AUTORITÉ DE SÛRETÉ NUCLÉAIRE
DIVISION DE BORDEAUX

RÉPUBLIQUE FRANÇAISE

Bordeaux, le 29 mai 2007

REPORT
concerning the radiotherapy incident at the university hospital centre (CHU) in Toulouse – Rangueil Hospital

1. The context : Calendar of events and description of the incident

1.1. Notification of the incident

The French Nuclear Safety Authority (ASN) was alerted by a call to ASN's Freefone number by Dr Igor Latorzeff, radiotherapist at Rangueil Hospital in the university hospital centre (CHU) in Toulouse on Friday 20 April 2007 at 11:55 (he also holds a licence (*DEP-DSNR Bordeaux –0494-2006*) to use radiotherapy equipment, issued by ASN on 7 April 2006 in accordance with the Public Health Code). The radiotherapist stated that the calibration file for the Novalis accelerator did not correspond to the manufacturer's file.

ASN's Bordeaux division was immediately informed and phoned back the radiotherapist. The hospital was not yet able to say whether the dose error consisted in an over- or underdosage. The division asked the hospital to put their material vigilance officer in contact with the French Health Products Safety Agency (AFSSAPS).

1.2. Detection and presentation of the incident

The incident involved the stereotactic surgery facility (http://www.chu-toulouse.fr/spip.php?article1695).

The manufacturer of the device, BrainLAB, carried out an intercomparison of the calibration files among the various European hospitals equipped with the device. At this point, they detected an anomaly in the files at the Toulouse CHU and informed the hospital on 17 April 2007. The anomalous file is used for the definition of microbeams (< 3 cm² of multi-leaf conformal radiation used in the treatment of the central nervous system). The potential consequences of the anomaly affect the calculation of the beam's monitor units.

The flaw had been present since the initial calibration of the device and the acceptance of the BrainSCAN software in April 2006 (the date when it was authorized). Only treatment in conformal mode using multi-leaf microbeams is concerned. This represents 145 patients of the 172 treated with the device since it began operation. The other 27 patients were given treatment using a conical collimator.

The report of the incident and facts relating to its handling by the team at Toulouse CHU reached the Bordeaux division of ASN on 20 April. The Departmental Health and Social Action Directorate (DDASS) in Haute-Garonne and the Midi-Pyrénées Regional Hospitalisation Agency (ARH) were contacted by the Bordeaux division in order to ensure rapid exchange of information on the same day as it was reported by the hospital.

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1.3. Immediate measures

Operation of the device was halted by the hospital on the morning of 18 April in order to carry out a complete reinitialization, which was the only way of evaluating the consequences of the anomaly. The radiophysicist carried out a simulation of the patients who had already been treated, using the new parameters. It was only subsequently that it would be possible to confirm or not the health implications.

The Bordeaux division was subsequently regularly informed about the results of the team's work, and carried out a new review of the situation on 25 and 27 April to ASN headquarters. The radiophysicist and the physics team at BrainLAB completed the requisite correction of the calibration file and ensured that this lay within the range of tolerance laid down by the manufacturer. The team at the hospital (radiotherapist and radiophysicists) then went back over all the dosimetries of the patients treated before the 18 April 2007.

On 1 May 2007, preliminary data for the recalculated doses for the 172 patients were transmitted to ASN. These concern, for each location treated and for each patient, the volume of the lesion, the target dose-volume histogram, the type of organ at risk affected and the volume concerned by a dose exceeding the limits laid down.

A reactive inspection, announced beforehand, took place on the afternoon of May 3, with a view to examining the circumstances of the incident and to clarifying the dosimetric consequences and the expected side effects. ASN referred the case to its technical support, the French Institute for Radiation Protection and Nuclear Safety (IRSN), in order to obtain an expert evaluation of the radiation physics and radiation pathology aspects connected to the incident. DDASS in Haute-Garonne and AFSSAPS took part in the inspection team.

2. The reactive inspection of 3 May 2007

2.1 Goals

The inspection led by ASN's Bordeaux Division, with technical support from IRSN, had three main goals:

- to identify the causes of the incident and its potential health effects;
- to evaluate procedures for informing patients and the associated follow-up;
- to specify the conditions for resumption of operation of the accelerator.

