rays) by linear accelerator and the standard technique of localised treatment is described as 3 dimensional conformal radiotherapy (3D-CRT). Further advances in 3D-CRT either aim to improve clinical outcome or aid the radiotherapy process by offering safer, faster and less labour intensive treatment.

The general objective of advances in 3D-CRT is to concentrate high dose irradiation onto the tumour and limit the amount delivered to surrounding normal tissues. This can be exploited to reduce treatment related toxicity, to allow for dose escalation to improve disease control and ultimately survival or a combination of both. Modern techniques of treatment delivery can also shape radiation to avoid specific critical normal structures in the vicinity of the tumour and vary the dose within the tumour to allow for differential doses to more radioresistant or more aggressive parts of the tumour although the latter approaches are at present somewhat speculative.

The radiotherapy process which can be considered akin to surgical intervention requires visualisation of the tumour and the surrounding normal tissues. This is achieved with CT, MRI and functional imaging prior to treatment and subsequently as close to the time of the delivery of treatment as possible to ensure radiation is accurately targeted onto the tumour. Imaging around the time of treatment is described as image guided radiotherapy (IGRT). Accuracy can also be improved with improved immobilisation of the patient and the tumour sometimes with the use of 3D “fiducial” markers and this has become known as stereotactic radiotherapy. Stereotactic radiotherapy has been initially used for the treatment of localised intracranial targets (cranial SRT) and more recently for extracranial tumours described as stereotactic body radiotherapy (SBRT).

New techniques of treatment suggested to be of clinical value should be introduced into routine practice after prior evaluation firstly to establish an improvement in physical parameters of dose delivery; secondly, studies should ensure that the physical benefit claimed is sustainable in a real clinical situation; and thirdly is likely to be of clinical significance. Ultimately, the presumed benefit should be demonstrated in appropriately designed prospective clinical studies. Notable examples of successful introduction of new technologies combined is radiotherapy of localised prostate cancer where the combination of highly conformal radiotherapy with dose escalation led to improved tumour control albeit with some increase in toxicity. The use of IMRT to avoid the parotid gland in the treatment of head and neck cancer resulted in preservation of salivary function.

While introduction of new technologies should be led by clinical need, technical advances are frequently commercialised and marketed without fulfilling the criteria for benefit. As in other commercially led ventures, new technologies tend to be marketed by the creation of new niche indications not previously

clinically validated. In a commercially driven health care system the boundaries between commercially and clinically driven advances tend to become blurred.

### Advances in the radiotherapy process

#### *Conformal radiotherapy*

The principal advances in conformal delivery of radiation have come from improved imaging. New generation fast CT scanners and advances in anatomical and functional MRI imaging together with the introduction of PET may provide new information of value to the treatment planning process. However, clinical practice should only be altered after the full evaluation to understand the clinical meaning of such advanced imaging modalities and this particularly applies to biological imaging.

3D computerised planning is part of standard RT practice. However, with modern algorithms dose-volume calculations have improved which has led to the recognition that previous dose prescriptions may not have provided accurate information on the actual dose distribution. The conformity of photon radiation has improved in some defined situations with intensity modulated radiotherapy (IMRT) and this is being exploited further for specific normal tissue avoidance.

Proton therapy (and to some extent heavy charged particle therapy) is considered as more conformal means of delivering radiation. The perceived clinical advantage is not always fully supported by benefit in physical dose distribution which is likely to be of clinical significance. At present, despite thousands of patients treated, there is absence of clinical evidence of benefit of protons over best photon radiotherapy in any of the clinical situations where it has been applied.

#### *Image guidance*

Imaging technology applied close to the treatment process with either megavoltage imaging, cone beam CT attached to the linear accelerator gantry or treatment room CT/MRI, has been described as image guided radiotherapy (IGRT) and this improves the accuracy of treatment delivery. It has also led to the recognition of temporal changes both within each treatment and during the course of fractionated radiotherapy not previously accounted for. The recognition of the importance of time factor has been embodied in the concepts of “4 dimensional (4D)” radiotherapy and “adaptive radiotherapy” allowing for adjustment of the treatment to the new circumstances during the course of radiotherapy.

### Introduction of new technology into clinical practice

#### *Requirements for new therapy*

The introduction of new systemic therapy into routine clinical practice is subject to a licensing process to satisfy criteria set by FDA (in US) and EMEA (in Europe). For new agents it needs to demonstrate safety and improved efficacy of new treatment. The introduction of new technology is not subject to such stringent requirements and only needs to demonstrate safety of the new equipment. This facilitated clinical introduction of new technologies which largely involve technical innovations and modifications of linear accelerator and cobalt radiation delivery technology. The introduction of new equipment into clinical practice is frequently accompanied by claims of benefit especially in niche markets. The current examples include irradiation of the spine with the Cyberknife (robotic arm mounted small linear accelerator), the treatment of some brain tumours with the gamma knife (multiheaded cobalt unit) and the treatment of skull base tumours with protons. The use of the internet and standard media for good news stories mostly by equipment users and

hard marketing by manufacturers are equivalent to “direct to patient” marketing which not infrequently precede evidence from clinical trials.

### *Improving radiation treatment*

The aim of improving treatment delivery is an entirely appropriate activity for research and development of radiotherapy and should be supported. However, new techniques of conventional external beam radiotherapy and new equipment should be subject to scrutiny and successful introduction should be accompanied by high level evidence of physical benefit (as above) and clinical benefit obtained from prospective studies perhaps mandated by regulatory authorities. The appropriate initial clinical endpoints should focus on gain in tumour control without increased toxicity; ultimately studies should demonstrate improved survival and quality of life of cancer patients.

In a commercially driven society, especially where patients seek solutions on an unregulated internet, there is a need for independent academic examination of new technologies. This should be supported by funding away from commercial interest to allow for impartial evaluation of new equipment independent of the manufacturers and of commercial medical interests.

Increased complexity of more sophisticated treatments and systems is subject to potentially unrecognised operator, equipment and system error. Independent system research can shed light on the whole process compared to the evaluation of new machinery on the basis of selective unidimensional endpoints of commercial interest. This should protect the individual patient and the healthcare system from the use of inappropriate and expensive technology and promote new treatments of real worth to the cancer patient. ■



## Advances in brachytherapy

by **Didier PEIFFERT**, Professor-Hospital Practitioner, Head of Radiology Department at the Centre Alexis Vautrin Regional Cancer Centre and, on an interim basis, at Jean Monnet Hospital in Epinal (France)

Brachytherapy is a cancer treatment involving the clinical use of radioactive isotopes to deliver a high radiation dose to small target volumes surrounded by radiosensitive structures. Radioactive sources (or seeds) are placed in or in contact with the tumour, while the dose to tissue around the target volume drops rapidly. The treatment thus offers several advantages compared with the best intensity-modulated, conformal, stereotactic radiation therapy techniques available today. The risk of radiation-induced cancer is minimal as the dose transmitted to the body from a distance is low. Brachytherapy delivers a fast, conformal, concentrated and hyper-fractionated dose of radiation with an optimum therapeutic index.

In use for 100 years, brachytherapy is improving with technological progress and changes in the medical world. Rules for determining the optimum source position and prescription have been defined, based on clinical correlations between the clinical stage, target volume, radiation dose and dose rate.

Brachytherapy offers another, unique, advantage: the position of the sources in relation to the target volume does not change, thus avoiding any problems due to organ or patient motion.

The technology has been made possible by source miniaturisation and the development of dose-computing systems based on 3D imaging. Also, dose-volume histograms can be used to study dose constraints regarding organs at risk and prospective research is being conducted in this area.

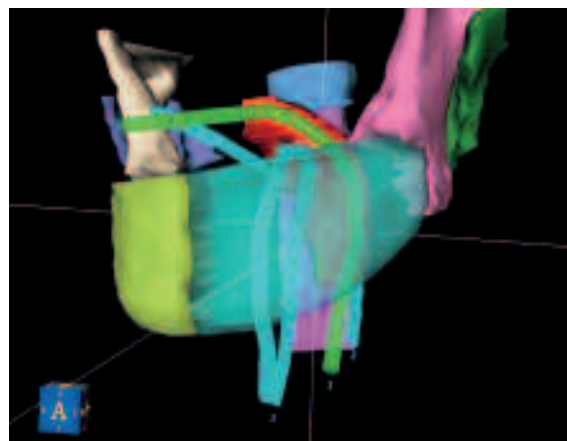
In the 1990s, experiments were carried out in France to test mobile, computer-controlled sources and optimised dosimetry systems in high dose rate (HDR) brachytherapy (dose rate  $> 12 \text{ Gy/h}$ ) and pulsed dose rate (PDR) brachytherapy ( $< 2 \text{ Gy/h}$ ). Progress in the field was boosted at the end of the 1990s with the use of permanent iodine-125 implants in prostate cancer treatment.

Changes in practices and techniques, together with the necessary investment, have made it possible to pool resources. These must now be organised to ensure that all patients for whom brachytherapy offers a curative or functional advantage over other radiation and cancer therapy techniques have access to it.

### New techniques

Shortly after Marie Curie discovered radium-226 in 1898, the first treatments were developed, using skin applicators and intracavitary utero-vaginal devices that were improved empirically to ensure optimum distribution of the radiation dose.

The 1970s saw a revolution with the appearance of radioactive sources, or seeds, made from man-made radioelements such as caesium-137, composed of pellets or strings of pellets and, more especially, iridium-192 wires. These were less than one millimetre in diameter, malleable and easy to insert into body tissue. They led to the increased use of interstitial brachytherapy in various indications, particularly in the head and neck, periorificial areas, the breast and skin. The same period saw the development of tomography, radioscopy and the use of orthogonal radiography to model source position. This led on to the clinical application of theoretical dosimetry models and then to the use of dedicated dose computing software. Implant geometry



Head and neck brachytherapy (velotonsillar carcinoma): 3D reconstructions of the target volume and organs at risk (lower jaw) prior to treatment plan dosimetry

has been optimised in clinical terms with the use of radioactive source afterloading to replace inactive “phantom” sources. Treatment plan dosimetry is used for any subsequent fine-tuning required.

With recent developments in 3D imaging technology, implants can now be viewed directly (ultrasonography, scanner, IRM) as they are placed. Tumours that were once inaccessible can now be treated. The use of brachytherapy in the treatment of prostate cancers, in conjunction with endorectal ultrasonography systems, is a perfect example of this. Methods guaranteeing good reproducibility, novel implantation systems and progress in rules relating to the prescribed doses to the target volume and organs at risk have led to rapid improvements and development built on retrospective and prospective studies. The use of brachytherapy in the treatment of prostate cancer now serves as a reference model for the development of a more elaborate, optimised, conformal technique. The use of real-time imaging is also used for other interstitial applications. In gynaecological brachytherapy, the use of diagnostic MRI and ultrasonography during implantation has improved seed positioning accuracy and the use of optimised applicators.

Brachytherapy can now be used to treat deep-seated, moving pulmonary, hepatic, thoracic and pelvic tumours.

The development of the first source projectors, originally intended for intracavitary gynaecological applications using caesium-137, guaranteed perfect protection for medical teams during treatment procedures. Another improvement came with the arrival of computer-controlled projectors using highly radioactive, miniature iridium-192 sources. These could adjust the dwell time of the source along the implant catheters and thus ensure optimum dose distribution. The use of less radioactive controlled sources reproduces the biological effect of exposure to low dose rates, which are known for their role in the local control of tumours and the side effects on organs at risk. The dose rate can now be prescribed.

Dose distribution calculation and optimisation systems are used to deliver the prescribed dose to the target volume and organs at risk and guarantee a uniform dose. Reverse dosimetry systems are now appearing, making use of the geometry of the implants on an empirical basis or serving as a guide for optimum implant positioning.

Overall, these innovations lead to the concept of intensity-modulated, conformal radiation therapy in which the system delivering the radiation dose is directly connected to the target volume.



Prostate cancer brachytherapy using permanent implants

## New advantages

The main clinical advantage for brachytherapy patients is to do with the use of 3D imaging and systems for computing and optimising dose distribution, either directly, in the case of prostate implants, or at a later stage in the case of HDR or PDR techniques using point sources. In order to observe the dose constraints given in the dose-volume histograms, the dose distribution within the target tumour and the organs at risk must be known.

Local control is improved with the factual demonstration of the benefit of increased dose, as seen in implants for prostate [ref. Stone] and cervical [ref. Potter] cancers. In the prostate, for example, 90% local control is attained if the D90 (dose delivered to 90% of the prostate) is above 140 Gy, compared with only 61% if it is lower. Similarly, for locally advanced cases of cervical cancer, 85% local control is attained if a higher dose is delivered using the HDR technique.

This increased dose is possible provided the constraints regarding the organs at risk are known. These are defined for long series of prostate cancer and are currently being updated for gynaecological brachytherapy [STIC PDR].

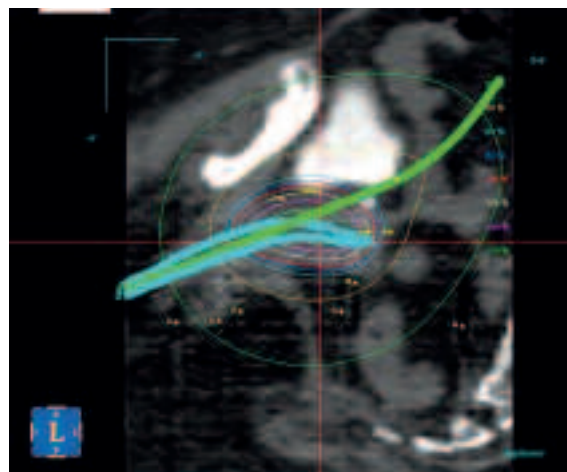
Apart from the purely clinical advantages they offer, these new techniques allow prostate cancer treatment and HDR brachytherapy to be carried out under outpatient conditions. Spread over several days, PDR techniques also allow nursing care to be given between each period of treatment (or pulses), which leave 30 to 45 minutes free every hour.

Lastly, HDR and PDR techniques avoid any risk of radiation exposure for the personnel and visitors.

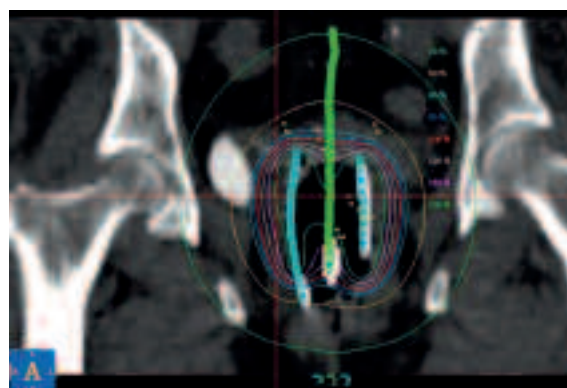
## New risks

The minimum activity of the point sources used in HDR or PDR radiotherapy is respectively 10 Ci (370 GBq) and 0.5 Ci (18.5 GBq). There is no comparison between these values and the radioactivity of the iridium-192 wires used earlier, which is in the region of 1 to 2 mCi/cm. In addition to possible calibration uncertainties (difference between the radioactivity measured by the supplier and user) [7], minor changes to the dwell time in the predefined positions can significantly affect dose distribution inside body tissues. The worst-case scenario where the source becomes trapped in a given position or is even lost in the catheter (as in an accident in the USA) has extremely serious, if not fatal, consequences. For this reason, the automatic verification of source return must be supplemented by external detection.

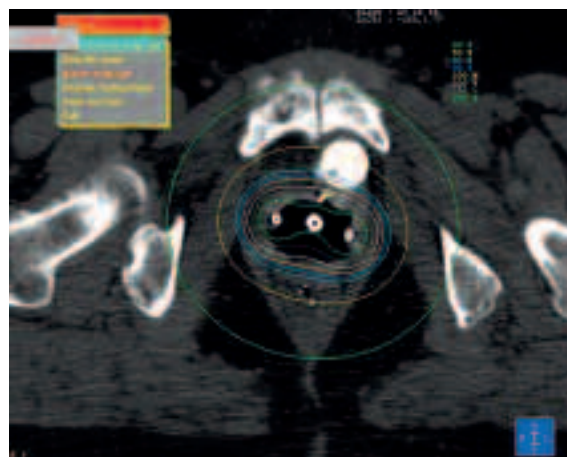
The use of sources with different radioactive levels for several projectors in the same department induces a risk of error (activity error during dosimetry).



a.



b.



c. Intracavitary, gynaecological PDR brachytherapy of epidermoid cervical cancer: reconstruction of catheter position and 3D dosimetry for treatment plan (a) sagittal, (b) frontal-oblique, (c) transverse

Brachytherapists are aware of the risk of source positioning errors; the tube's position in the patient can shift during treatment. Although the risks of HDR or PRD point source or implant positioning errors may be real, they are hard to detect. Declarations have been recently submitted to the ASN for each of these systems. Precise procedures have been drawn up concerning these points.

While it is possible to check total Kerma rate data for these new techniques, there may be some risks concerning the local instantaneous effects in patients.



There is no additional risk to personnel, except in the case of emergency procedures requiring an HDR or PDR source to be removed from a patient manually. Rooms are equipped with a container, screen and long forceps and cable-cutter for this purpose.

On the whole, the latest brachytherapy techniques are of clinical benefit to the patient. Their use does, however, involve some risks of error that could have more serious clinical consequences.

For this reason, these techniques call for the use of procedures prepared by a specially trained and evaluated team. ■

## References

- Ahmad F., Aletti P., Charra-Brunaud C., Van der Laarse R., Lapeyre M., Hoffstetter S., Peiffert D., Noel A.: Influence of dose point and inverse optimization on interstitial cervical and oropharyngeal carcinoma brachytherapy. *Radiother Oncol* 73:331-7, 2004
- Charra-Brunaud C., Peiffert D.: Résultats préliminaires de l'étude STIC PDR intitulée "Utilisation de la curiethérapie pulsée gynécologique (PDR) avec optimisation de la répartition de la dose et dosimétrie tridimensionnelle" pour les cancers du col utérin. *Cancer Radiother* 12:527-31, 2008
- Cosset J.M., Flam T., Thiounn N., Gomme S., Rosenwald J.C., Asselain B., Pontvert D., Henni M., Debre B., Chauveinc L.: Selecting patients for exclusive permanent implant prostate brachytherapy: the experience of the Paris Institut Curie/Cochin Hospital/Necker Hospital group on 809 patients. *Int J Radiat Oncol Biol Phys* 71:1042-8, 2008
- Cosset J.M., Gomme S., Peiffert D., Guerif S., Labib A., Hannoun-Levi J.M., Martin P., Quetin P., Nguyen T.D., Flam T., Thiounn N., Henni M., Rosenwald J.C., Housset M., Pontvert D., Asselain B., Chauveinc L.: Analyse clinique et dosimétrique de 469 patients traités en France en 2005 par implantation prostatique de grains d'iode 125 IsoSeed Bebig : rapport pour le Comité économique des produits de santé (CEPS). *Cancer Radiother* 11:206-13, 2007
- Haie-Meder C., Peiffert D.: Nouveautés en curiethérapie gynécologique : nouvelles technologies, curiethérapie pulsée, imagerie, définitions de nouveaux volumes d'intérêt et leur impact sur la dosimétrie : applications dans le cadre d'un STIC. *Cancer Radiother* 10:402-9, 2006
- Haie-Meder C., Pötter R., Van Limbergen E., Briot E., De Brabandere M., Dimopoulos J., Dumas I., Hellebust T.P., Kirisits C., Lang S., Muschitz S., Nevinson J., Nulens A., Petrow P., Wachter-Gerstner N.: Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. *Radiother Oncol* 74:235-45, 2005
- Métayer Y., Meyer P., Brunaud C., Peiffert D.: Contrôle de qualité en curiethérapie de débit de dose pulsé. *Cancer Radiother* 13:318-22, 2009
- Pötter R., Dimopoulos J., Georg P., Lang S., Waldhausl C., Wachter-Gerstner N., Weitmayer H., Reinthaller A., Knoke T.H., Wachter S., Kirisits C.: Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. *Radiother Oncol* 83:148-55, 2007
- Pötter R., Haie-Meder C., Van Limbergen E., Barillot I., De Brabandere M., Dimopoulos J., Dumas I., Erickson B., Lang S., Nulens A., Petrow P., Rownd J., Kirisits C.: Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol* 78:67-77, 2006

### The impact of new technologies on the risk of accident

by René Amalberti, Prof., MD, PhD, Senior Adviser Patient Safety at the French National Health Authority (HAS) – La-Plaine Saint-Denis (France)

#### The question of innovation and its relation to safety remains complex

The methods and scope of patient safety may be considered in a narrow sense or globally.

From a narrow perspective, patient safety involves correcting and gradually reducing the defects in solutions that are already known and readily available.

Viewed from a broad perspective, patient safety entails significant progress to reduce, directly (by improving instruments and methods) or indirectly (by radically changing instruments and methods), errors and unpleasant consequences hitherto recorded in practice.

This is as true in medicine as it is in industry. The use of reinforced concrete in construction has led to improved safety of buildings by reducing the risk of prematurely increased wear in the materials used in the past, enabled taller buildings to be constructed and meant that they are more resistant to earthquake. The use of cyclosporine A in liver transplants has meant reduced transplant rejections and has led to increased survival rates by a factor of 10.

In this broader view, most innovations bring with them major gains in safety, whether they involve new health products (drugs), new equipment (medical devices), or new working practices (often linked to technological progress).

This outlook is shared by all health professionals.

For most of them, innovation is perceived as a tool to enable a potentially considerable breakthrough in the advancement of safety, while traditional Quality and Safety methods are simply the means of optimisation.

Whereas innovation can tilt the balance in the direction of safety by several orders of magnitude (e.g. the discovery of blood groups increasing the safety of blood transfusions exponentially), Quality and Safety processes more often than not only result in a small-time benefit as regards the final prognosis (compared to gains as a result of innovation, the “safety first” quality approach rarely results in gains amounting to more than a few percent) [1].

Nonetheless, the qualitative contribution to safety made by both approaches is not exactly the same and fully justifies their complementary use. Innovation quickly removes problems related to techniques previously used by changing the paradigm (“let’s start with a tabula rasa”), whereas the Quality approach slowly removes existing problems by optimising the available methodology (specifically by combating the faults and failures related to actual practice). It is worth noting that with innovation, the new situation may have simply shifted the risk: the former risk has disappeared, and the overall benefit is positive, but new errors and failures appear, once again requiring implementation of a Quality approach in order to resolve them. This is typically the case with laparoscopy in surgery.

#### The conflict between the Quality approach and Innovation is more evident in medicine than elsewhere

Innovation is particularly difficult to manage in medicine due to a rate of innovation which far exceeds that in the ultra-safe nuclear and aviation industries which are usually used as benchmarks.

For example, major innovations in nuclear power occur at 30-year intervals, while in civil aeronautics the figure is just under 20 years. In surgery, in the last 15 years alone we have seen the emergence of laparoscopy, a full range of guided and robotic exploration, and more recently techniques involving non-invasive intervention, not to mention developments in equipment (endoprosthesis) and techniques of anaesthesia (blocks, combination blocks, etc.). For some surgical interventions, dramatic changes in technology occur over a cycle of less than 5 years.

But the conventional complete cycle (the PDCA, or Deming wheel) to deploy a Quality approach is more than 8 to 10 years, especially if this involves full national deployment including all sites and all professionals (plus their training). This means that the short cycles of medical innovation come into conflict with the long cycles of Quality, and it is the latter that are sacrificed. Time is never taken to safely stabilize methodology, rapid change is preferred.

Shaken by the intense pace of innovation and the extent of the progress that it has enabled (which is high on miraculous compared to what had gone before), doctors have naturally adopted a culture that is very supportive of these innovations, and are naturally inclined to neglect the limited - but real - benefits of a formal Quality and Safety approach to care. Not merely do they have only limited belief in the benefits that result from formal approaches, but they even come to regard these as potentially in conflict with those that result from innovation: for example, a surgeon who would like to use a new prosthesis with a cost-benefit ratio that is well supported by randomised trials published in a major journal in the field will be reproached by the quality expert for not following the quality approach, because this is breaching guidelines concerning the expected safety benefit that has resulted from standardising procurement and rationalising medical equipment stored in the operating theatre. In this case, few surgeons would consider the argument advanced by the quality team to be valid.

Worse still, in the numerous cases where one holds back innovation on the basis of being cautious, particularly when introducing health products where the standards imposed on the market are severe, we see that the results remain highly debatable. For example, Vioxx® was quickly withdrawn by the laboratory following a few negative side-effects, but this left on the market drugs of the same sort that were much less effective and in any event much less evaluated (under old AMM QA procedures), such that the American authorities have issued several reports ultimately regretting the withdrawal of the molecule and the rejection of innovation [2,3].

This acknowledgement forms the basis of the main topic of discussion in this article.

#### Controlling the specific innovation

It will be understood that an attitude of excessive caution regarding innovation is irrelevant in medicine. The safety gains related to innovation and included in time for the patient are unquestionably superior to the gains that the quality-based approach can provide.

At the same time, the quality approach involving the reduction of the defects and adverse effects associated with a method,



technique, or given organizational structure, at some point between two stages of innovation, remains absolutely necessary and is a legitimate objective.

The real debate therefore hinges on the suitability of innovation and the conditions of its introduction so as to remain compatible with the efforts of quality control to instill a 'win-win' dynamic, on the potentiation of the two approaches [4, 5].

We can learn from safe industries, even if their pace of innovation is at a lower level. Safe industries control innovation using two strategies:

- The decision regarding the adoption of innovation is completely removed from the hands of frontline players, and completely entrusted to those charged with regulating the system, whether private or public (those providing certification, national and international authorities, the central management of companies). These bodies grant permission for use, determine the conditions of such use, and the specific conditions of introduction applicable to each industrial site or economically involved stakeholder.
- Once the decision has been taken by these bodies, a national or international training plan for all personnel concerned must precede its introduction.

In the sphere of medicine, one must admit that such conditions are completely lacking. At best, the authorities give permission for medical devices and products entering the market (even then, there is a huge gap between the very restricted introduction of health products, and the more liberal introduction of innovative devices). There is virtually no authorisation for the use of innovations, with each individual participant choosing his moment and his way of getting to grips with a product that has recently been launched on the market. The participants are scattered, their autonomy is still extensive, scientific journals and lobbyists remains considerable weight in incentivising use (with all their influence in terms of access and endorsement). The advertising and marketing policies of innovative companies continue to focus primarily on professionals since they make the final decision. Professional bodies and authorities often intervene, after some delay, to eliminate the most critical aspects of risk and

sometimes by sponsoring training. In short, nothing is required to engage in the use of a new technique or a new medical product (insofar as it is authorised for use), no term of supervised training, still less verification of knowledge by the authorities.

This anarchic introductory mechanism logically clashes with efforts of the quality approach by constantly shifting the goalposts in terms of the errors and failures to be overcome, leaving no time to deal with the actual safety of the techniques involved.

A mere statement of these defects serves to explain the problems encountered. It also points towards three sensible recommendations that all address the need for an enhanced role for professional bodies and authorities.

- It should be the case that professional bodies and authorities have an enhanced role in the interpretation and review of scientific journals and proposals for innovation in the industry, to inform and regulate innovation collectively, possibly with test areas under strict experimental supervision. The economic evaluation aspects of innovation are also crucial both from an ethical perspective (equal opportunity for client access) as well as in terms of the overall cost effectiveness balance of the system. This aspect is sorely lacking in scientific journals and in the commercial aims of innovators.
- There should be a validation process that not only focuses on the marketing of health products and equipment, but also focuses on the use of the product, including the early establishment of a concerted quality approach suitable for the particular innovation, including personalised evaluation.
- Lastly, individual certification of usage - a license - should be given to professionals after (supervised) training and prior to use of the device.

Efforts are being made here and there in the medical profession to adopt these recommendations, but in medicine the road is still rather long, when it comes to mastery of the marvellous tool that innovation represents [6]. There is no shortage of examples of poor control of such innovation in radiotherapy both in France and abroad and these lend support to the present argument. ■

## References

1. Degos, L., Amalberti, R., Bacou, J., Bruneau, C. Carlet, J., *The frontiers of patient safety : breaking the traditional mold, British Medical Journal* 2009;338:b2585.
2. Kourilsky P., Giry, I. Safety standards: an urgent need for Evidence-Based Regulation, *Surv. Perspect. Integr. Environ. Soc.*, 1, 105-115, 2008.
3. Strom, B.: How the US drug safety system should be changed, *JAMA*, 295, 2072-2075, 2006.

4. Schlich T. Tröhler, U. The risks of medical innovation, Routledge, NY, 2006.
5. Crosby, E. Innovation in medical practice: from new idea to standard of care, *Can J. Anesth*, 2008, 328-36.
6. Amalberti, R., Quel futur et quelle stratégie de sécurité pour un système devenu ultra-sûr? *Transfusion Clinique et Biologique*, 16 (2009) 80-85.

# SESSION I. PARADIGMS OF EXTERNAL RADIOTHERAPY AND BRACHYTHERAPY: “NEW TECHNIQUES, NEW BENEFITS AND NEW RISKS”

## Highlights of the IAEA International Conference on Advances in Radiation Oncology (ICARO)

by **Rethy K. Chhem**, Director, Division of Human Health, IAEA, Vienna (Austria)

The International Atomic Energy Agency (IAEA) organized a conference called the 'International Conference on Advances in Radiation Oncology' (ICARO) in Vienna on April 27-29, 2009. The Conference dealt with the requirements demanded by the transition from conventional radiotherapy to advanced technologies, staff training, treatment planning and delivery, quality assurance and optimal use of available resources. The current role of advanced technologies in clinical practice and future trends were discussed.

It was emphasized that advanced technologies in radiation medicine should not be universally adopted until certain requirements have been met. These include; 1) the availability of adequate diagnostic imaging services, 2) experience with 3D conformal radiation therapy and advanced treatment planning, 3) that clinical studies demonstrate a universal benefit of advanced technology, 4) that the staff have adequate training in planning, implementation, and quality assurance of advanced technology, and 5) continuous medical education and self-assessment occurs.

Implementation of advanced radiation technologies requires good diagnostic imaging facilities, modern treatment planning capabilities, ongoing quality assurance processes, and experience with three dimensional techniques, all of which require increased levels of training, support and quality assurance. It was underscored that more clinical studies are needed to demonstrate a clinical and cost- benefit advantage prior to implementing advanced technologies in general practice.

The meeting was organized by the IAEA and co-sponsored and supported by European Society for Therapeutic Radiology and Oncology (ESTRO), American Society for Radiation Oncology (ASTRO), American Brachytherapy Society (ABS), American Association of Physicists in Medicine (AAPM), International



International Conference on Advances in Radiation Oncology (ICARO)

Association of Radiation Research (IARR), and International Commission on Radiation Units and Measurements (ICRU), with cooperation from Asociacion Latino Americana de Terapia Radiante Oncologica (ALATRO), European Association of Nuclear Medicine (EANM), Asia-Oceania Federation of Organizations for Medical Physics (AFOMP), European Federation of Organisations for Medical Physics (EFOMP), International Network for Cancer Treatment Research (INCTR), International Organization for Medical Physics (IOMP), Trans Tasman Radiation Oncology

Overview	Topics
Clinical sessions/clinical practice	Advances in Chemo-RT in Cervical and H&N cancer Current Trends in Brachytherapy Radiotherapy in Paediatric Oncology Reducing Late Radiation Toxicities Altered Fractionation in Cure and Palliation
Training sessions/educational	How to set up a QA programme Commissioning and Implementing a QA Programme for New Technologies Transition from 2D to 3D and IMRT Training, Education and Staffing: Getting ready for new technologies Cost and Economic Analyses in Radiation Oncology
Planning future activities	PACT meeting with manufacturers of diagnostics and radiotherapy equipment Clinical Trials: Global Quality Improvement
"Controversial" topics Debates	Co-60 - No time for retirement? IMRT- Are you ready for it? Do we need proton therapy?

Table 1: Topics covered at ICARO 2009



Group (TROG), and International Union Against Cancer (UICC). Additional financial support was given from several industries and manufacturers. Participants submitted research contributions, which were reviewed by members of the scientific committee and presented via 46 lectures and 103 posters. There were 327 participants from 70 Member States (29 high income and 41 low- and mid- income MSs).

The programme included multiple sessions, or refresher courses with the opportunity for audience participation, covering topics as shown in Table 1. Invited speakers were known for their expertise within their field, many with experience in LMI countries. Parallel sessions were held in specialized topics directed towards a relevant audience (medical physicists and radiation oncologists) along with side events to discuss very specific issues such as QA in clinical trials and collaboration with commercial companies.

## Main points:

- There are many low income countries with no or very basic diagnostic and treatment facilities.
- Low and middle income (LMI) countries have an increasing number of cancer patients many with advanced stage disease and with fewer radiation facilities per capita. Palliative treatment is common, but there are an increasing number of curative patients.
- Demand for radiotherapy service in LMI countries will increase dramatically over the next 20 years.
- There is a worldwide shortage of qualified medical physicists, dosimetrists, therapists, nurses, and radiation oncologists.
- Improved education and training must increasingly be provided to match the demand for technology development. Distance learning may help meet some of this demand in the short term but in the longer term there will be a large increase in the demand for teachers and trainers in all component fields of radiation oncology.
- There is competition for health care resources, so radiation treatment must be affordable, safe and of good quality.

- Equipment and technical support has to be adapted to the level of development and to the infrastructure (available resources and staff) of each country.
- In LMI countries, service and maintenance are often not available and must come from large distances. Spare parts are often not available. For curative treatment, the impact of “down-time” may be significant and measurably detrimental.
- There remains a role for Cobalt teletherapy. New technical developments may allow the introduction of highly-conformal treatment techniques with Cobalt.

## Recommendations

1. The minimum of basic radiation therapy services should be made available to all patients with cancer who need them.
2. Assistance should be made available to LMI countries, to develop education and training programs to enable radiation therapy services to be improved.
3. Advanced technologies in radiation therapy should not be universally adopted until the following conditions are met
  - 3.1. That a need for the advanced technology exists (i.e., curative patients).
  - 3.2. That experience with 3D conformal radiation therapy and advanced treatment planning exists before implementation of advanced technologies.
  - 3.3. That adequate diagnostic imaging services are available.
  - 3.4. That studies demonstrate a universal advantage to each aspect of advanced technology, either in improving local control or in reducing toxicity.
  - 3.4. That personnel have adequate training in planning, implementation, and quality assurance of the advanced technology.
  - 3.5. That continuous medical education and self-assessment occurs
4. Clinical studies should be done to demonstrate a clinical and cost-effective benefit to advanced technologies.
5. Each country must decide whether adequate resources exist for implementation of advanced technology. ■



## The range of radiosensitivity in the human population: hyper- and hypo-sensitivity

by **Simon Bouffler**, Head of the Radiation Effects Department, Health Protection Agency, Centre for Radiation, Chemical and Environmental Hazards, Chilton, Didcot, Oxfordshire (United Kingdom)

### Radiosensitivity

Some clear examples exist in the human population of extreme radiosensitivity. The inherited genetic condition Ataxia telangiectasia (AT) is characterised by extreme cellular radiosensitivity (Woods and Taylor, 1992) and these individuals show extreme reactions to radiotherapy. The original findings of the association of extreme reaction to therapy and cellular sensitivity (Taylor et al., 1975) were followed by several similar studies (e.g. Woods et al., 1988; Plowman et al., 1990). ATM is involved in DNA damage signalling and therefore provided the model for DNA damage response as being critical to radiosensitivity. Recent investigations have identified human disorders such as Cornelia de Lange syndrome and dyskeratosis congenita as having links to DNA damage response through sister chromatid cohesion and the telomerase complex respectively (Vrouwe et al., 2007; Kirwan and Dokal, 2008). Furthermore genetic screens for novel radiosensitivity genes using lower eukaryotes have identified new genes in pathways that affect radiosensitivity such as chromatin remodelling, RNA processing and protein degradation (Bennett et al., 2001; van Haaften et al., 2006). New cellular radiosensitivity syndromes with DNA damage response defects continue to be identified (e.g. Stewart et al., 2007).

Syndromes exhibiting sensitivity to radiation carcinogenesis also exist, for example Gorlin Syndrome where multiple skin cancers form in radiation fields and retinoblastoma where soft tissue sarcomas frequently occur in radiation fields (e.g. Kleinerman, 2009).

More subtle radiosensitivity might be expected to be observed in heterozygous carriers of the genes mutated in the extremely radiosensitive conditions. The possibility of elevated breast cancer risk in heterozygous carriers of AT disease causing mutations has been a topic studied and discussed over many years. While the situation remains controversial a recent large study identified a ~2.4 fold elevated breast cancer risk in AT mutation carriers (Renwick et al., 2006). Some cellular assays such as the G2 chromosomal radiosensitivity, apoptosis and cell cycle delay assays can detect a modest elevation in radiosensitivity in AT heterozygote populations (e.g. Scott et al., 1994; Finnon et al., 2008).

### Population surveys

Wider surveys of cellular radiosensitivity in clinically normal individuals not known to be carrying any specific genetic predisposition have been carried out. Despite initial optimism no relationship between cellular radiosensitivity and normal tissue reactions has been reliably established (e.g. Peacock et al., 2000). Studies of this type established that there is a range of cellular radiosensitivity in the human population. Other surveys have focused on alternative measures of radiosensitivity, often with a focus on the relationship with cancer risk. For example, reports exist indicating that G2 chromosomal radiosensitivity (Scott et al., 2004), radiation-induced apoptosis (Camplejohn et al., 2003) and radiation-induced cell cycle delays (Hu et al., 2002) each correlate with cancer risk.

The relationship between the severity of clinical reaction to radiotherapy and subsequent cancer risk is of course uncertain. Nonetheless several studies have now made estimates of the contribution of heritable factors to the range of cellular radiosensitivity. These studies have frequently exploited the power of human twin studies. Monozygotic twins are genetically identical while dizygotic twins share 50% of their genes. Well established methods are available for the analysis of twin data sets that allow estimation of the contribution of genetic factors and environmental factors to specific phenotypes.

Using a G2 chromosomal radiosensitivity assay Wu et al., (2006) estimated that genetic factors accounted for ~59% of the phenotypic variation in radiosensitivity identified. Using an assay for apoptosis in lymphocytes Camplejohn et al., (2006) estimated an 81% contribution of genetic factors to radiosensitivity. The work of Finnon et al., (2008) provides estimates of a 68% contribution of genetic factors to radiation-induced cell cycle delay and a 59% contribution of genetic factors to radiation-induced apoptosis. Therefore genetics plays a significant role in determining individual radiosensitivity. This opens the way in principle for the development of genetic tests for radiosensitivity.

It has been suggested that variation in telomere length, DNA damage response and radiosensitivity are linked (e.g. Slijepcevic, 2004, 2006). However one limited study did not observe a relationship between telomere length and acute skin reactions to radiotherapy (Iwasaki et al., 2008).

### Gene expression analysis

The potential power of newer genomic-based methods for prediction of reactions to radiotherapy is now being explored and many reports are now available. For example Svensson et al., (2006) developed gene expression array classifiers for late tissue reactions in prostate cancer patients. Reiger et al., (2004) report the development of a gene expression classifier for prediction of acute reactions to radiotherapy. While these studies identify a range of genes that associate with reaction severity there is not yet a consensus of those that are predictive for differing types of reaction. The genes identified span a wide range of pathways and networks including DNA damage response, apoptosis, ubiquitination and stress signalling amongst others. In some cases even single gene assays, in this case for the cell cycle regulator CDKN1A, appear to hold promise for the prediction of acute skin reactions to radiotherapy (Badie et al., 2008).

### Conclusions

In radiotherapy practice it is commonly held that approximately 5% of patients will show severe normal tissue reactions. Human population studies confirm that there exists a range of human cellular radiosensitivity and that genetic factors contribute significantly to the observed variation. Searches for markers predictive of normal tissue reactions to therapy have tended to focus on identifying the sensitive sub-group. However, it is clear that there must also exist a relatively hyposensitive portion of the population.

While we have this knowledge that there is a range of radiosensitivity we as yet have only a very incomplete knowledge of the genes, proteins and pathways that determine radiosensitivity. It is entirely possible that each of the clinically important aspects of radiosensitivity – i.e. acute normal tissue reactions, late normal tissue reactions and induced cancers may have different causes and indeed these may be different in different tissues. To help resolve some of these uncertainties Barnett et al., (2009) advocate that large genome-wide association studies seeking genes that associate with severe normal tissue reactions to radiotherapy are needed.



In developing a more complete understanding of human radiosensitivity it will be important to determine the relationship between the different aspects of radiosensitivity. It is notable that many of the cellular assays showing some relationship to reactions to radiotherapy also appear to associate with cancer susceptibility. One further area where it will be important to gain further knowledge is in the relationship between the intrinsic radiosensitivity of an individual and the radiosensitivity of tumours occurring in the individual. For example, in an individual intrinsically hyposensitive, are tumours also likely to be relatively hyposensitive? Some early studies indicate some correlation

between somatic fibroblast radiosensitivity and tumour radiosensitivity (Fertil and Malaise, 1981). Further it is known that cancer phenotype is affected by the nature of inherited mutations in Li-Fraumeni syndrome and this is likely to also affect tumour radiosensitivity (Monti et al., 2007)

Fuller understanding of the mechanisms and genetics of human radiosensitivity should help the refinement of treatments to maximise rates of cure by radiotherapy while minimising severe normal tissue reactions. ■

## References

- Badie C., Dziwura S., Raffy C., Tsigani T., Alsbeih G., Moody J., Finnon P., Levine E., Scott D., Bouffler S. (2008). Aberrant CDKN1A transcriptional response associates with sensitivity to radiation treatment. *Br. J. Cancer* 98: 1845-1851.
- Barnett G.C., West C.M., Dunning A.M., Elliott R.M., Coles C.E., Pharoah P.D., Barnett N.G. (2009). Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. *Nature Rev. Cancer* 9: 134-142.
- Bennett C.B., Lewis L.K., Karthikeyan G., Lobachev K.S., Jin Y.H., Sterling J.F., Snipe J.R., Resnick MA (2001). Genes required for ionizing radiation resistance in yeast. *Nature Genet.* 29: 426-434.
- Camplejohn R.S., Gilchrist R., Easton D., McKenzie-Edwards E., Barnes D.M., Eccles D.M., Arden-Jones A., Hodgson S.V., Duddy P.M., Eeles R.A. (2003). Apoptosis, ageing and cancer susceptibility. *Br. J. Cancer* 88: 487-490.
- Camplejohn R.S., Hodgson S., Carter N., Kato B.S., Spector T.D. (2006). Heritability of DNA-damage-induced apoptosis and its relationship with age in lymphocytes from female twins. *Br. J. Cancer* 95: 520-524.
- Fertil B., Malaise E.P. (1981). Inherent cellular radiosensitivity as a basic concept for human tumor radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* 7:621-629.
- Finnon P., Robertson N., Dziwura S., Raffy C., Zhang W., Ainsbury L., Kaprio J., Badie C., Bouffler S. (2008). Evidence for significant heritability of apoptotic and cell cycle responses to radiation. *Hum. Genet.* 123: 485-493.
- Hu J.J., Smith T.R., Miller M.J., Lohman K., Case L.D. (2002). Genetic regulation of ionizing radiation sensitivity and breast cancer risk. *Environ. Mol. Mutagen.* 39: 208-215.
- Iwasaki T., Robertson N., Tsigani T., Finnon P., Scott D., Levine E., Badie C., Bouffler S. (2008). Lymphocyte telomere length correlates with in vitro radiosensitivity in breast cancer cases but is not predictive of acute normal tissue reactions to radiotherapy. *Int. J. Radiat. Biol.* 84: 277-284.
- Kirwan M., Dokal I. (2008). Dyskeratosis congenital: a genetic disorder of many faces. *Clin. Genet.* 73: 103-112.
- Kleinerman R.A. (2009). Radiation-sensitive genetically susceptible paediatric sub-populations. *Pediatr. Radiol.* 39, Suppl 1: 527-531.
- Monti P., Ciribilli Y., Jordan J., Menichini P., Umbach D.M., Resnick M.A., Luzzatto L., Inga A., Fronza G. (2007) Transcriptional functionality of germ line p53 mutants influences cancer phenotype. *Clin. Cancer Res.* 13: 3789-3795.
- Peacock J., Ashton A., Bliss J., Bush C., Eady J., Jackson C., Owen K., Regan J., Yarnold J. (2003). Cellular radiosensitivity and complication risk after curative radiotherapy. *Radiother. Oncol.* 55: 173-178.
- Plowman P.N., Bridges B.A., Arlett C.F., Hinney A., Kingston J.E. (1990). An instance of clinical radiation morbidity and cellular radiosensitivity not associated with ataxia-telangiectasia. *Br. J. Radiol.* 63: 624-628.
- Reiger K.E., Hong W.J., Tusher V.G., Tang J., Tibshirani R., Chu G. (2004). Toxicity from radiation therapy associated with abnormal transcriptional responses to DNA damage. *Proc. Natl. Acad. Sci. USA* 101: 6635-6640.
- Renwick A., Thompson D., Seal S., Kelly P., Chagtai T., Ahmed M., North B., Jayatilake H., Barfoot R., Spanova K., McGaffey L., Evans D.G., Eccles D., The Breast Cancer Susceptibility Collaboration (UK), Easton D.F., Stratton MR, Rahman N. (2006). ATM mutations that cause ataxia-telangiectasia are breast cancer susceptibility alleles. *Nature Genet.* 38: 873-875.
- Scott D., Spreadborough A.R., Roberts S.A. (1994). Radiation-induced G2 delay and spontaneous chromosome aberrations in ataxia-telangiectasia homozygotes and heterozygotes. *Int. J. Radiat. Biol.* 66, Suppl 6: S157-S163.
- Scott D. (2004). Chromosomal radiosensitivity and low penetrance predisposition to cancer. *Cytogenet. Genome Res.* 104: 365-370.
- Slijepcevic P. (2004). Is there a link between telomere maintenance and radiosensitivity? *Radiat. Res.* 161: 82-86.
- Slijepcevic P. (2006). The role of DNA damage response proteins at telomeres – an 'integrative' model. *DNA Repair* 5: 1299-1306.
- Stewart G.S., Stankovic T., Byrd P.J., Wechsler T., Miller E.S., Haisson A., Drayson M.T., West S.C., Elledge S.J., Taylor A.M.R. (2007). RIDDLE immunodeficiency syndrome is linked to defects in 53BP1-mediated DNA damage signalling. *Proc. Natl. Acad. Sci. USA* 104: 16910-16915.
- Svensson J.P., Stalpers L.J., Esveltd-van Lange R.E., Franken N.A., Haveman J., Klein B., Turesson I., Vrieling H., Giphart-Gassler M. (2006). Analysis of gene expression using gene sets discriminates cancer patients with and without late radiation toxicity. *PLOS Med.* 3: e422.
- Taylor A.M., Harnden D.G., Arlett C.F., Harcourt S.A., Lehmann A.R., Stevens S., Bridges B.A. (1975). Ataxia telangiectasia: a human mutation with abnormal radiosensitivity. *Nature* 258: 427-429.
- Van Haaften G., Romeijn R., Pothof J., Koole W., Mullenders L.H., Pastink A., Plasterk R.H., Tijsterman M. (2006). Identification of conserved pathways of DNA damage response and radiation protection by genome-wide RNA. *Curr. Biol.* 16: 1344-1350.
- Vrouwe M.G., Elghalbzouri-Maghrani E., Meijers M., Schouten P., Godthelp B.C., Bhuiyan Z.A., Redeker E.J., Mannens M.M., Mullenders L.H., Pastink L.H., Darrroudi F. (2007). Increased DNA damage sensitivity of Cornelia de Lange syndrome cells: evidence for impaired recombinational repair. *Human Mol. Genet.* 16: 1478-1487.
- Woods W.G., Byrne T.D., Kim T.H. (1988). Sensitivity of cultured cells to gamma radiation in a patient exhibiting marked in vivo radiation sensitivity. *Cancer* 62: 2341-2343.
- Woods C.G., Taylor A.M.R. (1992). Ataxia telangiectasia in the British Isles: the clinical and laboratory features of 70 affected individuals. *Quart. J. Med.* 82: 169-179.
- Wu X., Spitz M.R., Amos C.I., Lin J., Shao J., Gu J., deAndrade M., Benowitz N.C., Shields P.G., Swan G.E. (2006). Mutagen sensitivity has high heritability evidence from a twin study. *Cancer Res.* 66: 5993-5996.

## Radiation-induced sequelae and predictive tests: toward an individual profile

by David Azria, Val d'Aurelle Regional Cancer Centre (CRLC) – Montpellier (France) and Mahmut Ozsahin, Vaudois University Hospital – Lausanne (Switzerland)

Whether radiotherapy is successful or not largely depends on the total dose delivered and evenly distributed to the tumour. However, dose delivery is limited by the degree to which healthy tissue, in the irradiated area, can tolerate the dose [16].

Radiotherapy can cause various side effects [34], without it being possible to identify the risk of toxicity at an individual level. In fact, radiotherapy treatments are prescribed according to general protocols that do not take account of specific phenotypes or genotypes [5].

Two types of radiation-induced deterministic side effects (acute and late) are monitored from the start of a course of radiotherapy treatment, but only late side effects are described in detail in this review, in light of their irreversible nature and the impact they have on the patient's quality of life [13, 14, 24]. Acute reactions appear during or immediately following radiotherapy, and then usually disappear in the months following treatment without leaving any sequelae [24].

It is with this in mind that various predictive radiosensitivity tests performed on healthy tissue are being or have been developed to identify patients at an inherently high risk of late toxicity [15].

### Late radiation-induced side effects

Damage is usually caused to healthy tissues at a lower dose than that required to sterilise a tumour. Following a course of radiotherapy, the late side effects usually appear after a period of three months, although this is disputed (some people say the period is longer than six months). The symptoms may be mild or severe and become worse in the course of time. Late side effects occur in tissue with slow renewal rates, such as the superficial fascia, fatty tissue, the muscles or tissue that also contains tissue with fast renewal rates, such as the wall of the digestive tract [29]. There are many forms of microscopic late radiation-induced lesions, including fibrosis, necrosis, atrophy and vascular damage [29]. Little is known about the mechanisms involved in the occurrence of late radiation-induced lesions although several avenues of research support the hypothesis of perpetual localised production of cytokines and growth factors. In addition, the physiopathology of late-response radiation-induced lesions in healthy tissue is characterised by the direct destruction of stem cells, vascular impairment and the progressive formation of an interstitial fibrosis [24]. This kind of radiation-induced fibrosis, which is practically always found in irradiated tissue, is an abnormal accumulation of the extracellular matrix. Remodelling the matrix deposits is a permanent process that spontaneously evolves towards a deterioration due to disruption of local homeostatic equilibrium. In clinical terms, this can be extremely variable in terms of time (from the inflammatory phase to the “aged” fibrosis) and intensity (from simple induration to disabling retractile sclerosis) [9, 10, 14].

The key objective of a number of studies is to reveal and assess the side effects induced by radiation [32]. The “National Cancer

Institute (NCI) Common Toxicity Criteria system (CTC v1.0)” was first developed in 1983 to help assess and grade the side effects of chemotherapy treatment. This was brought up-to-date and improved upon in 1998, as version 2 (CTC v2.0), still focused on acute side effects [31]. Recently, and with a view to creating a single classification system that would include late toxicity, the NCI has developed a third version of the CTC: the CTCAE v3.0 for Common Terminology Criteria for Adverse Events version 3.0 (Table 1).

The CTC v3.0 [32] has several advantages over earlier toxicity assessment scales:

- The RTOG/EORTC, LENT-SOMA and CTC v2.0 scales gave inconsistent assessment results, hence the interest in developing a common classification system [11].

They list acute and late side effects together under a single classification, without factoring in the amount of time before the onset of symptoms. Investigators can thus describe and grade the side effect observed at each consultation without concerning themselves with the “time” parameter.

- This new classification system is the result of broad international consensus among oncologists and has been validated by all the clinical research groups. Many people from all over the world have been involved in its development, including the RTOG (Radiation Therapy Oncology Group), the EORTC (European Organisation for Research and Treatment of Cancer), the ACOSOG (American College of Surgeons Oncology Group), the ESTRO (European Society for Therapeutic Radiology and Oncology) and the ASTRO (American Society for Therapeutic Radiology and Oncology).

- In daily clinical practice, it is easy to use and gives fast results. There are other techniques used to assess late toxicity, mainly in breast disease, but they are very difficult to use on a large scale and fail to fully reflect what we are capable of in a clinical environment [15].

### Radiosensitivity factors in healthy tissue

Radiosensitivity factors can be divided into two subgroups that remain intricately interrelated during radiotherapy treatment. Thus, there are factors related to the treatment and factors related to the patient.

#### *Factors related to the treatment*

The risk, severity and nature of delayed reactions is intimately dependent on the irradiation procedures used. There are four factors that determine these reactions:

- **The total dose:** The majority of late side effects are deterministic and occur above a threshold dose. In addition, the slope for the dose-effect relationship is more inclined in the case of late-response tissue than for early-response healthy tissue [30]. A moderate reduction of the dose delivered to the healthy tissue may thus have a substantial impact on the incidence and seriousness of late damage.

- **Fractionation and the time gap between fractions:** The fractional dose is usually between 1.8 and 2 Gy. Late-response healthy tissues are especially sensitive to modifications in this fractional dose. In fact, using a fractional dose below 1.8 Gy (hyperfractionation) reduces the incidence and the severity of radiation-induced sequelae while maintaining the same total therapeutic dose. In addition, using a hyperfractionation also makes it possible to deliver a higher total dose to the tumour without increasing late toxicity.

The interval between fractions is not fully understood, but there is a great deal of experimental and clinical data that confirms that an interval of at least 6 hours between two fractions leads to repair of at least 50% of radiation-induced lesions. This interval is a major factor in late toxicity due to the correlation between



the considerable capacity of DNA to repair radiation-induced lesions and the sensitivity of late-response healthy tissue to fractionation [13].

– **Protraction:** or the total treatment time, has very little influence on the risk of late lesions occurring in healthy tissue. However, the fact of speeding up treatment may cause extremely acute toxicity and, therefore, late reactions following such a hyperreaction (or “consequential late effect”) [29].

– **The volume irradiated:** The volume of healthy tissue irradiated may influence the risk of complications during radiotherapy. Many mathematical models have been applied to the dose–volume–effect relationship to try and predict the risk of complications involved in a given irradiation scheme. The most fully-developed models concern the late effects of irradiation. Certain complications are directly dependent on volume: this is so in the case of radiation hepatitis, the severity of which depends on the hepatic volume irradiated. In the case of the lung, it is possible to predict the risk of clinical Grade 2 radiation pneumonitis (using the RTOG, or Radiation Therapy Oncology Group, classification) based on the dose–volume histograms. Apart from effects on the differentiated cellular compartment, the irradiation volume may also affect an organ’s functional reserve. For example, in the case of haematopoietic marrow and the salivary glands, complications are avoided due to the volume of healthy tissue spared from irradiation. This type of direct relation between volume and effect concerns organs with parallel architecture. Its role is thought to be minor, or even nonexistent, in the case of serial organs [20].

## Factors related to the patient

Two main frameworks can be mentioned under this section:

– The genetic framework: some genetic illnesses are characterised by anomalies in cellular mechanisms triggered to repair radiation-induced molecular damage and are associated with hypersensitivity in healthy tissue. Patients that carry a mutation in the ATM gene (Ataxia Telangiectasia) are at a higher risk of late radiation-induced toxicity [6, 21].

– Predisposing factors: The risk of complications or sequelae following irradiation appears to be higher when a certain number of predisposing factors, such as advanced age, treatments associated with chemotherapy [24] or hormone therapy [1–3], smoking, microvascular disorders (diabetes, arterial hypertension) and systemic sclerosis [14].

## Predictive toxicity tests

Cancer treatments, including radiotherapy, are mainly limited by the dose tolerated by healthy tissue, especially tissue that has a late response. In addition, the doses are not very well understood and are based on estimates developed a relatively long time ago [16]. In a population group treated using the same technique and assessed by the same team, there is clearly a difference in the intrinsic radiosensitivity of healthy tissue. Research is being developed into a possible deficit or gene modification and may result in a high-risk fringe group being identified.

On the technical level, studying the cellular radiobiological characteristics of healthy tissue poses less of a problem at first sight than studying those of tumours, mainly in view of tissue accessibility, the quantity of material available and the homogeneity of cell populations. Moreover, if we assume that there is a genetic anomaly underlying individual hypersensitivity, diagnosis could be based on lymphocytes or fibroblasts from a skin biopsy [14].

Lymphocytes would seem to be the most suitable tissue, given the simplicity of taking samples and the quantity available. Radiation-induced lymphocyte apoptosis has been examined over the last few years and represents the type of cell death that is sensitive and reproducible [27, 33]. Furthermore, lymphocyte sub-types CD4 and CD8 can be completely separated from other sub-types using a flow cytometry technique [7, 26]. Other cell types (especially fibroblasts) and several other assessment methods (micronuclei or lethal chromosomal aberrations) have

been looked at but the results, in terms of predicting late side effects remain contradictory [12, 17, 19, 22, 23]. Moreover, initial studies concerning the lymphocyte apoptosis test showed that this test is fast and reproducible unlike the other methods mentioned above [8, 26, 28].

## Ongoing studies

In a prospective study, based on preclinical and clinical (retrospective) data, we demonstrated the potential advantages of the radiation-induced CD8 lymphocyte apoptosis test in predicting toxicity [25]. In this study, predicting late side effects following radiotherapy was assessed on the basis of the *in vitro* radiation-induced CD8 lymphocyte apoptosis rate. Thus, a 5 ml tube of heparinised blood was taken from 399 patients who had undergone external radiotherapy for curative purposes. Each sample was prepared and then irradiated by a single 8 Gy dose. Forty-eight hours later, the lymphocytes were isolated and the apoptosis level measured by flow cytometry. All the patients had been regularly monitored and any late toxicity had been recorded and rated according to the RTOG/EORTC classification. Six patients refused external radiotherapy after the blood samples were taken and were excluded from the analysis. The area under curve (AUC) for ROC analyses was used to calculate the prediction of late effects based on the radiation-induced CD8 lymphocyte apoptosis rate. Competitive risk analysis gave an estimate of the cumulative incidence of late side effects depending on radiation-induced apoptosis. The majority of the patients had breast cancer (n=149, 147 women and 2 men), ENT cancer (n=75) or prostate cancer (n=36). The rates of Grade 2 and 3 late toxicity were 31% (121/393) and 7% (28/393) respectively. A low radiation-induced CD8 lymphocyte apoptosis rate was statistically correlated to the percentage of late toxicity of Grade  $\geq 2$  ( $p < 0.0001$ ). A radiation-induced CD8 lymphocyte apoptosis rate over 24 was found in all the patients who did not present toxicity of Grade 3 ( $p < 0.0001$ ). The AUCs were 0.827 for patients presenting late toxicity of Grade  $\geq 2$ . The positive predictive value was 83% for a radiation-induced CD8 lymphocyte apoptosis rate  $\leq 16\%$  and the negative predictive value was 86% for a radiation-induced CD8 lymphocyte apoptosis rate  $> 24\%$ . The cumulative incidence rates of late toxicity of Grade  $\geq 2$  at two years were 70, 32 and 12% respectively for lymphocyte apoptosis rates of  $\leq 16$ , 16–24 and  $> 24\%$ .

Of the 399 female patients in the study described above, 147 with breast cancer were treated by conservative surgery and adjuvant radiotherapy, and 90 had been started on tamoxifen (TAM, 20 mg/day) before beginning radiotherapy [1]. Fibrosis-free survival at two years was 51% in the group that received radiotherapy + TAM compared with 80% in the group not given TAM ( $p = 0.029$ ). Furthermore, this difference was distinct in the female patients at risk of developing late side effects. In the subgroup of 147 female patients, the women with markedly lower fibrosis-free survival rates were those who also had a low radiation-induced CD8 lymphocyte apoptosis rate. The fibrosis-free survival rates depending on whether or not the patient had been given tamoxifen and on the radiation-induced CD8 lymphocyte apoptosis rate showed that the patients with a radiation-induced CD8 lymphocyte apoptosis rate  $< 16\%$  and who had received concomitant TAM and radiotherapy had only a 20% rate of fibrosis-free survival. On the other hand, the female patients with high radiation-induced CD8 lymphocyte apoptosis rates showed very little sensitivity to the concomitant prescription of TAM and radiotherapy.

More recently, a phase II random study assessed the risk of late cutaneous toxicity due to the concomitant or sequential combination of radiotherapy and an aromatase inhibitor (Letrozole) in 150 female patients treated with conservative surgery for localised breast cancer. In this study, there were several stratification factors including the radiation-induced CD8 lymphocyte apoptosis rate. The results, with a two-year median follow-up study, will be presented at the ASTRO 2008 congress.



Given these initial results, we are keen to develop this test in clinical practice. However, there is not a single very large-scale multi-centre trial available to date. A hospital-based clinical research programme is currently at the inclusion stage and will then help us answer several questions:

- the relevance of this test in two pathologies requiring an escalating dose (breast and prostate cancer);
- the use of the same toxicity scale (CTC v3.0) at several sites with an independent assessment by two doctors at each consultation;
- the feasibility of a single biological test (centralised at the CRLC Val d'Aurelle in Montpellier to begin with) and the involvement of the French oncology community in this type of study.

## Genetic perspectives

This section is covered in detail in the article by Janet Hall of the Institut Curie. It is remarkable to note that two complementary approaches have been developed to determine the patients at risk of developing late radiation-induced toxicity: (i) low radiation-induced CD8 lymphocyte apoptosis rate (ii) four or more SNP [Single Nucleotide Polymorphism] alterations. We proposed correlating these two approaches [3]. Of the 393 patients included in the prospective study presented above, 16 developed Grade  $\geq 3$  radiation-induced toxicity (group A). All had a radiation-induced CD8 lymphocyte apoptosis rate  $< 16\%$ . We selected a further 18 patients with no late toxicity as a control group (group B). A blood test was taken to isolate the DNA and look for

SNP alterations in the ATM, SOD2, TGF $\beta$ 1, XRCC1, XRCC3 and RAD21. In group A, 15/16 patients (94%, 95%CI: 70-100) presented four or more SNPs compared with 6/18 (33%, 95%CI: 13-59) in group B ( $p < 0.001$ ). The probability of developing a Grade 3 toxicity was significantly higher (OR 9.3, 95%CI: 1.4-62,  $p = 0.003$ ) in patients with four or more SNPs (0.71, 95%CI: 0.48-0.89) compared with those with less than four SNPs (0.08, 95%CI 0.01-0.32). The median (range) radiation-induced CD8 lymphocyte apoptosis rate was 11% (6-42) and 25% (5-43) for the patients with four or more SNPs and less than four SNPs ( $p = 0.004$ ) respectively. The number of SNPs and the radiation-induced CD8 lymphocyte apoptosis rate were inversely linked ( $r = -0.53$ ,  $p = 0.0011$ ). Considered individually, the total number of SNPs detected on the ATM, SOD2, TGF $\beta$ 1, XRCC1, XRCC3 and RAD21 was 2 to 4 times higher in group A. Lastly, the median (range) radiation-induced CD8 lymphocyte apoptosis rates for the patients with toxicity of Grade  $\geq 3$  and carriers of four or more SNPs were 9% (5-16.5) and 11% (6-42%) respectively. We have shown that, on a healthy tissue model, the low radiation-induced CD8 lymphocyte apoptosis rate was correlated with the high risk of late toxicity and corresponded to over four SNP alterations in ATM, SOD2, TGF $\beta$ 1, XRCC1, XRCC3 and RAD21.

Studies are in progress to confirm these initial results in collaboration with Mount Sinai Hospital in New York (Professor B. Rosenstein) [18]. Analysis based on the total genome, rather than simply the candidate genes, is being developed. ■

## References

- [1] Azria D., Gourgou S., Sozzi W.J., Zouhair A., Mirimanoff R.O., Kramar A., et al. Concomitant use of tamoxifen with radiotherapy enhances subcutaneous breast fibrosis in hypersensitive patients. *Br J Cancer* 2004;91:1251-60.
- [2] Azria D., Ozsahin M., Gligorov J., Zaman K., Llacer Moscardo C., Lemanski C., et al. How to combine hormone therapy and radiation treatment in adjuvant breast cancer? *Cancer Radiother* 2008;12:37-41.
- [3] Azria D., Ozsahin M., Kramar A., Peters S., Atencio D.P., Crompton N.E., et al. Single Nucleotide Polymorphisms, Apoptosis and the Development of Severe Late Adverse Effects Following Radiotherapy. *Clin Cancer Res* 2008; sous presse.
- [4] Azria D., Rosenstein B.S., Ozsahin M. Radiation-induced side-effects with or without systemic therapies: Primetime for prediction of individual radiosensitivity! *Int J. Radiat Oncol Biol Phys* 2008; sous presse.
- [5] Buchholz T.A. Finding our sensitive patients. *Int J. Radiat Oncol Biol Phys* 1999;45: 547-8.
- [6] Cesaretti J.A., Stock R.G., Lehrer S., Atencio D.A., Bernstein J.L., Stone N.N., et al. ATM sequence variants are predictive of adverse radiotherapy response among patients treated for prostate cancer. *Int J. Radiat Oncol Biol Phys* 2005;61:196-202.
- [7] Crompton N.E., Ozsahin M. A versatile and rapid assay of radiosensitivity of peripheral blood leukocytes based on DNA and surface-marker assessment of cytotoxicity. *Radiat Res* 1997;147:55-60.
- [8] Crompton N.E., Shi Y.Q., Emery G.C., Wissner L., Blattmann H., Maier A., et al. Sources of variation in patient response to radiation treatment. *Int J. Radiat Oncol Biol Phys* 2001;49:547-54.
- [9] Delanian S., Balla-Mekias S., Lefaix J.L. Striking regression of chronic radiotherapy damage in a clinical trial of combined pentoxifylline and tocopherol. *J. Clin Oncol* 1999;17:3283-90.
- [10] Delanian S., Porcher R., Balla-Mekias S., Lefaix J.L. Randomized, placebo-controlled trial of combined pentoxifylline and tocopherol for regression of superficial radiation-induced fibrosis. *J. Clin Oncol* 2003;21:2545-50.
- [11] Denis F., Garaud P., Bardet E., Alfonsi M., Sire C., Germain T., et al. Late toxicity results of the GORTEC 94-01 randomized trial comparing radiotherapy with concomitant radiochemotherapy for advanced-stage oropharynx carcinoma: comparison of LENT/SOMA, RTOG/EORTC, and NCI-CTC scoring systems. *Int J. Radiat Oncol Biol Phys* 2003;55:93-8.
- [12] Dewey W.C., Ling C.C., Meyn R.E. Radiation-induced apoptosis: relevance to radiotherapy. *Int J Radiat Oncol Biol Phys* 1995;33:781-96.
- [13] Dubray B. Late complications of radiotherapy. Role of the time factor. *Bull Cancer Radiother* 1995;82:98-100.
- [14] Dubray B., Delanian S., Lefaix J.L. Late effects of mammary radiotherapy on skin and subcutaneous tissues. *Cancer Radiother* 1997;1:744-52.
- [15] Dubray B., Pavy J.J., Giraud P., Danhier S., Cosset J.M. Predictive tests of response to radiotherapy. Assessment and perspectives in 1997. *Cancer Radiother* 1997; 1:473-83.
- [16] Emami B., Lyman J., Brown A., Coia L., Goitein M., Munzenrider J.E., et al. Tolerance of normal tissue to therapeutic irradiation. *Int J. Radiat Oncol Biol Phys* 1991;21:109-22.
- [17] Floyd D.N., Cassoni A.M. Intrinsic radiosensitivity of adult and cord blood lymphocytes as determined by the micronucleus assay. *Eur J. Cancer* 1994;30:615-20.
- [18] Ho A.Y., Atencio D.P., Peters S., Stock R.G., Formenti S.C., Cesaretti J.A., et al. Genetic predictors of adverse radiotherapy effects: the Gene-PARE project. *Int J. Radiat Oncol Biol Phys* 2006;65:646-55.
- [19] Hoeller U., Borgmann K., Bonacker M., Kuhlmeier A., Bajrovic A., Jung H., et al. Individual radiosensitivity measured with lymphocytes may be used to predict the risk of fibrosis after radiotherapy for breast cancer. *Radiother Oncol* 2003;69:137-44.
- [20] Huchet A., Caudry M., Belkacemi Y., Trouette R., Vendrely V., Causse N., et al. Volume-effect and radiotherapy [III]. Part II: volume-effect and normal tissue. *Cancer Radiother* 2003;7:353-62.
- [21] Iannuzzi C.M., Atencio D.P., Green S., Stock R.G., Rosenstein B.S. ATM mutations in female breast cancer patients predict for an increase in radiation-induced late effects. *Int J. Radiat Oncol Biol Phys* 2002;52:606-13.
- [22] Johansen J., Bentzen S.M., Overgaard J., Overgaard M. Relationship between the in vitro radiosensitivity of skin fibroblasts and the expression of subcutaneous fibrosis, telangiectasia, and skin erythema after radiotherapy. *Radiother Oncol* 1996;40:101-9.
- [23] Kiltie A.E., Ryan A.J., Swindell R., Barber J.B., West C.M., Magee B., et al. A correlation between residual radiation-induced DNA double-strand breaks in cultured fibroblasts and late radiotherapy reactions in breast cancer patients. *Radiother Oncol* 1999;51:55-65.
- [24] Lartigau E., Dubray B., Mornex F. Biological mechanisms of late effects of ionizing radiations. *Cancer Radiother* 1997;1:669-76.
- [25] Ozsahin M., Crompton N.E., Gourgou S., Kramar A., Li L., Shi Y., et al. CD4 and CD8 T-Lymphocyte Apoptosis Can Predict Radiation-Induced Late Toxicity: A Prospective Study in 399 Patients. *Clin Cancer Res* 2005;11:7426-7433.
- [26] Ozsahin M., Ozsahin H., Shi Y., Larsson B., Wurgler F.E., Crompton N.E. Rapid assay of intrinsic radiosensitivity based on apoptosis in human CD4 and CD8 T-lymphocytes. *Int J. Radiat Oncol Biol Phys* 1997;38:429-40.
- [27] Radford I.R., Murphy T.K. Radiation response of mouse lymphoid and myeloid cell lines. Part III. Different signals can lead to apoptosis and may influence sensitivity to killing by DNA double-strand breakage. *Int J. Radiat Biol* 1994;65:229-39.
- [28] Slonina D., Gasinska A. Intrinsic radiosensitivity of healthy donors and cancer patients as determined by the lymphocyte micronucleus assay. *Int J. Radiat Biol* 1997;72:693-701.
- [29] Stone H.B., Coleman C.N., Anscher M.S., McBride W.H. Effects of radiation on normal tissue: consequences and mechanisms. *Lancet Oncol* 2003;4:529-36.
- [30] Thames H.D., Hendry J.H., Moore J.V., Ang K.K., Travis E.L. The high steepness of dose-response curves for late-responding normal tissues. *Radiother Oncol* 1989;15:49-53.
- [31] Trotti A., Byhardt R., Stetz J., Gwede C., Corn B., Fu K., et al. Common toxicity criteria: version 2.0. an improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;47:13-47.
- [32] Trotti A., Colevas A.D., Setser A., Rusch V., Jaques D., Budach V., et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* 2003;13:176-81.
- [33] Trowell O.A. The sensitivity of lymphocytes to ionising radiation. *J Pathol Bacteriol* 1952;64:687-704.
- [34] Withers H.R., Taylor J.M., Maciejewski B. Treatment volume and tissue tolerance. *Int J Radiat Oncol Biol Phys* 1988;14:751-9.





## Human radiosensitivity: new concepts and new tools to predict over-acute reactions after radiotherapy

by **Nicolas Foray**, Radiology Group, U836 Inserm, Grenoble Institute of Neurosciences (France)

### Some definitions to reconsider?

There was about 12 millions new cases of people suffering from cancer in the world in 2007. A great majority of them were treated with radio-chemotherapy. However, 1–10% patients may exhibit some over-acute tissue reactions, which may limit the application of the full scheduled treatment. The most frequent over-acute tissue reactions do not necessarily concern skin with erythemas and dermatitis but can rectites with prostate cancers, fibrosis with oesophagus cancer, etc. [e.g. RTOG/EORTC, 1995]. Post-treatment over-acute tissue reactions were longer divided into early and late ones. However, there is now evidence that their occurrence may cover a continuum of occurrence time and intensity from the first treatment session to some years after. Furthermore, the development of innovating anti-cancer strategies based on massive and local deposition of the radiation dose has complexified the previous definition of these early and late reactions [Dörr, 2001]. Lastly, radiodiagnostic sessions that are intimately included in radiotherapy treatment has changed drastically the assessment of the exact radiation dose that is delivered effectively to the patient. Consequently, despite of a number of attempts and notably a number of efforts provided by the French authorities after the recent events in the Epinal and Toulouse anti-cancer centres, the definition and the classification of these over-acute reactions is still not consensual: in practice, to recognize that a patient effectively suffers from over-acute tissue reactions is still done on the only basis of the local experience of the clinician. The exact occurrence of the over-acute tissue reactions in each national anti-cancer centre remains unknown. Lastly, since some over-acute tissue reactions observed after standard radiotherapy may look like some tissue reactions occurring after irradiation accidents, they are too frequently associated with dosimetry errors [Ash, 2007]. To conclude, biological endpoints correlated quantitatively to over-acute reactions are needed.

### Some molecular approaches to avoid?

The clinical response to radiation is undoubtedly dependent upon the organ, the tissue and the genetic status of each individual. While individual variations and the notion of continuum in the responses suggested the development of individual treatments, one must admit that the practical and economical necessities have progressively hidden these notions to the benefit of standards of anti-cancer treatments. In parallel, although many works on genetically modified yeasts and rodents have undoubtedly contributed to increase our knowledge in DNA damage repair and signalling and in the control of genomic stability, they erased the notion of the continuum of responses to radiation. The use of *in vivo* and *in vitro* animal models, maybe very sophisticated, has indeed over-simplified the clinical reality. Consequently, a number of works have caricatured the response to radiation as an all-or-none phenomenon with very radioresistant and hyper-radiosensitive cases. Worse, the most

hyper-radiosensitive animal models generally show mutations of proteins whose identical homologues did not exist in humans (e.g. Ku70, Ku80, Rad51, Rad52, etc.). Finally, the obvious necessity to quantify and describe each level of severity of radiation responses disappeared behind a number of “monogenic” studies that represent, still to date, the great majority of papers in radiobiology [Joubert, 2007, 2008].

### Some requirements to link tissue reactions with molecular endpoints

Unlike the all-or-none view described above, the notion of radiosensitivity is a relative notion that requires quantifications and intercomparisons. The evidence of the individual susceptibility, the specificity of the effects to the irradiated organs and tissues and the expected continuum in the severities of reactions oblige together:

- 1. To work with the widest range of radiosensitivity in order to define reliable parameters that would predict any situation (from radioresistance to hyper-radiosensitivity).
- 2. To work with human cells to avoid any biases that would be due to interspecies differences.
- 3. To choose models and protocols that would be as closest as possible to the clinical situations (dose, fractionation, tumour, relevant tumour models generally treated with radiotherapy, normal tissues, etc...).
- 4. To provide a universal and clear (operational) definition of the notion of radiosensitivity that would be quantitatively correlated with the clinical radiocurability of tumours and radiation-induced over-reactions in normal tissues.

This last point summarizes the first 60 years of radiobiology (from 1896 to 1956 exactly) when the radiobiologists became aware that a quantitative approach should succeed to the descriptive period during which cellular and tissue effects of radiations were described meticulously. However, endpoints related to the radiobiological death remained to be defined.

In 1956, by defining the radiobiological death as the loss of proliferation capacities of irradiated cells, Puck and Markus developed the clonogenic survival assays consisting in irradiating a given number of cells and thereafter scoring the resulted colonies some days after irradiation [Puck, 1956]. Thank to such assays, the relationship between dose and the post-irradiation clonogenicity, as a survival curve, enabled comparisons between cells, radiation type, experimental protocols, etc. Hence, the survival assays became the “gold standards” to define the radiosensitivity *in vitro*. Since the tumour local control (i.e. the post-irradiation decrease of tumour volume) was longer considered as a reliable parameter to account for tumour radiocurability *in vivo*, a number of research groups began systematic studies to verify the potential link between *in vivo* and *in vitro* observations. A quantitative correlation between tumour local control and clonogenic cell survival was pointed out in 1981 [Fertil, 1981]. In this paper, it was strongly suggested that radiosensitivity of normal tissues may be predicted by *in vitro* clonogenic cell survival assays.

### Some attempts to link tissue reactions with molecular endpoints

Unfortunately, the clonogenic assays appears rapidly too time-consuming to be applied in routine. In order to make faster the prediction of the clinical response to radiation, considerable efforts were thereafter provided to “molecularize” these *in vivo* approaches by developing faster assays. To summarize, three groups of molecular predictive assays were tested: those based on gene expression, on gene mutation or on gene functions.

## Assays based on gene expression

If the hypothesis that expression of a given gene is able to predict all the human radiosensitivity range is relevant, it implies *stricto sensu* that the expression of this gene varies with radiation dose like the clonogenic survival. However, the major proteins required for the upstream radiation-induced events (i.e. DNA damage recognition, DNA repair) are very abundant and do not show convincing variations with radiation dose. By contrast, some downstream actors of the radiation response (i.e. proteins involved in cell cycle checkpoint or cell death pathways) are radio-inducible. Nevertheless, there is still no convincing data showing correlation between gene expression and clonogenic cell survival for a large range of radiation dose. Lastly, since most of these assays are based on blood samples, it should also be investigated further whether the choice of the blood model adequately predicts over-acute reactions observed on other tissues.

## Assays based on gene mutation

The recent findings about single nucleotide polymorphisms (SNPs) has rendered punctually relevant the first approach evoked. Originally, considerable efforts have been made to identify mutations and polymorphisms in individuals suffering from particular cancers. In fact, some SNPs of the ATM, XRCC1, XRCC3, SOD2, RAD21, TGF-1 and PARP genes have been identified and eventually associated with abnormal response to radiation [e.g. Azria, 2008]. While SNPs may account for certain cases of radiosensitivity, there is still no quantitative general correlation between SNPs and intrinsic radiosensitivity. Moreover, some patients showing the same SNPs may exhibit different degrees of severity of tissue reaction [e.g. Azria, 2008]. Hence, it is too early to draw any final conclusion but it seems obvious that the relative impact of each SNP upon the general radiation response needs to be better estimated. Altogether, the available data present some promising evidence that some SNP may be aggravating factors of the radiation response but, again, a quantitative

link remains to be established: *per se*, a single SNP would not be sufficient to describe all the human radiosensitivity.

## Assays based on gene function

Apoptosis is a spectacular cell death pathway, easily detectable by microscopy. Such phenomenon became so popular in the radiobiology research area that some authors consider it as a synonym of radiosensitivity. However, there is still no general correlation between radiosensitivity (clonogenic survival) and apoptosis [eg. Schmitz, 2008]. As a representative example, the skin cells from patients suffering from ataxia-telangiectasia, the syndrome associated to the highest radiosensitivity in humans, do not elicit any apoptosis bodies but a number of micronuclei [Joubert 2007, 2008]. Besides, apoptotic bodies are still too frequently confounded with micronuclei from mitotic death pathway: this misinterpretation has been notably amplified by the development of assays based on the use of cytometry with which DNA fragments are detected. Since micronuclei systematically contain unrepaired DNA fragments, some false-positive apoptosis data may be simply explained by the presence of micronuclei and the predominance of mitotic death [Joubert 2007, 2008]. Since most of the apoptotic assays are performed with blood cells, it has rendered again more difficult an objective interpretation of data [Gera, 1992].

Through a plethora of studies, it must be stressed that cytogenetics (though chromosomal breaks and micronuclei) provided early the most reliable indicators of the human radiosensitivity [Fenech, 2006]. However, a classical argument against the extensive use of such assays is that a certain period of time (some hours) after treatment is required for getting metaphases, indispensable for visualizing chromosomes. During such period of time, some phenomena like repair may occur. Since chromosome damage generate from DNA damage, it appears therefore natural to investigate the repair of DNA double-strand breaks (DSB), responsible for the formation of chromosomal breaks and

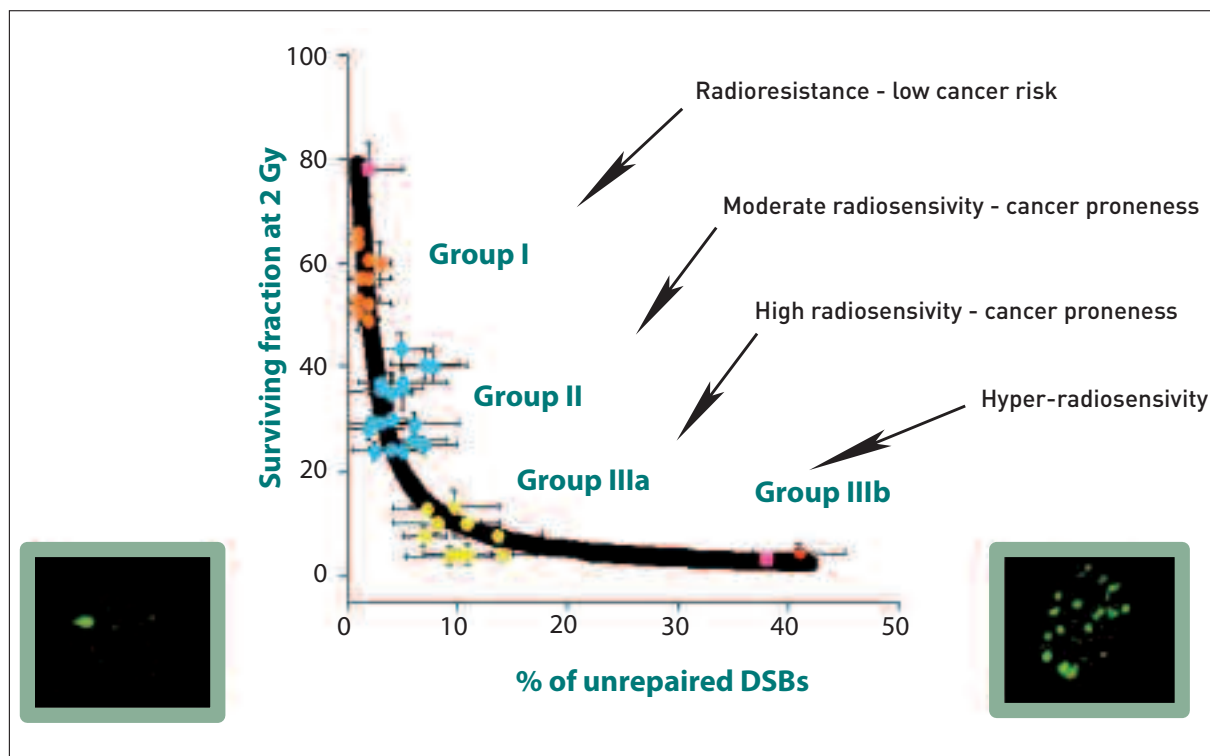


Figure 1. Relationship between survival fraction at 2 Gy (SF2) and unrepaired DSB per Gy calculated from pH2AX immunofluorescence technique applied to untransformed human fibroblasts irradiated at 2 Gy followed by 24 h for repair. Data are from [Joubert, 2008]. Arrows indicate the group of radiosensitivity (group I: SF2 ranging from 45.2 to 65.6%; group II: SF2 ranging from 45.2 to 7.4%; group III: SF2 ranging from 3.7 to 7.4%. Group III contains ATM-mutated cells (IIIa) but also any cells in which NHEJ repair proteins like LIG4 or DNA-PK are mutated (IIIb). Pink squares represent the most radioresistant and the most radiosensitive rodent cell lines (CHO-K1 and CHO-xrs5, respectively). SF2 was found to be inversely proportional to unrepaired DSB. Solid line result from a general data fitting. Lower inserts show representative example of nuclei with pH2AX foci for radioresistant and radiosensitive cells.



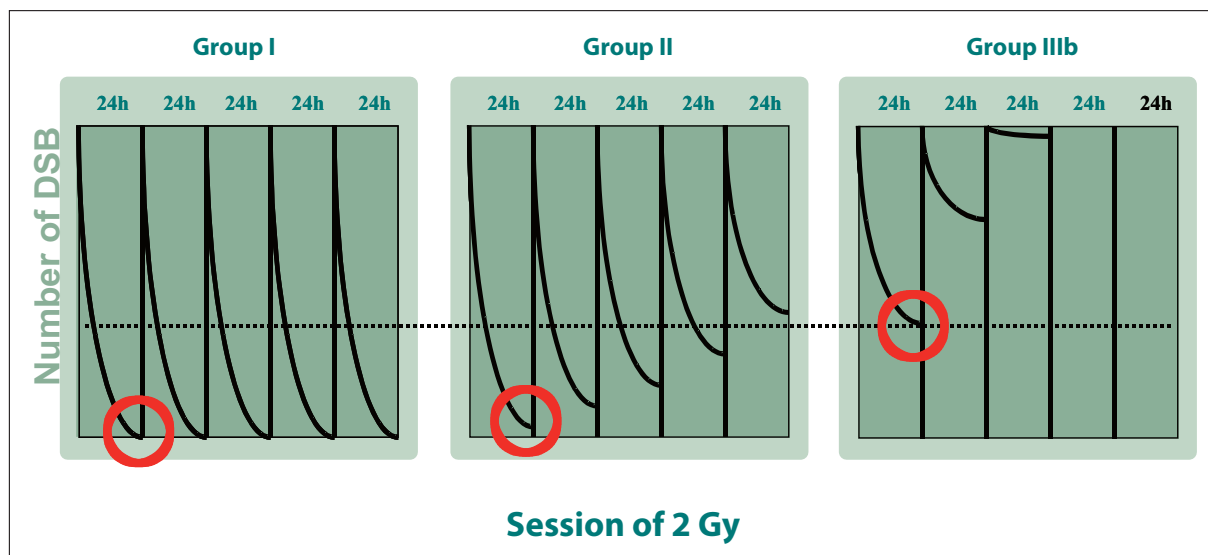


Figure 2. Schematic illustrations of the number of unrepaired DSB observed after several sessions of standard radiotherapy treatment (2 Gy per session, 24 h between sessions) according to the group of radiosensitivity. The number of unrepaired DSB reached in one session for group III patients is obtained more rapidly in the case of group II than group I.

micronuclei [Fenech, 2006]. However, while our understanding of DSB repair process has considerably progressed all along the last years, some unresolved questions remain to finally consider DSB repair as a reliable predictive factor of intrinsic radiosensitivity: Notably, mammalian cells were long believed to possess two major mechanisms for repairing DSB, namely, homologous recombination (HR) and non-homologous end-joining (NHEJ). However, since HR is only active in S-G2/M phase, this NHEJ or else HR paradigm that came from molecular models from rodent and yeast data cannot explain the radiosensitivity of human cells in G1 that would be NHEJ-proficient [Joubert 2007, 2008]. More recently, it was shown that radiation-induced DSB can be determined from the number of nuclear foci formed by the phosphorylation of the variant histone H2AX (pH2AX) and easily quantifiable using immunofluorescence [Rothkamm, 2003]. The pH2AX immunofluorescence technique revolutionized our estimation of the radiation-lethal events since it allows the determination of each individual DSB inside cell nuclei with a one-to-one correlation between DSB and pH2AX foci. Unfortunately, again, although successfully tested in hyper-radiosensitive cells and presented as powerful predictive assay, some preliminary data showed us that pH2AX immunofluorescence does not necessarily predict the whole range of human radiosensitivity [Joubert 2007, 2008].