2.1 Participants

Dr Martine SERVAT	DDASS in Haute-Garonne
Cyril BESNIER	AFSSAPS – Hospital inspection
Hélène BRUYERE	AFFSAPS – Material vigilance
Jeanne FALIU-JANS	ASN – Bordeaux Division
Thierry LECOMTE	ASN – Bordeaux Division , deputy head of division
Franck LHOSTE	ASN – Bordeaux Division
Cécile ETARD	IRSN – Radiophysicist
Marc BENDERITTER	IRSN - Radiopathologist
Régis COCHET	BrainLAB France
Jean HOOKS	BrainLAB
Pr Yves LAZORTHES	CHU Toulouse – Neurosurgeon
Dr Igor LATORZEFF	CHU Toulouse – Radiotherapist
Dr Philippe BOUSQUET	CHU Toulouse - Neurosurgeon
Pr Isabelle BERRY	CHU Toulouse – Biophysics
Dr Jean-Albert LOTTERIE	CHU Toulouse – Neurologist
Dr Alain REDON	CHU Toulouse – Radiotherapist
Anne VITTET	CHU Toulouse – Quality and Strategy Department
Claude RIEUX	CHU Toulouse - Quality and Strategy Department (material vigilance)
Pierre DUTHIL	CHU Toulouse – Radiophysicist, specialist in medical radiation physics for the NOVALIS device and qualified radiation protection officer for the hospital.
Emmanuelle CASSOL	CHU Toulouse - Radiophysicist

2.2 Presentation of the activity of the stereotactic radiosurgery centre

Stereotactic radiosurgery is a non-invasive image-guided technique with millimetre-scale precision, and is an alternative to normal surgery. Defining the target is of great importance. In Toulouse, stereotactic radiosurgery is mainly used in the treatment of intracranial tumours, and also of brain malformations.

The therapeutic support and protocols are based on feedback from techniques and from literature from all over the world, since this technique is used in around a hundred identical centres around the world. The prescriptions are precisely adapted to the particular pathology; the precision of the treatment is all the greater if the volume is small and the single shot is precisely adjusted.

A weekly interdisciplinary meeting is held, which intensifies consultation among the professionals involved in following up the patients.

The centre is open on Mondays, Wednesdays and Fridays.

2.3 Origin of the incident

During the initial acceptance test of the device, the hospital physicist carries out the calibration of the beams. In order to do this, he/she initially carries out measurements of the doses produced by the machine for every size of beam, in every possible position and with all the accessories which may be used (collimators). He/she must therefore use measuring tools (ionisation chambers) which are appropriate, in particular for the size of the beam to be measured. The measurements carried out are subsequently used to insert parameters into the files which will be used by the computer software that drives the accelerator during treatment. In the case of the stereotactic surgery accelerator at Rangueil Hospital, the calibration stage required the use of several ionisation chambers of sizes that were appropriate, especially for extremely narrow beams, which are not generally used to calibrate beams in conventional radiotherapy. This places complex constraints on the calculations required to obtain the right parameters to be inserted into the accelerator's files.

The BrainLAB instruction manual which comes with the equipment gives general advice on the measurements to be carried out, but does not recommend a standard procedure for the calibration of the beams. The machine is delivered without any parameters, and it is up to the physicists to configure it according to the tools at their disposal and the therapeutic techniques that will be used. Under no circumstances does the manufacturer carry out a validation of the tests: BrainLAB ensures customer support to the hospital in order to solve any problems regarding the mechanical working of the machine, but never ventures into the field of radiation physics. BrainLAB can put their customers in contact so as to compare dosimetric values obtained during tests and the parameters contained in the various files in the machine.

Treatment was therefore carried out for a year with a discrepancy between the prescribed dose and the actual output dose, until BrainLAB proceeded to improve the protocol and discovered the anomaly by comparing the Toulouse files with those at other identical centres.

Although the origin of the event is clearly identified (use of a measuring device which was inappropriate for calibrating microbeams), the underlying causes remain to be determined; this, however, was not the main goal of the inspection. The letter following the inspection therefore asks the CHU to analyse the organisational and human factors, especially human resources, work load, skills and training.

An annual external quality control for the sizes of specific fields had been planned for August 2007 with the Equal Estro company, the only body accredited for the whole of France for stereotactic surgery accelerators. Would this control have brought the anomaly to light ? Not necessarily, since the company uses thermoluminescent dosimeters that are sent to radiotherapy departments, which irradiate them by positioning them according to a specific protocol: the company then develops them. The CHU has asked Equal Estro whether this methodology is applicable to the specific nature of its microbeams, and is currently awaiting a response.