### Two DSB repair assays instead of one!

From 2003, unlike the majority of studies focusing on mutations of one single gene, we have deliberately chosen to extend our investigations to the largest spectrum of radiosensitivity of human cells, independently of any gene mutation. The relationship between cellular radiosensitivity and DSB repair data was examined in a collection of 40 non-transformed human fibroblasts representing at least 8 different genetic syndromes [Joubert, 2008]. The systematic application of the most extensively used molecular assays, namely immunofluorescence, electrophoresis and plasmid assays allowed us to propose a quantitative correlation between molecular and cellular radiosensitivity that is relevant for all mammalian cells: survival fraction at 2 Gy [SF2] was found to be inversely proportional to the amount of unrepaired DSB, whatever the genes mutations and the assays applied (Figure 1). Our findings support that the choice of a specific molecular assay conditions the nature of this correlation. However, no single assay discriminated the full range of human radiosensitivity. Particularly, pH2AX immunofluorescence does not predict well the moderate radiosensitivities [Joubert,

2008]. Our findings suggested the existence of an alternative DSB repair pathway, active in G1, independent of NHEJ and whose impairment may favour genomic instability. Notably, the MRE11-dependent pathway appears to be good candidate but this was in clear contradiction with the NHEJ or else HR paradigm evoked above.

Interestingly, the yield of MRE11 foci was found correlated to genomic instability and cancer proneness and with moderate radiosensitivity in all the syndromes tested [Joubert, 2008]. A classification of diseases according their cellular radiosensitivity, their molecular response to radiation and the functional assays permitting their evaluation was therefore proposed (Figure 1). In the frame of radiotherapy sessions, the group II cells may notably accumulate a large number of unreparable damage up to a level at which clinical overreactions become significant (Figure 2).

### Conclusions

The molecular and cellular bases of radiosensitivity are incredibly complex. However, their elucidation will render possible the development of reliable assays to predict the efficiency of anti-cancer radio-chemotherapy against tumours but also to predict and prevent the occurrence of over-acute reactions in surrounding normal tissues. We have learned from the already long and rich history of radiation research that:

1. even if they are "time-consuming" features, the clonogenic assays remain the "gold standard" to reflect quantitatively the radiocurability of tumours and the in vivo intrinsic radiosensitivity of normal tissues;
2. because of the predominance of mitotic death pathway for tumours and most of normal tissues, the micronuclei, cytogenetics and DSB repair assays remain the most reliable approaches to reflect the widest range of radiosensitivity;
3. gene expression, gene mutation (SNPs) and apoptosis assays generally performed from blood cells present some considerable advantages like rapidity of data acquisition but literature suggests that they are still punctually related to a certain range of radiosensitivity only, if any;
4. the study of a plethora of genetic syndromes has consolidated the conclusion that predictive assays based on the functionality of the DSB repair pathways involved in the response of radio- and chemo-therapy will permit to quantify and prevent the over-acute reactions occurring after irradiation. However, such approach with skin fibroblasts is longer than apoptosis blood

cells but seems to be more relevant for predicting a wide range of radiosensitivity: further investigations are therefore needed to better establish the quantified relationships between data from these two approaches

From our findings, we proposed therefore to apply systematically the double pH2AX and MRE11 immunofluorescence assays, at least, to cells from known syndromes and from skin biopsies of patients [Joubert, 2008]. To date, after gathering and testing 120 cell lines, no exception to our model has been observed [Foray et al., personal communication]. ■

## References

- ASH D. Lessons from Epinal *Clin Oncol.*, 2007; 19: 614-615.
- AZRIA D., OZSAHIN M., KRAMA A., PETERS S., ATENCIO D.O., CROMPTON N.E., MORNEX F., PELEGRIN A., DUBOIS J.B., MIRIMANOFF R.O. and ROSENSTEIN B.S. Single nucleotide polymorphisms, apoptosis, and the development of severe late adverse effects after radiotherapy. *Clin Cancer Res.* 2008; 14: 6284-6288.
- DORR W. & HENDRY J.H. Consequential late effects in normal tissues, *Radiother Oncol.*, 2001; 61 :223-231.
- FENECH M. Cytokinesis-block micronucleus assay evolves into a "cytome" assay of chromosomal instability, mitotic dysfunction and cell death. *Mutat Res.*, 2006; 600: 58-66.
- FERTIL B. & MALAISE E.P. Inherent cellular radiosensitivity as a basic concept for human tumor radiotherapy. *Int J Radiat Oncol Biol Phys* 1981; 7: 621-629.
- GEARA F.B., PETERS L.J., Ang K.K., Wike J.L., SIVON S.S., Guttenberger R., Callender D.L., Malaise E.P. and Brock W.A. Intrinsic radiosensitivity of normal human fibroblasts and lymphocytes after high- and low-dose-rate irradiation. *Cancer Res.* 1992; 52: 6348-6352.
- JOUBERT A. & FORAY N. [Intrinsic radiosensitivity and DNA double-strand breaks in human cells]. *Cancer Radiother* 2007; 11: 129-142.
- JOUBERT A., ZIMMERMAN K., BENCOKOVA Z., GASTALDO J., RENIER W., CHAVALAUDRA N., FAVAUDON V., ARLETT C.F., FORAY N. DNA double-strand break repair defects in syndromes associated with acute radiation response: at least two different assays to predict intrinsic radiosensitivity? *Int J Radiat Biol* 2008; 84: 1-19.
- PUCK T.T. & Marcus PI. Action of x-rays on mammalian cells. *J Exp Med*, 1956; 103: 653-666.
- ROTHKAMM K. & LOBRICH M. Evidence for a lack of DNA double-strand break repair in human cells exposed to very low x-ray doses. *Proc Natl Acad Sci U S A*, 2003; 100: 5057-5062.
- RTOG/EORTC. Late effects consensus conference: RTOG/EORTC, *Radiother Oncol*, 1995; 35: 5-7.
- SCHMITZ A., BAYER J., DECHAMPS N. and THOMAS G. Intrinsic susceptibility to radiation-induced apoptosis of human lymphocytes subpopulations. *Int J Radiat Oncol Biol Phys.* 2008;57:769-778.



## Evaluation and management of secondary cancer risk in modern radiotherapy: elaboration of an ICRP/ICRU publication

by **Jean-Marc Cosset** Vice-Chairman, ICRP Committee 3, chair of the Task Group and **André Wambersie** Member of ICRU, co-chair of the task group, for the *ad hoc* ICRP/ICRU Task Group – Paris (France)

The previous ICRP report dealing with Radiotherapy procedures was Publication 44, produced in 1985. Since that time, new techniques of external Radiotherapy have emerged and some of these have already been introduced into routine practice.

However, a possible disadvantage to a number of these new techniques is the increase in size of the volume of healthy tissues receiving low doses, and thus the theoretical potential to increase the risk of radiation-induced second cancers in those areas. Several authors have calculated that this risk could be doubled when using new procedures such as intensity-modulated radiation therapy (IMRT) (Hall 2003 and 2006, Kry 2005).

ICRP and ICRU each have an interest in this topic and both can offer complementary experience and competence. Hence, taking available data into account, they have decided to elaborate a document aimed at evaluating, as precisely as possible, the risks of second cancers related to the newly introduced techniques, and to propose solutions to manage this risk.

Firstly, the document will have to analyze the available clinical data, taking advantage in particular of the recent NIH publication “New malignancies among cancer survivors” (2006). Recent data on second cancers occurring after radiotherapy appear to confirm the usual clinical experience that “The majority of second induced cancers occur in or close to the high-dose treatment volume” (Hall, 2006). This important point should be kept in mind when comparing different techniques of irradiation; while it is certainly relevant to try to calculate the risks linked to the irradiation at low doses of large volumes located far away from the beams, it appears to be at least equally important to focus on those areas receiving “appreciable” dose (MP Little, 2001), close to the irradiated fields.

This clinical data also emphasizes the role of age, with children being much more sensitive to the carcinogenic effect of ionizing radiation than adults.

A last important point is that the “relative risks tend to be lower in the medical series than in the Japanese A-Bomb survivors” (MP Little, 2001). A similar observation has also been reported by Preston (2002) and Rubino (2003). The fractionation/protraction of most of the therapeutic irradiations, contrasting sharply with the extremely brief irradiation linked to the atomic bombs, might explain, at least in part, such a discrepancy.

The second section of the document will focus on the physical characteristics and on the dose distributions achieved by various techniques.

In order to aid the comparison of the various techniques and, after having considered the various dose distributions outside the beam, we propose to split the dose regions (outside the target volume) into three groups (the limits given here are still under discussion):

- “low dose” region: < 1 Gy;
- “medium dose” region: > 1 Gy and < 30 Gy (this last dose grossly corresponding to the 50% isodose according to the usual radiotherapy prescriptions);
- “High dose” region: > 30 Gy (up to the target dose).

An important point to be considered here is that a number of technical parameters can introduce large variations in the doses received by the healthy tissues outside the target volumes, variations which could actually be much larger than those introduced by the simple choice of a given technique.

The document will therefore have to include the scattered dose delivered by; the type of wedges, the number of beams and the modern IGRT (Image-guided Radiotherapy) techniques.

The third section of the document will deal with the risk models and the radiobiological aspects; the authors showing a potential doubling of the risk with some modern radiotherapy techniques (see above) have been using the linear-no threshold (LNT) model. However, other risk models have been proposed; schematically, models taking into account the “cell killing” at high doses (often called “competition” models), offering “bell-shaped” curves with a decrease of the risk at high doses, and models also based on this competition at high doses, but introducing corrections for repopulation and/or repair. Recent literature has shown that different conclusions could be drawn from the same subset of data when using different models (For example, the risk varying from double to identical). The ICRP/ICRU task group will aim at calculating the risks for a number of representative cancer sites, using the main proposed models.

The fourth section of the document will focus on recommendations; it will include a chapter on risk acceptability in the context of the treatment of a life-threatening disease, a chapter on specific recommendations on the various techniques, and a specific chapter about one of the most important parameters when dealing with radiation-induced tumors after radiotherapy; patient’s age. Children (up to about 15 years of age) are much more prone than adults to develop a radio-induced cancer after a given dose of irradiation. The causes for this include a higher “general” radiosensitivity of children, more frequent genetic syndromes linked to a higher susceptibility to irradiation at that age (See ICRP Publication 79) and a higher impact of scattered dose due to the smaller size of the children’s body.

This ICRP/ICRU document, still in a draft form, is not anticipated to be published before 2010. Of note, close contacts have been developed with the NCRP group working on the same topic. ■



## Risk acceptability in radiotherapy

by **Klauss Rüdiger Trott**, UCL Cancer Institute, University College London (UK) and Università di Pavia (Italy)

Cure from Cancer comes with a price tag. The nature and the timing of therapy-induced morbidity differ between the different treatment options such as surgery, chemotherapy, molecular therapies and radiotherapy, as do their frequency, their dependence on age, on co-morbidity, their impact on the quality of life after cure, their risk of fatal outcome, and the challenges they pose to the responsible doctor. Whereas most treatment-related side effects of surgery and chemotherapy occur early after treatment, the most serious side effects of radiotherapy occur late.

These differences make any comparison of treatment related morbidities of different treatment modalities a very difficult, often emotional and irrational affair. There is no common denominator on which the risks of say surgery and radiotherapy of prostate cancer, and their acceptability by doctor and patient, can be compared, yet both yield similar chances of cure from cancer.

The first to analyse the dilemma of chances of cure versus risk of late radiation damage in radiotherapy was Dr. Holthusen in 1936. Starting with the clinical observations that the probability of cancer cure as well as the probability of late normal tissue damage increase with dose, and assuming that both probabilities depend only on dose and volume but not on each other, he calculated the dose dependence of probability of uncomplicated cure and found a bell-shaped curve. This concept has since become the basis of all cure/risk arguments in radiotherapy since.

Yet, the main lesson from this argument is that good radiotherapy is not the one which does not cause any serious side effects in any patient, nor one which cures all patients. Therefore, dose and dose distribution in radiotherapy are not prescribed on the basis of which dose the tumour may require for cure but by the dose which would cause an acceptable level of serious late morbidity.

Whereas the failure of cure is a clear yes or no, the only other variable being time to recurrence, late morbidity has numerous clinical features. The spectrum of severity of each type of morbidity in any organ varies enormously between patients, so does timing, impact on quality of life etc. All this makes a purely quantitative approach to the problem of risk acceptability in radiotherapy obsolete.

Micro-vascular radiation damage is the hallmark of late and very late normal tissue damage after radiotherapy. It is always associated with telangiectasia which are visible in the skin but which occur in all organs. Yet, the clinical consequences vary between the different organs, from cerebrovascular incidents to rectal haemorrhage to cosmetic dysfiguration. Telangiectasia is always associated with a decrease in capillary density, micro-vascular insufficiency and subsequent atrophy. Micro-vascular radiation damage is steadily progressive for at least ten to fifteen years. None of the existing NTCP models is compatible with this most common and most important mechanism of very late normal tissue damage after curative radiotherapy.

This manifestation of very late radiation damage may also be closely related to another very late radiation damage, which recently has received considerable attention: cardiovascular radiation injury. The clinical and radiobiological investigation of

the dependence of very late cardiovascular radiation damage on dose and volume as well as its pathogenesis is the aim of two large European FP-7 research projects which are called RACE which is co-ordinated by Per Hall in Stockholm and CARDIO-RISK which is co-ordinated by Michael Molls in Munich. The most informative data which lead to this sudden interest of radiotherapists in cardiovascular injury come from the study of Sarah Darby in more than 100.000 breast cancer patients who received postoperative radiotherapy. The study compared the mortality from heart failure after radiotherapy of left-sided breast cancer with the mortality from heart failure after radiotherapy of right-sided breast cancer. With increasing follow-up, the mortality from heart failure in those patients with cancer of the left breast increased steadily by more than one-third in the radiotherapy group whereas there was no difference between right and left breast cancer in those patients who did not receive any radiotherapy. The only reasonable explanation for this side difference is that radiation caused heart failure ten or twenty years after radiotherapy of cancer of the left breast, this means, after mean radiation doses of the heart of less than 5 Gy (i.e. below the 10% isodose). It appears very likely that modifications of dose distributions can decrease or increase the risk of very late cardiovascular radiation damage. Yet, we do not know and have no means to know now, whether the current treatment techniques which are very different from those investigated in the study of Dr. Darby carry a lower risk, or the same risk or even a higher risk. Any strong statement in this direction now would be pure speculation. Moreover, volume as such is most unlikely to be a useful criterion of risk, the few experimental studies so far demonstrate that different anatomical structures in the heart which are not randomly distributed display very different radiosensitivities. The current research in Europe aims at solving some fundamental questions:

- What is the nature of radiation-induced heart disease after radiotherapy?
- Is very late cardiovascular radiation damage caused by radiation damage to the coronary arteries or to the microvasculature?
- How should the heart dose be specified for treatment plan optimisation?
- how can the risk of very late heart failure be included in the definition of an acceptable risk, an overall index of harm?

A large number of clinical / epidemiological studies provided indisputable evidence that patients who have been cured from their cancer by radiotherapy have an increased risk of developing a second cancer. Yet, treatment-related second cancers are the direct consequence of treatment success. Moreover, in most clinical situations (with the possible exceptions of lymphomas and childhood cancers) more patients die from failure of curing the first cancer than from treatment-induced second cancers.

In adult cancer patients, the crude absolute risk of developing a treatment-induced new cancer within the remaining life expectancy of the cured patient is well below 1% and thus much smaller than many risks of commonly accepted life style factors such as diet. The situation is entirely different in children and young adults. The cumulative incidence of treatment-associated second solid tumours increased dramatically as the patients progressed into their thirties. Cautious extrapolation would suggest that every patient who had been cured by radiotherapy from childhood cancer and has a normal life expectancy will develop a radiation-induced second cancer, later in life. The most critical organs for radiation-induced second cancers in paediatric radiotherapy in the first 25 years are breast, brain, bone, soft tissues and thyroid - yet there are great differences in sensitivity with age and in dose dependence: while sarcomas and brain tumours



tended to develop in the high-dose volumes of 30 Gy or more, carcinomas tended to occur in the intermediate to low-dose volumes. Each organ probably has a different dose effect relationship which changes with age. In view of this evidence it cannot be justified to use one shape of dose response relationship for all organs and all ages in risk estimation. We need organ, age and sex specific dose risk relationships before we can even start considering the acceptability of risk of radiotherapy-induced second cancers in the context of an overall index of harm. The ongoing European project ALLEGRO is a first attempt to explore the feasibility of such research.

The main scientific problem is not so much the shape of the dose risk relationship, even more critical is the specification of dose. In preventive radiation protection planning procedures, the mean organ dose has been recommended by ICRP for dose specification, if only as it is so simple. But the risk of radiation-induced second malignancies varies enormously with dose distribution within the critical organ. The leukaemia risk after the same mean bone marrow dose by more than a factor of ten. This question has not been well investigated, so far, the European FP7 project ALLEGRO is arguably the first which attempts to address this fundamental problem of the most serious though very late normal tissue risk after radiotherapy, the induction of a new cancer by the treatment of an existing cancer.

It is high time to stop modelling second cancer risks on the basis of no or inadequate data and rather concentrate on performing well controlled clinical, epidemiological studies such as the one which has been going on for more than ten years now in the Institut Gustave Roussy and those exploratory studies within the ALLEGRO project. They will require perseverance and hard work and have to focus on simple practical questions such as the dependence of the second cancer risk on dose, on dose-volume-distributions, on age and sex. We have to face reality rather than gambling in silico.

The ultimate aim of the Allegro project is to develop new criteria for treatment plan optimisation and patient information on which he may accept or reject treatment which would include, besides the risk of radiation-induced severe early and late normal tissue damage as is currently done also the risk of radiation-induced heart disease and radiation-induced second cancer. At present, no method has been proposed which could be considered safe or even suitable for this task.

I conclude that radiotherapy is a very effective treatment, similar to surgery for many common cancers and can cure many more patients than medical oncology. However there is a price for cure which in some situations can be very high. In most cases, the price appears acceptable, yet there is good evidence that improved treatment planning will be able to decrease overall risk and increase acceptability. However, despite of decades of research, there is no acceptable method to optimise treatment plans on the basis of clinical evidence and radiobiological science.

A major research effort, such as presently prepared by the ALLEGRO project is required to identify and resolve the main problems which, in my eyes are:

In any treatment, several, often independent side effects of different latency, of different severity and of different impact on quality of life may occur. How can these be combined to arrive at a simple measure of risk or an index of harm on which to optimise radiation treatment plans and discuss acceptability?

Treatment plans are presently compared on the basis of dose volume histograms, however, this does not make biological sense. We need to develop new methods to relate anatomical dose distributions rather than dose volume histograms to the different potential late normal tissue risks after curative radiotherapy. ■

## Round table on “Challenges in radiotherapy”

by **Pr Michel Bourguignon**, ASN Commissioner – Professor of Medical Physics

Radiotherapy is in a class of its own when we look at medical treatments. It is used to treat more than half the total number of cancers, a family of diseases that affects 30% of men and 25% of women. It is also an effective method of treatment as it succeeds in curing some 80% of the patients treated. Radiotherapy offers high quality treatment. We need it to be perfect!

The radiotherapy accidents in Epinal and Toulouse highlighted the risk of human and organisational errors. They have severe consequences for patients. Furthermore, radiotherapists have observed serious side effects in about 5% of patients (or around 10,000 people in France) which are not due to errors in the dose delivered or in the irradiated volume. These side effects could be related to individual hypersensitivity to ionising radiation.

At a time when the latest models of accelerators used in radiotherapy allow us to increase the doses delivered to tumours and thus increase the chances of a cure, it is important to ensure that the radiation protection of patients progresses at the same pace. The most likely way of achieving this is to assess each patient's radiosensitivity before radiotherapy begins.

## “Ethical justification: an urgent challenge for radiotherapy”

by **Santiago Sia**, Professor and Dean of Philosophy: Milltown Institute – Dublin (Ireland)

In line with the general call for ethical thinking in the various professions, there has been an acknowledgement in radiotherapy of the urgency and importance of justifying present practice. This is indeed a welcome development. But in addition to the difficulty of establishing an ethical criterion that will guide practice is the complexity of the ethical task itself. Unlike the search for specific guidelines or the establishment of agreed policies, the issue of ethical justification involves the individual practitioner as well as the professional body much more since it involves making a judgment or arriving at a decision. This particular challenge therefore needs to be addressed both by those already in practice and those still in training. There is a need not just to regulate professional practice but also to develop ethical awareness and sensitivity.



## Lessons learned from accidents in conventional external radiotherapy

by **Ola Holmberg**, Head, Radiation Protection of Patients Unit, Radiation Safety and Monitoring Section and **Renate Czarwinski**, Head, Radiation Safety and Monitoring Section, IAEA Vienna (Austria)



Headlines involving accidents in conventional external radiotherapy from recent years

When considering risks in radiotherapy, it should always be remembered that the patient is also gaining a major potential benefit from the radiotherapy. A patient receiving therapy with ionizing radiation will be exposed to many potential sources of harm throughout the medical procedures. While the probability of harm occurring might be low in many instances in radiotherapy, the consequences of that harm can be very serious for the individual patient, considering the high doses involved in therapy and the serious malignant conditions treated in many cases. The combination of the probability of harm occurring and the consequence of that harm, constitutes the risk for the patient. In order to prevent future accidents in radiotherapy, it is necessary to learn from accidents that have occurred in the past. When aiming to learn from these past accidents, it is of value to analyze the specific case histories and find the causes, contributing factors, actual circumstances of discovering the accident as well as methods for future prevention.

A number of accidents in conventional external radiotherapy have been extensively investigated and the lessons learned have been disseminated by the International Atomic Energy Agency (IAEA) [1-4]. The International Commission on Radiological Protection (ICRP) has also summarised causes and contributory factors for conventional external radiotherapy accidents [5]. When a hazard is realised there is usually an initiating event,

which is an act that occurred at some point in time and eventually led to the realisation of the hazard. While the IAEA in Safety Report Series 17 [4] is separating the terms “initiating event” and “contributing factor” (which is defined as “any circumstance, condition, action or omission which plays a part in the precipitation of an accident”), the ICRP [5] uses the term “cause” in order to describe a combination of events contributing to the realisation of the hazard. In this study, a number of past accidents have been reviewed. This information was subsequently systematically evaluated for generalized lessons to learn.

A review of lessons learned from accidents in conventional external radiotherapy [1-6], indicate patterns showing that most of these accidents have occurred under certain conditions. These conditions can be grouped into four categories:

1. Working with awareness and alertness: Accidental exposures have occurred due to inattention to details, and lack of alertness and awareness. This condition could also be made worse if the health professionals have to work in circumstances prone to distractions.
2. Procedures: Accidental exposures have occurred when there is a lack of procedures and checks, or when they are not sufficiently comprehensive, properly documented or fully implemented.
3. Training and understanding: Accidental exposures have occurred when there is a lack of qualified and well-trained staff, with necessary educational background and specialised training.
4. Responsibilities: Accidental exposures have occurred when there are gaps and ambiguities in the functions of personnel along the lines of authority and responsibility. In these cases, safety critical tasks have been insufficiently covered.

Learning from accidents that have occurred in the past, means addressing the above four conditions systematically, so that the occurrence of accidents in radiotherapy becomes minimized. ■

### References

1. IAEA. The overexposure of radiotherapy patients in San José, Costa Rica. IAEA, Vienna (1999).
2. IAEA. Investigation of an accidental exposure of radiotherapy patients in Panama, IAEA, Vienna (2001).
3. IAEA. The accidental overexposure of radiotherapy patients in Bialystok, IAEA special publication, IAEA, Vienna, (2002)
4. IAEA. Lessons learned from accidents in radiotherapy, Safety Reports Series No. 17, IAEA, Vienna (2000).
5. ICRP. Prevention of Accidental Exposures to Patients Undergoing Radiation Therapy. ICRP Publication 86, Volume 30 No.3 2000, Pergamon, Elsevier, Oxford (2000).
6. Holmberg, O. Accident prevention in radiotherapy. Biomed Imaging Interv J 2007; 3(2):e27.

## Lessons from accidental exposure in modern external radiotherapy

by **Pedro Ortiz López, PhD<sup>1</sup>**, Chairman of the Task Group of the International Commission on Radiological Protection on Preventing Accidental Exposures from Newer External Beam Radiation Therapy Technologies – Madrid (Spain)

### Building on solid ground

Radiotherapy brings unquestionable benefits to cancer patients; on the other hand, radiotherapy has unique safety-critical features requiring specific consideration: It is the only application of radiation, in which humans are deliberately given very high radiation doses, of the order of 20 to 80 Gy; often, normal tissue receives radiation doses that are on the upper edge of tolerable doses, as a result of which, accidental overdosage has had sometimes devastating consequences. In addition, underdosage, which may not always be timely detected, can also have severe consequences [ICRP, 2002]. Recent improvements in radiotherapy are associated with ever increasing complexity in both equipment and techniques and, despite of the fact that radiotherapy equipment is provided with standardized interlocks, safety in radiotherapy remains highly dependent on human actions, involving a complex interrelation among professionals of a multidisciplinary team through a large number of steps.

Keeping awareness of these features is essential for hospital administrators and heads of radiotherapy departments, when setting up a radiotherapy programme and when introducing new technologies and techniques. Publication ICRP, 2002, stated that “purchasing new equipment without a concomitant effort on education and training and on a programme of quality assurance is dangerous”. Without these key elements, no radiotherapy practice should be build up and operate, and therefore, they should be mandatory requirements by international standards and equivalent national regulations [IAEA, 1996]. These requirements should not be restricted to measurements on equipment, but should embrace the whole treatment process, the assignment of responsibilities, training and competence and systematic approaches for purchasing, acceptance testing, calibration, commissioning, and maintenance.

Moreover, accidental exposures have even occurred in well structured radiotherapy departments, when procedures or verifications are omitted [ICRP, 2009, in press]. Provisions are thus needed for supervising that the safety features stay effective over time, especially when workload increases and when new technologies and techniques are introduced.

### Lessons from major reported accidental exposures

Lessons from events with major consequences occurred with conventional radiotherapy have been reported [ICRP, 2002; IAEA, 2000, 1998, 2001, 2003] with the purpose of helping health administrators and heads of radiotherapy departments achieve confidence that these types of events are not likely to occur in their radiotherapy departments. This approach of using the lessons from past events to prevent reoccurrence can be called ‘retrospective approaches’. The following examples of lessons from

conventional radiotherapy are also applicable to new technologies:

- mistakes in beam calibration and commissioning of radiotherapy equipment with catastrophic consequences have shown the need to have in place an independent determination of the absorbed dose to the reference point. Some countries have even made this requirement mandatory;
- reports on major events due improper use of treatment planning system have taught that there is a need for thorough understanding of the TPS functionalities, for ensuring that the TPS is commissioned, tested and used according to instructions, and when deviations from instructions is unavoidable, the deviations should be validated before clinical use;
- a reported accelerator repair error has provided the lesson that it is indispensable to ensure notification to the physicist about any repair, together with a report of the nature of the repair, so that the physicist can infer the need for control checks, before resuming patient treatment;
- significant increase in workload and introduction of new techniques may lead to serious mistakes. Revisiting staff needs both in terms of number of professionals and training and competence is indispensable.

Serious accidental exposures with new technologies have also been recently reported, including the following lessons:

- a reported accidental exposure was caused by errors in determining the absorbed dose in small beams used for radiosurgery [ASN, 2007, Derreumaux, 2008]. These errors were related to using conventional protocols for standard sized beams and an ionization chamber of too large cross section. This event points to the need for developing specific dosimetry protocols for small and non-standard radiation fields, and for a thorough review of the training in radiotherapy physics, before introducing new technologies;
- an accidental exposure resulting in patient’s death occurred after an oral request for a collimator setting of “40-40” [meant to be 40 mm x 40 mm around a radiosurgery applicator], but a beam of 40 cm x 40 cm was applied instead [Derreumaux, 2008]. This event points to the need for ensuring proper communication and recording, together with a thorough understanding by staff of new techniques;
- fatal multiple patient accidental exposure occurred after the selection of and dose calculation for conventional physical wedges in treatment plans, for which dynamic wedges were meant to be used [Ash, 2007, ASN, 2007a, SFPM, 2006, Ash, 2007, Derreumaux, 2008]. One of the reasons for the mistake was the lack of understanding of the English abbreviation of EW (enhanced wedge), and of the fact that in this particular design of equipment, the number of MU required to deliver a dose with EW was substantially lower than with physical wedges;
- another accidental exposure occurred when data integrity was lost after a “computer frozen” event. The missing data included information on the multileaf collimator setting. This resulted in a treatment with the maximal collimator opening. In addition, the established procedure to perform a so called “verification hybrid plan” was not followed [CP, 2005, NYC-DHMH, 2005]. Thus, methods for verification of data integrity after a “computer crash” are needed and safety-critical quality control procedures should never be omitted;
- a number of new problems have been reported with regard to the increased used of imaging for radiotherapy. These problems include the misunderstanding of coordinates and marks from virtual simulation, the possible errors in tissue density because

1. The following group of authors collaborated in writing the report from the International Commission of Radiological (in press) from which part of the information is reproduced in this paper: P. Ortiz López, O. Holmberg, J.C. Rosenwald, J.M. Cosset, P. Dunscombe, L. Pinillos, J.J. Vilaragut and S. Vatnitsky.





of image artefacts, possible geometrical errors due to image distortion and significant excess in dose given by daily imaging for verification [NRC, 2007, ROSIS, 2008a, CIB, 2007], Derreumaux, 2008].

Making case histories and lessons from accidental exposures part of the training of radiotherapy staff is an effective tool to raise and maintain awareness.

## Lessons from events without major consequences

As described above, lessons from major accidental exposures are important, but information from other events without major consequences is also required. Moreover, focusing only on major events with catastrophic consequences may lead to overlook other, more frequent, errors with lower consequences, which may become severe if occurred elsewhere. Sharing information on events without major consequences forms the basis for keeping safety under continuous improvement. An example is the radiation oncology safety information system, ROSIS ([www.clin.radfys.lu.se/default.asp](http://www.clin.radfys.lu.se/default.asp)). When a new technology or technique emerges, it is important that users efficiently share experience and lessons in the first months/years and early disseminate a concise advice from their experience. Professional bodies can be instrumental in gathering these efforts.

## Anticipating, quantifying and making risk-informed decisions

The retrospective approaches described above are highly valuable but have the intrinsic limitation of being confined to reported experience, thus unreported events or other latent risks remains unaddressed. This type of risk can only be identified by proactive methods of finding out “what else could go wrong” or “which other potential hazards might be present”. These methods are the subject of other sections of this Conference. Three common approaches have applied to radiotherapy, namely the failure mode and effect analysis [Huq, 2008], the risk matrix [Ortiz López, 2008], and the probabilistic safety assessment [Vilaragut, 2008].

## Conclusions

Key requirements for the prevention of accidental exposure should be mandatory in form of standards and regulations. Lessons from accidental exposure should be incorporated into the education and training curricula. First users of a new technology should collect experience, and disseminate an early advice to other future users. Proactive safety assessments should be used, especially for new technologies. ■

## References

- ASH D., (2007) Lessons from Epinal. Clin Oncol 19:614-615.
- ASN (2007) Report concerning the radiation therapy incident at the university hospital centre (CHU) in Toulouse – Rangueil Hospital. Autorité de Sûreté Nucléaire, France.
- ASN (2007a) Summary of ASN report n° 2006 ENSTR 019 - IGAS n° RM 2007-015P on the Epinal radiation therapy accident. G. Wack, F. Lalande, M.D. Seligman.
- CP (2005) [Treatment Facility] Incident Evaluation Summary, CP-2005-049 VMS, 1-12.
- CUSTOMER INFORMATION BULLETIN (Nucletron) (2007): Incorrect creation of DRR using GPU-based methods. CIB-OTP 192.047-00.
- DERREUMAUX S., ETARD C., HUET C., TROMPIER F., CLAIRAND I., BOTTOLIER-DEPOIS J.-F., AUBERT B., GOURMELON P., (2008). Lessons from recent accidents in radiation therapy in France. Rad Prot Dosim.
- HUQ M.S., FRAASS B.A., DUNSCOMBE P.B., et al. (2008) A method for evaluating quality assurance needs in radiation therapy. Int. J. Radiat. Oncol. Biol. Phys. 70, S170-S173.
- IAEA. “International Basic Safety Standards for Protection against Ionizing Radiation and for the Safety of Radiation Sources”. Jointly sponsored by the Food and Agriculture Organization of the United Nations, International Atomic Energy Agency, International Labour Organisation, OECD Nuclear Energy Agency, Pan American Health Organization, World Health Organization. IAEA Safety Series 115, IAEA, Vienna 1996.
- IAEA, (1998). “Accidental overexposure of radiotherapy patients in San José”, Costa Rica.
- IAEA (2000). “Lessons learned from accidents in radiotherapy”, Safety Reports Series No. 17.
- IAEA (2001). “Investigation of an Accidental Exposure of Radiotherapy Patients in Panamá”.
- IAEA (2003). “Investigation of an accidental exposure of radiotherapy patients in Bialystok”.
- IAEA, (2006). Case Studies in the Application of Probabilistic Safety Assessment: Techniques to Radiation Sources. TECDOC 1494.
- ICRP, (1997). Protection from Potential Exposure: Application to Selected Radiation Sources, ICRP Publication 76. Annals of the ICRP 27 (2), [Pergamon Press, Oxford].
- ICRP, (2002). “Prevention of Accidental Exposure to Patients Undergoing Radiation Therapy, ICRP Publication 86. Annals of the ICRP 30 (3), Pergamon Press, Oxford.
- UNITED STATES NUCLEAR REGULATORY COMMISSION (2007) Gamma knife treatment to wrong side of brain. Event Notification Report 43746.
- NEW YORK DEPARTMENT OF HEALTH AND MENTAL HYGIENE (2005) Information Notice 2005-01. Office of Radiological Health, NYC Department of Health and Mental Hygiene.
- ORTIZ LÓPEZ P., DUMÉNIGO C., RAMÍREZ M.L., MCDONNELL J.D., VILARAGUT J.J., PAPADOPULOS S., PEREIRA P., GONÇALVES M., MORALES J., FERRO R., LÓPEZ MORONES R., SANCHEZ R., DELGADO J.M., SANCHEZ C., LARRINAGA E., SOMOANO F., GUILLÉN A., RODRÍGUEZ M. (2008). Radiation safety assessment of cobalt 60 external beam radiation therapy using the risk-matrix method. IRPA 12.
- PEIFFERT D., SIMON J.M., ESCHWEGE F. (2007) “Epinal radiotherapy accident: passed, present, future”. Cancer Radiother. Nov;11(6-7):309-12. Epub 2007 Oct 24.
- ROSIS (2008), Radiation Oncology Safety Information System (ROSI) [www.rosis.info](http://www.rosis.info)
- VILARAGUT LLANES J.J., FERRO FERNÁNDEZ R., RODRÍGUEZ MARTÍ M., ORTIZ LÓPEZ P., RAMÍREZ M.L., PÉREZ MULAS A., BARRIENTOS M., SOMOANO F., DELGADO RODRÍGUEZ J.M., PAPADOPULOS S., PEREIRA P., LÓPEZ MORONES R., LARRINAGA CORTINA, RIVERO OLIVA J.J., ALEMANY J., (2008). Probabilistic Safety Assessment of radiation therapy treatment process with an electron linear accelerator for medical uses. IRPA 12.

## Accidents, Lessons of the Past

### Lessons learned from accidents in Brachytherapy

by Luis Pinillos, Director Radiotherapy and Nuclear Medicine, National Cancer Institute (INEN) Lima, (Peru)

Brachytherapy, term defined by Forsell in 1931, can be administered at different dose rates\* that have been grouped as low dose rate (LDR), medium rate (MDR) high dose rate (HDR) and pulsed high dose rate (PDR) depending of the dose administered in one hour. (ICRU Report 38).

Although HDR is defined as more than 12 Gy/h the usual dose rate employed is around 100-300 Gy/h. (Nag. S., et al 1999a).

Brachytherapy came into use soon after the discovery of radium by Pierre and Marie Curie in 1898. The “hot loading” radioactive material is inserted directly into tumors or into cavities but has the inconveniences of irradiating the medical caregivers, that no correction of implants is possible, great experience needed, and in some permanent implants there are problems with the discharge of patients. (ICRP Publication 97.)

Manual LDR large temporary hot sources of radium or caesium procedures are still in use in a few countries particularly for cervix cancer treatment. (Pinillos L. 1997.)

To reduce the exposure hazard and allow for corrections of the implants, manual after loading was introduced.

Manual after loading caesium is used mainly for cervix and vaginal cancers and seeds and wires or plaques are used for prostate, soft tissues and ocular treatments using, 192Ir, 125I, 103Pd as radioactive sources. (Pinillos L. 2000.)

More than 50,000 patients are treated yearly with hot sources but few sources have been reported lost and no severe accidents have been reported. The doses to caregivers and comforters are below 1 mSv/years. (ICRP Publication 98.)

As younger patients are diagnosed and treated with brachytherapy, special precautions have to be taken regarding the pregnant partner.

The small sources can migrate into the lung, urine, semen or gastrointestinal tract, rare event for which no adverse effect has been reported as the activity and photon energy of the source is small. (Eschleman 2004, Grimm 1993.)

The use of condoms is recommended for the first 5 ejaculations.

Fertility is another issue, and although patients are or become infertile, fathering is still possible being the risk of genetic effects, for the child very low. (ICRP Pub. 98, UNSCEAR 2001.)

Cremation is an issue in many countries as activity can be found in patient ashes as well as airborne dose that can be inhaled by cremation staff. To overcome it, cremation is recommended 3 months after a 105 Pd implant or 12 months after 125I. If the time is less, it is indicated to remove the prostate and only scatter the cremation remains 20 months after. (ICRP Pub. 98.)



Patient in a Brachytherapy suit

As mentioned, in order to reduce exposure, manual after loading was first introduced using hollow needles or tubes that were inserted in patients and then the radioactive material was inserted. Sievert in 1937 proposed the concept of remote manual after loading in which the sources that are housed in a shielded container are driven through transfer cables into the hollow tubes in the tumors. (ICRP Pub. 97.)

In the 1980, automated remote control was developed that allows the use of very high activity sources and after-loading procedures of MDR, HDR and PDR came into use.

Here considering the high source activity, the concept of protection acquired new dimensions as not only the caregiver, comforters and patients are at risk as the technique implies a much longer chain of events and procedures from the production, the transport of over 10,000 sources per year, 3 to 4 source replacements a year, 3 to 4 new calibrations per year, over 500,000 procedures per year, new areas of clinical utilization and due to the development of the area, many more than 1000 centers using brachytherapy having different levels of training (ICRP 97).

The high activity also implies that minor errors in the time the source remains in a given position can severely affect the patient.

It is here where we will emphasize our topic identifying the risks and the origins of events and accidents.

Although many events have been reported using the high activity sources it is thought that there is a large under reporting of problems being noticeable that most reports come from big and prestige centers with good QA programs and not from centers without a large experience where more problems are expected to arise being it an indirect proof of under reporting (ICRP 97).

The reported events have origin in the different phases of the process needed to administer a treatment and they start with the manufacture, handling and transport of the sources, inadequate shielding during transport or in the safe or defects of the bunker, problems with sources in transit from the safe to the patients and its return, doses incorrectly prescribed or delivered or duplicated, failure identifying patients or even treatments to a different anatomical location. (NRC 2002, ICRP 97).

With this great spect of possibilities of exposure, event or accident, very strict adherence from radiation oncologists, medical physicists, technical and administrative staff to a QA program is

\*LDR: 0.4 TO < 2 Gy/h  
MDR: 2 to < 12 Gy/h  
HDR: > 12 Gy/h



mandatory and the importance of reporting events should be emphasized. (IAEA 2001). A key focus of accident prevention has long been the use of multiple defences against the consequences of failures. (ICRP 103.)

## **We will present some examples reported during the different phases**

### **Packing and transport**

As previously stated, over 10,000 shipments of radioactive sources occur every year. It is clear that for transport, the sources have to be installed and secured properly in the shielded position, the package adequately identified and signaled as containing radioactive material.

Due to accidental damage of containers or sources inadequately packaged or secured or due to intentional actions as theft many persons have been exposed including drivers, handling operators, administrators and public (ICRP 97).

Some of the reported events include a source outside the transport safe and not secured that was detected and the source moved to the shielded position, another reported case was a source being returned, a high dose was detected after 32 persons had been exposed, a driver to a dose of 5.8 mSv, a crating employee 46.13 mSv in several hours another driver 0.8 mSv (NRC 2002).

Another reported event was overpack damage after falling from conveyor that required a new overpack to continue with the shipment.

### **Source Exchange**

During the process of source exchange, personnel has been exposed for example as a consequence of backward connection of the transfer guide.

### **Bunker**

Regarding the bunker, there is a report of a case where as a consequence of a defect in the bunker design and construction, a public waiting area received a high exposure (260 Sv/h on the floor of the waiting area above the facility) (NCR 2002).

### **Operation**

Events during operation are the most reported ones, being the greatest cause of misadministration and or accidents. They are due to mechanical problems or human errors.

### **Mechanical**

The mechanical events are dependent of the control unit or the computer, the source cable or the catheter or the applicators and can be represented by reports of loss of power to the control unit that stopped its operation requiring a manual procedure to interrupt the treatment. In other case the power failure affected the computerized security program which allowed incorrect calculation after wrong data entry another report specified that the stop button in the console did not retract the wire source.

Regarding the source cable errors reported, this are due to disconnection or kinked or interlock failure with the source staying in the exposure position with resultant clinical consequences.

Dislodged applicators have resulted in irradiation of unrelated areas.

Other issues reported are blood contaminating the source tube and the source during the use of open ended catheters that now are not in use.

Premature and abrupt termination of treatments has also been reported.

Human errors reported include incorrect medical indication, patient identification, wrong diagnosis or area of treatment, wrong prescription or data entry or incorrect catheter or applicator.

The reports include a lip treated instead of the nasopharynx, a vulva irradiated instead of the uterine cervix, gastric irradiation instead of the esophagus the cheek instead of the bronchus, etc.

There are reports on double treatment to the same patient, higher doses because of failure to immediately calibrate a replacement source, errors in dwell times programming due to introducing the data inversely or programming the steps incorrectly.

Most of the reported events were part of a fractionated treatment and as such these errors are seldom fatal and maybe compensated eliminating or adjusting subsequent doses or fractions.

### **Multiples errors**

One case of death has been reported related to administration of HDR brachytherapy. The patient had received pelvic teletherapy for anorectal cancer. She had flexible tubes inserted transperineally to the anorectal region for an interstitial implant. One of the planned treatments was aborted because of source transfer "problems". The patient was returned to the nursing home and did not re-attend. A flexible tube fell from the patient 4 days later and was placed in a waste container. The patient died the subsequent day. After the source was noted to be missing, it was tracked through the patient to the waste incinerator. As the most severe case, for its characteristics, we can consider it as an event that illustrates equipment, human, and organizational errors. The failure of the weld between the transfer wire and the source was the initial precipitating event. Subsequently, the staff ignored the machine and room radiation monitors that registered the failure of return of the source to the safe, and the external monitors that identified residual radiation after treatment. These external monitors had malfunctioned previously but had not been repaired or replaced. The staff had failed to monitor the patient for radiation emission after treatment (NRC 2002).

Other accumulation of errors had also been reported as a cause of events or accidents.

As another example an equipment failure reported as failure of the weld between the transfer wire and the source was followed by human errors as staff ignored both machine and room monitors that showed failure of source return and then as an organizational error the patient was not monitored after the procedure.

Other examples of not following the established order of procedures are reported as connecting transfer wire backwards leading the engineer to briefly touch the guide so as to return the source receiving 21 mSv to the left thumb and index, 419 mSv to the tip of the left index finger and 1 mSv whole body.

### **Other cases**

Cases were reported of defective cable in the production as the source wire was not sufficiently stiff to resist looping which lead to replacement of the cable it in the 37 machines where the cable had been installed.

The source has also stuck in extended position as a consequence of a defective model of HDR that required a technician flown from the factory to the hospital to replace the assembly.

Other reports show the wire slipped from the wheels that protract and re undersized transfer cable diameter.

Regarding applicators, it has been reported they can kink inside cavities or tissues.

Once the needle is removed the source returns but an overdose of up to 73% has been reported.

Inadequate default position for start of dwell sites made the treatment start 6 cms beyond the intended location, a patient with a double catheter, one for the urethra and one for the bladder. The source was placed in the bladder instead of the urethra; an applicator was placed in the rectum instead of the vagina a wrong length catheter was chosen and the check and eye were irradiated instead of the bronchus.

In summary, remote MDR, HDR and PDR brachytherapy is a rapidly growing technique with over 500,000 procedures per year with sources delivering a very high dose per minute where mistakes can lead to severe clinical adverse events.

Accidents have been reported in the whole chain of procedures including one death being human error the prime cause of events.

An integrated team following QA procedures is necessary to prevent accidents and reporting accidents and incidents is important to share the lessons learned to prevent similar mistakes. ■

## References

- ESCHLEMAN J.S., Davis B.J., Pisansky T.M., et al, Radioactive seed migration to the chest alter transperineal interstitial prostate brachytherapy: extraprostatic seed placement correlates with migration in Int. J. Radiat. Oncol. Biol. Phys 2004; 59: p.419-425.
- GRIMM P.D., Blsko J., Ragle H., et al. Migration of iodine-125 and palladium - 103 seeds to the lung after transperineal brachytherapy for prostate cancer in Endocrine/Hypertherm. Oncol.1993; 9, p.90.
- IAEA, 2001. Implementation of Microsource High-Dose-Rate Brachytherapy in Developing Countries. IAEA-TECDOC-2001:1257. International Atomic Energy Agency, Vienna.
- ICRP Pub 97. Prevention of high-dose rate Brachytherapy Accidents. 2005;35(2) p3,5,23,25,30.
- ICRP Pub 98. Radiation safety Aspects of Brachytherapy for prostate cancer using permanently implanted sources. 2005;35(3) p 5-7.
- ICRP Pub 103. The 2007 Recommendations of the International Commission on Radiological Protection. 2007;37:p130.
- ICRU, 1985. Dose and Volume Specification for Reporting Intracavitary Therapy in Gynecology. ICRU. Report 38 International Commissions on Radiation Units and Measurements, Bethesda, MD.
- NAG S., Orton C., Young D., Erickson B., 1999a. American Brachytherapy Society survey of brachytherapy practice for carcinoma of the cervix in the United States. Gynecol. Oncol. 1999; 73: p111-118.
- NRC. Events Reported to NRC Involving HDR units 1/19903/2002. Nuclear Regulatory Commission.
- PINILLOS Ashton Luis in Capítulo de Radioterapia in Obstetricia y Ginecología José Pacheco, 1997 [Ed].
- PINILLOS Ashton Luis in Capítulo de Radioterapia in Principios Terapéutica Quirúrgica. Eduardo Barboza [ed] Primera Edición, 2000.



## WHO Radiotherapy risk profile

by **Michael Barton**, Professor of radiation Oncology, University of New South Wales, Collaboration for Cancer Outcomes Research and Evaluation, **Jesmin Shafiq**, Collaboration for Cancer Outcomes Research and Evaluation, **Douglas Noble**, **Claire Lemer**, World Health Organization Patient Safety Programme (Australia)

Radiotherapy saves lives, prolongs lives and improves the quality of life. It is widely known to be one of the safest areas of modern medicine, yet, for some, this essential treatment can bring harm, personal tragedy and even death. Radiotherapy treatment is a multi-stage, complex, process (Figure 1) that involves treatment of a wide range of cancer conditions through utilization of various technologies and related professional expertise. A high level of accuracy is needed at every step so that the maximum tumour control is produced with minimal risk to normal tissue. Risks should be managed prospectively and dose errors should be maintained within acceptable tolerances; the radiation dose should be delivered within 5% of the prescribed dose [8]. Several studies have concluded that, for certain types of tumours, the accuracy should be even better (up to 3.5%) [6,10,11]. The literature in the area of radiation oncology safety is limited, and relates mainly to developed countries, or is the result of investigations of major errors.

According to the IAEA safety standards[1], an “incident” is defined as:

*Any unintended event, including operating errors, equipment failures, initiating events, accident precursors, near misses or other mishaps, or unauthorized act, malicious or non-malicious, the consequences or potential consequences of which are not negligible from the point of view of protection or safety.*

A “near miss” is defined as:

*A potential significant event that could have occurred as the consequence of a sequence of actual occurrences but did not occur owing to the plant conditions prevailing at the time.*

Other terms for medical errors include “events”, “mistakes”, “misadministrations”, “unusual occurrences”, “discrepancies”, and “adverse events”.

The WHO World Alliance for Patient Safety general patient safety taxonomy contained within the International Classification for Patient Safety uses the following definitions[14]:

*A patient safety incident is an event or circumstance which could have resulted, or did result, in unnecessary harm to a patient.*

*An adverse event is an incident which results in harm to a patient.*

*A near miss is an incident that did not cause harm (also known as a close call).*

*An error is a failure to carry out a planned action as intended or application of an incorrect plan, and may manifest by doing the wrong thing (an error of commission) or by failing to do the right thing (an error of omission), at either the planning or execution phase.*

We have used “incident” and “near miss” wherever possible within this report. However, this needs further discussion within the radiotherapy community to determine whether a uniform terminology as in other medical fields could be used in relation to radiotherapy safety.

A review of available literature showed that in the years 1976 to 2007, 3125 patients were reported to be affected by radiotherapy

incidents that led to adverse events. About 1% (N=38) of the affected patients died due to radiation overdose toxicity. Only two reports estimated the number of deaths from under-dosage. The number of incidents that occurred in the planning stage was 1702 (55%), and of the remaining 45% incidents were due to errors that occurred during the introduction of new systems and/or equipment such as megavoltage machines (25%), errors in treatment delivery (10%), information transfer (9%) or in multiple stages (1%).

In the years 1992 to 2007, more than 4500 near misses (N=4616) were reported in the literature and publically available data-bases. Misinformation or errors in data transfer constituted the greatest bulk of incidents in modern radiotherapy services. Of all incidents without any known adverse events to patients, 9% (N=420) were related to the ‘planning’ stage, 38% (N=1732) were related to transfer of information and 18% (N=844) to the ‘treatment delivery’ stage. The remaining 35% of the incidents occurred in a combination of multiple stages.

More system or equipment-related errors documented by medical physicists were reported, as compared to errors that occur during initial choice of treatment, dose prescription and other random errors not related to equipment or system faults. International safety guidelines have been developed and are regularly updated to deal with radiotherapy errors related to equipment and dosimetry. Much effort has been directed at QA of system and equipment related components of radiotherapy, such as planning computers, dosimetry audit and machine performance. Little effort has been made so far to standardize medical processes, including target drawing, the application of appropriate margins and the verification of setup involved in radiotherapy. These errors cause variations in time-dose-fractionation schedules, leading to changes in the biological doses that have the potential for a significant impact on patient safety. European experts also suggested that taking initiatives to improve the culture of clinical governance, and setting the standards of practice through medical peer review of target drawing and dose prescription, would be a significant positive step in improving quality in radiotherapy services [7,9]. There is no consensus as yet as to how best to deal with errors not covered by regular system quality assurance checks.

Several interventions are likely to be effective at reducing risks at multiple stages in the radiotherapy treatment process. *Planning protocol checklists* are relevant to 20 identified risks, *independent checking* to 12 risks, and specific *competency certification* to 11 risks. This may be because there are more risks in these areas or because the individual risks have been better identified.

Other high impact interventions include:

- Equipment quality assurance to reduce the risk of systematic errors such as miscalibration that may affect very large numbers of patients.

- Peer review audit to improve decision making that will have flow-on effects throughout the treatment process.

- In vivo dosimetry may mitigate 24 identified risk areas and provide an important independent check of the planning, calculation and delivery elements of the pathway and address 12 of 16 risks in planning, 5 of 10 in treatment transfer, 4 of 11 in patient set-up and 3 of 7 in treatment delivery. The costs of establishing and maintaining a program of routine in vivo dosimetry for all treatments is likely to be high and resource intensive, which may place it beyond the reach of services in some countries.

In addition there are safety processes that apply to all stages of the delivery of radiotherapy:



1. Patient identification
2. Audit of equipment commissioning and processes
3. Staff competency assessment
4. Process and equipment quality assurance
5. Information transfer with redundancy
6. Process governance
7. Error reporting and quality improvement
8. External checking
9. Adequate staffing

## Conclusions

This risk profile for the first time quantifies the process of care in radiotherapy, and systematically addresses the risks at each stage. Putting this knowledge to work will require innovative strategies on behalf of managers and health-care professionals alike.

Redesigning systems to reduce risk involves engaging policy-makers, managers and patients [13]. Central to this is an adequate and competent workforce, supported by an appropriate reporting and learning framework. Several efforts have been attempted, both nationally and internationally to this end, including the Radiation Oncology Safety Information System (ROSIS) [2], the Calgary incident learning system [4] and the recently described United Kingdom framework [12]. Technical solutions offer hope for the future, including in vivo dosimetry, which offers the opportunity to reduce some risk, but must be put in the context of an overall approach to patient safety in radiotherapy. The use of simple checklists has been proved to be successful in other areas of patient safety as a way of systematically reducing risk [3]. Similar systems have been suggested in radiotherapy and should be further promoted and developed [5]. ■

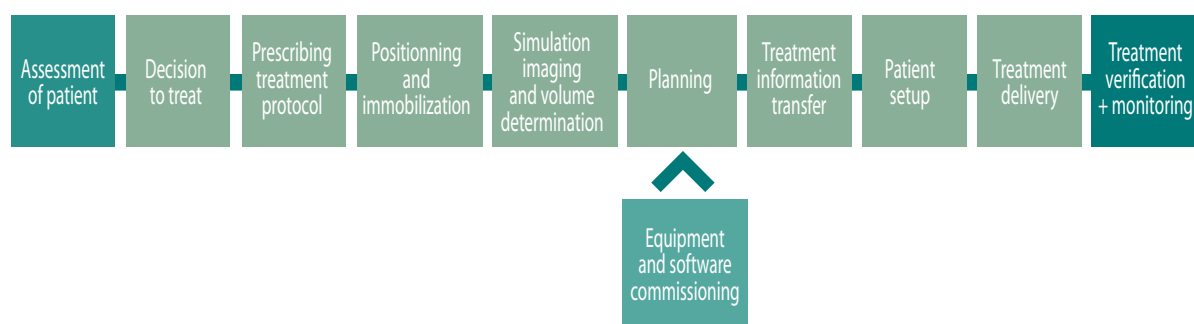


Figure 1: stages of radiotherapy treatment

## References

1. IAEA safety glossary: Terminology used in nuclear safety and radiation protection. [www.pub.iaea.org/MTCD/publications/PDF/Pub1290\\_web.pdf](http://www.pub.iaea.org/MTCD/publications/PDF/Pub1290_web.pdf). 2007. International Atomic Energy Agency. 30-7-2008.
2. ROSIS database: a voluntary safety reporting system for Radiation Oncology. [www.rosis.info](http://www.rosis.info). 2009. 10-9-2007.
3. World Health Organization World Alliance for Patient Safety. [www.who.int/patient-safety/challenge/safe.surgery/launch/en/index.html](http://www.who.int/patient-safety/challenge/safe.surgery/launch/en/index.html). 2009. 29-5-2008.
4. Alberta Heritage Foundation for Medical Research. A reference guide for learning from incidents in radiation treatment: HTA Initiative #22. [www.ihe.ca/documents/hta/HTA-FR22.pdf](http://www.ihe.ca/documents/hta/HTA-FR22.pdf). 2006. 27-7-2008.
5. Australian Commission on Safety and Quality in Healthcare. Expanding the Ensuring correct patient, correct site, correct procedure protocol: Draft patient matching protocols for radiology, nuclear medicine, radiation therapy and oral health. Consultation Paper. 14-1-2008. Sydney, Australian Commission on Safety and Quality in Healthcare.
6. Brahme A. Accuracy requirements and quality assurance of external beam therapy with photons and electrons. *Acta Oncol* 1988;27.
7. International Atomic Energy Agency. Comprehensive audits of radiotherapy practices: a tool for quality improvement: Quality Assurance Team for Radiation Oncology (QUATRO). 2007. Vienna, International Atomic Energy Agency.
8. ICRU. Determination of Absorbed Dose in a Patient Irradiated by Beams of X or Gamma Rays in Radiotherapy Procedures. 24. 1976. Bethesda, MD, ICRU.
9. McNee S.G. Clinical governance: risks and quality control in radiotherapy. Report on a meeting organized by the BIR Oncology Committee, held at the British Institute of Radiology, London, on 9 February 2000 [Commentary]. *BJR*. 2001;74:209-12.
10. Mijnheer B.J., Battermann J.J., Wambersie A. What degree of accuracy is required and can be achieved in photon and neutron therapy? *Radiother Oncol* 1987;8:237-52.
11. Mijnheer B.J., Battermann J.J., Wambersie A. Reply to: Precision and accuracy in radiotherapy. *Radiother Oncol* 1989;14:163-7.
12. The Royal College of Radiologists. Towards Safer Radiotherapy. [www.rcr.ac.uk/publications.aspx?PageID=149&PublicationID=281](http://www.rcr.ac.uk/publications.aspx?PageID=149&PublicationID=281). 2009. The Royal College of Radiologists.
13. Tylko K., Blennerhassett M. How the NHS could better protect the safety of radiotherapy patients. *Health Care Risk Report* 2006;18-9.
14. World Health Organisation (WHO). International Classification for Patient Safety (ICPS). [www.who.int/patientsafety/taxonomy/en/](http://www.who.int/patientsafety/taxonomy/en/). 2009. WHO. 24-6-2008.



## Methods of risk analysis applied to radiotherapy

by **María Luisa Ramírez Vera M.D.<sup>1</sup>**, Consejo de Seguridad Nuclear,  
FORO Iberoamericano de Organismos Reguladores Radiológicos y Nucleares –  
Madrid (Spain)

Lessons from major accidental exposures reported in the bibliography [IAEA1998, 2000, 2001, 2003, ICRP 2002] point to the fact that the event sequences leading to them had not been anticipated and, as a result, no sufficient safety provision were placed. In this report, a proactive approach to safety assessment is presented, which up to date has been used to a very limited extent in radiotherapy [USNRC 1995 a, 1995 b, 1995 c, Thomadsen 2003].

### Risk analysis methods

Proactive risk analysis methods [Gertman 1994, IAEA 2006, ICRP 1997, Vilaragut 2004] follow a common pattern, starting with a search for all potential failures and errors, followed by the estimation of their risk and by a prioritization of efforts to avoid accidental exposure from the events leading to higher risk. In this work, two proactive methodologies were used: risk matrix (RM) and probabilistic safety assessment (PSA).

### Risk matrix

The risk matrix (RM) is a screening method for discriminating lower-risk from higher-risk events, in order to focus efforts on detailed analysis of the higher-risk events. The risk matrix operates in three steps, 1) identification of all potential initiating events, 2) discrimination of higher-risk events, and 3) detailed analysis of the higher-risk events for reducing the risk to a lower level.

A four-level scale (very low, low, high and very high) was applied to the following parameters: the frequency of the initiating event, the failure probability of the safety provisions to detect it and the severity of the consequences of the accidental exposure, if the initiating event is not timely detected. The levels of the three parameters were combined by a logical relation into a level of risk, which was also expressed in a four-level scale. Events resulting in higher risk were separated for detailed analysis [Vilaragut 2006].

The detailed analysis of the higher-risk events consisted of further scrutinizing “how robust are the existing safety provisions?”; “can the frequency of occurrence of the event sequence or its consequences be reduced?”; “is there a need to add one or more safety provision to reduce the risk to an acceptable level (low or very low)?” The answers to these questions lead to additional safety provisions needed to lower the risk of the higher-risk events to an acceptable level.

The application of the method to high-dose-rate (HDR) brachytherapy resulted in the identification of 12 event sequences with

a ‘higher’ risk. These events were subject to a detailed analysis from which additional safety measures were found necessary. Only a summary of these safety measures is given below.

An error in preparing the input data tables for manual treatment (for example, wrong decay data for the sources) is an event leading to higher risk and catastrophic consequences, i.e. several deaths or irreversible damage to multiple patients in the case of HDR brachytherapy. Considering the complexity of the calculations for HDR brachytherapy, and given the large number of parameters to be considered, manual treatment planning is not recommended for HDR brachytherapy.

Verification of source intensity, as determined in the hospital, against the value given in the source certificate, is crucial to avoid accidental exposure caused by mistakes in the hospital calibration of brachytherapy sources. This verification is a very robust safety provision because a discrepancy in the value of the kerma rate would reveal an error in either the calibration in the factory or in the hospital.

### Probabilistic safety assessment

Probabilistic safety assessment (PSA) is a method for identifying initiating events that may trigger accident sequences, for modeling the sequences of events that can evolve to an accidental exposure if no obstacle stops this development, i.e., if safety measures fail and quantifying the risk from individual sequences and the global risk. In this work, the identification of initiating events was performed using failure modes and effects analysis (FMEA), a standard method to identify potential failure of an equipment, system or process and to analyze the resulting effects [Chiozza 2009, Spath 2003]. Once the initiating events were identified, the event sequences were modeled by means of “event trees”.

Once the event sequences were defined, the frequency of occurrence of the accidental exposure from each sequence was quantified, using fault-tree analysis. The risk of each event sequence was computed by means of Boolean equations, combining the frequency of the initiating event and the probability of failure of all safety measures involved in the sequence. An analysis of importance was done to evaluate how many times a risk is reduced or increased when a safety measure is added or removed. The following information summarizes the results of this study.

As many as 453 failure and human errors were identified which potentially might cause the undesired events defined. These failures and errors were grouped into 118 types of initiating events. 120 safety measures, also called “barriers” because they are actual obstacles to stop the event sequence and avoid the accidental exposure, were identified in the generic radiotherapy department. 259 failure and errors, which can lead to a failure of the barriers, were also analyzed and incorporated in the fault trees. All of this resulted in 434 potential accidental sequences, half of which involve patients.

Of all event sequences involving patients, the major contributor to their frequency are incidents which can be compensated for and therefore do not constitute accidental exposures. Only 0.3% of the potential accidental sequences involve multiple patients

1. The work described in this paper was done by the following group: Vilaragut, J.J.<sup>a</sup>; Duménigo, C.<sup>a</sup>; Ramírez, M.L.<sup>b</sup>; Ortiz López, P.<sup>c</sup>; Barrientos, M.<sup>b</sup>; Pérez Mulas, A.<sup>b</sup>; McDonnell, J.D.<sup>d</sup>; Papadopoulos, S.<sup>e</sup>; Pereira, P.P.<sup>f</sup>; Gonçalves, M.<sup>g</sup>; Morales, J.<sup>h</sup>; Ferro, R.<sup>i</sup>; López Morones, R.<sup>i</sup>; Sánchez, R.<sup>i</sup>; Miguel Rodríguez Ponce, R.<sup>i</sup>; Delgado, J.M.<sup>h</sup>; Sanchez, C.<sup>h</sup>; Larrinaga, E.<sup>h</sup>; Somoano, F.<sup>i</sup>; Guillén, A.<sup>h</sup>; C. Alvarez, Rodríguez, M.<sup>h</sup>

**a.** Centro Nacional de Seguridad Nuclear, La Habana, Cuba. **b.** Consejo de Seguridad Nuclear, Madrid, España. **c.** International Atomic Energy Agency, Viena, Austria. **d.** National University, Rosario, Argentina. **e.** Autoridad Reguladora Nuclear, Buenos Aires, Argentina. **f.** Instituto Nacional de Câncer, Brasil. **g.** Instituto de Radioproteção e Dosimetria, Comissão Nacional de Energia Nuclear (CNEN), Rio de Janeiro, Brazil. **h.** Instituto Nacional de Oncología y Radiobiología, La Habana, Cuba. **i.** Comisión Nacional de Seguridad Nuclear y Salvaguardias, Dr. Barragán, 779, México D.F., México. **j.** Instituto Nacional de Cancerología, México DF, México. **k.** Instituto Madrileño de Oncología, Madrid, España. **l.** ELEKTA, Madrid, España.



Treatment of a cerebral tumour with Gamma Knife

and severe or catastrophic consequences. Single patient event sequences, which can not be compensated for and therefore constitute accidental exposures, amount to 15% of the frequency of sequences involving patients, and are therefore 50 times more frequent than multiple patient accidental exposures. Although much more attention has been devoted so far to reports of catastrophic-type, low-probability accidental exposures involving multiple patients, other events, with less catastrophic, but still significant consequences, are much more likely to occur. They may be underreported and deserve increased attention.

As few as nine different imitating events are responsible for 90% of the potentially catastrophic accidental exposures involving multiple patients while 90% of the severe consequences on a single patient are triggered by 21 events.

Errors and faults involving the treatment planning system (TPS) can lead to a substantial number of accidental exposures. The study has shown that three safety measures can avoid 77% of the systematic or catastrophic accidental exposures. These three measures are: 1) periodic quality control of the treatment planning computer, the digitizer, and the revalidation of external beam (i.e. to check the constancy of external beam dose calculations to safeguard against inadvertent alteration or corruption), transfer of the treatment plan; 2) validation after any modification or update of the TPS; and 3) review and validation of any change in the procedure for the TPS use. Independent verification of the TPS calculation substantially reduces the risk of accidental exposure. Absence of this verification increases the risk by a factor of 10.

Three safety measures were identified that can avoid 55% of severe accidental exposures involving the whole course treatment of a single patient. These measures are the following: 1) clinical evaluation by the radiation oncologist; 2) in vivo dosimetry using reliable, calibrated detectors; and 3) approval of the

treatment plan at a discussion/meeting of radiation oncologist and physicist.

The following safety measures have a preventive effect on a large number of initiating event sequences: 1) portal imaging at the initial session and periodically thereafter; 2) dosimetric tests; and 3) interlocks of the beam monitoring system. Absence of such safety measures increases the risk in the initiating events where they apply by factors of 90, 30 and 6, respectively.

A number of errors relate to unclear delineation of target volumes and bear a significant contribution to single-patient accidental exposure. It is recommended: 1) to use a color code for those volumes and to make it mandatory in the radiotherapy department; 2) to include in the TPS acceptance tests a verification of compliance with the terminology of ICRU [ICRU 1993, 1999]; and 3) to incorporate into the design of the TPS interlocks and warnings to restrict manipulation of treatment volumes to alert staff on the potential omission of secondary treatment volumes.

The 'record and verify' system of medical accelerators drastically reduces the risk of nine initiating events related to daily treatment session delivery. Absence of this system increases the risk by a factor of 75. New equipment should, therefore, include record and verify systems.

The presence of two technologists during treatment preparation and delivery is very important. Failure to comply with this good practice increases the risk of accidental exposure by a factor of 10. At least one of the two technologists should be the same during the whole course of treatment, from the initial setup until the end of treatment.

*Important remark:* this particular study was devoted to the treatment process, and issues of calibration, commissioning and maintenance were not in the scope of the study. Therefore, the findings do not include errors and mistakes that can be made in these activities.

## Strengths and limitations of the risk-analysis techniques used in this study

### Probabilistic safety assessment

PSA provides quantitative information with numerical values about how much a given safety measure reduces the risk or how much the absence of a given safety measure may increase the risk. With this information, the cost-benefit analysis is objective. Moreover, PSA combines several tools to evaluate safety (qualitative, quantitative, and graphical) which allow complementary inputs to cover the limitations of each tool, if used separately. In spite of the fact that PSA is an ideal technique for safety assessment, its application is very complex, demands a time-consuming work and requires experts from outside the hospital.

### Risk matrix assessment

The method is relatively easy to apply by individual radiotherapy departments. Once the initiating events and typical safety measures are identified for a generic radiotherapy department, it can serve as template to be used by individual hospitals for tailored self evaluation. Although the risk matrix approach does not provide numerical values, it classifies events by risk levels or bands, and facilitates allocation of efforts on higher-risk event sequences.

### Both methods are complementary

All methods have in common the task of identifying initiating events and typical safety measures, for example using FMEA. Effort invested in this identification for a generic department can be used in individual departments. It is possible to gather a multidisciplinary team to perform a probabilistic safety assessment when introducing a new technique, and the insights and identified events can be used for individual departments.



## Conclusions

Risk analysis techniques are a valuable resource for risk identification, evaluation and quantification and risk reduction management. In this work, two proactive methods, traditionally used in the industry, risk matrix and probabilistic safety assessment have been adapted for radiotherapy treatments. Risk analysis tools contribute to identify vulnerable aspects of radiotherapy treatments and provide a fundament for decision making in choosing safety measures. Proactive methods are not meant to replace retrospective methods, but rather the strength of these approaches resides in the synergy among them to improve overall safety in radiotherapy practice. ■

## References

- CHIOZZA M.L., PONZETTI C.(2009) "FMEA: a model for reducing medical errors". Clin Chim Acta Jun 404 75-78.
- GERTMAN, D.I., BLACKMAN, H.S., Human Reliability and Safety Analysis Data Handbook, John Wiley & Sons, Inc., New York (1994).
- IAEA. "Accidental overexposure of radiotherapy patients in San José", Costa Rica, (1998).
- IAEA. "Lessons learned from accidents in radiotherapy", Safety Reports Series No. 17, [2000].
- IAEA. "Investigation of an Accidental Exposure of Radiotherapy Patients in Panamá", [2001].
- IAEA. "Investigation of an accidental exposure of radiotherapy patients in Białystok", [2003].
- IAEA. Case Studies in the Application of Probabilistic Safety Assessment: Techniques to Radiation Sources. TECDOC 1494, [2006].
- ICRU. Prescribing, Recording and Reporting Photon Beam Therapy, Rep. 50, ICRU, Bethesda, MD (1993).
- ICRU. "Prescribing, Recording and Reporting Photon Beam Therapy [Supplement to ICRU Report 50]", Report 62, ICRU, Bethesda, MD, ICRU 62 (1999).
- ICRP. Protection from Potential Exposure: Application to Selected Radiation Sources, ICRP Publication 76. Annals of the ICRP 27 [2], [Pergamon Press, Oxford], (1997).
- ICRP. "Prevention of Accidental Exposure to Patients Undergoing Radiation Therapy, ICRP Publication 86. Annals of the ICRP 30 [3], Pergamon Press, Oxford (2002).
- SPATH P.L. (2003) Failure mode and effects analysis to improve patient safety. AORN J Jul;78:16-41.
- THOMADSEN B., et al, Analysis of Treatment Delivery Errors in Brachytherapy Using Formal Risk Analysis, Int. J. Radiation Oncology Biol. Phys., Vol. 57, No. 5, pp. 1492-1508 (2003).
- UNITED STATES NUCLEAR REGULATORY COMMISSION. NUREG/CR -6323 UCRL-ID-120051 Relative Risk Analysis in Regulating the Use of Radiation - Emitting Medical Devices. A preliminary application, USA, (1995).
- UNITED STATES NUCLEAR REGULATORY COMMISSION. NUREG/CP -0144 INEL-94/0111 A Workshop on Developing Risk Assessment Methods for Medical Use of Radioactive Material, USA, (1995).
- UNITED STATES NUCLEAR REGULATORY COMMISSION. Human Factor Evaluation of Teletherapy: NUREG/ CR-6277, USA (1995).
- VILARAGUT J.J, FERRO R., LOZANO B., De la FUENTE A., DUMÉNIGO C., TRONCOSO M., PEREZ Y., ALEMAÑY J., LEÓN L., AMADOR R.M, LASO R., LABRADOR F., BLANCO A., BETANCOURT L., CASTRO D., SILVESTRE I. (2004); Results of the probabilistic safety assessment to the cobalt-therapy process, NUCLEUS No. 36.
- VILARAGUT J.J, FERRO R., TRONCOSO M., Aplicación de matrices de riesgo para evaluar la seguridad del tratamiento con teleterapia, Revista NUCLEUS No. 39, [2006].

## Radiation safety issues linked to the omnipresence of computers

by Jean-Claude Rosenwald, honorary consultant in medical physics,  
consultant to Dosisoft, Curie Institute – Paris (France)

Radiotherapy is one medical speciality where the computers have been used from the very beginning of informatics, as early as around 1950. They were originally designed to replace the manual time consuming task of 2D dose summation from different beams. Computers are now omnipresent in radiotherapy. In external therapy, at the planning stage, the “Treatment Planning Systems” (TPS) are used to choose the “best” beam setup allowing to achieve an optimal irradiation of the target volume while keeping the dose at the organs at risk below an acceptable threshold and the dose at the rest of the body at minimal level. Advanced imaging methods, also based on computerised systems, are required to allow accurate delineation of the volumes of interest and to provide a reference for subsequent patient alignment. Computerised water phantom systems are used to measure the 3D dose distribution that is required to tune the beam models incorporated into the TPS. At the beam delivery stage “Record and Verify Systems” (RVS) are linked to the accelerators; they check that the accelerator parameters are consistent with the prescription and they record all accessible technical data at each fraction. Electronic Portal Imaging Devices (EPID), attached to the accelerator arm, are used to provide 2D or 3D “cone beam reconstructed” images to be compared with electronic images coming from the TPS or from any other “virtual simulation” system. The accelerator itself embarks several computers, used for beam control, gantry and/or multileaf collimator control and communication with other devices. In brachytherapy, image based planning is routinely performed with computerised TPS, followed by treatment completion with a computer driven afterloading system.

Computers are not any longer standalone system. They are all interconnected and many data exchanges take place between the various pieces of equipment, including communication with the data management systems : administrative hospital information system, patient medical record database, etc. Fortunately the development of standards has greatly facilitated such exchanges : most technical hardware or software problems can now be solved relatively easily thanks to Ethernet or WiFi networks, TCP/IP solutions and DICOM or DICOM RT protocols. On the other hand, the multiplicity of systems, the large quantity of exchanged data, the wide spectrum of possibilities offered by each system, makes it impossible to guarantee an error free process from the radiotherapist’s prescription to the actual patient’s treatment delivery.

### Learning from experience

In response to the increased complexity of the techniques and of the tools that are made available for an up-to-date radiotherapy, in spite of the efforts of the manufacturers to provide user-friendly secure solutions, one can fear an increase in the risk of accident caused directly or indirectly by computerised systems. Actually, a significant numbers of such accidents has been reported. The most dramatic of them, all related to the misuse of a TPS, are given in Table 1.

The common point of these severe incidents is that they are related to an error on treatment time (or monitor units) which is clearly the most important parameter. Only in one case, the error was on the treatment site (treating the wrong side) which is also a fundamental issue. The introduction of beam modifiers (wedge filters, dynamic MLC) is an additional factor of risk. Another common characteristic, found from the detailed case description, is that the errors were always related to the introduction a new procedure.

This list is by no mean complete. It shows only some significant examples. Many less severe incidents or near misses have been reported and may be found for instance in the ROSIS database ([www.rosis.info](http://www.rosis.info)) where it has been observed that almost half of the reported incidents were “considered to have an element of

Year	Country	Reference(s)	Description
1982-1991	UK	Ash and Bates 1994, ICRP 2001, Rosenwald 2002	Underdosage (-5 to -30%) due to a wrong interpretation of the TPS treatment time calculation algorithm for isocentric treatments (1045 patients)
2000	Panama	IAEA 2001, Rosenwald 2002	Overexposure (by a factor 2) of 28 patients treated with irregular field, due to a misuse of the TPS and absence of interlock for this situation
2003	France	Derreumaux 2008 (case 1)	Overexposure (+20%) of one patient planned with a motorized wedge filter but treated without wedge because of a data exchange failure between TPS and RVS
2004-2005	France	Ash 2007, Peiffert 2007, Derreumaux 2008 (case 4.1)	Overexposure (>20%) of 24 patients planned with mechanical wedges but treated with dynamic wedges, because of incorrect interpretation of the TPS requirement
2005	UK	Williams 2007, Mayles 2007	Overexposure (+57%) of one patient due to application of an inadvertent manual correction to monitor units calculated by TPS and transferred to RVS
2005	USA	Will be described in a forthcoming ICRP report (see footnote 3)	Overexposure of a head and neck patient during at least 3 consecutive fractions (around 13 Gy/fraction instead of 2 Gy) due to absence of leaf movement (open field) for an IMRT plan that was modified on TPS and retransferred to RVS after a computer crash occurred
2007	USA	NRC 2007a	High dose irradiation of the wrong size of the brain due to incorrect MR image transfer (understatement of orientation issues) for one patient scanned “head first” and treated “feet first”
2007	USA	NRC 2007b NRC 2009	Overexposure (45 Gy instead of 25 Gy) during brachytherapy complementary vaginal irradiation (after 56 Gy IMRT) due to lack of consistency between the TPS dose rate factor and the units used for source specification

Table 1: examples of dramatic accidents caused (mostly indirectly) by computerised systems





data transfer which either directly caused or contributed to the occurrence of the incident" (ROSIS Newsletter- January 2007). Errors in patient identification have also been recognised as a relatively frequent cause of misadministration due to the introduction of computerised systems (ROSIS Newsletter – August 2006), especially when using a RVS. Actually several authors have insisted on the fact that the introduction of the RVS, which is precisely designed to increase the patient safety since it compares prescribed and actual treatment parameters, prevents from most random errors but induces other types of error that may be more serious because they tend to become systematic (Fraass 1998, Patton 2003, Fraass 2008).

## Preventive actions

Learning from experience is important to avoid a repetition of past accidents, but the variety of the situations and the rapidity of the technological changes make it difficult to anticipate what could cause future accidents.

Recommendations for quality assurance of TPS have been issued by several groups (IAEA 2004, ESTRO 2004). They describe the tests that should be done during the acceptance and commissioning phase of a TPS and give some advices about periodic checks and quality control of individual treatment plans. They are somewhat difficult to follow strictly since the intent was to cover as many cases as possible with an impressive number of tests to be repeated in many situations. More recently, the IAEA suggested a much more pragmatic approach for TPS acceptance (IAEA 2007) and commissioning (IAEA 2008). The SFPM is about to release a report<sup>1</sup>, inspired by these recommendations but making a clearer distinction between the risk to produce inaccurate dose distributions and the risk of "accident". This report flags the necessity to have a good perception of the most critical components in using a TPS and provides a tentative risk analysis. This must be followed by the acquisition of a good understanding of the TPS functions by browsing all recommended tests while keeping in mind the possible pitfalls.

To my knowledge, there are no similar recommendations for quality assurance of RVS. A safety standard IEC document, originally directed to manufacturers, exists (IEC 2005), but user's verification of RVS is usually treated as an extension of the TPS quality assurance with a simple statement that the data transfer must be validated. Actually many more issues should be considered and IAEA plans to publish a dedicated report.

The French legislation has introduced a requirement for systematic constancy check of the MU calculated by the TPS and of its

transfer to the RVS. This must be repeated at least annually and after each software or hardware update. The most important aspect of this measure is to bring the user's attention on the potential risk of TPS MU miscalculation or erroneous transfer. This should help to induce a cultural change with an evolution from retrospective analysis of incidents and systematic extensive quality assurance programmes, towards more focused programmes supported by proactive approaches of risk assessment<sup>2</sup> (Amols 2008).

Since most (if not all) incidents have a strong component involving human and environmental factors, in spite of the efforts to improve procedures, communication and training, there is still a significant risk of human failure (e.g. undetected problem during systematic manual/visual checks of plan data) for such a complex multifactor environment in a situation where resources are limited. In vivo measurements are likely to detect some of the more serious errors. Secondary MU calculations are also helpful but their degree of independency relative to the principal MU calculations must be carefully assessed. The power of the computer-based solutions could be oriented towards safety and efficiency improvement by providing automatic solutions of database mining or filtering of data exchanges, and searching for any anomaly with respect to "reference protocols". Such solutions could be used wisely as a complement and not a replacement of human judgment.

## Conclusions

The development of computer based radiotherapy information systems with a multiplicity of data exchanges between many components is meant to improve treatment quality and productivity while preserving or improving treatment safety. In the same time, there is a risk, that the increase of complexity leads to a loss of human control of the process and that accidents would occur, mainly due to an insufficient understanding from the user and/or to a lack of resources. This should be counterbalanced by a proactive approach, involving both manufacturers and users, where the major risks must be identified and publicised, complemented by the introduction of computer aided solutions oriented specifically towards safety management. ■

1. "Recommandations pour la mise en service et l'utilisation d'un système de planification de traitement en radiothérapie" to be published shortly by the Société Française de Physique Médicale (www.sfp.m.fr).

2. The overall problem of the risks related to new technologies and the use of proactive approaches to reinforce accident prevention will be discussed in a new ICRP report that will be published shortly.

## References

- Amols H.I. [2008], New technologies in radiation therapy: ensuring patient safety, radiation safety and regulatory issues in radiation oncology, *Health Phys* 95(5), 658-665.
- Ash D. & Bates T. (1994), 'Report on the clinical effects of inadvertent radiation underdosage in 1045 patients.', *Clin Oncol (R Coll Radiol)* 6(4), 214-226.
- Ash D. (2007), 'Lessons from Epinal.', *Clin Oncol (R Coll Radiol)* 19(8), 614-615.
- Derreumaux S., Etard C., Huet C., Tromprier F., Clairand I., Bottollier-Depois J.-F., Aubert B. & Gourmelon P. (2008), 'Lessons from recent accidents in radiation therapy in France.', *Radiat Prot Dosimetry* 131(1), 130--135.
- ESTRO 2004 Quality assurance of treatment planning systems; practical examples for non-IMRT photon beams – European Society of Therapeutic Radiation Oncology, Booklet n°7
- IAEA 2001 Investigation of an Accidental Exposure of Radiotherapy Patients in Panamá. IAEA, Vienna.
- Fraass B. A., Lash K. L., Matrone G. M., Volkman S. K., McShan D.L., Kessler M.L. & Lichter A.S. 1998 'The impact of treatment complexity and computer-control delivery technology on treatment delivery errors.', *Int J Radiat Oncol Biol Phys* 42(3), 651-659.
- IAEA (2004) Commissioning and Quality Assurance of Computerized Planning Systems for Radiation Treatment of Cancer - Technical Reports Series n° 430 IAEA, Vienna
- IAEA (2007) Specification and acceptance testing of Radiotherapy Treatment Planning Systems - TECDOC n° 1540 IAEA, Vienna
- IAEA (2008) Commissioning of Radiotherapy Treatment Planning Systems: Testing for Typical External Beam Treatment Techniques - TECDOC n° 1583 IAEA, Vienna
- ICRP (2001) International Commission on Radiological Protection.. Prevention of accidental exposure of patients undergoing radiation therapy, ICRP Publication 86. Annals of the ICRP 30(3), (Pergamon Press, Oxford).
- IEC (2005). Medical Electrical Equipment: Safety of Radiotherapy Record and Verify Systems. International Electrotechnical Commission, Publication IEC-62C/62274, Geneva
- Mayles W.P. M. (2007), 'The Glasgow incident--a physicist's reflections.', *Clin Oncol (R Coll Radiol)* 19(1), 4-7.
- NRC 2007a Gamma knife treatment to wrong side of brain. Event Notification Report 43746. United States Nuclear Regulatory Commission
- NRC 2007b Misadministration in brachy due to wrong unit for specification. Event Notification Report 43301. United States Nuclear Regulatory Commission
- NRC 2009 Reportable medical events involving treatment delivery errors caused by the confusion of units for the specification of brachytherapy sources, Information Notice 2009-17, United States Nuclear Regulatory Commission
- Patton G.A., Gaffney D.K. & Moeller J.H. (2003), Facilitation of radiotherapeutic error by computerized record and verify systems, *Int J Radiat Oncol Biol Phys* 56(1), 50-57
- Peiffert D., Simon J.-M. & Eschwege F. (2007), 'Epinal radiotherapy accident: passed, present, future', *Cancer Radiother* 11(6-7), 309-312 (in French).
- Rosenwald J.C. (2002), Safety in radiotherapy: Control of software and informatics systems, *Cancer Radiother* 6 Suppl 1, 180s-189s (in French).
- Williams M.V. (2007), 'Improving patient safety in radiotherapy by learning from near misses, incidents and errors.', *Br J Radiol* 80(953), 297-301.

## Quality and safety in radiotherapy: precursor events and feedback from experience

by Pr Eric Lartigau, University Department of Radiotherapy Oscar Lambret Center and Faculty of Medicine, Université Lille II – Lille (France)

Treatment safety is a major challenge for the medical world. In France every year thousands of patients present secondary events of varying severity directly attributable to the management of their pathology (drug toxicity, nosocomial infections, etc.). Despite all the difficulties inherent in medical practice and its lack of comparability with the world of industrial production, the majority of such events are probably avoidable by the introduction of a management quality/safety policy.

The place and the sequence of the various therapies implemented in cancer treatment are at present defined in a collegial process (multidisciplinary discussion meeting) and lead to an individual care programme. The choice of this sequence is based on shared, published and assessed baselines. The implementation of the treatment scheme necessitates the involvement of various specialists (surgeon, chemotherapist, radiotherapist, radiologist, anatomic pathologist, etc.) in an organised and coordinated environment. Obtaining optimum therapeutic value involves quality control on persons (assessment of professional practices), equipment (drug, machines, implantable devices, etc.) and organisations (accreditation, etc.). Oncology-radiotherapy occupies a central place in this multidisciplinary management of cancer: in 2008 more than 190,000 patients benefited from such treatment. The discipline is particularly sensitive to quality and safety because of its specific features: management of all types of tumour, patients of all ages, repetition of therapeutic procedures (fractions) over several weeks using very high-technology equipment (linear accelerators).

### Quality & safety

Radiotherapy has experienced recently-notified accidents that have raised questions in the media and the public. A complex

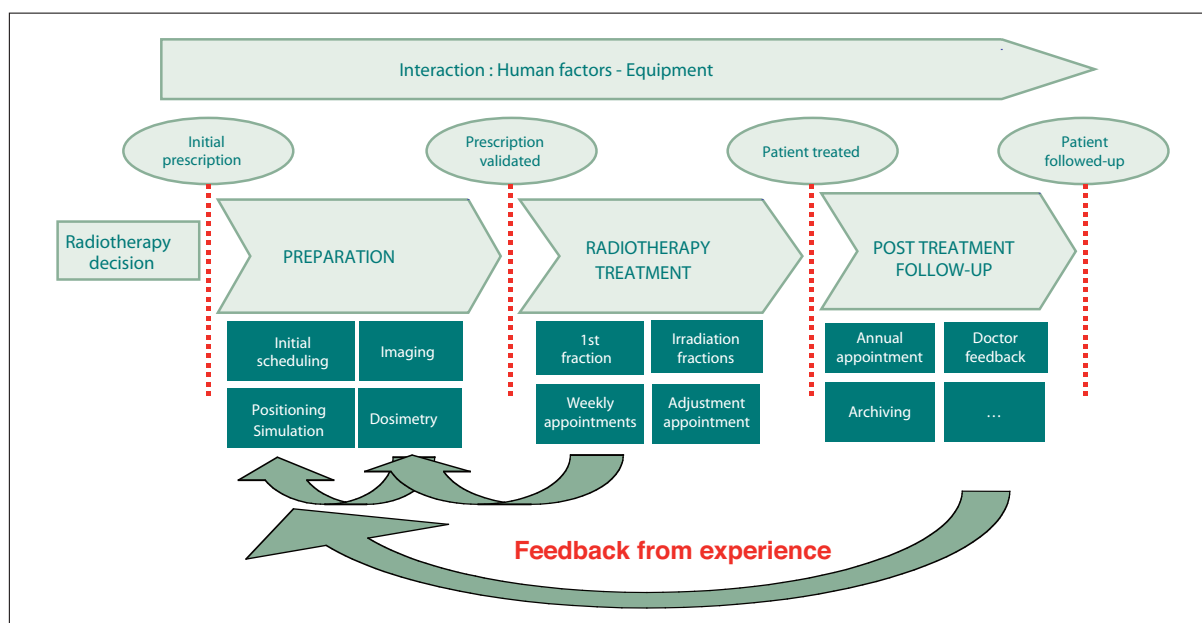
process, radiotherapy involves various professions (doctor, physicist, operator, technician, secretary and administrative personnel). It is a complex system in which there are a number of risks of deviation from the required baseline. Nevertheless, the risk of radiotherapy should not be exaggerated: it is similar to that of other therapeutic strategies. For example, the incidence of drug-related iatrogenic errors per hospital admission varies between studies from 1.8% to 7%. The effects of iatrogenic drug errors are serious: fatal for 1% to 2.7% of the patients and life-threatening in 12% to 46.8% of cases.