2.4 Handling of the incident

The aftermath of the incident was handled satisfactorily by the hospital (report, analysis of the impact on all the patients, setting up of corrective measures, preparation of information for the patients within a very tight time limit, conditions for resumption of operation).

As soon as the incident was discovered, the device was recalibrated with a so-called 'pinpoint' ionisation chamber, appropriate for microbeams. IRSN was not able to examine the new calibration procedures during the inspection. The new configuration of the facility first enabled the true output doses during treatment to be recalculated, which was verified by IRSN.

For 10 days, from 20 April to 1 May, the CHU team proceeded to recalculate the doses received by 172 patients treated since the accelerator began operation. This work led to the setting up of a data base with, for each patient, the prescribed dose for the target organ, the dose actually received by the organ, as well as the dose received by healthy organs and the proportion of these organs affected. The inspection team did not evaluate these documents on the spot during the inspection. However, the CHU presented them and there was an initial discussion.

2.5 Analysis by the Toulouse CHU of the dosimetric consequences and expected side effects

According to information provided by the CHU during the inspection, the actual output doses were within the limits of output doses in other centres, particularly one of the pioneers, the San Francisco centre, where the CHU team had taken part in training and exchange sessions. These dose ranges apply to target organs.

With regard to neighbouring healthy organs, any increase in dose to the target organ is likely to affect them. Dose limits are therefore defined in order to limit the impact of doses received by healthy organs to levels below that which have any adverse health effect. Although with the doses initially prescribed for the target organs the CHU had been careful to remain below this dose limit with regard to healthy organs (with some justified exceptions), the configuration incident led to the predetermined dose limits being exceeded, but only, according to the CHU, in very small proportions of volume of the healthy organ, in the region of a few per cent. 6 cases were identified where over 5 % of the volume of the healthy organ was probably affected.

It is difficult to be sure on the basis of these data whether a health effect may occur, since the volume of the organ affected is very small, and because there is currently insufficient scientific knowledge in this field.

Those centres that treat target organs at such high dose levels, and where as a result healthy organs receive the same dose levels as in the case of the Toulouse incident, have not observed any adverse health consequences, which is incidentally the reason why they treat patients with such high doses.

ASN will nevertheless refer the case to IRSN in order to obtain a more in-depth expert evaluation of the data provided by the hospital, and in particular of the cases of the 6 patients for whom over 5% of the volume of healthy organs may have been affected.

2.6 Discussions with the manufacturer of the accelerator

Prolonged discussions also took place with the representatives of the manufacturer of the Novalis accelerator, the BrainLAB company. It turns out that the operating instructions for the machine, in this case entirely translated into French, recommend a certain number of steps for the calibration of the beams, without it being compulsory to keep to a single procedure. In the final analysis, the calibration of the beams and the methodology implemented are a matter for the team of physicists who are going to use the accelerator. BrainLAB is present during the setting up of the machine and accompanies the hospital during the acceptance test. However, it is merely a question of ensuring that the mechanical and software operating parameters are correct. The physics team then has to regulate the machine and complete the computer files using the measurements that it carries out.

An additional check by IRSN and AFSSAPS nevertheless ensures that the operating instructions contain the minimum amount of information needed to carry out the calibration of the beams. BrainLAB were advised to review the operating instructions with a view to including feedback from the incident, apparently the first of its kind even though BrainLAB has already set up 87 similar facilities throughout the world.

2.7 Patient information

With regard to information to the patients about the calibration anomaly, the hospital informed the inspectors that they wished to proceed with this before any public announcement, by using the exceptional procedure of calling the patients in by post, which would enable them to be accompanied when informed about the reassessment of the dose. The doctors will carry out a complete health check-up, on top of the standard quarterly clinical and medical imaging follow-up procedure.

Approximately twenty new treatment sessions were cancelled while the machine was out of operation. From the standpoint of medical ethics, it was desirable to resume treatment as quickly as possible, once it was certain that the machine was safe, which was the case on 14 May.

3. The follow-up to the inspection

The authorisation granted in 2006 in accordance with the Public Health Code to the Toulouse CHU for the use of the accelerator was not suspended, since the CHU itself decided to halt all treatment until such time as the situation was back to normal. Once the inspection team had observed that the new procedure for calibrating the microbeams was satisfactory, and had been informed about all the work carried out by the CHU in order to assess the health impact on the patients concerned and ensure their medical follow-up, they did not object to operation being resumed.