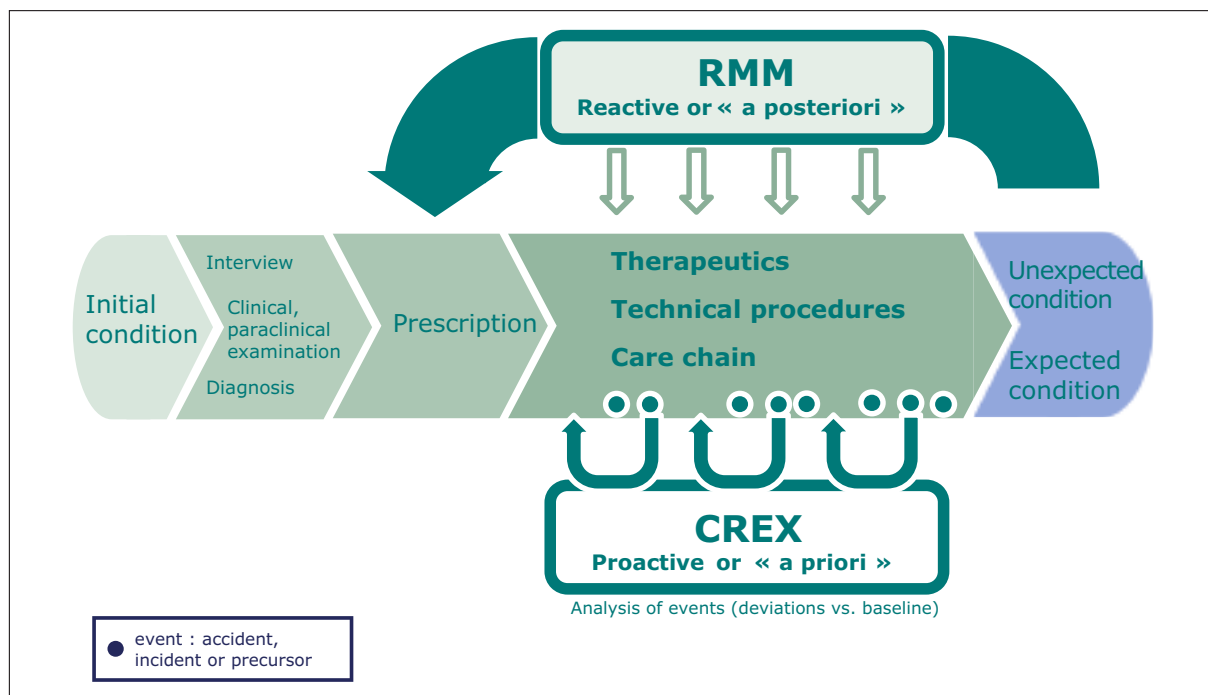
There are a number of analogies between the world of air transport and that of medicine, including radiotherapy. Accidents are experienced as unacceptable, generate extreme media coverage and have very substantial consequences on organisations. Waiting for such an event before reacting is not an option. Only prospective recording of events deviating from the norm for the purposes of analysis and correction can be considered (concept of precursor events), in preference to analysis, essential though that remains, of an accident that has occurred (morbidity-mortality meeting).

Such events occur in a context where the routine treatment (radiotherapy session) has many analogies with an airline flight. The patient must be received, identified, directed to the appropriate waiting room. He or she is confronted with a machine, the use of which is regulated by documents and quality controls, both internal and external to the establishment. The personnel includes posts tasked with supervision, real-time management, equipment maintenance, etc.

When the session (flight) ends, the patient leaves, and repeats the process the next day, sometimes with different personnel (crew) but in an environment that must provide the same quality and the same safety of management.

In addition to human, financial and technical resources, a safety policy necessitates a rigorous, validated methodology. A number of models of safety of practices have been developed in the industrial world. After assessment of the existing models, the model developed in the aviation world seemed without doubt to be the most robust and the most adaptable to radiotherapy. In Air France Consulting we found the willingness to work on the transposition of the model to the medical world and, thanks to the support of the MEAH, it was possible to run this experiment





between 2005 and 2007 on three pilot sites of the national federation of cancer treatment centres in Angers, Villejuif and Lille.

## The experience feedback committee: CREX

The methodology, based on the use of feedback from experience, thus comes from the aviation world, where it was developed from the mid-1970s.

The tasks of the experience feedback committee (CREX) are to:

- collect priority precursor events;
- monitor the system analyses performed each month;
- decide and follow up the corrective actions undertaken.

The committee consists of a multidisciplinary team of pairs (one representative and one substitute per sector of activity): radiotherapist, physicist, secretary, technician, supervisor, quality manager. Each member of the committee has received Orion (method of systemic analysis of precursor events) training given by Air France Consulting. To encourage exchanges between everyone, there must be no hierarchy within this group. A quality coordinator is appointed, with the role of collecting and prioritising events, preparing and chairing the meetings and drafting the minutes. This person is also tasked with monitoring the introduction of corrective actions and making sure that they are properly applied (assessment). The quality coordinator can collect precursor events in various ways (adverse event notification form, e-mail, case analysis, etc.). The precursor events are entered in a database.

The meetings last 1.5 hours and are monthly. All the items are discussed at the meetings (presentation of the events of the month, prioritisation of an event, choice of the person responsible for the analysis, presentation of the analysis of the event selected the previous month with proposed corrective actions, choice of corrective actions by the group, selection of the person responsible for implementing the selected corrective action(s) and definition of the timetable, and lastly follow-up of corrective actions undertaken at previous meetings).

In 2007, the recording of 403 precursor events at the Centre Oscar Lambret revealed a preponderance of events related to treatment prescription (20%), medical presence (15%), dosimetry validation (11%) and transmission of information. All these precursor events were analysed in order to select the events that the working unit considered the most important to correct

(11 CREX meetings and 8 adverse events selected for corrective actions). The Orion analysis identified corrective actions defined by CREX and then implemented by one of the members. After implementation of the corrections, a follow-up assessment was conducted over time. This action follow-up also recorded factors associated with treatment quality, such as the production of control images in the example in table 3.

One of the principal causes of potential reluctance to report events is the difficulty of considering them not as individual faults but as system failures. The punitive culture present too often in our organisations is a potential hindrance to experience feedback. Radiotherapy Resources Management (RRM) training has been a powerful lever of change by visual demonstration of situations that might pose a risk.

Once this step has been taken, the most sensitive is certainly regular feedback of information to the teams in order to maintain continuous mobilisation. The results must be discussed at the monthly team meetings. To maintain active participation by all the personnel, it has been essential to inform all the teams by means of notices, e-mail, meetings, etc.

The establishment of an experience feedback committee thus seems to us to be an essential step for the implementation of a safety policy in radiotherapy. It raises team awareness of compliance with and monitoring of procedures. Analysis of precursor events is a powerful tool for throwing light on organisational dysfunctions. Their correction and the communication about them is an essential management tool within the “no punishment” framework, a guarantee of trust and loyalty of the personnel.

Held upstream of the morbidity-mortality meetings, its meetings reinforce the safety system within the quality policy of the establishment. It is currently being introduced in FNCLCC radiotherapy departments. Its sustainability will depend on the involvement of the professional personnel and on the resources allocated to this “activity”, essential for the future of our discipline.

## Conclusion

As we have seen, safety in radiotherapy is a long-standing concern. The concept of feedback from experience corresponds to an overall process organised around systematic prospective

notification of observed incidents (precursor events) occurring during or in association with (secretariat, appointments, etc.) the healthcare activity. These events are recorded, prioritised, analysed (ORION method) and addressed (corrective actions) by the experience feedback committee (CREx) in order to avoid their repetition and eliminate progression to an accident. Feedback has the enormous advantage of raising the awareness of all personnel by making them contributors to safety. The aim is not to leave this field only to "quality specialists", but rather to make everyone, every day, vigilant participants in the detection and processing of incidents.

Requiring perfect document management (still in too embryonic a state in our organisations) and personnel awareness-raising (radiotherapy resource management), it is very certainly the indispensable base before rollout of "defence in depth" actions. Pooling of corrective actions is under way in the FNCLCC. ■

## References

1. Debouck F., Petit H.-B., Roy V. ORION – *Méthode d'analyse systémique*, - Publibook 2009.
2. Lartigau E., Sarrazin Th. *Qualité et sécurité en radiothérapie*. Risques & Qualité 2006, 2 : 101-106.
3. Lartigau E., Coche-Dequéant B., Dumortier V., Giscard S., Lacornerie T., Lasue A. et al *Le CREX : un outil indispensable à la sécurité en radiothérapie : une évaluation à 2 ans* Cancer Radiother. 2008;12:610-3.
4. MEAH *Améliorer la sécurité en radiothérapie*. Rapport de fin de chantier, Mai 2007. [www.meah.fr](http://www.meah.fr)
5. *Practical guidelines for the implementation of a quality system in radiotherapy*. Rapport ESTRO.
6. *Principes méthodologiques pour la gestion des risques en établissement de santé*. Rapport ANAES (Janvier 2003).
7. Revue *Contrôle* n°168 "le risque" téléchargeable sur le site de [www.asn.fr](http://www.asn.fr)
8. Yeung T.K., Bortolotto K., Cosby S., Hoar M., Lederer E. *Quality assurance in radiotherapy: evaluation of errors and incidents recorded over a 10 year period*. Radiother Oncol. 2005 ; 3:283-291.
9. Woynar S., Debouck F., Cellier P., Bourhis J., Cauterman M., Lartigau E. Vers une "politique sécurité" en oncologie-radiothérapie. *La mise en œuvre du retour d'expérience*. Cancer Radiother. 2007 ; 11:320-32.



## Accident reporting system: the ROSIS experience

by **Mary Coffey**, Director Division of Radiation Therapy, School of Medicine, Trinity College Dublin, and **Joanne Cunningham**, Lecturer, Division of Radiation Therapy, School of Medicine, Trinity College Dublin (Ireland)

The ROSIS project was initiated in 2001 by Ola Holmberg and Mary Coffey as part of a wider ESTRO project. One of the main aims of the project was error reduction and learning from the experiences of others in this respect. Incidents and near incidents are a fact of life and ROSIS aspired to utilise the experience gained from these incident to change practice at a local, national and international level through a confidential, voluntary, reporting and learning web based system. The aims of this system were defined as:

- establish an international reporting system in radiation oncology and;
- use the system to reduce the occurrence of incidents in radiation oncology by:
  - enabling all radiation oncology departments to share reports on incidents with other departments as well as with other stakeholders such as scientific and professional bodies;
  - collecting and analysing information on the occurrence, detection, severity and correction of radiation oncology incidents;
  - disseminating these results and generally promoting awareness of incidents and a safety culture in radiation oncology.

The first task carried out by the ROSIS group was an evaluation of the existing legislation at European level relating to incident and near incident reporting. This was based on a review of the European Directive on patient safety 97/43/EURATOM to identify the radiotherapy specific aspects and to try to determine how these had been translated or incorporated into national legislation. Questions were devised to illicit information on the laws of each country which underpinned incident reporting and whether these laws were based on or independent from EU Directives on radiation protection.

An extensive search was carried out to try to identify the Government department/s, in the then 15 member states, responsible for this legislation. Questionnaires were then circulated to the relevant government ministries, the radiological protection agencies and to a representative group of clinical departments to illicit information on incident reporting practices. Nine responses were received all indicating mandatory reporting of incidents and two indicating mandatory reporting of near or potential incidents. Simultaneously a review of incident and near incident reporting in other high reliability organisations was carried out. An ESTRO mail shot then sought expressions of interest to participate in a pilot project with forty five responses, sixteen

of whom already had an active incident reporting system in place. Twenty seven sample report forms were received from 22 clinics spanning 9 countries and from these the ROSIS departmental and incident report forms were developed.

The initial forty five respondents were then invited to participate in a three month pilot project to validate the ROSIS report forms. Following analysis of the pilot project the forms were refined and the web forms and database were put in place.

Consistent with the initial aim of the ROSIS project and the key aims of a reporting system as identified by Leape [1] the system is:

- independent of any regulatory activity or authority;
- confidential;
- a learning system focusing on system safety rather than individual actions.

ROSION takes a systems approach to safety and considers the occurrence of incidents in the context of the infrastructure and procedures within a clinic. The department form has been designed to reflect this approach by collecting information that includes the equipment levels, staff numbers, patient numbers, the complexity of the procedures carried out, the level of electronic connectivity and the quality assurance programme. This form is completed on registration and the clinic is then allocated an identification code which is used to submit subsequent reports thus ensuring anonymity.

The initial incident form, completed each time an incident or near incident occurs, collected the following information:

- treatment modality;
- date of occurrence;
- discipline (s) and QA method (s) that detected the incident;
- where in the process it occurred.

Over a six year period a total of 120 clinics registered with ROSIS and over 1200 reports were submitted. Almost 98% of the reports relate to external beam. To provide feedback to participants the anonymised reports can be accessed directly through the website, [www.rosis.info](http://www.rosis.info), and a series of spotlight cases have been prepared and circulated. In addition a short course in risk management in radiotherapy, based on ROSIS, has been developed and is in its sixth year.

An analysis of the database and a survey of ROSIS departments identified some areas where additional functionality would improve the system. The original forms relied heavily on free text information making analysis and cross correlation difficult. It was decided to revise the structure of the database and the report form to reduce the amount of free text space and to introduce a more comprehensive hazard classification system. This would facilitate a higher level of analysis, cross correlation and feedback and would, to a large extent, be language independent.

Future plans for ROSIS include the development of a local reporting form that links with the ROSIS database and the introduction of a prospective risk assessment component. In the future ROSIS will provide the system in languages other than English. ■

### References

- [1] Leape, LL. Reporting of adverse events. *New England Journal of Medicine* 2002; 347: 1633-1638.



## Use of adult stem cells in the treatment of radiation-induced skin burns

by **Pr Jean-Jacques Lataillade**, Percy Military Hospital, Armed Forces Blood Transfusion Centre, Research and Cell Therapy Department – Clamart, **Dr Marie Prat**, Percy Military Hospital, Armed Forces Blood Transfusion Centre, Research and Cell Therapy Department – Clamart, **Pr Patrick Gourmelon**, French National Institute for Radiological Protection and Nuclear Safety (IRSN), Fontenay-aux-Roses and **Pr Eric Bey**, Percy Military Hospital, Plastic Surgery Department – Clamart (France)

### Mesenchymal stem cells: adult stem cells with much to offer

First identified in bone marrow, Mesenchymal Stem Cells (MSCs) have also been detected in many other types of tissue (cartilage, thymus, spleen, adipose tissue, etc.) and, more recently, in placental blood. The name MSC alone covers the chief properties of this mesodermal cell type: self-renewal, high proliferation capacity and multipotency. The number of these cells can be significantly increased under standard culture conditions (*in vitro* expansion) and their ability to differentiate not only into various other types of mesodermal cell (such as chondrocytes, osteoblasts and adipocytes) but also endodermal or ectodermal cells (through the recent concept of cell plasticity) has been well defined for specific culture media.

MSCs are characterised *in vitro* as adherent cells similar to fibroblasts in appearance. Their antigenic profile is clearly defined by the expression of membrane molecules such as CD105 (SH2), CD73 (SH3, SH4) and CD90 (Thy1). These cells are part of the medullary microenvironment. In addition to the specifically structural role they play, they provide functional support for haematopoiesis by producing a variety of cytokines and growth factors. Actually, MSCs fulfil this trophic role in many types of tissue, helping to support the specific and inductive microenvironment of each one.

Phase I and II clinical trials have shown that MSCs amplified *ex vivo* can be safely administered on a systemic basis. The trials also pointed to the potential benefits to be gained from their use in a vast array of fields, as far apart as reparative medicine and the treatment of malignant disorders. Recent revelations of chromosomal anomalies after culture have, however, somewhat dampened enthusiasm concerning the use of MSCs in humans.

With regard to skin lesions caused by ionising radiation, we recently had occasion to treat victims of radiation burns who exhibited acute, radiation-induced skin syndromes. The cell therapy approach developed for these patients could be advantageously put to use at a later date in the treatment of other types of lesion such as thermal burns and lesions related to overexposure during radiotherapy. Despite the wide range of allogeneic and autologous transplantation methods available, the prognosis for deep and extensive radiation-induced burns is not quite satisfactory, owing to recurrent inflammations leading to graft failures. Clinicians and researchers are working to overcome these problems by developing new techniques for treating burns, involving the use of MSCs in particular.

### Cell therapy for radiation-induced skin burns

Acute, high-dose irradiation accidents have occurred with increasing frequency in recent years [Georgia (1998), Turkey (1999), Peru (2000), Panama (2001), Poland (2001), Georgia (2002), Chile (2005), Senegal (2007), France (2006-2007), Tunisia (2008)]. These have been due in particular to the misuse of radioactive sources in industry and hospitals. While the phenomenon is generally limited as far as numbers are concerned, its effects are catastrophic in human terms and particularly difficult to treat.

Although the literature provides quite good descriptions of the pathogenesis of acute localised radiation burns, the medical treatment of this type of pathology remains extremely complex and delicate. Feedback from the clinicians in charge of these patients at the burns treatment centre at Percy Military Hospital highlights the need for new therapeutic strategies. Cell therapy could bring about significant progress in this area.

One aspect of skin response to localised, high doses of radiation is the onset of tissue necrosis. This occurs after a clinically silent phase and develops in successive episodes that are hard to predict. It is related to an intense local inflammatory process and characterised by its recurrence. In view of the risks associated with radiation-induced necrosis and the development of lesions, underpinned by the feedback given in the literature and the very precise dosimetric data now available, the use of a new therapy combining the symptomatic conservative treatments already implemented and localised cell therapy with mesenchymal stem cells can now be contemplated.

MSCs are considered for use in this therapy not because of their multipotency but because they play a trophic role. The cytokines and growth factors they produce would help to control the local inflammations that are characteristic of radiation burns. The therapeutic potential of MSCs was thus studied from a radiopathology point of view by teams at the Army of the Service Health research centre (CRSSA) and the French National Institute for Radiological Protection and Nuclear Safety (IRSN) using animal models. In the past two years, several patients have benefited from cell therapy of this type, in conjunction with surgical treatment involving exeresis and an epidermal autograft. Each case concerned severe, highly localised radiation-induced burns (hands, arms, buttocks) with a high probability of radical amputation surgery being required later. The MSCs were taken from autologous bone marrow samples following *in vitro* expansion from 15 to 17 days. The culture medium included 8% clinical-grade platelet lysate. The quality control checks, including in particular the karyotypes, were all normal and the cells produced could therefore be administered. 150 to 180 x 10<sup>6</sup> cells were injected locally into the lesions following surgical removal of the necrotic tissue and an epidermal autograft. This cell administration was repeated two to five times depending on the severity of the case of each patient and the rate of progress. The effect on pain was spectacular in all patients and observable as of the day following injection. This antalgic effect disappeared, however, after a few days and additional injections were necessary. Surgeons also noticed the significant impact on how quickly and how successfully the epidermal graft took. No recurrence of necrosis was observed in these patients - after a period of four years in the case of the first. It is our opinion that MSCs played a role in the local control of inflammation. They also promoted successful grafting and overall healing of lesions.

There is no doubt that these advances in cell and tissue bio-engineering will be used to great advantage in the treatment of severe burns of this type in the future. In this type of therapeutic approach, multipotent stem cells such as MSCs, integrated into



overall skin models, would promote the survival and proliferation of specialised epidermal, dermal and muscle cells. Animal experiments are under way to confirm that MSCs injected locally into lesions play a role in controlling inflammation and helping grafts to take. The results obtained from animal models are expected to confirm the positive role of MSCs regarding not only local-regional inflammation and grafting success, but also reactive fibrosis in chronic, radiation-induced lesions following radiotherapy. ■

## Radiation therapy equipment: safety, commissioning, calibration; the medical physicist's point of view

by **Albert Lisbona**, Medical Physicist – Nantes-Atlantique Regional Cancer Centre (France)

In the past few years, technological progress has led to some major developments in radiotherapy, including innovations such as helical tomotherapy and robotic radiotherapy. The objective, however, remains unchanged: to deliver the highest possible dose of radiation to the target while minimising the risk of damage to nearby healthy tissue.

Radiotherapy involves a complex therapeutic process. It provides patients with treatment based on increasingly sophisticated equipment (Figure 1), techniques and human skills that are closely interconnected through various machine-machine and human-machine interfaces.

In the past thirty years, various publications have described commissioning and start-up procedures for linear accelerators designed for medical use and for other key medical devices used in radiotherapy. A number of organisations have largely contributed to this extensive literature, including the International Electrotechnical Commission (IEC) (1-5) for the preparation of standards, the ICRU (6) and learned societies in the medical physics field (AAPM (7 – 12), IPEM, SFPM,...) for the publication of recommendations to users.

The acquisition, commissioning and start-up (and operation) procedures are identical for all types of equipment. The first step involves preparing the specifications for the equipment to be

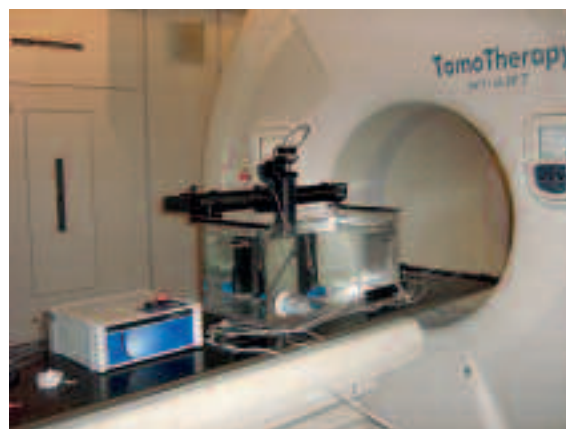


Figure 2: validation setup on a helical CT scanner

purchased. These are based on IEC-type standards and recommendations such as quality assurance and quality control procedures proposed by learned societies in medical physics. In particular, the specifications stipulate the performance levels required of the equipment and provide a list of its characteristics, taking into account the medical purpose it is to serve and planned radiotherapy methods, such as 3D conformal radiotherapy, intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT) and intra- and extracranial stereotactic radiation therapy.

Once the equipment has been purchased, the commissioning and acceptance procedure is the next step. This entails verifying and validating equipment performance to ensure that it complies with specifications (Figure 2). This step is carried out jointly by the supplier and the user, represented by the medical physicist. A commissioning report is then written up.

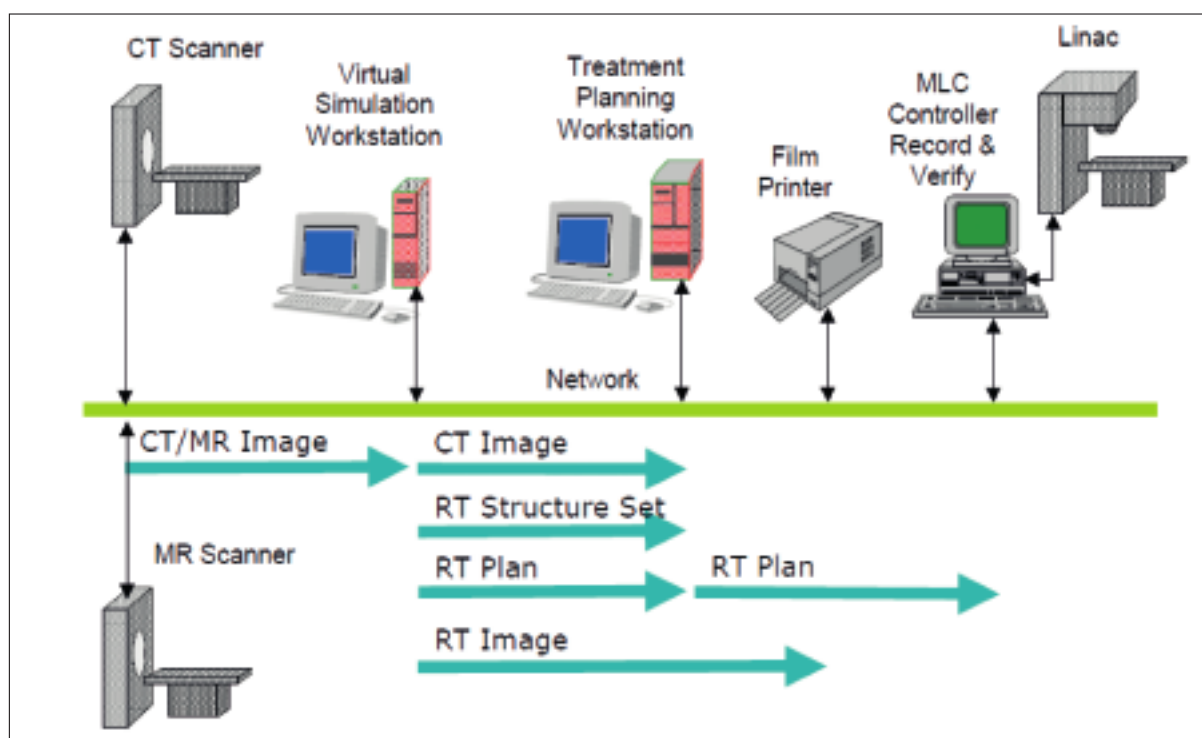


Figure 1: connections between main items of RT equipment (after J.A. Purdy)

Radiotherapy is seeing such fast innovation that for some of the most recent and sophisticated equipment, like Accuray's Cyberknife or TomoTherapy's HiArt II system, commissioning procedures rely on the manufacturers' knowledge (in addition to IEC standard documents) of their systems (they are in the best position). Similarly, quality control programmes, based on a consensus of expert opinions, are not yet ready for the use of this new equipment.

Commissioning also represents the first step in setting up the quality control programme. The purpose of this programme is to guarantee reliability, consistent mechanical and dosimetric performance (in the case of medical linear accelerators) and technical safety throughout the lifetime (ten years) of the equipment, in conjunction with the contractual maintenance programme.

From the administrative point of view, equipment commissioning or acceptance opens the equipment guarantee period.

In the case of linear accelerators designed for medical use, physical commissioning of the equipment alone does not allow pre-clinical validation. In addition, the main dosimetric characteristics of the radiation beams to be used in treating patients [13] need to be measured. These measurements are used to make a mathematical model in the treatment planning system (TPS) of the dosimetric characteristics of the radiation beams delivered by the linear accelerator at the radiotherapy centre. The TPS uses special calculation algorithms to simulate the medical prescription in terms of the dose to be given to the patient. The patient's anatomical data must be available to perform these personalised calculations. This is obtained from scanner images, increasingly in conjunction with functional imaging (MRI, PET).

The linear accelerator and TPS are connected (the X-ray scanner, which is essential for treatment preparation, may also be included) using the radiation therapy information system (RTIS). This system regulates the flow of radiotherapy patients and checks and records the dose fractions the patient receives during treatment. Nowadays, radiotherapy simply could not exist without the RTIS. This system is at the heart of the radiotherapy centre and must consequently follow the same purchasing and commissioning procedures as the linear accelerators described above.

Before any clinical use is possible, equipment commissioning procedures must be supplemented by the validation of the planned radiotherapy techniques. This is done through process-oriented checks, such as IMRT, intra- and extracranial stereotactic radiation therapy [14], etc. The aim is to use a test object and appropriate dosimetric equipment to validate the different stages of the patient's RT pathway (the test object represents the patient), from the scanner used in preparation, through the TPS and data transfer to the RTIS, up to delivery of the dose by the linear accelerator.

Radiotherapy equipment must be purchased, selected, installed, commissioned and calibrated following meticulous procedures. Any mistakes or oversights during commissioning and calibration can prove very costly. The medical physicist in charge of such procedures must assume his/her responsibilities fully and allow no compromise on any aspect of the process. ■

## References

1. IEC 60601-2-1: Medical electrical equipment – Part 2-1: Particular requirements for the safety of electron accelerators in the range 1 MeV to 50 MeV Amendment 1 [2002].
2. IEC 60977, Medical electrical equipment – Medical electron accelerators in the range 1 MeV to 50 MeV – Guidelines for functional performance characteristics [2008].
3. IEC 61217, Radiotherapy equipment – Coordinates, movements and scales [1996].
4. IEC 60976, Medical electrical equipment – Medical electron accelerators – Functional performance characteristics [2007].
5. IEC 62083, Medical electrical equipment – Requirements for the safety of radiotherapy treatment planning systems [2000].
6. ICRU report 42: Use of Computers in External Beam Radiotherapy Procedures with high Energy Photons and Electrons [1987].
7. Purdy J.A., Biggs P.J., Bowers C., et al. Medical accelerator safety considerations: Report of AAPM Radiation Therapy Committee Task Group No. 35. *Med Phys* 1993; 20:1261–1275.
8. Nath R., Biggs P.J., Bova F.J., et al. "AAPM code of practice for radiotherapy accelerators: Report of AAPM Radiation Therapy Task Group No. 45," *Med. Phys.* 1994, 21, 1093–1121.
9. Kutcher G.J., "Comprehensive QA for radiation oncology: Report of AAPM Radiation Therapy Committee Task Group 40," *Med. Phys.* 1994, 21, 581–618.
10. Kubo H.D., Glasgow G.P., Pethel T.D., et al. High dose-rate brachytherapy treatment delivery: Report of the AAPM Radiation Therapy Committee Task Group No. 59. *Med Phys* 1998;25: 375–403.
11. Das I., Cheng J.C., Watts R.J., et al. "Accelerator beam data commissioning equipment and procedures: Report of the TG-106 of the Therapy Physics Committee of the AAPM," *Med. Phys.* 2008, 35, 4186–4215.
12. Klein E.E., Hanley J., Bayouth J., et al, Task Group 142 report: Quality assurance of medical accelerators *Med. Phys.* 2009, 36, 4197–4212.
13. IAEA-TECDOC-1540 Specification and Acceptance Testing of Radiotherapy Treatment Planning Systems 2007.
14. Williamson J.F., Dunscombe P.B., Sharpe M., et al. Quality Assurance Needs for Modern Image-Based Radiotherapy: Recommendations From 2007 Interorganizational Symposium on "Quality Assurance of Radiation Therapy: Challenges of Advanced Technology". *Int J Radiat Oncol Biol Phys* [2008] 71:S2–12.

## The Radiation Therapist profession: a challenge and an opportunity to improve the safety and the patient care in Radiation Oncology

by **Gianfranco Brusadin**, RTT, European Federation of Radiographer societies (Italy)

The European Federation of Radiographer Societies (EFRS), which is invited to speak at this occasion, was founded in 2007. EFRS represents 29 radiographer societies from 27 European Countries and about 100.000 people in the profession of medical imaging and radiotherapy. An educational wing is now being set up with, as affiliate members, educational institutes that provide radiographer education. The role of the EFRS is to represent, promote and develop the profession of radiographers in Europe, within the whole range of medical imaging, nuclear medicine, and radiotherapy ([www.ehrs.eu](http://www.ehrs.eu)). The EFRS aims are among others: promoting patient safety and radiation protection, promoting the use of the EFRS reference code of ethics, developing European standards of professional practice, promoting evidence based practice and the principle of 'science in society' and promoting harmonisation of initial and post-graduate education. The EFRS aspires to achieve these aims in cooperation with all related organisations and groups in Europe. As a result patients will benefit of a good standard of care delivered by high quality professionals.

### Developments in Radiation Oncology (RO)

RO was practically born with the discovery of X-rays in 1895 [Despeignes, 1896]. Since RO highly evolved and, especially in the last two decades, has known a strong acceleration in technological evolution. This brought about an exponential growth in complexity of the process to provide the treatment in which multiple disciplines and professionals interact. All this has certainly improved the overall quality and the results of the process of care, but it also increased the risk of preventable adverse events. The elements of complexity in the system are many. Some are inherent to RO such as the therapeutic agent used, that requires high skills to be managed safely for the patients, without forgetting the potential danger to the staff, and the public. Others are related to the speed in which the technological progress takes place, the involved rapid changes and the high level of heterogeneity. The increased complexity of the equipment and software used, bring about new types of malfunction that may not be easily detected by the operators and which may involve several patients before being detected, notwithstanding the fact that the self checking systems of the equipment were increased.

Another development is the possibility of raising of the overall National investments for RO, particularly in countries in Eastern and Southern Europe who are now in a position to implement "ex novo" departments or to overhaul the equipment and the methods of therapy, bringing about the need to employ new personal or to radically adapt the training of the existing personnel. The increasing number of RO departments has increased the total number of patients treated but, at the same time, also the probability of patients to be involved in an avoidable adverse event. Nowadays a radiation treatment to be accomplished with success, is an activity that needs the involvement, the coordinated interaction and the sharing of ethical and deontological responsibilities of different professions. It is an activity in which not

one step is made entirely by a single independent professional. Many people work together contributing their part to the entire process.

The importance of proper professional interaction between these people is such that if the contribution of one of them is somehow lacking the whole quality of the radiation treatment will be affected. This characteristic of a strong multi professional interaction, represents another complexity and it can be a critical element, but in the same time an added value and an opportunity for adequate management of clinical risks and optimisation of the quality of care provided to cancer patients. In many European countries the profession of RT has been the subject of a profound change in terms of training and acquisition of autonomy and professional responsibility. The technological progress requires both the obsolescence and the creation of new roles and functions. Each professional group should therefore, periodically reassess the operational procedures in place, according to the developments and share the outcomes of the evaluation with the other professions in order to redefine the procedures in needed.

### Consequences for staffing RO departments

The above mentioned developments impose a thorough transformation of all the involved staff members in the RO departments in terms of indispensable knowledge and competences, work processes, the scope of practice and the intra-inter professional relationships. The multi professional team is generally composed of, at least, three professional groups: the Radiation Oncologist, the Radiation Therapist and the Medical Physicist. This team composition is substantially shared at international level [WHO, 2008]. The heterogeneity of the RT profession at European and world wide level as will be explained below, makes the definition of the quantitative RT staff needed for the safe delivery of radiation treatment very complex. An interesting point is made in an article [EORTC ROG, 2008]: "An insufficient number of radiation technologists appears to be the most hazardous link in a large number of RT departments. This shortage may be because national guidelines regarding the number of RTT are very diverse and depend by large on local organization, on differences in the qualification and specialisation of RTT in the countries, how the work is distributed between the various disciplines and on the complexity of the work done at the centres.

There is a large variety in the definition of the tasks assigned under the "title" of Radiation Therapist. In some countries these are highly skilled professionals with a recognised diploma, whereas in other countries they might be health care professionals who receive an in-service training without recognition of this as a separate entity. This also explains the variable transition zone between RTT and radiation physicists concerning their tasks." It is plausible that this heterogeneity and uncertainty about the content and social status of the RT profession and a lack of career perspectives obstructs the attraction of students and brings about departure of qualified staff and this explains the permanent shortage on the labour market in most EU countries. RO is a labour intensive activity, despite the presence of considerable technological devices. Moreover, the presence of a multi professional team requires special attention in the organization of human resources. In fact, with the introduction of new technologies one professional group may be subjected to an excessive workload and another group, perhaps eased or even underemployed. For the purpose of clinical risk management a clear and shared definition of the professional roles is essential in order to avoid conflicts in the allocation of tasks or dangerous "gaps" in the same. If not managed properly the natural resistance to change can lead to a latent failure condition. On a regular basis, the whole radiotherapy team should be invited to discuss and decide on the allocation of tasks based on the





principles of effectiveness and efficiency of operation of the entire system, within the limits imposed by the current national legislation.

## The RT profession

In the European Core Curriculum for RTs [ESTRO-EU Commission, 2003], currently under revision, the profession is defined as: "RT's are the group of professionals with direct responsibility for the administration of radiation therapy to cancer patients. This encompasses the technical delivery of the radiation dose, the clinical and the psychosocial care of the patient on a daily basis throughout the treatment preparation, the treatment and immediate post treatment phases. The RT is a member of the multidisciplinary team comprising essentially the clinician, physicist and RT. As the RT sees the patient on a daily basis he/she is also often a link person for the patient within the wider multidisciplinary team. They liaise with all the other associated professionals in ensuring the needs of the patient are met". The document also highlights the critical lack of a common name: "The lack of a single title creates difficulties in terms of identity and also in facilitating the free movement of personnel that is integral to the development of the European Community and a clearly identified aspiration." The content and level of education, the scope of practice and the professional responsibilities differ a lot from country to country and depend of the national or even local culture in RO departments.

## Quality assessment and risk management

The RT is the front line operator, in direct contact with the patient for several sessions and a reference to the same and is in a position to be the material author for several active failures that could happen in a Radiotherapy Department. But also the RT's have a key role in being the last effective barrier in the trajectory of accident opportunity of a possible hazard by detecting errors before they become effective. ROSIS data ([www.rosis.info](http://www.rosis.info)) seems to confirm this condition as much as 69% of accidents or near misses are detected by RT's at the therapy unit. Even though the events in the ROSIS system are not representative for the entire population of events, the above percentage is significant, enhanced by the fact that the percentage rises to 78% if incidents or near misses reported by RT's working in other phases of the process are included [dosimetrist/planner, Simulator-CT].

A common element is the relevant participation of RT's in almost all stages of the radiotherapy process. The WHO document shows that characteristic of the profession [WHO, 2008], since in eight out of the eleven stages in which the process is broken, the RTs are involved and professionally responsible. Of particular significance and synthesis are two publications on quality [Leer, 1995, 1998]. In these documents it is clearly indicated that the management should provide the highest degree of involvement and integration of all the professionals in the team. For example, the definition of the objectives of a RO Centre in terms of type and number of treatments must be made on the basis of the allocation of human resources, technology and available infrastructure. This definition should be shared with all staff of the Centre and compared with national and international guidelines. All staff should be involved in this important decision-making phase and have the opportunity to express their specific professional contribution. It should be underlined that this involvement should not be read in a "union" way but rather to ensure the safety and quality of service delivered to the cancer patient. The sharing among all staff of the objectives and the information on the achievements improves the motivation of the staff and helps to create a better organizational climate.

The technological equipment is a fundamental element in the quality of RO. The acquisition process and the management of the equipment, require careful design because many accidents which have affected several patients have been generated by malfunctioning equipment or by improper use. After defining what type of equipment should be acquired, all staff that will use

it should be involved in the acquisition process. A severe latent error condition can be generated by the lack of involvement of the end user of the equipment in this process. The acquired equipment might be in some respects inadequate for the task to be performed and thus create difficult working conditions with the risk of errors or even violation of security procedures in order to render the equipment suitable to the context of use. In some cases the equipment is underemployed, or even never used, as inappropriate to the intended use, which is a serious waste of resources. The purchase of large machinery, essentially LINAC, not only needs the involvement of all staff but of RT in particular and must include the specific training and the conditions of warranty and maintenance. The participation of the RT in the purchase process is crucial because of the fact that the end user of the equipment will have to manage the workflow in case of breakdown or scheduled maintenance.

## Education of RT's

The initial education is currently highly fragmented in Europe with regard to duration, content and level. (e.g. universities, in-service hospital schools or even only training on the spot). There are specialised three or four year specialised radiotherapy courses at various levels or three or four year combined courses also including all medical imaging modalities. Because these imaging modalities are becoming more and more integrated in treatment planning the latter is an interesting option. The education must always address the safety culture and clinical risk management in order to allow the reactive analysis of incidents or near misses occurred. It also should promote and stimulate research by RT's on aspects of daily clinical practice in order to be presented nationally or internationally or published in scientific literature. These research activities, besides being an effective instrument in strengthening the professional team, allow the critical review of the activities taking place and identification of specific weaknesses.

At the departmental level, in the process of defining the objectives of the Service, the ongoing training of RT's should be determined clearly, in terms of time and resources. The training must be clearly documented and incorporated in the activity. The RT's should receive proper training on the use of equipment and software and be provided an adequate learning time for the implementation of new methods or use of new acquired technology. Due to the considerable investments the temptation may be to exert pressure in order to rapidly introduce the new equipment into clinical practice. Inadequate training of personnel however creates a serious latent error condition as well as a risk of under-utilization or non-optimal use of the equipment. Each time newly hired staff must be properly trained in accordance with their education and experience. Often both the management and the professional groups consider newly hired or recently qualified staff as immediately operational, which may lead to a clear latent error condition. In some Countries, the RTs, are compulsory enrolled in professional registers and/or are represented by an official body, while in other countries they are organized into associations or scientific societies.

These entities may communicate directly with national institutions such as the Ministry of Health and/or Education by offering appropriate core curricula. Continuous Professional Development (CPD) is in only very few countries well established, but this counts not only for the RT profession. It is therefore the most important goal of the EU LifeLongLearning action plan. In relation to radiation protection however the Council Directive 97/43/Euratom is very clear: "Member States shall ensure that continuing education and training after qualification is provided and, in the special case of the clinical use of new techniques, the organization of training related to these techniques and the relevant radiation protection requirements.". This directive is currently under revision and it is expected that the implementation of the new directive in the member states will be checked more severely than in the past. The EU has since long time abandoned their original idea of harmonisation (professional) education in

the member states, because education is and remains a national responsibility and depends on the national culture and organisation of the society. On the other hand many European activities are stimulated and funded to exchange information and knowledge and to develop core elements of educational programmes at the European level. Member countries however can never be forced to implement these. Surely it would be desirable, given the rapid changes technology-related, that the national law provides flexibility, with a good degree of foresight.(e.g. by correlating the scope of practice to the state of the art).

## Conclusions

The evolution of RO technology leads to the need for strategic management of the limited financial and human resources to ensure safe and high quality treatment of cancer patients and motivated highly educated staff at all levels. Shortages on the labour market in specific countries may be solved by creating clearness about the content and social status of the RT profession and by offering good initial and continuous education, accompanied by interesting career perspectives, specialisation and research. Harmonisation of the RT education in Europe can only be brought about if the different cultures and working processes in RO departments are harmonised first, with clear procedures and role descriptions. For this representatives of all the RO team members would have to cooperate at the European level, each with the input of their national organisations and background. ■

## References

- DESPEIGNES V., "Observation concernant un cas de cancer de l'estomac traité par le rayons Rontgen", Lyon Medical, Lyon 1896; 428-506.
- EORTC, Radiation Oncology Group, "Profile of European radiotherapy departments contributing to the EORTC Radiation Oncology Group (ROG) in the 21st century", Radiotherapy and Oncology 88, 2008, 403-410.
- ESTRO – EUROPEAN COMMISSION, "Review of the European Core Curriculum for Radiotherapy Technologist", Directorate General Health and Consumer Protection, Europe against cancer Programme, Bruxelles 2003
- LEER J.W.H., SCALLIET P., THWAITES D., OVERGAARD J., "Quality assurance in radiotherapy", Radiotherapy Oncology. 1995; 35:61-73
- LEER J.W.H., MCKENZIE A.L., SCALLIET P., THWAITES D., "Practical guidelines for the implementation of a quality system in radiotherapy", ESTRO Booklet 4, 1998
- WHO, "Radiotherapy risk profile, technical manual", Geneva 2008



## EFOMP approach to reducing errors in Radiotherapy

by **Herman Van Kleffens**, School for Medical Physics & Engineering (SMPE/e), University of Technology Eindhoven – Eindhoven (Netherlands) and **Wil Van Der Putten**, Dept. of Medical Physics & Bioengineering, Galway University Hospitals – Galway (Ireland)

In several accidents in Radiotherapy it could be stated that amongst many complex factors leading to the accident also a lack of good professional behavior of a medical physicist plays a role (Exeter, North Staffordshire and Epinal). EFOMP recognizes the importance of good education and training and has spent a lot of effort in establishing conditions to achieve this. An example is the publishing of several policy statements (PS):

No. 1: Medical Physics Education and Training: The Present European Level and Recommendations for its Future Development, 1984.

No. 3: Radiation Protection of the Patient in Europe: The Training of the Medical Physicist as a Qualified Expert in Radiophysics, 1988.

No. 8: Continuing Professional Development for the Medical Physicist, [also available as Acrobat pdf-file: policy8.pdf], March 1998 [*Physica Medica* XIV (1998) 81-83].

No. 9: Radiation Protection of the Patient in Europe: The Training of the Medical Physics Expert in Radiation Physics or Radiation Technology [also available as Acrobat pdf-file: policy9.pdf] [*Physica Medica* XV (1999) 149-153].

No. 12: The present status of Medical Physics Education and Training in Europe. New perspectives and EFOMP recommendations.

No. 13: Recommended Guidelines on the Development of Safety and Quality Management Systems for Medical Physics Departments.

Another activity is EFOMP's support of the European School for Medical Physics (ESMP) and [co] organizing workshops and congresses to facilitate mutual exchange of experiences.

We will now discuss PS No 12 in more detail.

### PS No 12 The present status of Medical Physics Education and Training in Europe. New perspectives and EFOMP recommendations

PS No 12 was published in *Physica Medica* (2009) xx, 1-5. Two European issues will affect the still wide variety in education and training of Medical Physicists within Europe:

1. The harmonization of the architecture of the European Higher Education System, arising from the "Bologna Declaration", for 2010;
2. the recently issued European Directive: "Directive 2005/36/EC of the European Parliament and of the Council of 7 September 2005 on the recognition of professional qualifications.

The wide variety in education and training among the National Member Organizations (NMO) of EFOMP has recently been published (1) and was in accordance with former inquiries (2,3). It was concluded that not only a wide variety exists in education and training but also in professional practice. Here a task for all NMO's and EFOMP has to be fulfilled. This becomes more urgent in the spirit of the Bologna Declaration and Directive 2005/36/EC. Therefore EFOMP recommends all NMO's a five year university education (Master on Medical Physics or equivalent), a minimum of two year postgraduate training in Medical Physics which leads to a registration as Qualified Medical Physicist (QMP). Now an additional training with a minimum of two years can lead to a registration as Specialist Medical Physicist (SMP). EFOMP will now allow this only for an interim period and will use the full duration of a Continuous Professional Development (CPD) cycle of five years for registration as SMP. Not clear is now whether the CPD cycle starts immediately with the start of the two years training period for QMP, which will result in a total education and training period of 10 years, or with the start of the additional training after the registration as QMP, which will result in a total education and training period of 13 years! If the lack of Medical Physicists in most countries is taken into account, such a long period will have a negative influence on the number of available Medical Physicists.

### School for Medical Physics and Engineering in Eindhoven (SMPE/e)

In the Netherlands, as in other European countries the lack of Medical Physicists is severe. Due to a governmental limit in the number of trainees in Specialist Medical Physicists the problem will become even worse. Therefore, SMPE/e started in 2006 with the education of Qualified Medical Engineers (QME). Actually the QME is comparable with a QMP. The latter however is not recognized by the NMO in the Netherlands. Only SMP's are recognized after a minimum of 9 years total education and training. A level of professionals in between the MSc and the SMP resulting in a pyramidal build up of workforce can solve this problem. All trainees in Medical Physics (both for SMP and QME) will be educated in Safety and Risk Analysis. This course for trainees in Medical Physics was established in 2001 and supported by the Dutch Society for Medical Physics (NVKF). It was felt as a necessity to educate trainees in all aspects of safety and risks associated with the application of complex methods and techniques in health care.

EFOMP has embraced this initiative and supported a workshop on Safety and Risk Analysis during the second Mediterranean conference on Medical Physics from April 28-30, 2004. Also some other NMO's were interested in the subject and invited the organizer of the course to their country (Ireland and Denmark).

### Recommendation

EFOMP recommends all NMO's to incorporate a course in Safety and Risk Analysis in the education of all trainees in Medical Physics in order to reduce errors in health care in general and in Radiotherapy in particular. ■

### References

1. EUDALDO T., OLSEN K., "The present status of medical physics education and training in Europe: an EFOMP survey". *Physica Medica* 2008; 24(1): 3-20.
2. VAN KLEFFENS H.J., "Actual situation of implementation of EC Directive 97/43/Euratom [MED] in Europe". *Physica Medica* 2000; XVI(3):165-167.

3. VAN KLEFFENS H.J., "Implementation of the EC Directives 97/43/Euratom [MED] and 96/29/Euratom [BSS] in Europe". *Physica Medica* 2002; XVIII(4):149-152.



### Training of medical physicists in radiotherapy

Medical physicists with appropriate qualifications and clinical training are needed to ensure the safe and effective use of modern imaging and therapeutic equipment in hospitals. An entry level medical physicist should have an appropriate academic qualification at the postgraduate level followed by clinical training in a hospital and professional accreditation, recognition or registration with an appropriate authority in the country. While there are examples of countries with these academic, clinical and accreditation processes in place, most African countries have no programme at all while many countries in Asia, Europe and Latin America do not have the clinical or accreditation/registration programmes. The long-term strategy of the IAEA is to contribute to the establishment and harmonization of medical physics education programmes, including clinical training and professional accreditation/registration, in Member States while recognizing that this can be achievable and sustainable only in

countries where a critical mass of applications exists in medical use of ionizing radiation (treatment and imaging). For countries with a limited number of medical applications, the concept of consolidating medical physics education in the region is followed. Furthermore, the IAEA trains around 200 medical physicists per year through specialized short courses on imaging and therapy using ionizing radiation, excluding courses on radiation safety.

In addition to education and training through the provision of courses and material, the IAEA also supports training of medical physicists working in hospitals through fellowships. Education and training is an essential part of the overall quality management system in radiotherapy and emphasizes the balance of health benefits against radiation risks. This requires a systematic approach, in which education and training needs are clearly identified together with the means of meeting those needs. ■

### References

1. FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS, INTERNATIONAL ATOMIC ENERGY AGENCY, INTERNATIONAL LABOUR ORGANIZATION, OECD NUCLEAR ENERGY AGENCY, PAN AMERICAN HEALTH ORGANIZATION, WORLD

HEALTH ORGANIZATION, International Basic Safety Standards for Protection against Ionizing Radiation and for the Safety of Radiation Sources, Safety Series No. 115, IAEA, Vienna (1996).



## The IAEA quality audits in radiotherapy

by Joanna Izewska, TLD Officer and Unit Head, Dosimetry Laboratory,  
Dosimetry and Medical Radiation Physics Section, International Atomic,  
Stanislas Vatnitsky and Eeva Salminen

The quality audit is considered an essential part of quality management systems in radiotherapy. It is a method of checking that the quality of activities in a radiotherapy centre adheres to the standards of good practice. The quality audit in radiotherapy is equivalent to peer-review or evaluation of practice by independent auditors, typically professionals specializing in various aspects of radiotherapy, such as radiation oncology, medical radiation physics and radiotherapy technology. The main objective of the quality audit is to aid in quality improvement. Audit findings are documented and provided to the audited centres with recommendations for improvements. Usually, the auditors are independent and have no authority to enforce actions based on their findings. In this respect, the quality audit's nature differs from that of the regulatory inspection as the audit provides specific advice on quality improvement but does not serve as an enforcement tool (IAEA 2007 a).

The scope and focus of the quality audit can vary significantly. Audits may be initiated to review the entire radiotherapy practice at a facility (comprehensive audit) or particular, important parts of practice (partial audit). Comprehensive audit, also known as a clinical audit (Euratom Directive 97/43, 1997) covers the complete clinical pathway of the patient from dose prescription, through planning, dose delivery to the follow-up. The clinical audit addresses the three main elements of the practice: structure, process and outcome. In contrast, partial audit has a limited scope and it focuses on specific parts of the radiotherapy process. A typical example of such a partial audit is a dosimetry audit, which has the purpose of checking the beam calibration in external beam radiotherapy (Aguirre et al. 2002, Izewska et al. 2002 a). It is the most fundamental audit in radiotherapy since the success of radiation treatment depends strongly on assuring accuracy in dose measurements.

Dosimetry audits in radiotherapy have a long tradition (Aguirre et al. 2002, Izewska et al. 2003). Both on-site audit systems and mailed dosimetry programmes have proven to be very useful tools in quality assurance. Typically, on-site audits test dosimetry, electrical, mechanical and safety parameters of radiotherapy equipment and review local dosimetry systems. Some audit programmes also assess treatment planning systems and review the clinical dosimetry records. Many on-site audit programmes function at a national level and are available for a limited number of hospitals, whereas mailed TLD audits operate at a larger scale, involving hundreds or thousands of radiotherapy facilities (Aguirre et al. 2002, Izewska et al. 2002 a, Izewska et al. 2002 b, Molineau et al. 2005, Roue et al. 2004).

### IAEA/WHO TLD audit in radiotherapy dosimetry

The IAEA/WHO TLD postal dose audit programme has now been in operation for 40 years. It uses mailed thermoluminescence dosimeters (TLD). Hospital users irradiate TLDs with a given dose under known irradiation conditions and then return them to the IAEA for evaluation. To-date the calibration of over 7500 radiotherapy beams in 1650 hospitals in 120 countries have been audited through this programme.

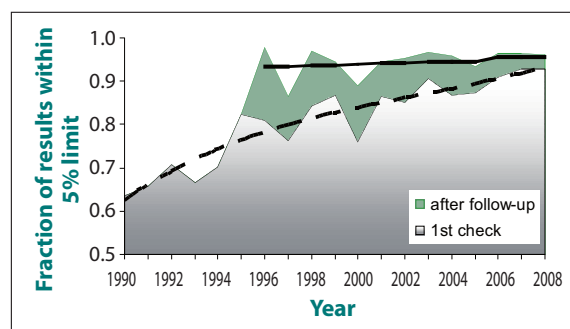


Figure 1. Fraction of TLD results within 5% acceptable limit in the IAEA/WHO TLD postal dose audit programme. After the regular follow-up of poor TLD results was introduced in 1996, the fraction of acceptable results increased to about 0.96.

At present, approximately 93% of TLD results meet the acceptance criterion of 5% (see Figure 1). An integral part of the auditing process is resolving discrepancies in the beam calibrations that are discovered. The discrepancies are monitored by the IAEA (IAEA 2007 b), and their causes are traced, understood and corrected. Through the follow-up procedures, several participants have improved their abilities to accurately deliver radiation dose, and the percentage of acceptable results has increased from 80% in 1995 to 96% in 2008 (Figure 1). However, 4% of the poor results remained uncorrected either due to a failure to respond to the IAEA efforts or due to local problems that could not be resolved without allocation of appropriate resources. In addition some centres work within practical limitations such as insufficient availability of qualified medical physicists or lack of adequate dosimetry equipment, which hampers quality. Nevertheless, significant improvements have been observed in dosimetry practices in radiotherapy centres worldwide (see Figure 1).

Another dosimetry audit programme that has been developed by the IAEA is one based on a semi-anthropomorphic phantom. It assesses the entire external beam radiotherapy workflow for conformal radiotherapy techniques, from patient data acquisition and computerized treatment planning to dose delivery. The experience gained in audits for these techniques (Gershkevitch et al. 2008) has highlighted the need for careful attention to basic aspects of dosimetry and treatment planning.

### QUATRO: comprehensive audit in radiation oncology

It has been recognized by the IAEA that accurate beam dosimetry and treatment planning alone, although critical for the radiotherapy process, cannot guarantee the required outcome of the patient's treatment. It is equally important that the clinical, as well as the physical and technical aspects of patient treatment are adequate. Consequently, a comprehensive audit methodology was developed by the IAEA (IAEA 2007 a) within the framework of the Quality Assurance Team for Radiation Oncology (QUATRO). QUATRO audits involve assessment of radiotherapy infrastructure, including patient-related aspects and equipment-related procedures, together with radiation safety and patient protection, where appropriate. Staffing levels and professional training programmes for radiation oncologists, medical radiation physicists and radiation therapists are also reviewed.

Since 2005, the IAEA has organized more than 30 QUATRO audits in response to requests from radiotherapy centres from all over the world. Most audits took place in Central and Eastern European countries. These audits included assessment of the ability of centres to maintain their radiotherapy practice at the level corresponding to the best clinical practice in the economic circumstances of a given country.



During the process of QUATRO audits, inadequacies in infrastructure, equipment, human resources and procedures are identified at the audited centres and areas for improvement are documented. Some centres have been acknowledged for their operation at a high level of competence, while others received comprehensive set of recommendations for needed improvements. Based on the audit results, it was also possible for the IAEA to identify common issues and items needing improvement and to address them internationally. An example of this is the training of radiation therapists in Central and Eastern Europe, now being implemented through the IAEA's cooperation with the European Society for Therapeutic Radiology and Oncology (ESTRO).

## Conclusion

Radiation oncology requires a strong commitment to quality assurance, including active participation of all staff directly involved in the radiotherapy process together with supporting specialists. The establishment of regular audit system enables continuous improvement through assessment and implementation of planned and systematic actions necessary to provide sufficient assurances that the radiation treatment satisfies quality requirements.

In particular, dosimetry audits have proven to be a useful tool for the improvement of dosimetry practices worldwide. It is of importance for all radiotherapy centres to have access to long-term dosimetry auditing programmes, particularly when installing new equipment and implementing new procedures. ■

## References

- AGUIRRE J.F., TAILOR R., IBBOTT G., STOVALL M., HANSON W., 2002, Thermoluminescence dosimetry as a tool for the remote verification of output for radiotherapy beams: 25 years of experience, Proc. Int. Symp. Standards and Codes of Practice in Med. Rad. Dosim., IAEA-CN-96/82, Vienna: IAEA: 191-99
- EURATOM DIRECTIVE 97/43, 1997, On health protection of individuals against the dangers of ionising radiation in relation to medical exposures. Official Journal Of The European Communities no L180: 22
- GERSHKOVITCH E., SCHMIDT R., VELEZ G., et al., 2008, Dosimetric Verification of Radiotherapy Treatment Planning Systems: Results of IAEA Pilot Study, Radioth. Oncol., 89: 338-346
- IAEA, 2007 a, Comprehensive Audits of Radiotherapy Practices: A Tool for Quality Improvement, Quality Assurance Team for Radiation Oncology (QUATRO), Vienna: IAEA
- IAEA, 2007 b, On-Site Visits to Radiotherapy Centres: Medical Physics Procedures, Quality Assurance Team For Radiation Oncology (QUATRO), TECDOC 1543, Vienna: IAEA
- IZEWSKA J., SVENSSON H., IBBOTT G., 2002 a, Worldwide Quality Assurance Networks for Radiotherapy Dosimetry, Proc. Int. Symp. Standards and Codes of Practice in Med. Rad. Dosim. IAEA-CN-96/76, 139-156, Vienna: IAEA
- IZEWSKA J. AND THWAITES D.I., 2002 b, IAEA Supported National Thermoluminescence Dosimetry Audit Networks for Radiotherapy Dosimetry, Proc. Int. Symp. Standards and Codes of Practice in Med. Rad. Dosim, IAEA-CN-96/137: 249-268 Vienna: IAEA
- IZEWSKA J., ANDREO P., VATNITSKY S., SHORTT K.R., 2003, The IAEA/WHO TLD Postal Dose Quality Audits for Radiotherapy: A Perspective of Dosimetry Practices at Hospitals in Developing Countries, Radioth. Oncol. 69: 91-97
- MOLINEU A., FOLLOWILL D.S., BALTER P.A., et al., 2005, Design and Implementation of an Anthropomorphic Quality Assurance Phantom for Intensity-Modulated Radiation Therapy for the Radiation Therapy Oncology Group, Int. J. Rad. Onc. Biol. Phys. 63 (2): 577-583
- ROUE A., VAN DAM J., DUTREIX A., SVENSSON H., 2004, The EQUAL- ESTRO External Quality Control Laboratory in France, Cancer Radiother. 8, Suppl 1: 44-49

## Equal-Estro: a dosimetry laboratory keeping pace with modernisation in radiotherapy

by Attila Veres, Equal-Estro Laboratory, Villejuif (France)

Quality Assurance (QA) in radiotherapy has always been recognised as a crucial factor in guaranteeing the necessary degree of dosimetric accuracy and optimum treatment results [1, 2]. Verification results acquired over the past ten years demonstrate the significant role played by the Quality Control (QC) programme proposed by Equal-Estro for quality assurance in external radiotherapy systems [3].

The Equal programme began with the use of thermoluminescent dosimeters (TLDs) for the purpose of dose verification for external radiotherapy units. This quality assurance service was then extended to include brachytherapy [4, 5].

Recent advances in therapeutic irradiation methods have spurred Equal-Estro to commit itself even further to keep pace with progress [6]. New dosimetry methods are now available or being developed. These are based on film dosimetry or the use of special solid TLDs. These techniques have already been adopted for the dosimetry audit on accelerators using the IMRT technique and TomoTherapy systems and are being developed for CyberKnife® machines.

The dosimetric verification of small X-ray beams, which is potentially capable of performing dose measurements on beams as small as 3 mm [6], and the verification of proton beams are the latest challenges that Equal-Estro intends to tackle.

### Verification of radiotherapy systems using the postal TLD method

The Equal-Estro laboratory uses a dosimetry method first developed at the Gustave Roussy Institute in Villejuif [1, 2, 7-10]. After being irradiated at radiotherapy centres, dosimeters are returned to the Equal-Estro laboratory where they are read. The laboratory uses lithium fluoride (LiF) powder as a TL material.

Thermoluminescent dosimetry is a relative dose measurement method in which the dose is determined by comparing the signal from a given dosimeter with that of a reference dosimeter. The reference dosimeter must therefore be irradiated under reference conditions and with the highest degree of accuracy [11].

Intercomparison tests are performed by similar national and international laboratories on a regular basis to guarantee the traceability of the metrological references used at Equal-Estro [12]. The tests are two-way tests: dosimeters are irradiated by Equal and read by the participating laboratory and dosimeters irradiated by the participating laboratory are read by Equal. The relative standard deviation is below 1% for all results to date and whatever the case considered (Fig. 2.1 & 2.2).

### Verification of conventional external radiotherapy systems

Acceptability criteria, determined as a function of the observed dose deviation ( $\delta$ ), are as follows:

- if  $0\% < |\delta| \leq 5\%$ , the results are within the tolerance range;
- if  $5\% < |\delta| \leq 10\%$ , the results are outside the tolerance range;
- if  $|\delta| > 10\%$ , the results have reached emergency level.

In the second and third case, repeat checks are mandatory. Use of the machine concerned by the third case must be suspended

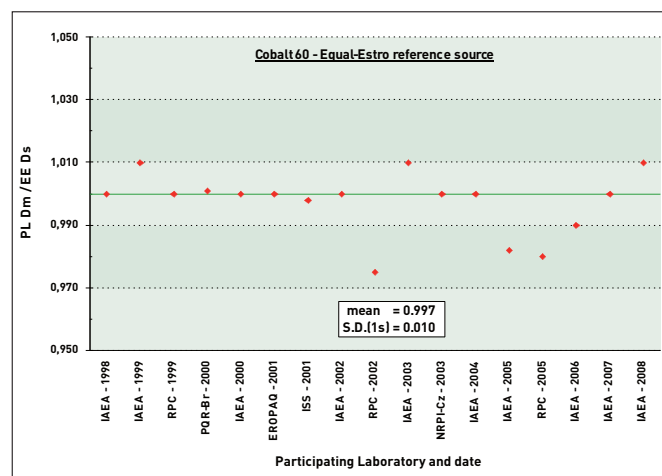


Figure 2.1: results of comparisons between the Equal-Estro dosimetry laboratory and other national and international dosimetry laboratories. The TLDs were irradiated by Equal-Estro and read by participating laboratories

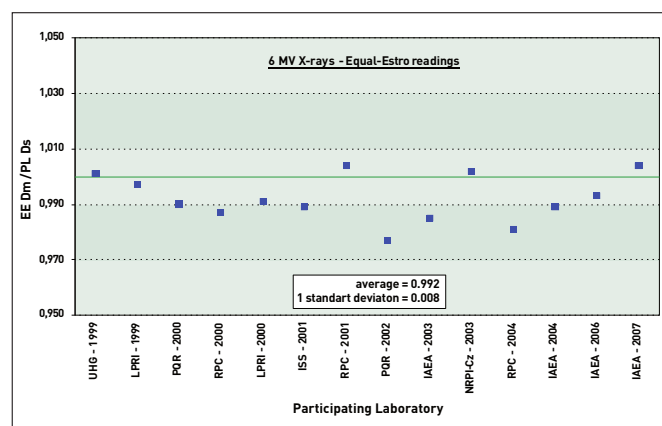


Figure 2.2: results of comparisons between the Equal-Estro dosimetry laboratory and other national and international dosimetry laboratories. The TLDs were irradiated by participating laboratories using a 6 MV photon beam then read by Equal-Estro

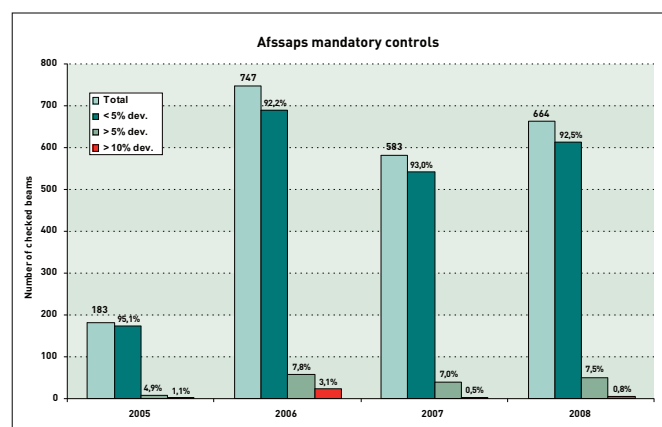


Figure 2.3: results of dosimetry tests performed by the Equal-Estro laboratory in France since external dosimetry audits became mandatory (2004). The total number of beams checked (photon and electron beams) is shown for each year



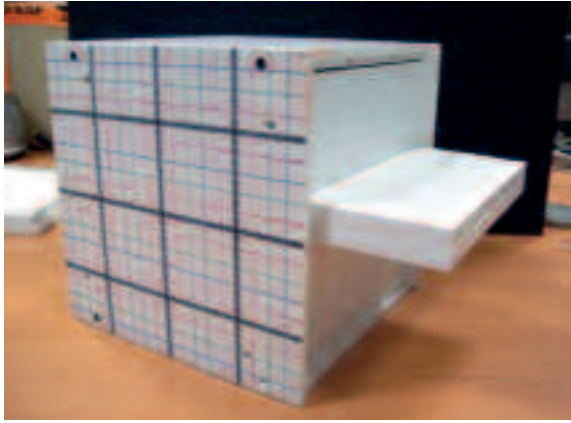


Figure 3.1: EasyCube® phantom

and may only be resumed when measurement results meet acceptability criteria.

Between the date on which external dosimetry auditing became mandatory in France (2004) [13, 14] and the end of 2008, a total of 2,177 high-energy photon and electron beams were tested, in accordance with the AFSSAPS decision. Of this total, 92.7% of beams were within the tolerance range and 7.3% were outside it. All the beams that had reached the emergency level (1.5% of all beams checked) passed the tests after a second or third verification (Fig. 2.3).

Most of the deviations observed concerning external radiotherapy units were due to TLD positioning errors during irradiation at the centre. Some, however, were due to the wrong data being used in treatment planning systems (TPS).

#### Verification of brachytherapy systems

The dose deviation classification method used for brachytherapy systems is similar to that used for external beam auditing:

- $|\delta| \leq \pm 5\%$ : optimum level;
- $5\% < |\delta| \leq 7\%$ : tolerance level;
- $7\% < |\delta| \leq \pm 10\%$ : outside the tolerance range;
- $|\delta| > 10\%$ : emergency level.

The upper tolerance threshold is higher in brachytherapy owing to the greater uncertainty in measurement results [4, 5].

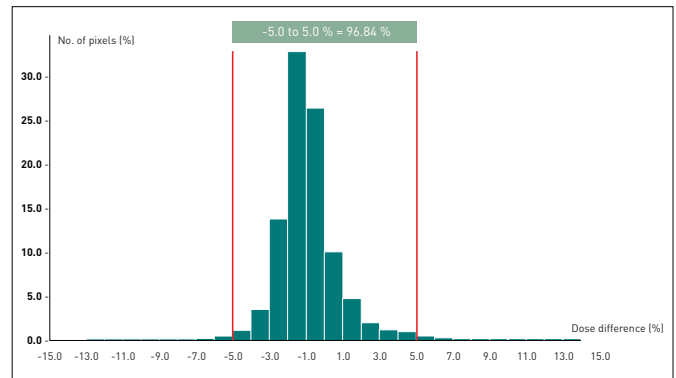


Figure 3.3: histogram showing dose difference with acceptability limits

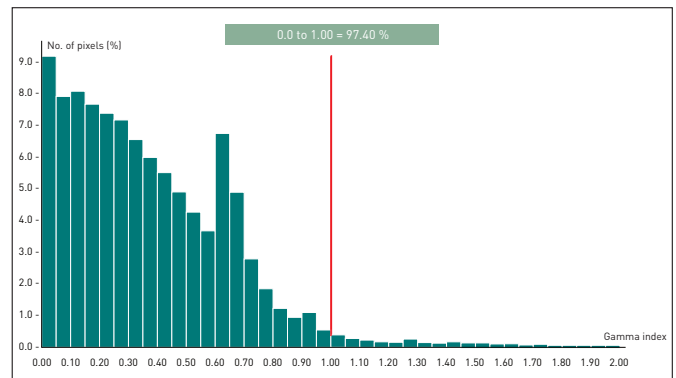


Figure 3.4: histogram of gamma index

#### Film dosimetry

Dose distribution is a very important factor in dosimetry verification for systems used for special treatment techniques like intensity-modulated radiation therapy (IMRT) or tomotherapy. In this respect, film dosimetry remains one of the most accurate tools for performing external dosimetry audits. In some cases, it may be useful or necessary to combine film measurements with TLD measurements.

#### Verification of IMRT and tomotherapy systems

Both types of system are verified in exactly the same way. Dosimetric films are placed in an EasyCube® plastic-water

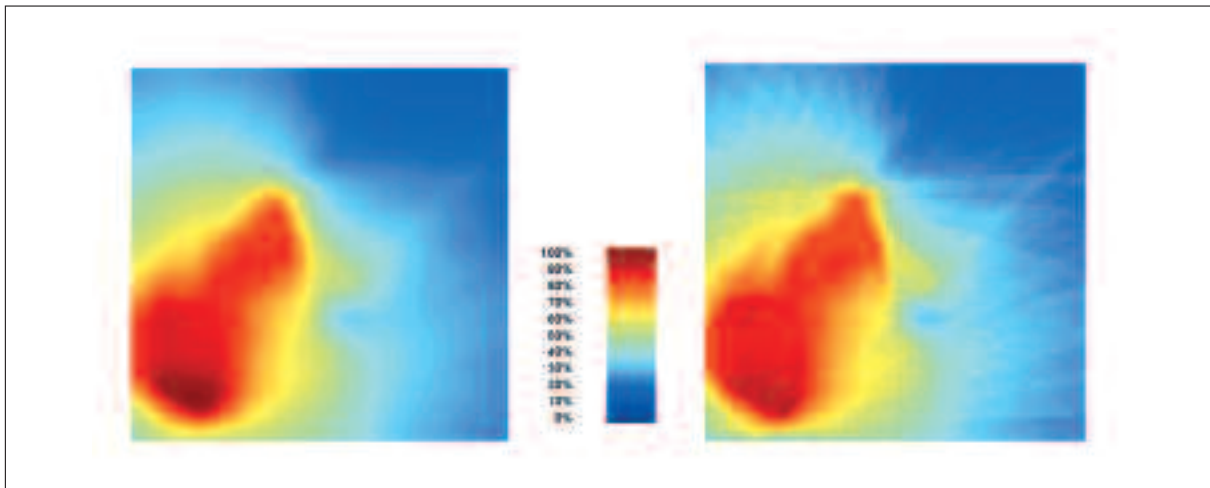


Figure 3.2: film image on the right; computed image (TPS) on the left

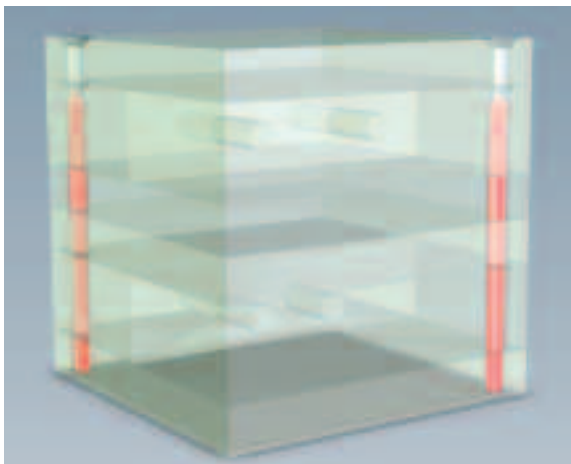


Figure 3.5: TL dosimeters

equivalent phantom (Fig. 3.1), which is then irradiated on the machine to be verified. Irradiation is carried out using a real patient's treatment plan and applying it to the scanned images of the phantom.

TL dosimeter tubes are used to check the reference dose of the machine by taking measurements in water or in water-equivalent phantoms.

The control of dose distribution with films is done using Gafchromic® films which are irradiated then compared with the dose distribution computed by the TPS. A software program capable of processing TPS data and scanned images of the films (Fig. 3.2) is used to perform this comparison. This means that two images (one computed and one measured) are compared in terms of dose difference (Fig. 3.3.) and gamma index (Fig. 3.4.).

The acceptability criteria for IMRT and tomotherapy systems are as follows:

- dose distribution: deviations of more than 5% above the planned dose are tolerated on no more than 10% of the area of the irradiated films;
- deviations in dose measurements obtained by TLD must be within the 0-5% range.

#### *Verification of Cyberknife and proton beam systems*

A method for verifying Cyberknife systems is being developed in collaboration with the radiotherapy centres of Lille (Centre Oscar

Lambret), Nancy (Centre Alexis Vautrin) and Nice (Centre Antoine Lacassagne).

Equal-Estro has designed a new plastic phantom that fits the anthropomorphic phantom commonly used for dosimetry on these machines. The phantom is designed to allow dosimetry films and TL dosimeters to be irradiated at the same time (Fig. 3.5.). The films are used to verify the dose distribution on various planes of the irradiated volumes, while the four TLDs are positioned so that certain dosimeters receive a maximum dose, imposing a minimum dose on the others.

Preliminary tests are underway.

We are working with the Orsay Proton Therapy Centre to develop a dosimetric verification method for proton beams. Dosimetric film is the tool used but simultaneous or parallel use of TL dosimeters is being considered.

#### **Dosimetric verification of small beams**

Some radiotherapy methods involve the use of very small beams shaped by micro-multileaf collimators. In view of the particular dosimetric problems related to the use of this type of beam, centres should apply for dosimetric verification with regular external audits.

Based on our experience, the working group set up for this purpose has suggested using TLDs specially adapted for this type of method. Irradiation will be carried out using plastic phantoms similar to those used in film dosimetry and each dosimeter (in the form of a chip) will be enclosed in a mini-phantom (Fig. 4.1).

In addition to TLD characterisation work (for repeatability, etc.), the initial dosimetry checks based on comparisons with ionisation chambers are in progress and a comprehensive dosimetry audit methodology is being prepared. Repeatability tests have so far allowed us to identify which dosimeters produce a consistent signal over a series of readings when irradiated with the same dose (Fig. 4.2).

This service will soon be available to radiotherapy centres interested in validating the use of this type of beam.

#### **Conclusion**

The postal TLD method used by the Equal-Estro laboratory for auditing radiotherapy systems is subject to constant evaluation under a quality assurance programme that includes national and international intercomparisons.

Dose distribution tests using films are a good way of checking treatment plan quality on IMRT machines. This type of check is already among the services offered by Equal-Estro.

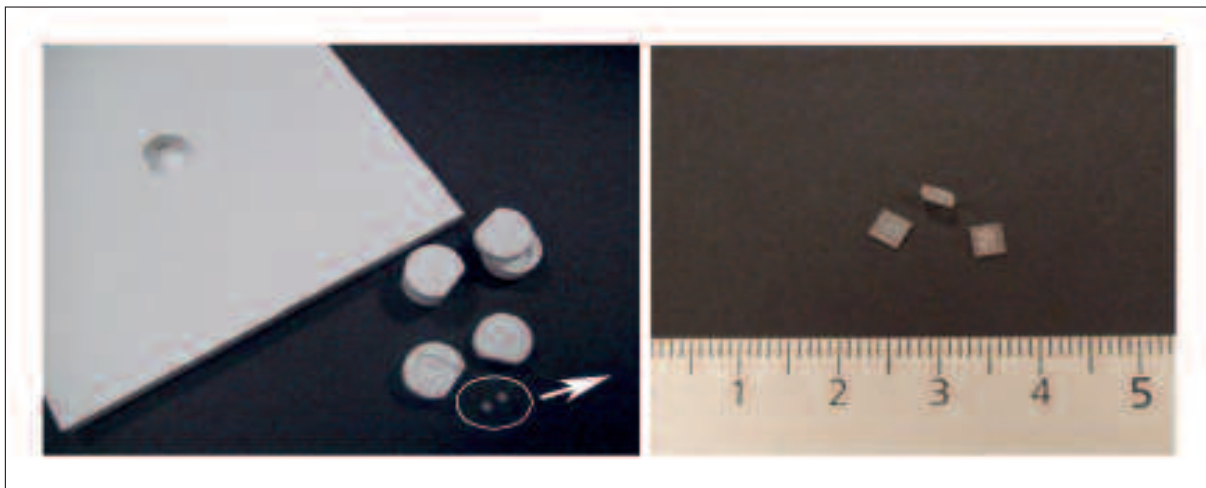


Figure 4.1: TLD chips and their mini-phantoms



Tests on doses delivered using small beams or photon beams will soon be available to the centres concerned

The main purpose of quality assurance in radiotherapy is to prevent any major deviations between the prescribed dose and the dose delivered by treatment systems, thereby lowering the risk of radiotherapy accidents. ■

- [1] A. DUTREIX, E. VAN DER SCHUEREN, S. DEREUMAUX, J. CHAUDAUD, *Preliminary results of a quality assurance network for radiotherapy centres in Europe*. Radioth. Oncol., 1993, Vol 29, pp 97-101.
- [2] I. H. FERREIRA, A. DUTREIX, A. BRIDIER, J. CHAUDAUD and H. SVENSSON. *The ESTRO-QUALity assurance network (EQUAL)*. Radioth. Oncol., 2000, Vol. 55, : pp 273-284.
- [3] A. VERES, A. ROUE, I. FERREIRA, A. BRIDIER, J. CHAUDAUD, H. SVENSSON and A. DUTREIX. *EQUAL - Ten years of dosimetry audits in radiotherapy*. Proceedings of the 14th International Congress of Metrology, Paris - France, June 22-25, 2009.
- [4] A. ROUÉ, J.L.M. VENSELAAR, I.H. FERREIRA, A. BRIDIER and J. VAN DAM, *Development of a TLD mailed system for remote dosimetry audit for 192Ir HDR and PDR sources*. Radioth. Oncol., Vol. 83, 2007, pp. 86-93.
- [5] A. ROUÉ, I.H. FERREIRA, J. VAN DAM, H. SVENSSON and J.L.M. VENSELAAR, *The EQUAL-ESTRO audit on geometric reconstruction techniques in brachytherapy*. Radioth. Oncol., Vol. 78, 2006, pp. 78-83.
- [6] A. VERES, A. BRIDIER, N. CAUSSE, I. FERREIRA, A. LISBONA and M. TOMSEJ, *Implémentation d'un audit dosimétrique externe postal pour les faisceaux délimités par les collimateurs micro-multilames: Méthodologie et résultats préliminaires*. Poster - SFPM (French Medical Physicists Society) Scientific days, Marseille 2008.
- [7] A. DUTREIX, S. DERREUMAUX, J. CHAUDAUD, E. VAN DER SCHUEREN, *Quality control of radiotherapy centres in Europe: beam calibration*, Radioth. Oncol., Vol. 32, 1994, pp 256-264.
- [8] S. DERREUMAUX, J. CHAUDAUD, A. BRIDIER, V. ROSSETTI, A. DUTREIX. *A european quality assurance network for radiotherapy: dose measurements procedure*. Phys. Med. Biol., Vol 40, pp 1131-1209. 1995.

- [9] I. H. FERREIRA, A. DUTREIX, A. BRIDIER, D. MARRE, J. CHAUDAUD, and H. SVENSSON. *THE ESTRO EQUAL results for phantom and electron beams checks in European Radiotherapy beams*. The International Conference on Radiological Protection of Patients in Diagnostic and Interventional Radiology, Nuclear Medicine and Radiotherapy, Malaga 26-30 March 2001. IAEA - CN-85-48, 2001, pp 625-630.
- [10] D. MARRE, I. H. FERREIRA, A. BRIDIER, A. BJÖRELAND, H. SVENSSON, A. DUTREIX, J. CHAUDAUD. Energy correction factors of LiF powder TLD irradiated in high energy electron beams and applied to mailed dosimetry for quality assurance networks. *Phys. Med. Biol.*, Vol 44, 2001, pp 3657-3674.
- [11] A. BRIDIER, I.H. FERREIRA, A. BEAUDRE, C. DAGNEAUX and J. CHAUDAUD, *Tracabilité des références métrologiques en dose absorbée dans l'eau dans le cadre d'un réseau européen de contrôle de qualité en radiothérapie externe - Expérience de l'IGR*, Proceedings of the 10th International Congress of Metrology, BNM, Saint Louis - France, October 22-25, 2001.
- [12] J. IZEWSKA, P. ANDREO, *The IAEA/WHO postal programme for radiotherapy hospitals*, *Radioth. Oncol.*, Vol. 54, 2000, pp 65-72.
- [13] Décision AFSSAPS, *Décision du 2 mars 2004 fixant les modalités du contrôle de qualité externe des installations de radiothérapie externe*, JORF n° 94 du 21 avril 2004.
- [14] Décision AFSSAPS, *Décision du 27 juillet 2007 modifiant la décision du 2 mars 2004 fixant les modalités du contrôle de qualité externe des installations de radiothérapie externe*, JORF n° 187 du 14 août 2007.

## The Norwegian Program on Quality Assurance in Radiotherapy (KVIST) – Organisation, Benefits and Experiences of this initiative for stakeholder's involvement

by Hilde Merete Olerud, Norwegian Radiation Protection Authority, Institute of physics, Biophysics group, University of Oslo, Sverre Levernes, Taran Paulsen Hellebust, Norwegian Radiation Protection Authority, Oslo University Hospital – DNR, Montebello, I.E. Heikkela, Norwegian Radiation Protection Authority, Dag C. Johannessen, Norwegian Radiation Protection Authority, Oslo University Hospital, Hans Bjerke, Norwegian Radiation Protection Authority, B.L. Rekstad, Oslo University Hospital, E. Sundqvist, Radiography Programme, Faculty of Health Sciences, University College, Oslo, Gunilla Frykholm, Norwegian Radiation Protection Authority, Oslo University Hospital, St.Olav University Hospital (Norway)

### NRPA as authority and professional body responsible for QA and audit

The Norwegian radiation protection regulation [1] is founded on the basic recommendations of the International Commission on Radiological Protection (ICRP), and even though Norway is not an EU member, the relevant EURATOM directives are reasonably well implemented in the RP legislation. NRPA has the authorization to ask for information about the annual number of treatments and diagnostic examinations carried out in various medical areas and has made regular assessments of the use of both radiotherapy, nuclear medicine and diagnostic radiology in order to explore trends in the use of different modalities, looking for possible regional variations and the effects from the introduction of new technology or procedures. NRPA has a central administration located in the Oslo area, and a staff about 100 people in total. Radiotherapy centres need a certain authorisation, as well as nuclear medicine and advanced X-ray departments do, while dentists and simple use of X-ray in primary health care only are object to notification. NRPA do inspections to the licensees on various periodicities, according to a risk based judgment.

In addition to NRPA's administration of the RP legislation, we also have certain duties as professional body within radiation dosimetry, quality assurance and audits. In the nineties, the capacity in

radiotherapy was considered to be low in Norway. It was also revealed some serious incidents in treatments of breast cancers. According to the national cancer strategy, the number of radiotherapy centres has been doubled since then. Furthermore, NRPA was asked to develop a national quality assurance programme in radiotherapy (acronym KVIST). The population of 4.8 million people now has a good accessibility to RT. Norway has a centralized public founded health care system, with 26 public hospital trusts and 72 hospitals. Radiotherapy is performed in 10 RT centres holding 40 linear accelerators in total. Co-60 sources are no longer in use in Norway for external therapy. All RT centres have external radiotherapy, four departments provide brachytherapy. All RT centres have conventional simulators and dedicated computed tomography (CT) for treatment planning. Three of the departments also have a dedicated MR scanner.

### Method: Organisation of quality assurance and clinical audits in radiotherapy

The central part of the QA program at NRPA is a group called KVIST, organized in the section for quality assurance in radiology to sort it from NRPA's authority functions. A national reference group with representatives from all radiotherapy centers is established as a formal link to the RT centers. Working Groups are defined and prioritised to solve certain tasks. The work is based on active cooperation of specialists from all centers aiming at national consensus for the resulting reports and guidelines. This model shortens the distance between different professional communities and challenges them to define "good medical practice". The costs for the KVIST initiative are shared between the NRPA and the radiotherapy centres, i.e. NRPA hosts the meetings and covers travel expenses for all participants, while the RT centres covers the personnel costs.

The KVIST group at NRPA:

- Is multidisciplinary (oncologists, medical physicists, radiation technologists)
- Consists of part time employees shared with different radiotherapy departments
- Acts as secretariat and coordinates the Working Groups for all types of QA projects within radiotherapy
- Secures close cooperation between the radiotherapy community and national public bodies

### Results: Outcome of the KVIST initiative

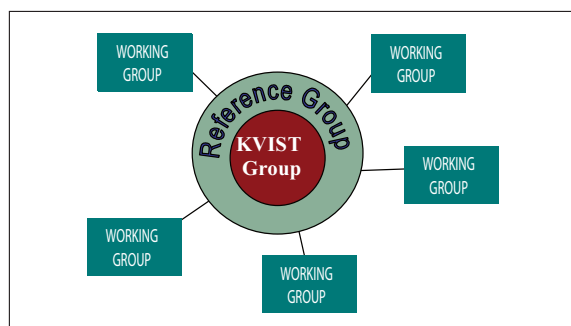
The KVIST initiative has been a driving force in improving the quality of radiation treatment of cancer patients on a national basis, and has caused a range of harmonised national recommendations. This is achieved through a wide range of activities [2, 3], in summary:

#### *External dosimetry audits at all radiotherapy centers in Norway*

In close collaboration with NRPA's secondary standard dosimetry laboratory (SSDL), external dosimetry audits were performed in 2004 after the implementation of the IAEA dosimetric protocol (TRS 398) [4], and again in 2008 including the use of radiochromatic films [5]. KVIST also provides two phantoms for quality control of the non-dosimetric information exchange between different data systems in the radiotherapy chain [6].