ASN sent a follow-up letter to the hospital on 29 May 2007 (see attached document) containing a number of requests for corrective action and for additional information.

AFSSAPS is carrying out an analysis of the manufacturer BrainLAB's instruction manuals. AFSSAPS may request the BrainLAB company to review its documents.

3.1 Points for further examination

The hospital has been asked to draw up a report on the incident. It should present an analysis of the causes of the incident, the lessons that have been learnt from the event, and should lay out the corrective action taken to ensure that such a situation does not happen again.

In order to analyse in more detail the incident and the potential consequences expected, ASN considers that further information should be provided:

- The values for the doses initially prescribed in addition to the table of dosimetric data,
- Confidentially, the medical records of the six patients for whom the dose limits for organs at risk were exceeded, for significant volumes of the organ. The records will be sent to a radiation pathologist at IRSN for an expert evaluation regarding possible side effects.

Rangueil Hospital was asked to provide this information in the follow-up letter.

3.2 Epidemiological follow-up study of the cohort of patients concerned

The Health Monitoring Institute (Institut de Veille Sanitaire, InVS) will carry out a follow-up of the cohort of patients concerned from the health standpoint. InVS will propose an epidemiological surveillance protocol which will last for a minimum post-treatment period of two years, which corresponds to the time taken for the appearance of the side effects to be feared after this type of treatment.

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APPENDIX

Follow-up letter to the inspection of 3 May 2007
CHU de Toulouse - Hôpital de Rangueil

RÉPUBLIQUE FRANÇAISE

AUTORITÉ DE SÛRETÉ NUCLÉAIRE

DIVISION DE BORDEAUX

Docteur Igor LATORZEFF
Hôpital de RANGUEIL
1 avenue Jean-Poulhès - TSA 50032
31059 TOULOUSE Cedex 9

Bordeaux, le **29 MAI 2007**

Subject: Inspection INS-2007-ENTBOR-082 of 3 May 2007 further to incident report 20 April 2007

Authorisation DEP-DSNR Bordeaux-0494-2006 7 Apri1 2006

Ref : [1] - Letter DEP-Bordeaux-0460-2007 dated 27 April 2007
[2] - Letter DGSNR/SD7/n°1027/2006 dated 19 April 2006 relating to the prevention of serious radiotherapy risks via an approach based on organisational and human factors.

Dear Dr Latorzeff,

As was announced in the letter whose reference is given above, Officers from the Nuclear Safety Authority (ASN) carried out on 3 May 2007 a reactive inspection in accordance with protection against ionizing radiation after a notification of an incident involving the stereotactic radiosurgery accelerator.

I am writing to provide you with a summary of the visit, as well as to inform you of the main requests and comments resulting from the observations made on this occasion.

Summary of the inspection

The inspection followed a notification of an incident concerning the calibration of the Novalis stereotactic radiosurgery facility, which led to a large number of patients receiving higher doses than those prescribed. The information obtained between the time of the notification and the inspection was clarified and explanations were given regarding the detection and causes of the event.

The use of an ionisation chamber of inappropriate dimensions for the size of the microbeams produced for most treatment led to a calibration error from the moment the facility began operation in April 2006. The error came to light during an intercomparison with other similar facilities used throughout the world carried out in April 2007 by the BrainLAB company, the provider of the facility.

Once the correction of the calibration had been carried out by the CHU working with the manufacturer, the dosimetric data were recalculated for all 172 patients treated since the facility began operation. Taking into account the type of beams affected by the error, the team in charge of treatment identified 145 patients who had been subject to an overexposure the size and length of which depended on the size of the fields, the location of the lesion and the type of pathology.

The patients treated by stereotactic radiosurgery at the Toulouse CHU are undergoing a quarterly medical checkup and the ASN inspectors have taken note of the fact that until now no functional clinical event has been reported for the 145 patients.

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A summary report presenting the recalculated dosimetric parameters for the 145 patients was handed over to the inspectors by the CHU during the meeting.

It was agreed that resumption of operation of the accelerator was possible, after implementation of the acceptance procedure for the dosimetry software. A comparison of the isodoses of patients' medical records with another Novalis centre would also provide a further guarantee for ensuring the safety of treatment.