#### *Patterns of care data, available equipment, staff and QA routines*

Since 2001 all radiotherapy centres are annually reporting patterns of care data together with data about personnel, equipment and QA routines, according to thoroughly discussed and well agreed parameters [7]. This will for example involve the definition of a "linear accelerator equivalent", LAE= 1 standard linac, staffed with 4 RT technologists, used 7.5 hours per day. While the number of Linacs was increased from 26 to 38 between 2001 and



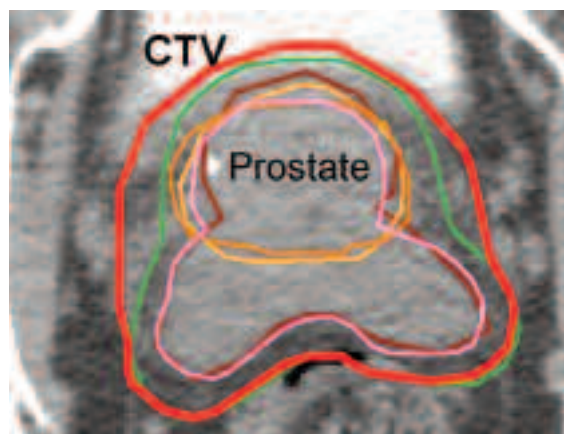
The organisation of the KVIST initiative: the reference group and all WG's have representation from all disciplines and centres



2008, the LAE increased from 24.9 to 35.0. We also count both man-labour year and number of persons employed of various professions, normalized to LAE. The key figures for the number of treatments are defined as the number of "new patients" (patients never been treated before), "patients" (patients who started treatment that year), "cases" (treatments against a volume), "patient attendances" (fractions) and "field exposures". The KVIST group processes such data and presents them in special reports. A password protected web based solution for reporting and presentation has been developed serving the national reference group, the working groups, the RT departments, the medical society and the health authorities (<http://kvist.nrpa.no/Main/Default.aspx>). The data is used for comparison and discussions about quality and production, resource allocation and hospital administration.

## National system for incident handling and reporting

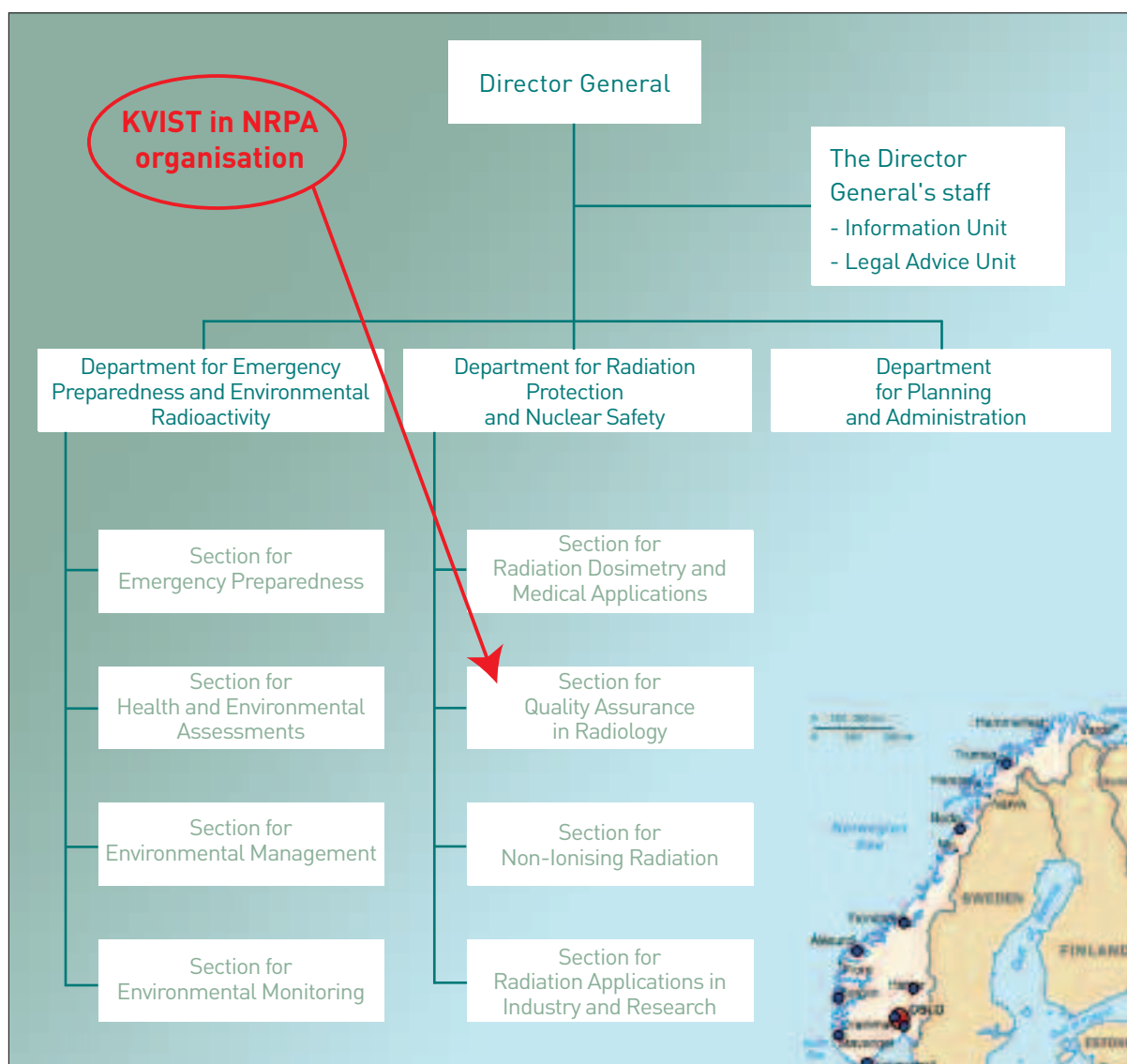
A unified system for classification and coding of incidents and accidents in radiotherapy has been worked out in close cooperation with the clinics [8], and implemented as a part of the hospitals quality system. Local groups are established to act on problems, do internal audits and learn from mistakes. Condensed statistics of more serious errors are sent to KVIST annually to give a national overview and report to international organizations like IAEA.



KVIST work-shop in 2007: the target volume in terms of "clinical target volume" (CTV) delineated at six different RT centres in Norway

## The Norwegian Radiotherapy Meeting and workshop for comparing treatment plans

A post-qualifying educational system for medical physicists with calculus exercises has been developed [9]. Furthermore, KVIST has established the Norwegian Radiotherapy Meeting, an annual



The Norwegian Radiation Protection Authority (NRPA)'s organisation. The map shows NRPA (red dot) and the ten radiotherapy centres in Norway (blue dots).

meeting where oncologists, RT technologists and physicists meet to discuss radiotherapy related issues. Workshops dedicated specific cancer diagnoses are also arranged as part of these meetings. Selected clinical cases are anonymised and distributed to all radiotherapy centers telling them to work out a complete treatment plan according to local guidelines. The resulting plans are collocated by KVIST and results are discussed in the workshops [10].

## *Clinical guidelines and audits in radiotherapy*

The target volume definitions were harmonized in 2003 [11], and will be revised in 2009 according to the new ICRU report. These are important elements in the national guidelines for radiotherapy that have been drafted in cooperation with national professional groups for different diagnoses. Guidelines have been worked out for lung, prostate and gastrointestinal cancers, more are in the pipeline. This work is part of a larger program for national guidelines for cancer care. The guidelines shall reflect good medical practice, they are a reference for clinical audits, and will

be revised regularly based on new knowledge and techniques. A system for clinical audits was developed and tested on the treatment of bone metastases in 2003–04 [12], and for treatment of breast cancer in 2008–09. Furthermore, a common radiotherapy prescription form with necessary parameters for radiotherapy is published, to be used as a tool to register intended treatment [13]. This report will also be used for future audits.

## **Conclusion**

The KVIST initiative is now a well established national QA program in RT. It is an example of stakeholder involvement and collaboration between a governmental body, health professions and health providers. The fact that members of the KVIST group are part time employed in both hospital and governmental body facilitates the objective. The work is partly performed by the radiotherapy community itself, thus creating an atmosphere of ownership. The KVIST group secures funding, accomplishment and regularity of the work. ■

## **References**

1. Regulations no. 1362 of 21 November 2003 on radiation protection and use of radiation. Oslo: Ministry of Health, 2003. [www.nrpa.no/archive/Internett/Publikasjoner/Annet/act\\_eng.pdf](http://www.nrpa.no/archive/Internett/Publikasjoner/Annet/act_eng.pdf) [10.02.2002]
2. NRPA bulletin 8:2008 "Quality Assurance in Radiotherapy – eight years outcome" Østerås: Norwegian Radiation Protection Authority (2008) [www.nrpa.no](http://www.nrpa.no) [Publications]
3. Lervenes S., Hellebust T.P., Heikkilä I.E., Johannessen D.C., Frykholm G., Bjerke H., Rekstad B.L., Sundqvist E., Olerud H.M. The Norwegian Program on Quality Assurance in Radiotherapy (KVIST) – Organisation, Benefits and Experiences During Seven Years. In: Book of abstracts (no 49). International Workshop on Clinical Audit, Tampere 7-10 September 2008. Helsinki: STUK, 2008.
4. Bjerke Hans. Dosimetry in Norwegian radiotherapy. Implementation of the absorbed dose to water standard and code of practice in Norway. StrålevernRapport 2003:11. Østerås: Norwegian Radiation Protection Authority, 2003.
5. Mauring Alexander. Dosimetric control with radiochromic film: Results and analysis from 10 radiotherapy hospitals in Norway. StrålevernRapport 2009:10. Østerås: Norwegian Radiation Protection Authority, 2009. Language: Norwegian.
6. Klebo Espe I. Quality control of non- dosimetric parameters in CT-based treatment planning in radiotherapy. StrålevernRapport 2006: 13. Østerås: Norwegian Radiation Protection Authority, 2006. Language: Norwegian.
7. Lervenes S., Hellebust T.P., Johannessen D.C., Espe I.K. Activity reporting for radiotherapy in Norway 2003-2004. StrålevernRapport 2006:11. Østerås: Norwegian Radiation Protection Authority, 2006. Language: Norwegian.
8. Lervenes S., Johannessen D.C. Incident handling at Norwegian radiotherapy centres. StrålevernRapport 2006:3. Østerås: Norwegian Radiation Protection Authority, 2006. Language: Norwegian.
9. Hellebust T.P., Frengen J., Heggdal J., Knutsen B.H., Klebo Espe I., Rekstad B. Guidelines for training of medical physicists in radiotherapy in Norway. StrålevernRapport 2005:6. Østerås: Norwegian Radiation Protection Authority, 2005. Language: Norwegian.
10. Rekstad B.L., Lervenes S., Heikkilä I.E., Johannessen D.C., Sundqvist E., Bjerke H., Hellebust T.P., Olerud H.M., Frykholm G. Norwegian Experiences with Workshop as a Clinical Audit Tool for Radiotherapy of Specific Cancer Diagnoses. In: Book of abstracts (no 42). International Workshop on Clinical Audit, Tampere 7-10 September 2008. Helsinki: STUK, 2008.
11. Lervenes S., Johannessen D.C. Volumes and doses for radiotherapy. Definitions, guidelines for usage, documentation and reporting. StrålevernRapport 2003:12. Østerås: Norwegian Radiation Protection Authority, 2003. Language: Norwegian.
12. Johannessen D.C., Hellebust T.P., Bremnes R., Bergersen V., Tausjø J., Bruland Ø. A pilot study on clinical audit in radiotherapy. StrålevernRapport 2004:9. Østerås: Statens strålevern, 2004.
13. Heikkilä I.E. High energy radiotherapy requisition – planning aim and treatment prescription. StrålevernRapport 2009:12. Østerås: Norwegian Radiation Protection Authority, 2009. Language: Norwegian



## Clinical? Audits; who should control what? – european guidelines

by Järvinen Hannu, M.Sc. (Eng), Principal Advisor (for Radiation in Health Care), Radiation and Nuclear Safety Authority (STUK), Radiation Practices Regulation – Helsinki (Finland)

### Clinical audit and the European Guideline

The concept of *clinical audit* is not a new one but has long been applied in many health care practices. In the European Commission (EC) directive 97/43/EURATOM (MED) [European Commission, 1997], this concept has been introduced for the assessment of medical radiological practices. Simultaneously with the European development, the IAEA has developed comprehensive audit programmes under the term of clinical audit [IAEA 2007; 2009]. Further, several dosimetry or quality audit programmes traditionally applied in the field of radiotherapy (e.g. by the IAEA [Izewska et al. 2004] or the ESTRO [Ferreira et al. 2000]) have been recognized to form an important part of clinical audit.

In Europe, the EU Member States are required to implement clinical audits "in accordance with national procedures" (Article 6.4 of the MED). Despite the very precise definition of Clinical audit in the MED, a questionnaire to the Member States has revealed that there is a high diversity of approaches to clinical auditing and the lack of practical implementation in several Member States. While in some countries a systematic approach to clinical audit has been established (e.g. in UK, Germany, France and Finland), in most countries clinical audits have been only occasional or have not been implemented in practice. Several problems have also been identified, such as poor understanding of the purpose of clinical audits, lack of criteria for the standards of good practices and practical problems such as financing of audit work. In some countries, clinical audit seemed to be confused with internal quality assurance programmes or external assessments such as accreditations and regulatory inspections.

For these reasons, the EC conducted in 2007-2008 a special project to prepare further guidance on the principles of clinical audit and its practical implementation. Before submission to the EC, the draft Guideline was subjected to critical reviews by major scientific professional organizations (including ESTRO) and further introduced and discussed in an international Workshop. The published EC guideline [European Commission, 2009] provides a general framework for the Member States in order to establish sustainable national systems of clinical auditing of all radiological practices (diagnostic radiology, nuclear medicine and radiotherapy). It is sufficiently flexible and will enable the Member States to adopt the model of clinical audit with respect to their national legislation and administrative provisions.

The EC Guideline introduces the basic principles of clinical audit (objectives, coverage, standards of good practice etc) aiming at clarifying its profound meaning and recommended application. It defines the topics which should be covered while the criteria of good practice are discussed only on generic levels. It discusses the interrelation of clinical audit with other audit systems such as certification of quality systems, accreditation, peer review and quality award, and also its interrelation with regulatory control. Finally, it gives general advice for the practical implementation

of audits, including organization of audits, recommendations for auditors, models of financing, national coordination and the role of scientific and/or professional societies and regulatory authorities.

It is important to recognize that the EC guideline is not a legal requirement. It will only give recommendations and highlight some possible "national procedures" as expected by the MED.

### Clinical audit in radiotherapy

#### General purpose

The MED-directive defined clinical audit as "a systematic examination or review of medical radiological procedures which seeks to improve the quality and the outcome of patient care, through structured review whereby radiological practices, procedures, and results are examined against agreed standards for good medical radiological procedures, with modifications of the practices where indicated and the application of new standards if necessary".

In the EC Guideline, the general purpose of any clinical audit is further described as to

- improve the quality of patients' care
- improve the effective use of resources
- enhance the provision and organization of clinical services
- further professional education and training

Based on these aims, clinical audits should yield multiple benefits to the health care system such as:

- improvement of practice
- recognition for quality and awareness of good practices
- recognition of outdated practice
- motivation of staff to increase quality
- improvement of local standards and adherence to national standards
- prevention against litigation
- improvement of communication within the institution,
- revealing weak points and
- promoting development of quality systems.

Radiotherapy is a complex procedure requiring a multidisciplinary approach from clinical and radiation oncologists, radiotherapy medical physicists, diagnostic radiologists and RTTs with interaction with other disciplines as appropriate, and many current developments are adding significantly to the complexity. Within this complex framework, clinical audit will be an important tool of quality improvement and can have a major impact on developing the practices in compliance with the most recent data on good treatment practices, as well as improving the safety and efficacy of treatments. Clinical audits will evaluate the current status of the radiotherapy department with respect to delivery of radiotherapy to patients and to identify areas for future improvement.

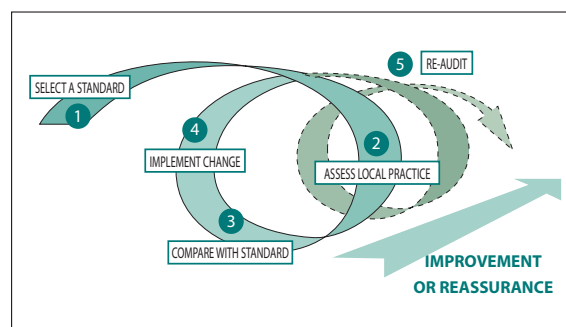


Figure 1: the audit cycle. Reprinted from Goodwin R., de Lacey G., Manhire A. (eds). *Clinical Audit in Radiology: 100+ recipes*, 1996 by permission of The Royal College of Radiologists.



Structure	<p>The mission of the unit for radiotherapy practices</p> <p>Lines of authorities and radiation safety responsibilities</p> <p>Staffing levels, competence and continuous professional development of staff, in particular for radiation protection</p> <p>Adequacy and quality of premises and equipment</p>
Process	<p>Justification and the referral process</p> <p>Availability and quality of treatment guidelines (protocols, procedures)</p> <p>Optimization procedures</p> <p>Procedures for dose delivery to the patient (beam calibrations, accuracy of dosimetry and treatment planning)</p> <p>Quality assurance and quality control programmes</p> <p>Emergency procedures for incidents in use of radiation</p> <p>Reliability of information transfer systems</p>
Outcome	Methods for the follow-up of outcome of treatments (short term and long term)

**Table 1: the priorities of clinical audit of radiotherapy practices**

## Coverage and priorities for radiotherapy practices

It is evident from the definition that clinical audit should be a multi-disciplinary and multi-professional activity [European Commission, 2009]. It should be a continuous activity for quality improvement (Fig 1). It should be carried out by competent experts with good experience in clinical practices. Both internal audits (auditors coming from inside a given health care unit) and external audits (auditors coming from outside the unit) should be implemented. These are of equal importance and should supplement each other. External audits are needed to remove possible "blindness" of internal experts to recognize weaknesses of own unit and to give more universal and broader perspectives.

Clinical audit should address the structure, process and outcome of the practices. For radiotherapy, the priorities should be as shown in Table 1. The main focus in radiotherapy should be an assessment of the overall performance of the radiotherapy department and how staff, equipment, procedures, outcomes, patient safety and comfort correspond to the aims and objectives of the department. Responsibilities and reporting structures within the department must be clearly defined. Clinical audit should also evaluate how the department interacts with external service providers. This will include relationships with referring clinics and clinicians, equipment providers, etc.

Clinical audits can be of various types and levels, either reviewing specific critical parts of the radiotherapy process (partial audit) or assessing the whole process (comprehensive audit). Audits can address various "depths" of the procedure, from generic features to details of a given treatment. The comprehensive clinical audit must include the full patient pathway from referral to follow up. All steps within this pathway are interlinked and interdependent. These include diagnosis, treatment decision, simulation, treatment planning, verification, treatment delivery, patient review during and at the end of treatment, and follow up. Dosimetry audit is an important example of partial audits and should be within the scope of a comprehensive clinical audit, as assured dosimetry is a vital component of accurate clinical practice.

The system of auditing inherently aims at improving the quality and safety of radiological procedures, thus minimizing the probability of adverse effects and incidents. In radiotherapy, the risk profile [WHO, 2000] calls for particular attention in the efforts of avoiding incidents due to their probable very serious consequences. Therefore, auditing the emergency preparedness and procedures will be of high value in the list of priorities for clinical audit.

For dosimetry and quality assurance of radiotherapy, at least the dose per monitor unit and associated parameters in external beam radiotherapy (also for IMRT fields) should be addressed,

and at least reference air kerma rate and geometric reconstruction in brachytherapy. At an advanced level of clinical audit, the treatment planning process, the correctness of input data, treatment delivery etc, should also be addressed.

It is appreciated that auditing the clinical *outcome* may be very difficult, in particular for external audits. In radiotherapy, the outcome includes the results both in terms of cancer status and in terms of the side effects of the treatment. For the former, this may be expressed in terms of cure with figures such as five years survival, disease free survival or local control. It may also be expressed in terms of symptom palliation or quality of life. With regard to toxicity assessment, outcomes can be expressed in terms of quality of life, specific toxicity scores including mortality, complication rates and interventions necessary to overcome complications. In is obvious from all this that the audits of outcome are often limited to auditing only the methods of follow-up and not its actual results.

Auditing the detailed practice for a given treatment can usually mean only a few selected treatment processes per audit run. Full details of the procedures should be assessed at least for the items of the procedure where a reasonable consensus on a good practice can be achieved for application as the criteria of assessment. Such items for a given treatment could be for example:

- adequacy of the evidence-based data available in the literature and the patient/tumour features which justify the treatment plan. Depending on the tumour type and clinical setting, good practice could include genetic or family history, clinical and pathological stage of tumour, tumour size and grade and performance status of patient;
- practices for dose prescription, specification of the target volume;
- achievement of normal tissue tolerance in dose planning;
- quality of the treatment delivery;
- follow-up practices (acute and late complications, recurrence): Adequacy of recorded data, follow-up model (frequency of examinations, clinical items, examination in a local health care unit or in a radiotherapy hospital, information flow etc), comparison of complication rates with expected.

## Aspects of practical organization

The practical organizing of external clinical audits can be through site visits of an audit team or, for a limited part of practices with relevant documented or measurable data, by mailed review and central analysis of the data. Besides the EC Guideline, comprehensive guidance for audit visits has been published by the IAEA [IAEA 2007]. The dosimetry audits by mailed thermoluminescent dosimeters are good examples of partial clinical audits with a limited scope [Izewska et al. 2004, Ferreira et al. 2000].



The standards of good practice should be derived from evidence based data, long term experience and knowledge gained. In practice, these can be adopted from legal requirements, results of research, consensus statements, recommendations by learned societies or local agreements (if there is no other more universal reference). However, in radiotherapy the consensus on good practices can often be difficult to achieve, in particular for the detailed clinical protocol of the treatment. The lack of confidence or clinical evidence can be the major reason for this, but a natural reason can also be the inevitable variation of local resources as for the availability and quality of necessary equipment and services. In such a situation, the criteria of good practice adopted should be regarded as giving only preliminary orientation, and the results of audit should then be used like a benchmarking tool to achieve improved evidence and possible adjustment of the chosen criteria.

## Who should control what?

In the jungle of the concepts of quality management, with diversity of approaches and procedures for trying to improve and maintain high quality, the meaning of concepts can easily be confused with each other and this has been particularly true for clinical audit. While it is obvious that clinical audit has some similarities with other quality assessments and controls, it is imperative not to confuse it with such activities as:

- research;
- quality control program for equipment;
- quality (system) audit to verify that the quality systems conform to a quality standard;
- accreditation;
- regulatory inspection nor any other regulatory activity.

The purpose of these other activities should be properly understood, and conversely to duplicating any efforts, clinical audits should be developed to supplement the other activities.

*Research* is a systematic investigation to increase the sum of our knowledge. For clinical audit, the aim of research is to determine what a good practice is, while audit itself should ask the question: "Are we actually following good practice?" The *quality control* of radiotherapy equipment aims at ensuring adequate performance characteristics and safe operation throughout the lifetime of the unit, and the responsibility for the checking lies solely on the health care organization, the user of the equipment or the practitioner. Any audit or external control does not remove or release this responsibility while, however, can give desirable confidence on the results of the quality control.

A quality system in conformance with international quality standards such as the ISO 9001 [ISO, 2000] is generally considered a

good basis for the overall quality management in a radiotherapy clinic. To ensure that the local quality system conforms to the specifications of the quality standard, certification by a certification body can be acquired by special quality (system) audits carried out regularly by quality system experts. These experts are usually not clinical experts and the assessment does not address the quality of the clinical practice but solely its conformance with the general quality rules. Conversely, in clinical audits, clinical experts concentrate on the evaluation of the conformance of the clinical practice to the agreed good practice.

The system of accreditation deals with the competence of the unit to perform certain practices, in accordance with given standards. This can become very close to the aims of clinical auditing, while usually the scope is narrower and limited to the definite standards. In radiotherapy, such standards are either very general or not very common and limit the applicability of accreditation in the sense of replacing the clinical audits.

Finally, a legislative and statutory framework is needed in each country to regulate the safety of facilities and activities, including medical use of radiation. The regulatory requirements will generally depend on the level of risk or complexity associated with the medical use, as determined by the regulatory body. In radiotherapy, the high risk profile justifies maximum regulatory efforts, including regulatory inspections. The purpose of such an inspection is to *verify* that various detailed requirements for radiation protection are being met. The methods of verification can include both documentary assessments and verification measurements. While the verification procedures can be partly similar to some clinical audit procedures, the basis of the review and the use of the results are quite different [European Commission, 2009] and clinical audits should not be confused with regulatory inspections.

## Conclusion

Clinical audit is a multi-disciplinary, multi-professional assessment of the radiotherapy practices for the improvement of the safety and quality of the practices. It should be a continuous activity whereby both internal and external audits are implemented. It should not be confused with other quality assessment or control activities such as regulatory inspections, accreditations or certifications of the quality system. The priorities include essential parts of the radiotherapy structure, process and outcome, such as the mission of the unit, quality assurance and dosimetry and methods of follow-up of treatments. The recent Guideline of clinical audit published by the European Commission gives guidance for clinical audit principles and practical implementation, and provides a general framework to establish a sustainable national system of clinical audits. ■

## Acknowledgements

The preparation of EC guideline reported in this article was financed by the European Commission (Contract N TREN/07/NUCL/S07.71512).

## References

- EUROPEAN COMMISSION. Council Directive 97/43/Euratom of 30 June 1997, on health protection of individuals against the dangers of ionizing radiation in relation to medical exposure, and repealing Directive 84/466/Euratom. Official Journal of the European Communities No L 180/22-27, 9.7.1997.
- EUROPEAN COMMISSION. "Guideline on Clinical Audit for Medical Radiological Practices [Diagnostic Radiology, Nuclear medicine and Radiotherapy]", to be published in EC Radiation Protection series, 2009, available from [http://ec.europa.eu/energy/nuclear/radiation\\_protection/publications\\_en.htm](http://ec.europa.eu/energy/nuclear/radiation_protection/publications_en.htm)
- FERREIRA I.H., DUTREIX A., BRIDIER A., CHAVALDRA J., SVENSSON H. The ESTRO-Quality assurance network (EQUAL). *Radiother. Oncol.* 2000; 55: 273-284.
- IAEA. Comprehensive Audits of Radiotherapy Practices: A Tool for Quality Improvement. Quality Assurance Team for Radiation Oncology (QUATRO). IAEA, Vienna 2007.
- IAEA. Guidelines for Clinical Audits of Diagnostic Radiology Practices: A Tool for Quality Improvement. IAEA, Vienna 2009.
- INTERNATIONAL STANDARDS ORGANISATION (ISO). Quality systems - Model for quality assurance in design, development, production, installation and servicing, ISO 9001:2000.
- IZEWSKA J., SVENSSON H., IBBOTT G. Worldwide quality assurance network for radiotherapy dosimetry, Standards and Codes of Practice in Medical Radiation Dosimetry (Proc. Int. Symp. Vienna, 2002), Vol. 2, IAEA, Vienna [2004], 139-155.
- International Atomic Energy Agency (IAEA). Guidelines for Clinical Audits of Diagnostic Radiology Practices: A Tool for Quality Improvement. IAEA, Vienna 2009.
- WHO. Radiotherapy risk profile. Technical Manual. WHO/IER/PSP/2008:12, WHO 2008.

## The ICRP take-home message

by **Pedro Ortiz-López, PhD<sup>1</sup>**, Chairman of the Task Group of the International Commission on Radiological Protection on Preventing Accidental Exposures from Newer External Beam Radiation Therapy Technologies – Madrid (Spain)

### Introducing new technologies

The decision to implement a new technology for radiation therapy should be based on a thorough evaluation of expected benefits rather than being driven by the technology itself. To ensure a safe implementation, a step-by-step approach should be followed.

### Lessons from conventional techniques that is applicable to new technologies

The following conclusion, drawn in the context of conventional radiation therapy, from publication ICRP No. 86 not only remains applicable but is even more critical for new technologies: “purchasing new equipment without a concomitant effort on education and training and on a programme of quality assurance is dangerous”.

### Staff training, availability and dedication

Major safety problems may arise from underestimating the staff resources required to implement and operate a new technology. Resources should be allocated so as to avoid substituting proper training with a short briefing or demonstration, from which important safety implications of new techniques cannot be fully appreciated.

Certain safety-critical tasks, such as calibration, beam characterization, complex treatment planning and pretreatment verification for intensity modulated radiotherapy, require a substantial increase in staff allocation. The reassessment of staff requirements, both in training and number of professionals, is essential when moving to new technologies.

### Safety awareness of responsible persons for radiotherapy departments

Radiation therapy staff and hospital administrators should remain cognizant of the fact that the primary responsibility for the safe delivery of treatment is with them. This responsibility includes investigating discrepancies in dose measurements before applying the beam to patient treatments. Independent verification of beam calibration remains essential.

Hospital administrators of radiation therapy departments should provide a work environment that encourages working with awareness, facilitates concentration and avoids distraction.

### Manufacturers

Manufacturers should be aware of their responsibility for delivering the correct equipment with the correct calibration files and accompanying documents. They also have a responsibility to provide correct information and advice to users. Procedures to meet these responsibilities should be developed and quality controlled.

### Programme of purchasing, acceptance and commissioning

Programmes for purchasing, acceptance testing and commissioning should not only address treatment machines but also

treatment planning systems, radiation therapy information systems, imaging equipment used for radiation therapy, software, procedures and entire clinical processes. Devices and processes should be re-commissioned after equipment modifications including software upgrades and updates.

### Need for new protocols for treatment prescription and dosimetry

Protocols for treatment prescription, reporting and recording, such as found in ICRU reports, should be revised to accommodate new technologies. They should be adopted at a national level with the support of professional bodies. Similarly, dosimetry protocols should be developed for small and non-standard radiation fields.

### Dose escalation

Target dose escalation without a concomitant increase in normal tissue complication probability generally implies a reduction of geometrical margins. Such a reduction is only possible with conformal therapy accompanied by precise, image-guided patient positioning and effective immobilization together with a clear understanding of the accuracy achieved in clinical practice. Without these features, target dose escalation could lead to severe patient complications.

### Safety-critical communication and notifications

Unambiguous, well structured communication is essential, considering the complexity of radiation therapy and the multidisciplinary nature of the health care environment. In particular, procedures to notify physicists of maintenance and repair activities, identified as crucial in conventional technology, are even more necessary with new technologies.

### Computers and data integrity

Procedures should be in place to deal with situations created by computer “crashes”, which may cause loss of data integrity and lead to severe accidental exposures.

### Updating of quality control tests

When conventional tests and checks are not applicable or not effective for new technologies, the safety philosophy should aim at finding measures to maintain the required level of safety. This may require the design of new tests or the modification and validation of the old ones.

### Using lessons from experience

Lessons learned from past accidental exposure should be incorporated into training. Radiation therapy facilities are encouraged to share their experiences of actual and potential safety incidents through participation in databases such as Radiation Oncology Safety Information System (ROSIS), often referred to in this report. Report formats and analytical tools should be further developed to maximize and facilitate the learning components of such databases.

### Overcoming the lack of experience when introducing new technologies

Prior to the introduction of new techniques and technologies, there is little or no operational experience to share. To maintain safety in this situation, two complementary measures are recommended:

The following group of authors collaborated in writing the report from the International Commission of Radiological (in press) which has served as the basis for this paper: P. Ortiz López, O. Holmberg, J. C. Rosenwald, J.M. Cosset, P. Dunscombe, L. Pinillos, J.J. Vilaragut and S. Vatnitsky.



1. Prospective safety assessments should be undertaken in order to develop risk-informed and cost-effective quality assurance programmes. Examples of these tools are Failure Modes and Effects Analysis, Probabilistic Safety Assessment and Risk Matrix.

2. Moderated electronic networks and panels of experts supported by professional bodies should be established in order to expedite knowledge sharing at the early phase of introducing a new technology. ■

---

### References

• ICRP. "Prevention of Accidental Exposure to Patients Undergoing Radiation Therapy". ICRP Publication 86. Annals of the ICRP 30 (3), 2002. Pergamon Press, Oxford.

• ICRP. "Preventing Accidental Exposures with Newer External Beam Radiation Therapy Technologies. Annals of the ICRP (in press), 2009. Pergamon Press, Oxford.

## Radiation protection in modern radiotherapy: a regulator's point of view

by Jürgen Griebel, Federal Office for Radiation Protection (BfS) (Germany)

Radiation therapy (also radiotherapy) is the medical use of ionizing radiation as part of cancer treatment, but also has several applications in non-malignant conditions. Concerning the treatment of malignant tumours, it is common to combine radiotherapy with surgery, chemotherapy, hormone therapy or some mixture of the three. Radiation therapy is commonly applied to the cancerous tumour, but may also include the draining lymph nodes if they are clinically or radiologically involved with tumour. It is necessary to include a margin of normal tissue around the tumour to allow for uncertainties in daily set-up and tumour motion. These uncertainties can be caused by internal movement (for example, respiration as well as colon and bladder filling) and movement of external skin marks relative to the tumour position.

### Radiation Techniques: An Overview

The three main divisions of radiotherapy are external beam radiotherapy or teletherapy, brachytherapy or sealed source radiotherapy, and systemic radioisotope therapy or unsealed source radiotherapy. Most recent developments include particle therapy, which is a special case of external beam radiotherapy where the particles are protons or heavier ions, and intraoperative radiotherapy (IORT), which is a special type of radiotherapy that is delivered immediately after surgical removal of the cancer.

Conventional external beam radiotherapy is delivered via two-dimensional beams using linear accelerator machines and mainly consists of a single beam of radiation delivered to the patient from several directions: often front or back, and both sides. Hereby, the treatment is planned or simulated on a specially calibrated diagnostic x-ray machine known as a simulator because it recreates the linear accelerator actions. The aim of simulation is to accurately target or localize the radiation to the volume which has to be treated. This technique is well established and is generally quick and reliable.

The planning of radiotherapy treatment has been revolutionized by the ability to delineate tumours and adjacent normal structures in three dimensions using specialized computed tomography (CT) and/or magnetic resonance imaging (MRI) scanners and planning software. This technique, denoted as virtual simulation, allows more accurate placement of radiation beams than is possible using conventional X-rays, where soft-tissue structures are often difficult to assess.

An enhancement of virtual simulation is 3-dimensional conformal radiotherapy, in which the profile of each radiation beam is shaped to fit the profile of the target from a beam's eye view using a multileaf collimator and a variable number of beams. When the treatment volume conforms to the shape of the tumour, the relative toxicity of radiation to the surrounding normal tissues is reduced, allowing a higher dose of radiation to be delivered to the tumour than conventional techniques would allow.

Intensity-modulated radiation therapy (IMRT) is an advanced type of high-precision radiation that is the next generation of three-dimensional conformal radiotherapy. Computer-

controlled linear accelerators distribute precise radiation doses to malignant tumours or specific areas within the tumour. The pattern of radiation delivery is determined using highly-tailored computer algorithms to perform optimization and treatment simulation. By use of this kind of treatment planning, the radiation dose is consistent with the 3D shape of the tumour by controlling, or modulating, the radiation beam's intensity. The customized radiation dose is intended to maximize tumour dose while simultaneously protecting the surrounding normal tissue. This may result in better tumour targeting, lessened side effects, and improved treatment outcomes as compared to even three-dimensional conformal radiotherapy.

Three-dimensional conformal radiotherapy is still used extensively for many body sites, but the use of IMRT is growing in more complicated body sites such as central nervous system, head and neck, prostate, breast and lung. Unfortunately, IMRT is limited by its need for additional time from experienced medical personnel. Proof of improved survival benefit from either of these two techniques over conventional radiotherapy is growing for many tumour sites, and the ability to reduce radiation toxicity is generally accepted. In contrast, there are concerns, particularly with three-dimensional conformal radiotherapy, about increased exposure of normal tissue to radiation and the consequent potential for secondary malignancy. In addition, overconfidence in the accuracy of imaging may increase the chance of missing lesions that are invisible on the planning scans - and therefore not included in the treatment plan or that move between or during a treatment - for example, due to respiration or inadequate patient immobilization. New techniques are being developed to better control this uncertainty - for example, real-time imaging combined with real-time adjustment of the therapeutic beams. This new technology is called image-guided radiation therapy (IGRT) or four-dimensional radiotherapy.

In particle therapy, ionizing particles (for example protons or carbon ions) are directed at the target volume. The dose increases while the particle penetrates the tissue, up to a maximum (the Bragg peak) that occurs near the end of the particle's range, and it then drops to - almost - zero. The advantage of this energy deposition profile is that less energy is deposited into the healthy tissue surrounding the target tissue. Ion beam therapy is the cutting edge of modern radiotherapy. It requires most recent technologies to accurately deliver the particles to the target volume and completely new approaches to clinical dosimetry.

### Biological Imaging: Impact on Radiotherapy

In radiation therapy, staging, treatment planning, monitoring and evaluation of response are traditionally based on CT and MRI. These radiological imaging techniques have the significant advantage to show the anatomy with a high resolution, being also called anatomical imaging. In recent years, so called biological imaging methods which visualize metabolic pathways have been developed. These methods offer complementary imaging of various aspects of tumour biology. To date, the most prominent biological imaging modality in use is positron emission tomography (PET), whose diagnostic properties have clinically been evaluated for years.

Biological imaging offers the potential to improve the detection and delineation of the tumour tissue and the visualization of heterogeneous tumour biology. Promising radiotracers in target volume delineation include fluorodeoxyglucose-PET in lung and head and neck cancer and amino acids-PET of brain gliomas. Increasing body of scientific evidence indicate that biological imaging may also characterize tumour tissue by visualizing tumour hypoxia and proliferation. In combination with most recent radiation techniques such as IMRT or ion beam radiation,





the visualization of heterogeneous tumour biology may revolutionize treatment planning as well as treatment monitoring and follow-up. However, to define the real impact of biological imaging on clinical outcome after radiotherapy, further clinical studies are required.

## Quality Management System: A Challenging Issue

As shown above, radiotherapy includes responsibility for a large variety of different steps such as tumour staging, treatment planning and simulation, treatment delivery of ionizing radiation and its ongoing verification, as well as treatment monitoring and follow up of the cancer patient. Hereby, most recent technical developments in radiation techniques and imaging procedures as well as highly sophisticated computer technology are applied. Furthermore, radiotherapy is an integral part of the multidisciplinary management of cancer patients, which comprises – in addition to radiotherapy – surgery, chemo- and/or immunotherapy and other novel treatment approaches. Thus, radiotherapy is a multi-step, multi-discipline procedure, which requires a demanding quality management system along the whole therapy line.

From a regulator's point of view, the outlined complexity of radiotherapy is a challenging issue which has to be met in radiation protection. Hereby, in particular, the:

- exposure of patients as part of their radiation treatment (medical exposures);

is of major interest. However, further potential exposure scenarios have to be taken into account:

- exposure of employees arising from radiotherapy practice (occupational exposures);
- exposure of members of the public arising from the use of medical radiation equipment and radioactive sources (public exposures).

A further consequence of radiotherapy being a multi-disciplinary approach is that input from a number of professional groups, interacting with manufacturers and suppliers of equipment, maintenance engineers, and the relevant regulatory authorities is required. All members of the multi-disciplinary team have an individual and joint responsibility to ensure their contribution to safe practices in the delivery of radiotherapy.

Concerning treatment delivery of ionizing radiation, demanding quality requirements of technical equipment including commissioning, acceptance testing, and quality controls, in particular calibration of radiation, as well as a comprehensive quality assurance programme with the participation of appropriate qualified experts have to be implemented to ensure that for each patient the exposure of volumes other than the planning target volume is kept as low as reasonably achievable, while delivering the prescribed dose to the planning target volume within the required tolerances. For example, a dose to the target volume being 5% too low may result in clinically detectable reduction in tumour control, while a dose to normal tissues being 5% too high may lead to significant increase in normal tissue complication probability, i.e. unacceptable side effects. So, deviations from prescribed dose may involve severe or even fatal consequences

and require prompt investigation in the event of an accidental medical exposure. Furthermore, sufficient staffing including radiological medical practitioners, medical physicists and medical radiation technologist as well as adequate and ongoing training and education of this personnel is essential.

All of these aspects are essential from a regulator's point of view. Nevertheless, it has to be appreciated that the fundamental principles of justification and optimization are the foundation of radiation protection in radiotherapy. In particular, the principle of justification is of pivotal importance to radiotherapy of patients. The decision to perform a radiotherapy rests upon a professional judgement of the benefits that accrue to the total health of the patient, while accounting for any detrimental biological effects that might be caused by the ionizing radiation. The benefits will include the direct health benefits to the individual as well as the benefits to society. The detriment will be the potential deleterious effects of ionizing radiation such as deterministic and stochastic effects. The objective of radiotherapy is to deliver a radiation dose to a selected target volume of an organ or tissue for the purpose of killing cells. Such therapy results in absorbed doses that are orders of magnitude greater than those encountered in diagnostic procedures. So, in radiotherapy, the potential for complications with normal tissue is significant. Some deleterious effects will often be an unavoidable part even of a properly justified procedure. As a consequence, the justification for each procedure should be carefully considered. In this decision process, other therapeutic approaches such as surgery or chemotherapy, either alone or in combination with radiotherapy, have to be considered.

There are special cases that warrant further justification, including the medical exposure of the pregnant or potentially pregnant patient. Likewise, radiotherapy involving children under the age of 18 years requires a higher level of justification since children may be more susceptible to radiation and have a longer life expectancy during which manifestation of possible harmful effects of radiation may occur.

Clinical research that exposes humans to therapeutic ionizing radiation should conform to the provisions of the Helsinki Declaration and should take into account the guidelines for its application prepared by Council for International Organizations of Medical Sciences (CIOMS) and World Health Organization (WHO), and the International Commission on Radiological Protection (ICRP). In addition, the therapeutic exposure of volunteers for clinical research is deemed to be not justified unless it is subject to approval by an ethics committee and/or by any other institutional body assigned similar functions by the relevant authority.

As outlined above, a demanding quality assurance programme along the whole line has to be an integral component of modern radiotherapy practice. This programme should include regular and independent auditing, whereby – amongst others – the adherence of the principle of justification has to be taken into account. In summary, this quality assurance programme needs to be linked to the radiation protection programme in order to strengthen safety while at the same time improving quality and efficiency. ■

## UK initiatives to improve patient safety in radiotherapy – the role of the Health Protection Agency

by Úna O'Doherty, Medical Exposure Department, Health Protection Agency (United Kingdom)

The Health Protection Agency (HPA) is an independent organisation whose role is to provide an integrated approach to protecting UK public health. Part of its remit includes the provision of independent advice on radiological practice and radiation safety. The HPA assists and supports a range of organisations and whilst the HPA is not a regulator, its scientific staff have helped develop radiation protection structures through work with the ICRP, IAEA, the European Commission and UK regulators to produce legislative frameworks and guidance documents.

In 2005, HPA incorporated the National Radiological Protection Board (NRPB) through the Health Protection Agency Act 2005 and later that year the Medical Exposure Department (MED) was formed. This department builds on the valuable work in radiation protection carried out by the NRPB. Whilst the NRPB's main focus was on diagnostic imaging and interventional radiology, the department's scope has grown to include nuclear medicine and radiotherapy (RT). In 2006, the Chief Medical Officer for England, Sir Liam Donaldson launched a range of initiatives relating to patient safety in RT. One of these initiatives involved the HPA recruiting clinically trained staff whose role is to support the RT community, making the HPA an impartial resource equipped with the knowledge and skills to work in partnership with health care professionals within the clinical setting.

These staff are equipped with an understanding of current RT practice and clinical issues thus enabling them to provide relevant up to date advice. This may be in the form of a telephone call or e-mail from an individual regarding a specific matter, or through working with a clinical department, more of which is described later in this paper. Whilst advice is mainly provided to healthcare professionals, professional bodies, government departments and agencies, members of the public also often contacts the MED for advice in relation to medical exposures that either they, or a family member have had or are about to undergo.