Finally, the issue of patient information linked to that of information about the incident was examined. The information should be made public within a reasonable time limit, while leaving the hospital enough time to inform and accompany the patients when the incident is announced. The communications strategy will be defined following consultation of the decision-making bodies of the Ministry of Health and ASN.

A. Requests for corrective action

Comparison before resumption of operation

Given the specific methodology required in order to calibrate the microbeams, as well as the errors which led to the problems that caused the incident, it is clear that a new intercomparison with other hospitals using the same equipment would appear to be a useful safety measure for the validation of the configuration of the accelerator.

Request A.1: I ask you to undertake a comparison of the estimated dosimetry of the patients concerned by the incident with another Novalis centre in order to confirm the correct configuration of your device.

The incident demonstrates, similarly to other incidents recently reported in France, sometimes with more serious consequences, the importance which should be granted to ensuring the safety of radiotherapy treatment, since such malfunctions can lead to situations which have a major impact on health. In the circular whose reference is given above [2], following the initial reports of incidents in Lyon and Grenoble, ASN alerted beam therapy departments to the importance of 'the role of people and of organisations' in making treatment safer. To this end, in the appendix to the letter it was proposed to set up a risk management procedure comprising phases of risk identification, analysis and treatment.

The need to analyse risks is in fact more necessary than ever, and should lead to the following topics in particular being covered:

- patient program: reception and first consultation, acquisition of morphological data, utilisation of images in order to determine volumes of concern, calculation of the dose distribution and MUs, definition of ballistics, treatment.
- materials: TPS, "record and verify", materials for immobilisation and marking, masks, portal imaging, treatment equipment, metrology. In this respect, the impact of computerization on changes in staff activity should be analysed;
- organization of the department.

Finally, I would like to point out that risk analysis should be open-ended in nature in order to take into account, on the one hand, changes in the department (materials, staff, organization, etc) and, on the other, both internal and external feedback. To this end, regarding the latter point, you might want to take into consideration any events (near-incidents and incidents) identified within your department. I would therefore ask you to set up a system for the reporting of such events (logbook).

Request A.2: I ask you to initiate an analysis of the risks within your department in order to formalize your work procedures, identify critical operations and on that basis take steps to set up the appropriate structural and organizational measures.

Request A.3: I ask you to set up a system for identifying and reporting any event which may be considered as a discrepancy which might possibly lead to an incident.

Patient follow-up

You should ensure that patients are systematically and regularly monitored following their treatment. Following the detection of the dose anomaly, an exceptional consultation should be proposed to all the patients, while the medical follow-up should be extended to several years, given the delay before the appearance of side effects potentially linked to the treatment.

Request A.4: I ask you to keep me informed of the results of the clinical follow-up of the patients following the exceptional post-incident consultation, and then on an annual basis or in the event of clinical signs which suggest the recent appearance of a radiation-induced complication.

B. Additional information:

Analysis of the incident

Request B.1: I ask you to draw up and send to me a report on the incident. It should present an analysis of the causes of the incident, the lessons that have been learnt from the event by the department and the CHU, and should lay out the corrective action taken to ensure such a situation does not happen again. The analysis of the causes should in particular examine human and organizational factors (workload, skills, training , etc). The report should also detail:

- **The precise experimental conditions under which the erroneous measurements leading to the calibration errors were carried out;**
- **The precise experimental conditions under which the measurements were corrected after the discovery of the incident;**
- **The results of measurements of scatter factor, before and after correction, for all the beams affected by the error.**
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Dosimetric data for patients

Request B.3: I ask you to add to the final summary table of the anonymous dosimetric data for the 145 patients an additional column which mentions, for each patient, the dose initially prescribed on the PTV envelope and the corresponding isodose.

Medical records

IRSN observed that, in the final summary table of dosimetric data, there are 6 patients for whom the dose restrictions for organs at risk that you selected were exceeded for significant volumes of the organ.

Request B.4: I ask you to send, in confidence, the complete records for these 6 patients containing the dose-volume histograms, the isodose curves, the treatment plan and the clinical records, to an IRSN doctor (Pr. Gourmelon).

C. Remarks.

None.

I would be grateful if you sent me your comments and responses regarding these points within **a time limit not exceeding 3 months**. With regard to any commitments you may make, I would ask you to identify them clearly and specify, for each one, the target date for its completion.

Yours sincerely,

For the President of ASN and acting on the authority of the head of the Bordeaux division

Julien COLLET