The MED staff are from a range of backgrounds including radiographers, physicists and radiobiologists. Collectively they possess dosimetric expertise, clinical knowledge and practical experience of all types of medical exposures, and the application of this within government policy. An awareness of current practical issues is maintained through radiographers employed by the department undertaking regular clinical placements and remaining registered with the Health Professionals Council (HPC). Liaison with manufacturers allows the MED staff to keep up to date as technology develops. This unique partnership of scientific and clinical staff from the HPA working together with those providing services in hospitals ensures a balanced and evolving approach to patient safety in RT.

This paper describes a number of MED initiatives relating to safety in radiotherapy and how it is working to improve radiation protection and patient safety at local, national and international levels.

### HPA contribution to Guidance Documents

MED has an established history of joint publications with the professions. To formalise the relationships which produce this type

of work, the department has Memoranda of Understanding with both the Society and College of Radiographers and the Royal College of Radiologists to allow and promote communication on matters relating to radiation protection in clinical practice and regulatory requirements as well as policy development. Recent examples of this may be seen in the publication of *A Guide to Understanding the Implementation of the Ionising Radiation (Medical Exposure) Regulations (2008)*<sup>1</sup> and *Towards Safer Radiotherapy (2008)*<sup>2</sup>.

### *Guide to Understanding the Implementation of the Ionising Radiation (Medical Exposure) Regulations*

Most UK RT centres have well established mechanisms in place for local review of radiotherapy errors (RTEs) however; the ability to share data at a national level was always constrained by an inconsistency in the terminology used in RTE.

This issue was in part answered by the casting of The Ionising Radiation (Medical Exposures) Regulations (IR(ME)R) 2000 & 2006. IR(ME)R is legislation intended to protect the patient from the hazards associate with ionising radiation in the UK. The Ionising Radiations Regulations 1999 address incidents due to equipment defect or malfunction and The Ionising Radiation (Medical Exposure) Regulations 2000 [IR(ME)R], focus on procedural failures. There is an inherent safety culture established in the Regulations, with employers providing a framework within which professional undertake their professional and legal responsibilities.

Under IR(ME)R major errors within RT where patients receive an exposure to ionising radiation "much greater than that intended" are reported to the appropriate authority. In England, the Care Quality Commission (CQC), as the regulator, receives these reports. The CQC publish on their website quarterly reports of their key findings from inspections of clinical departments.

UK regulations for medical exposures are made under the criminal law framework but these have not yet been tested through cases in the courts. It was agreed that further clarity was needed regarding legal responsibilities of RT professionals and to address this, an IR(ME)R working party was formed, bringing together representatives from the professional bodies representing clinical oncology, therapeutic radiography and RT physics and the MED with the intention of producing a guide to help employers and clinical staff understand IR(ME)R legislation and implement it as it pertains to RT. The document describes the duties and responsibilities of healthcare workers under IR(ME)R, the necessity for local procedures, protocols, training and auditing and how inspection and mandatory reporting of incidents is undertaken. 'A Guide to Understanding the Implementation of the Ionising Radiation (Medical Exposure) Regulations' was published in September 2008<sup>1</sup>.

### *Towards Safer Radiotherapy*

Following several high profile incidents in the UK, there was recognition within the RT professional community for the need to share information related to RTE's nationally. A multidisciplinary working party including representatives from the professional bodies, patients, the National Patient Safety Agency and the MED was established in 2006 to produce patient safety guidance. The working party agreed and standardised the following within a published document:

1. agreed terminology for use in reporting of RT incidents;
2. a coding system to describe the point on the RT pathway that the incident occurred;
3. a classification grid for severity grading of the RT incident;
4. recommendations to improve safety in RT.

To allow national sharing of information surrounding RTEs, terminology was clearly defined for the UK to reduce ambiguity.



This terminology is consistent with World Health Organisation definitions.

The RT pathway was broken down into 21 constituent processes, including treatment room design, patient referral for RT, planning and administration of RT and follow up. These processes were then given a number coding. Each process was then broken down further into its sub-processes, forming a total of 196 sub-processes each with a letter coding. In this way each activity involved in the planning and delivery of RT could be described by a unique alphanumeric code. This code describes where the error occurred and allows individual errors to be compared locally and nationally. It should be noted that for most RTEs there will be an initiating event, and a number of subsequent events that constitute the error; each of these events can be coded using this method.

A classification grid for severity grading of RTEs was defined to enable a grading to be applied to RTEs in a consistent way. There are five severity classifications, including a grading for near misses.

This combination of these three elements provides a standard approach by which RT incidents and near misses can be described, classified and coded locally. This in turn allows national analysis of these events, thus producing learning for the RT community.

Thirty-seven practical recommendations to improve patient safety in RT are also described in the document. The purpose of the recommendations is to identify ways of reducing errors in RT which are caused by human error or failure of systems of work.

'Towards Safer Radiotherapy' (TSRT) was published in April 2008<sup>2</sup>. It was immediately embraced by the RT professions and continues to be quoted and referenced locally, nationally and internationally.

## HPA contribution to Continuous Improvement and Safety Culture

Many initiatives and publications from national and international organisations and bodies have attempted to assist departments in achieving a safe and timely service, and new ones will continue to be published in the future. However, individual departments often have to interpret the advice and apply it locally without assistance. The MED offers support to clinical departments through:

1. analysis of working practices and guidance on translating national recommendations into local practice, through the provision of site visits;
2. analysis of incidents and near misses.

### Radiotherapy Site Visits

The assurance of patient safety combined with optimal service efficiency, whilst maintaining compliance with legislation are the cornerstones of everyday clinical practice. The ongoing demands facing healthcare professionals providing quality services in an efficient and timely manner are well known. The MED aims to support clinical departments, particularly as they adopt new technologies into existing care pathways and practices.

The MED's interaction with clinical departments depends on the type and needs of individual departments. Provision of advice can range from a response to a telephone enquiry from a healthcare professional to a comprehensive site visit. These visits are at the department's invitation and are intended to provide independent on-site support and reassurance on issues surrounding patient safety and process efficiency within the context of IR(ME)R.

The site visit provides a vehicle to deliver key safety messages to all those involved in the delivery of RT to patients. This face to face interaction with clinical departments allows the MED to positively influence local safety cultures and help clinical departments understand the safety implications of their own processes.

The MED offers a tailored service, with visits lasting 1-3 days. Each visit is planned in advance via email contact with a key stakeholder from the department and a programme for the visit is agreed. A site visit usually begins with a meeting with the heads of service and medical and physics leads for the department, to ensure that there is involvement from all staff groups. Visits consist of a series of observations of key areas within the clinical department, informal interviews with individual members of staff and a review of department procedures. Examples of good practice are shared between departments. At the end of the visit, feedback of findings and agreement of an action plan is achieved in consultation with representatives from the clinical department. There is also the provision for support and follow-up to these site visits.

MED site visits continue to evolve through consultation with the clinical community and are informed by working with key stakeholders. Feedback from the visits shows that clinical sites valued and benefitted from an independent review of all aspects of the pathway. The site visit identifies redundant processes so resources can be refocused into areas of potential weakness. Practical advice on the implementation of guidance documents was given and learning from shared experience of other clinical sites was valued. The flexible approach to the visit and receipt of achievable advice was also deemed beneficial. All sites note the importance of conducting visits and receiving advice outwith a regulatory programme of inspections, undertaken by staff with clinical backgrounds.

By working in partnership, real improvements can be made and any advice given is done in consultation with local sites and with local practice in mind. MED staff provide an independent overview of a clinical department's practices without preconceived ideas and draw on good practice from elsewhere, as well as their own experiences. Flexibility of approach when undertaking a site visit is a key factor in tailoring advice as each site or situation is unique. By giving individuals the confidence to challenge their existing practices and identify redundant work processes, more efficient ones can be implemented, but always within the appropriate legal framework and within the context of an enhanced safety culture.

### Reporting and Analysis of Incidents and Near Misses

In the UK, the National Patient Safety Agency (NPSA) has an established system of voluntary reporting of incidents and near misses, including those in RT, called the National Reporting and Learning Service (NRLS). The MED works with the NPSA on national collection and analysis of RT incidents, whether near misses or reportable events, and promulgating this experience across the community.

In 2008, the NPSA engaged expertise from the MED to undertake analysis of all RTEs and near misses reported to them. The classification and coding system from 'Towards Safer Radiotherapy' (TSRT) was successfully employed for the analysis of a sample dataset. The analysis of the first dataset highlighted areas where further improvements could be made both in terms of quality and quantity of reporting. In order to improve this further work has been undertaken by the MED and NPSA Steering Group on Patient Safety in Radiotherapy on how to implement the 'Towards Safer Radiotherapy' coding and classification locally and to streamline the submission of data to the NRLS.

This has involved working with the vendor systems used for upload of incident data to the NRLS by clinical departments. A guidance document was written and piloted in six RT departments to explain how to implement the classification and coding system from TSRT and how to improve submission of RT incidents to the NRLS. This document was then launched at a national workshop (June 2009) involving all UK RT departments.

The MED has a data sharing agreement with the NPSA to provide the expertise to undertake the analysis of data collected on radiation incidents on a regular basis. These reports will be

regularly published on the NPSA website<sup>4</sup>. National sharing of any lessons learnt from incidents and near misses will now be possible. By including near misses within the analysis, a much larger dataset can be produced which is more relevant to normal practice and broadens the opportunities for learning. In addition, this work facilitates the comparison of local and national incident analysis.

Further work in this area includes the development of additional codes to map causes of RTE's and to establish a coding revision process. Discussions have already begun with professional bodies from other healthcare modalities in the UK to share experience of this methodology. In addition the MED are working to establish a link with the international community to enable their work to contribute to international reporting for the benefit of global patient safety.

## Conclusion

The HPA's MED has established a national independent resource for the RT community, providing a unique approach to improving patient safety in radiotherapy, through joint publications with the professional bodies, site visits and analysis of incidents and near misses.

MED staff, who have RT expertise from clinical, scientific and healthcare policy backgrounds work in partnership with the entire RT community including healthcare professionals, professional bodies, government departments and agencies, and members of the public. This approach has been endorsed by the RT professional bodies and clinical departments alike.

As part of an independent agency, MED staff can work with clinical departments, from within their own environment and without threat, to provide a genuine opportunity for clinical staff to learn and develop their services and their own expertise with the objective of improving radiotherapy safety for patients. ■

## References

1. A Guide to Understanding the Implications of the Ionising Radiation (Medical Exposure) Regulations in Radiotherapy  
[www.rcr.ac.uk/publications.aspx?PageID=149&PublicationID=289](http://www.rcr.ac.uk/publications.aspx?PageID=149&PublicationID=289)
2. Towards Safer Radiotherapy, 2008  
[www.rcr.ac.uk/index.asp?PageID=149&PublicationID=281](http://www.rcr.ac.uk/index.asp?PageID=149&PublicationID=281)

3. Care Quality Commission  
[www.cqc.org.uk/](http://www.cqc.org.uk/)
4. NPSA Reporting and Learning System (RLS) Data Summary May 2008  
[www.npsa.nhs.uk/nrls/patient-safety-incident-data/quarterly-data-reports/](http://www.npsa.nhs.uk/nrls/patient-safety-incident-data/quarterly-data-reports/)



## The system of radiological events evaluation in radiotherapy in the Czech Republic

by **Karla Petrová, Lenka Hobzová**, State Office for Nuclear Safety and  
**Josef Novotný**, Hospital Na Homolce – Prague (Czech Republic)

The paper will briefly describe the regulatory approach to the licensing and control of the radioterapeutic departments in the Czech Republic and will be more specifically focused to the prevention of the radiological events (incidents and accidents) in this area. The use of sources of ionizing radiation in radiotherapy is traditionally activity with the highest preference and attention from the side of regulatory authority. There are very strong and high legislative requirements defined for the technical quality of sources and their regular control as well as for the workers and their appropriate qualification. It is clear that the fault can be never definitely excluded – mainly the human error – however a big effort is invested to the prevention and minimization of the probability that the error occur.

One of the most important document requested with the application for the licensing of radiotherapy is the Program of quality assurance where all procedures must be described and prevention of the faults shall be included. The inspections are organized at least once per year at these workplaces and the inspectors pay big attention also to the registration of all radiological events which happened at the workplace. The registration of these events is obligatory. The radiological events are classified in accordance with their importance into several groups – the most important (category A) group shall be reported to regulator (the State Office for Nuclear Safety - SUJB).

Of course there is always a problem with the completeness of this reporting. SUJB is searching the ways how to receive as much information as possible. There is long term effort to communicate directly through the seminars or national conferences with the workplaces performing the radiotherapy, to explain them the importance of the sharing of lesson learned from radiological events between the workplaces as an essential part of the effective prevention.

There is also good co-operation between regulator and professional societies. SUJB has also differentiated approach to the workplaces which honestly announced the event and to them which conceal the information and the event is found during the inspection or it is announced by the patient or somebody else.

The survey of radiological incidents has been organized during the years 2006-2008 in the Czech Republic and it is showing that majority of incidents is caused by human errors appearing at different stages of radiotherapy process (85%). Altogether 160 events were registered on the workplaces (25 workplaces participated in the survey) during these three years. Errors appearing at the beginning of process can cause radiological incidents with serious consequences for patients (category A) contrary to incidents occurring during fractionated treatments, which might be usually compensated. There were 6 serious events (category A) during past three years investigated by SUJB – 4 of them properly reported. More detailed description will be done in the paper. The possibilities for limitation of radiological incidents will be also discussed on the basis of proposed human error model. ■



## Inspecting radiotherapy treatment safety: a priority for ASN for several years to come

by **Jean-Luc Godet**, Head of Ionising Radiation and Health Department, **Carole Marchal**, Deputy director of Ionising Radiation and Health Department and **Mathias Lelièvre**, Head of the Paris Division – French Nuclear Safety Authority – Paris (France)

The inspections carried out by ASN in the medical sector have, since 2005, also included radiological protection for patients. Between 2002 and 2005, ASN saw it as important to publish the new regulatory framework required to transpose Directive 97/43 Euratom<sup>1</sup>, while also carrying out inspections focusing mainly on radiological protection regarding healthcare professionals, the technical compliance of facilities with license requirements issued by ASN and the management rules applying to radioactive sources.

Safety problems in radiotherapy treatment, brought to light following the accidents that occurred at Epinal Hospital (2004-2005) and Rangueil Hospital in Toulouse (2006-2007), together with other incidents notified to ASN since 2005, have led ASN to shift the focus of its inspections in radiotherapy to radiological protection for patients. Since 2007, the 180 radiotherapy centres in France have been subject to annual inspections and inspections are carried out immediately whenever warranted by the nature of significant radiological protection events notified to ASN.

ASN has therefore defined a new aim for inspections of French radiotherapy centres, drawing on a major portion of its resources to implement its objectives. This priority resulted in ASN providing a response to new needs: a need for transparency with regard to the public, the renewed need for coordination with other administrative entities in the healthcare sector and the need to share its experience, with professionals and stakeholders at regional, national and international level.

### New radiotherapy inspection practices (2007 to 2009)

**New objectives** - Inspections have gradually evolved from an inspection focused on the accelerators used in radiotherapy to a comprehensive inspection of both the technical aspects and the organisational and human factors. As a result, inspections are not only focused on checking the radiological protection and quality aspects of the equipment, checking traceability relative to maintenance operations and establishing formal rules for equipment use, but also on team organisation, including the medical physics team, the stages in the patient care pathway, the information sharing system within departments and the progressive implementation of a quality management system. This broader scope has been supported by solid regulatory measures introduced by the Order approving ASN Ruling No.2008-DC-0103 of 1st July 2008.

The inspections have also served to monitor the development of various initiatives promoting feedback, based on analysis of events liable to result in radiation overexposure or exposure affecting healthcare professionals. The criteria for notifying a



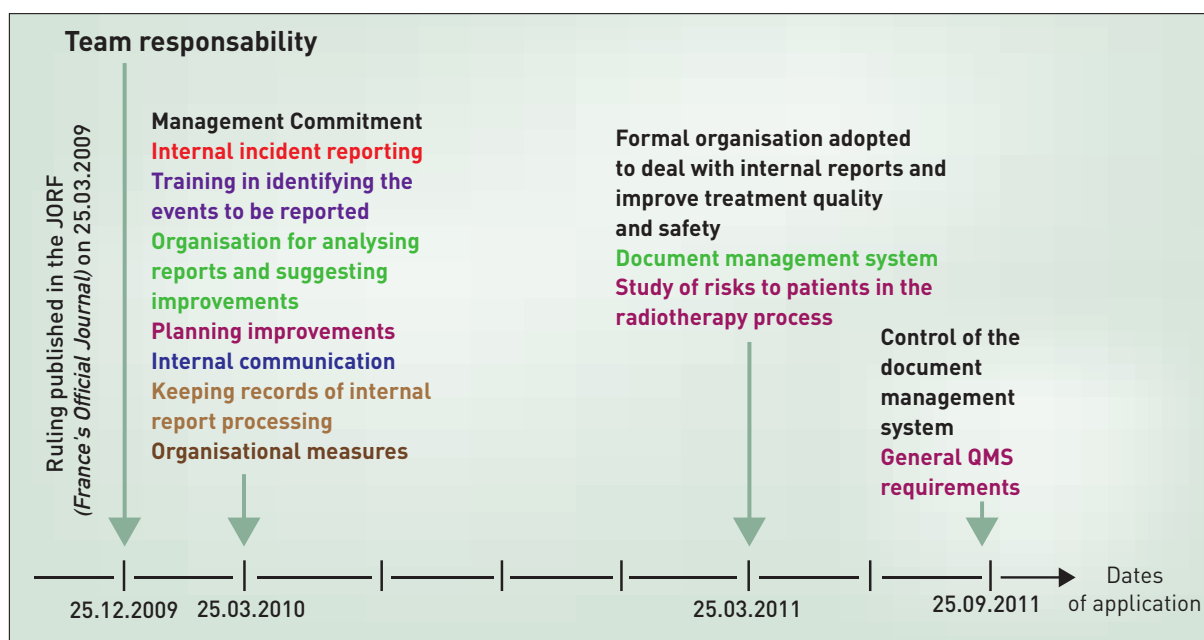
ASN inspection of the radiotherapy Department at the Henri Mondor University Hospital in Créteil, August 2008

significant event to ASN were defined (July 2007) and then revised (September 2009) and a reporting and rating scale divided into eight levels, known as the ASN/SFRO scale, has been developed. Implementing an initiative such as this implies establishing a policy on internal reporting at radiotherapy centres to ensure that any problems are recorded and known, together with team organisation to analyse such problems and then supervise implementation of corrective measures designed to prevent a similar incident from occurring again in the future. In 2008, ASN was notified of two hundred and eight events, the majority of which (98%) were rated Level 1 on the ASN/SFRO scale (no consequences for patient health), with the rest (2%) being classified Level 2 incidents (possible moderate alteration to an organ or physiological function). The inspections carried out to date have aimed to encourage transparency at the centres, so that they will report their incidents, and to check analyses performed and ensure that corrective measures really are implemented.

**Relations between inspectors and healthcare professionals** - Monitoring implementation of quality assurance initiatives and of measures promoting feedback and experience-sharing have brought about a radical change in relations between ASN and staff at the radiotherapy centres inspected, including management representatives, physicians, medical physicists, radiotherapists and operators in charge of dosimetry. The period 2007-2009 has been an extremely stressful time for the professionals inspected, with increased media and public attention focused on

1. Directive 97/43 Euratom of 30 June 1997 on health protection of individuals against the dangers of ionising radiation in relation to medical exposure.





Schedule for application of ASN ruling no. 2008-DC-103

radiotherapy. In spite of this, a relation of mutual respect has gradually developed between ASN inspectors and staff at radiotherapy centres : acknowledgment of the expertise of ASN personnel, of the added value generated by the inspection process, and also of the constraints affecting radiotherapy departments, especially in terms of human resources and funding. Relations between ASN and the radiotherapy centres, which may occasionally, by their very nature, be fraught, have, in the majority of cases, enabled repeated inspection campaigns to proceed in a calm and professional atmosphere, conducive to achieving considerable progress on the part of the radiotherapy departments to ensure radiological protection for staff and patients.

**The resources implemented** - Having defined its objectives, ASN has been able to deploy the appropriate resources. To begin with, a huge effort has been made to ensure that every radiotherapy centre is inspected at least once a year. Thus, since 2007, ASN has carried out over 500 inspections at radiotherapy departments. Performing inspections on this annual basis has made it possible to closely monitor changes to the services, thanks to the responses given by the departments to inspection follow-up letters and then the following year's inspection, to observe the real impact of action taken since the previous inspection.

Although prior notice of inspection was given more or less systematically prior to 2007, the radiation protection inspectors have since employed all the tools available to them: surprise inspections, reactive inspections following incidents, inspections involving experts (radiotherapists or medical physicists), inspections in conjunction with other inspection bodies, such as the medical inspectors from the local health and social services offices (DDASS). Knowing the exact situation of each department has enabled the ASN to adapt its inspection procedures according to the stakes and issues involved at each. For example, surprise inspections have been conducted to check the actual presence of professionals, in compliance with the regulatory requirements. In addition, where the situation has justified such action, decisions have been taken with regard to a number of radiotherapy centres : thus, in 2009, three of them had to temporarily stop all activity, since the ASN suspended their licences to use their accelerators because they did not have any more medical physicists.

Since 2007, ASN has also been developing new training programmes so that its personnel can develop the skills required

for more efficient and comprehensive inspections of radiotherapy centres. Inspector training, which is required in order to be a certified radiationprotection inspector, has thus integrated a module on organisational and human factors. Inspectors can also take an advanced training course on risk analysis in radiotherapy. Lastly, immersion training at radiotherapy centres has provided ASN inspectors with a better understanding of the constraints under which the healthcare professionals work, as well as improving their technical knowledge. Inspection tools have been updated each year, by means of national workgroups. These tools include an inspection guide, which is enriched each year thanks to feedback from centres that have notified incidents. Every year, ASN also draws up a report on the inspections carried out, in a monograph containing a review of the improvements made by the centres and identifying recurring problems to be checked during inspections carried out the following year.

## Review of inspections carried out in 2007 and 2008

In April 2008, ASN published the review of inspections carried out in 2007 at radiotherapy centres, focusing on the subject of organisational and human factors. This review has led to the following observations in particular:

- staff appear to be fully in control of the steps involved in planning and providing treatment, together with their related responsibilities, even though these are rarely defined in formal procedure;
- individual medical follow-up of patients following treatment is generally well-organised;
- it is essential to increase the number of medical physicists staff working in radiotherapy teams, especially radiation physicists, as well as the number of radiotherapy oncologists and radiotherapists;
- internal checks relative to procedures involved in planning and providing treatment are carried out at the centres, but, in most cases, are still not set out in written procedures;
- analysis of the risks related to radiotherapy, based on the compilation and analysis of undesirable events, is performed at too few of the centres.

This review has revealed contrasting situations at different radiotherapy centres : at some centres, steps have been taken to make treatment safer; while at others, although fewer in number, organisational weaknesses have built up which must be addressed as a priority.

All the radiotherapy centres inspected in 2007 were reviewed in 2008. ASN was thus able to monitor the actions implemented by the radiotherapy centres following the inspections carried out in 2007, making it a priority to examine, during the first six months of 2008, the situation of those centres where shortfalls in terms of human resources and organisation had been found. The conclusions drawn by the inspections of these "priority" centres were immediately sent to the Regional Hospital Agencies (ARH) and to the national support unit set up by the National Cancer Institute (INCa). The work carried out by this unit, of which ASN is a member, has served to identify nine centres for which the French Health Minister then demanded immediate action be taken to make up the shortages of staff specialising in medical radiation physicists.

The inspections carried out in 2008 covered six specific subjects: human resources, how medical physics is organised, training in radiological protection for patients, skilled use of equipment, managing treatment safety and quality and risk management.

The review of these inspections, published in November 2009, reveals even greater contrasts in the situation than in 2007. Staff (radiotherapy oncologists, radiation physicists and radiotherapists) are still having to cope with serious problems. The continuing acute shortage of radiation physicists causes insecurity among the medical physics teams and is still, for around 20% of radiotherapy centres, a critical factor affecting the strength of the organisation.

*"Plans d'organisation de la radiophysique médicale"* (POPM, organisational plans in medical radiation physics), required under French regulations, often lack any prospect of improvement or updating, notably with regard to progress achieved compared with the situation in previous years.

Between 2007 and 2008, ASN inspections showed that safety had improved insofar as concerns treatment. Nonetheless, these improvements vary from one centre to the next and from one region to the next. Organised management of treatment safety and quality is a critical factor for between 10% and 20% of the centres where the introduction of such an approach is long overdue.

Insofar as concerns the application of regulatory requirements relative to internal quality control on equipment, these checks, regarding radiotherapy facilities and the related scanners, are far from exhaustive at practically all the centres.

Implementation of the procedures for notifying ASN of significant radiological protection events was widespread in 2008 but the centres have difficulty in organising and performing in-depth analysis and undertaking any improvements required on a regular basis. At the end of the first six months of 2009, 50% of the centres had notified ASN of at least one event (compared with 18% between June 2007 and July 2008).

## Key points regarding the inspection programme for 2009 to 2012

In 2009, ASN pursued its monitoring of all the radiotherapy departments, targeting inspections primarily on the application of the recently-introduced requirements relative to quality assurance, looking ahead to the staged implementation of the requirements set out in technical ruling 2008-DC-103 of 1st July 2008.

This ruling was approved in January 2009 by the French Health Minister and has been enforceable since March 2009. A guide, drawn up in liaison with healthcare professionals and published by ASN in March 2009, provides a specific reference framework for managing safety and treatment quality. It comes with a second methodology document focusing on risk analysis in external radiotherapy, which was also drawn up in conjunction with healthcare professionals.

The schedule for application of this new ruling (see box) will be checked during future ASN inspections, up to 2011.



Treating prostate cancer with brachytherapy: the radioactive rods stored in the container are implanted around the tumour

The year 2012 should be thought of, by all radiotherapy centres, as a cut-off year: after this date, in order to be authorised to practice radiotherapy, the regulatory quality criteria, defined by the INCa must be satisfied in their entirety. ASN, in liaison with the inspection departments of the new regional healthcare agencies (ARS), is planning a comprehensive review of the centres to check these criteria and reassess treatment safety.

## Providing information to the public and public health agencies

- ASN was concerned to report on its inspection activities, within the framework of its public information policy, as defined by France's Act of 13 June 2006 on Transparency and Security in the Nuclear Field. Accordingly, the follow-up letters to inspections carried out at radiotherapy centres since 1 January 2008 have been published on the ASN's website ([www.asn.fr](http://www.asn.fr)). These follow-up letters formally list any noncompliance identified together with the remarks of the radiation protection inspectors. They also report on improvements made at the centres inspected, the extent to which ASN's requirements have been dealt with, without detriment to the medical quality of radiotherapy treatment and its outcome for the patient. As on 31 August 2009, ASN had published 222 inspection follow-up letters. Inspections were also carried out in the presence of journalists, with a view to informing the public of the ASN's monitoring practices.

A general report on Level 1 events (on the ASN/SFRO scale) notified to ASN is published every quarter ([www.asn.fr](http://www.asn.fr)). Events classified as Level 2 or above are reported in a specific newsletter available on the ASN website or in press releases.

As a result of the expertise built up in the course of its inspections and its detailed knowledge of how each one of the 180 radiotherapy centres in France, (including French overseas *départements*) functions, ASN has developed stronger relations with other administrative bodies which have authority in the matter of radiotherapy. Thus, in the regions, the ASN's regional divisions work in liaison with the Regional Hospital Agencies (ARH) and medical inspectors from the DDASS. Such cooperation results in more efficient monitoring. For example, inspections have frequently been carried out jointly with the medical inspectors, making it possible to compare findings at the same radiotherapy centre, which may vary according to their specific fields of expertise.

At national level, ASN has signed cooperation agreements with the French National Authority for Health - (HAS, December 2008), the French Agency for the Safety of Health Products (AFSSAPS, July 2009), the National Institute for Public Health Surveillance (InVS, September 2009) and, in the near future, an agreement will be signed with the National Cancer Institute (INCa). Such cooperation should, especially, make it possible to implement and consolidate reciprocal information-sharing



procedures between ASN inspections and the healthcare establishment accreditation system coordinated by the HAS, controls on medical devices performed by the AFSSAPS, surveillance of undesirable events carried out by the InVS and INCa's national monitoring of the situation at radiotherapy centres facing the most serious problems.

Additionally, ASN has also been keen to report information to stakeholders in the broadest sense of the term. In the regions, seminars are regularly held by the ASN's regional divisions to bring together healthcare professionals and partner administrations to discuss the inspections carried out, the improvements and problems found, to develop individual initiatives implemented by some centres, in the area of quality assurance and information-sharing management, for example.

At national level, ASN has developed links with certain learned societies, including the French Society of Radiation Oncology (SFRO) and the French Society of Medical Physics (SFPM), for example. The meetings provide an opportunity to listen to the professionals' needs and to explain ASN's desire to work together to improve radiological protection at radiotherapy centres.

Lastly, at international level, ASN, in conjunction with several partners, is organising a conference on treatment safety in radiotherapy in December 2009, aimed at sharing its experience with healthcare professionals (SFRO, SFPM, SFRP) and international partners (IAEA, WHO, EU).

### Changes required

ASN has less than three years' experience in inspection in the area of treatment safety in radiotherapy. Its inspectors have quickly developed specialised skills in new areas involving treatment plans, taking account of organisational and human factors and risk analysis, for example. They have also had to deal with complicated situations and analyse events involving issues relative to radiation protection and medical device vigilance at the same time, based on the observation of anomalies in dose planning software, for example, or incompatibility between accessories used in stereotactic radiotherapy. To deal with all this and build up its own expertise, ASN has developed specialised training for its inspectors (in risk analysis and HOF). It has also taken on new staff with specific expertise (HOF) or sound experience in the hospital environment (medical physicists and radiotherapists). This drive to ensure that the most experienced inspectors develop specialised skills must be sustained, for example in the area of risk analysis.

In certain situations, expertise from outside ASN has been required during inspections, calling on learned societies (medical physicists and radiotherapy oncologists). Work is in progress to define a legal framework for coordinating such expertise (legal protection and ethics) as well financing it.

The aim of an ASN inspection is not to assess the quality of clinical practice, especially insofar as concerns application of the principle of justifying all therapeutic indications. Eventually, ASN nonetheless hopes that clinical audits, performed in conditions that still need to be defined in France (HAS), and based on the latest EU recommendations, will also be carried out to make the ongoing initiatives to ensure treatment safety as comprehensive as possible. This assessment of professional practice, combined with ASN's inspection system, will thus ensure that radiotherapy in France enjoys a high level of quality and safety.

### Conclusions

Inspecting treatment safety in the field of radiotherapy has, since 2007, become one of ASN's priorities. This will continue to be the case until at least 2012, when the criteria defined by the INCa must be scrupulously satisfied in order to be authorised to practice radiotherapy treatment. The continuing acute shortage of medical physicists, which it will take five to ten years to fill, is still a critical factor affecting the strength of the organisation, one that receives particular attention during ASN's inspections in this area.

Since 2007, ASN has noted significant improvements at many centres that reflect the real development of a safety culture, mainly focused on better traceability of controls on planning and carrying out treatment, the gradual implementation of an internal system to record and analyse problems and notifying ASN of certain events.

For ASN, after making the regulatory framework clearer and stricter in 2008, the next challenge to be met, in close cooperation with the healthcare professionals, is to organise a system for sharing experience at national level, based on events recorded and notified, which will be of benefit to all the radiotherapy centres.

Lastly, ASN will continue to play its part in keeping the public informed, by systematically publishing inspection follow-up letters and reports on the events notified to it online. ■

## Informed consent process: a patient centred approach of the therapeutic decision

by Dr Marie-Charlotte Bouësseau, Ethics and Health, Team leader,  
World Health Organization (WHO) – Geneva (Swiss)

As any other treatment, radiotherapy requires the patient's informed consent. The process of informed consent refers to a free decision made by the patient, after an open dialogue with the health professionals. It includes several steps: provision of clear information to the patient focussed on risks and benefits, modalities of the treatment and other therapeutic options. The patient is also expected to express questions and concerns. It is important to ensure consistency between the information provided by the different teams taking care of the patient. The second step gives the opportunity for the patient to consult other persons who can help him to take his decision (e.g. members of his family, family doctor, patients' organizations). The third step aims to formalize the decision, most of the time a written document will be signed by the patient. The process does not end with this third step, the exchange of information has to continue during the treatment. Cultural and personal aspects should be taken into consideration, for example the patient's family may have a different role depending on cultural settings.

Specific modalities for patients unable to give consent will be discussed, as well as complex situations such as palliative radiotherapy. ■





*Contrôle* review's articles present the ASN view of the subject covered and gives an opportunity for the various stakeholders concerned to express themselves freely with regard to the law.

## C O N T R Ô L E .

the French Nuclear Safety Authority Review

6, place du Colonel Bourgoin, 75572 Paris Cedex 12 – France

Broadcasting: Phone: 33.1.40.19.86.53 – Fax: 33.1.40.19.86.32

E-mail : ASN.PUBLICATIONS@asn.fr

Publishing director:

André-Claude LACOSTE, Chairman

Deputy publishing director: Alain DELMESTRE

Coordinator: Jean-Luc GODET

Editor: Pascale LUCHEZ

Editorial staff: Fabienne COVARD

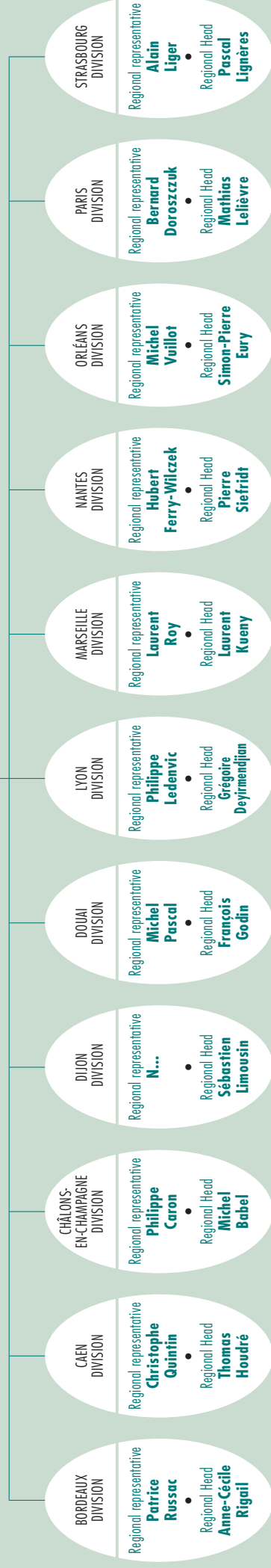
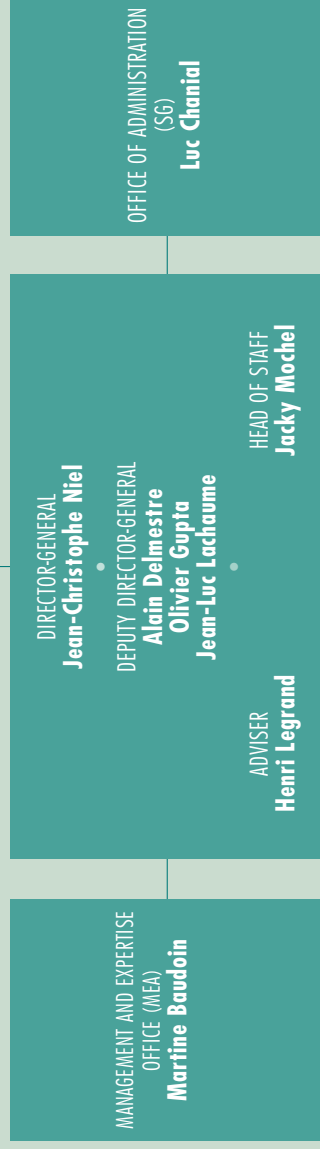
Photos: cover: ASN

p. 1: ASN/CEil Public-M. Zumstein, p. 2: Siemens, p. 5: F. Marvaux/REA, p. 7: Lebrecht Music & Arts/Corbis, p. 10: Noak/Le Bar Floréal/Institut Curie,  
p. 12: O. Seignette/M. Lafontan/IRSN, p. 13: IRSN, p.19: ASN, p. 23: P. Grollier/Architecte: cabinet A. Béchu, p. 24: ASN, p. 26: SFR0,  
p. 31: Siemens, p. 32: SFPm, p. 34: BSIP/L. Oigny, p. 36: FHF, p. 44: BSIP/Phototake/Levy, p. 45: La ligue contre le cancer, p. 47: Médiateur de la République,  
p. 48: F. Tondre/REA, p. 51: ASN/CEil Public – M. Zumstein, p. 53: AIEA, p. 55: OMS, p. 57: Commission européenne, p. 58: Institut Curie,  
p. 62/63: D. Peiffert, p. 67: IAEA, p. 82: O. Holmberg, p. 85: L. Pinillos, p. 91: Raguet/Phanie, p. 101: A. Lisbona, p. 107: O. Holmberg,  
p. 112/113: A. Veres, p. 116: HM. Olerud, p. 129: ASN/P. Dubreuil photographies, p. 131: Garo/Phanie.

ISSN : 1254-8146 – Commission paritaire : 1294 AD – Realization : ARTYG, Paris 2<sup>e</sup> – Printing-Office: FABREGUE, 87500 Saint-Yrieix-la-Perche

# ASN organization chart

at November 1st, 2009



Name ..... First Name .....  
 Address .....  
 Zip Code ..... Town ..... Country .....

**Send to: ASN : Centre d'information et de documentation du public**  
**6, place du Colonel Bourgoïn, 75572 Paris Cedex 12 – Fax: 33 (0)1 40 19 86 92**

Les dossiers de la revue <b>CONTROLE</b>		Select quantity			Select quantity
100-101	La communication*	out of stock	149	La surveillance radiologique de l'environnement (11.2002)	out of stock
102	Les déchets faiblement et très faiblement radioactifs (12.1994)*	out of stock	150	Sûreté et compétitivité (01.2003)	
103	Le rapport d'activité 1994 de la DSIN (02.1995)*	out of stock	151	La sûreté nucléaire et la radioprotection en France en 2002 (03.2003)	
104	Les commissions locales d'information (04.1995)*	out of stock	152	Le démantèlement des installations nucléaires : le nouveau panorama (05.2003)	out of stock
105	La sûreté des réacteurs du futur, le projet EPR (06.1995)		153	Le radon : évaluation et gestion du risque (06.2003)	
106	L'organisation du contrôle de la sûreté et de la radioprotection (08.1995)		154	Les enjeux de la maintenance (09.2003)	
107	Les réacteurs en construction – le palier N4 (10.1995)		155	Les études probabilistes de sûreté (11.2003)	
108	La crise nucléaire (12.1995)*	out of stock	156	Épidémiologie et rayonnements ionisants (01.2004)	
109	L'activité en 1995 de la DSIN (02.1996)*	out of stock	157	Rapport de l'ASN sur la sûreté nucléaire et la radioprotection en France en 2003 : extraits (03.2004)	
110	Le retour d'expérience des accidents nucléaires (04.1996)		158	La radioprotection des travailleurs (05.2004)	
111	Les rejets des installations nucléaires (06.1996)*	out of stock	159	L'harmonisation de la sûreté nucléaire en Europe (07.2004)	
112	Les exercices de crise (08.1996)*	out of stock	160	La recherche en sûreté nucléaire et en radioprotection (09.2004)	
113	Déchets radioactifs : les laboratoires souterrains de recherche (10.1996)		161	Contamination radioactive : quelles actions pour les sites pollués ? (11.2004)	
114	La communication sur les incidents nucléaires (12.1996)		162	La sûreté du cycle du combustible (01.2005)	
115	L'activité de la DSIN en 1996 (02.1997)		163	Rapport de l'ASN sur la sûreté nucléaire et la radioprotection en France en 2004 : extraits (03.2005)	
116	La sûreté du cycle du combustible 1 <sup>re</sup> partie (04.1997)*	out of stock	164	Le réacteur EPR (05.2005)	
117	La sûreté du cycle du combustible 2 <sup>e</sup> partie (06.1997)*	out of stock	165	La gestion des déchets radioactifs en France (07.2005)	
118	La gestion des déchets très faiblement radioactifs (08.1997)		166	Contrôler la sûreté nucléaire et la radioprotection (09.2005)	
119	Le démantèlement des installations nucléaires (10.1997)		167	La radioprotection internationale : les acteurs internationaux (12.2005)	
120	Le transport des matières radioactives (12.1997)		168	Le risque (02.2006)	
121	L'activité de la DSIN en 1997 (02.1998)		169	Rapport de l'ASN sur la sûreté nucléaire et la radioprotection en France en 2005 : extraits (03.2006)	
122	Le contrôle de la construction des chaudières nucléaires (04.1998)		170	La radioprotection internationale : les autorités nationales de radioprotection (05.2006)	
123	Radioprotection et INB (06.1998)		171	Protéger la population en situation d'urgence (07.2006)	
124	Les relations internationales bilatérales (08.1998)		172	La radioprotection des patients : pour une meilleure prise en compte de la radioprotection des patients dans les pratiques médicales (09.2006)	
125	25 ans de contrôle de la sûreté nucléaire (11.1998) ( épuisé)		173	L'utilisation de sources radioactives dans l'industrie et la recherche (12.2006)	
126	La gestion des matières radioactives et son contrôle (12.1998)		174	La sûreté des transports des matières radioactives (02.2007)	
127	La sûreté nucléaire en 1998 (03.1999)		175	Rapport de l'ASN sur la sûreté nucléaire et la radioprotection en France en 2006 : extraits (04.2007)	out of stock
128	Les réacteurs expérimentaux et de recherche (04.1999)		176	Les réacteurs expérimentaux et leur contrôle (07.2007)	
129	Le vieillissement des installations nucléaires (06.1999)		177	Les rejets radioactifs en France (11.2007)	
130	Sites contaminés et déchets anciens (08.1999)*	out of stock	178	Les relations entre l'ASN et les différents acteurs, un an après la loi TSN (01.2008) version  sur <a href="http://www.asn.fr">www.asn.fr</a>	
131	Les systèmes informatiques dans l'industrie nucléaire (10.1999)		179	Rapport de l'ASN sur l'état de la sûreté nucléaire et de la radioprotection en France en 2007 : extraits (04.2008) ( épuisé)	
132	Le retour d'expérience des exercices de crise nucléaire (01.2000)		180	La gestion post-accidentelle d'un accident nucléaire (07.2008)	
133	La sûreté nucléaire en 1999 (03.2000)		181	Le démantèlement des installations nucléaires de base (11.2008)	
134	La gestion des déchets radioactifs : l'état des recherches début 2000 (04.2000)		182	Contrôle du nucléaire : l'inspection par l'ASN (02.2009)	
135	Les relations internationales multilatérales (06.2000)		183	Rapport de l'ASN sur l'état de la sûreté nucléaire et de la radioprotection en France en 2008 : extraits (04.2009)	
136	Le risque d'incendie dans les installations nucléaires (09.2000)		184	La poursuite d'exploitation des centrales nucléaires (07.2009)	
137	Les rejets des installations nucléaires (11.2000)				
138	Le plutonium (01.2001)				
139	Rapport sur la sûreté nucléaire en France en 2000 (03.2001)				
140	L'homme, les organisations et la sûreté (05.2001)				
141	Sûreté nucléaire et transparence (07.2001)				
142	La protection contre les risques externes (09.2001)				
143	Le contrôle de l'utilisation des rayonnements ionisants (11.2001)				
144	L'inspection des installations nucléaires (01.2002)				
145	Rapport sur la sûreté nucléaire en France en 2001 (03.2002)				
146	Transport des matières radioactives (05.2002)				
147	Les réexamens de la sûreté des installations nucléaires (07.2002)				
148	La radioprotection des patients (10.2002)	out of stock			

(1) Maximum 5 issues

\* The out of stock issues can be consulted at ASN's Information and Documentation Center (Paris, France)

also available in english