The Medical Follow-up of the Radiological Accident: Épinal 2006

Authors: Tamarat, Radia, and Benderitter, Marc

Source: Radiation Research, 192(3) : 251-257

Published By: Radiation Research Society

URL: https://doi.org/10.1667/RR15262.1

RADIATION RESEARCH **192**, 251–257 (2019)
0033-7587/19 $15.00

DOI: 10.1667/RR15262.1

The Medical Follow-up of the Radiological Accident: Épinal 2006

Radia Tamarat[1] and Marc Benderitter

Radioprotection and Nuclear Safety Institute (IRSN), Health Division, Fontenay-aux-Roses, France

INTRODUCTION

The radiation overdoses that occurred during radiotherapy at the Public General Hospital in Épinal has been considered the most severe in France. This accident was rated 6/7 on the French Society for Radiation Oncology Scale (ASN/SFRO), whereby radiological events are rated from 1 to 7 based on established consequences (including death of individuals) and the potential effects of the events (*1*).

This accident was linked to errors in the treatment process, which led to different levels of overexposure for more than 5,000 patients (*2–5*). Three patient cohorts, Épinal I, II and III, were defined according to chronological discovery, as follows:

Épinal I. In this cohort, 24 patients who received radiotherapy for prostate cancer between May 2004 and August 2005 were exposed to an additional radiation dose of 20% to 30% due to an error in operating the treatment planning software (calculation of the treatment time with physical wedges, radiation with dynamic wedges).

Épinal II. In this cohort, 409 patients receiving radiotherapy for prostate cancer between October 2000 and October 2006 were exposed to an additional radiation dose of 0.17 to 0.34 Gy (8 to 10%) due to daily portal imaging. This overdose was not considered in the patient's final dosimetry.

Épinal III. In this cohort, 5,012 patients received radiotherapy for cancer between 1987 and July 2000 using an isocentric technique. Here, a calculation error inserted into the ''in-house'' IT program for monitor unit (MU) calculation led to an overdose of 3% (1,100 patients), 5.5% (3,600 patients) and 7.1% (312 patients).

ACCIDENT CIRCUMSTANCES

Two accelerators, a 6-MV Clinac 600 CD® and a 6- and 25-MV Clinac 2100 C® equipped with a portal imaging system, a multi-leaf collimator and dynamic wedges with an ''intensity modulation'' option were embedded at the Radiation Oncology Department in 1999 and 2000, respectively. These two new machines were in addition to the existing 12-MV Saturne machine that was in operation in the department. The accident resulted from a convergence of different human errors. There were three main sources of error, discussed below. These were related to inaccurate ''in-house'' calculation of the MU, improper use of portal imaging and inadequate use of dynamic wedges for IMRT.

Inaccurate In-house Calculation

The first error was related to an inaccurate in-house calculation of the MU. Prior to 2001, a correction factor linked to the radiation beam calibration was systematically omitted in the calculation of the MU number for the isocentric technic. As a consequence, 5,012 patients received additional dose of 5.5% (3,600 patients treated with the Saturne 12-MV), 3% (1,100 patients treated with the Clinac 600 CD) and 7.1% (312 patients treated with the Clinac 2100 C).

Improper Use of Portal Imaging

Patient positioning on the Clinac 600 CD and Clinac 2100 C machines was controlled using both portal imaging (matching) and radiography checks. In 2001, matching for the patient positioning was performed daily, for each radiation session, based on two orthogonal images generated by 6-MV beams (front and side). In addition, radiography checks were performed weekly, using four treatment beams and double exposure (6 and 25 MV). At the time the errors occurred, the dosimetric impact of the check and matching was considered negligible. In fact, the doses corresponding to the weekly check and daily matching were calculated *a posteriori* and corresponded to doses of 0.38 and 0.17 Gy, respectively. In November 2006, the dosimetric contribution of the check and matching was considered to calculate the MU for each session, according to best practices. As a result, it was determined that four patients from 2001 to 2006 received an additional dose of 8–10% compared to the dose prescribed by the radiation oncologist.

Inadequate Use of Dynamic Wedges for IMRT

The Clinac 2100 C machine was initially used to treat prostate cancer patients by 3-dimensional (3D) conformal radiotherapy using the static wedge technique. In 2004, this machine was employed to treat prostate cancers by 3D conformal radiotherapy with intensity modulation (IMRT), using dynamic wedges. The switch from static to dynamic

[1] Address for correspondence: IRSN, Health Division, BP17, 92262 Fontenay aux Roses Cedex, France; email: radia.tamarat@irsn.fr.

wedges without changing the dosimetry parameters resulted in an error in the dose delivered to 24 patients, which was 20% higher than the dose initially prescribed by the radiation oncologist.

Simulation of the different radiation sequences, using treatment planning software (TPS), was performed to calculate the MU necessary to configure the linear accelerator. The planning considered the dose prescribed by the radiation oncologist, the type of wedge (static or dynamic) used on these machines and the characteristic of the radiation beam. An error in the selection of the type of wedge used for the treatment was introduced during the parameter settings of the TPS. Finally, each radiation fraction planned for delivery with the dynamic wedge, according to the prescription of the radiation oncologist, was delivered by the machine parameterized with the MU calculated to conform with the use of the static wedge. *In vivo* dosimetry check was not performed at that time to control the radiation exposure.

Discovery and Subsequent Actions Taken

The first symptoms related to radiation overdose appeared in January 2005, when gastroenterologists reported unusual occurrences of rectitis. A high number of unusual, serious cases of rectitis began to occur in May 2005, increasing from 5 to 10 within a few months. The French Nuclear Safety Authority (ASN) was notified of the accident and inspected the Radiation Oncology Department in July 2006.

In October 2006, the Ministry of Health requested that the French Radioprotection and Nuclear Safety Institute (IRSN) conduct an assistance mission at the hospital and provide the patients with the best medical care possible. A total of 425 overexposed patients were identified. Among these patients, four died, 11 were left with severe late health consequences and nine with moderate health consequences. None of the 24 highly effected patients from the Épinal I cohort escaped uninjured. These patients received conventional treatment, including corticotherapy, hyperbaric oxygen therapy (HBO), argon laser or surgery. Since these treatments were not sufficient, a multidisciplinary medical committee was organized to propose new strategies for the medical management of these patients.

All radiotherapy at the Radiation Oncology Department of Épinal Hospital was suspended in late January 2007. In addition, the ASN and the French Society of Oncological Radiotherapy (SFRO) were asked to assess the consequences for each patient who received radiation overdoses and identify recommendations concerning safety improvements at the Radiation Oncology Department (*6*).

DOSE RECONSTRUCTION

Radiation dose was recalculated for the majority of patients comprising the Épinal I and II cohorts who suffered from severe complications, as reported by Derreumaux *et al*. (*7*).

Patient treatment planning included radiotherapy (6 and 25 MV Clinac 2100 C) for prostate adenocarcinoma combined or not with hormonotherapy or prostatectomy. Five convergent complex fields collimated by a multileaf collimator, including four wedged beams, were used, allowing for precise conformity to the tumor shape. Radiation dose was planned for each patient according to tumor grade. Dose planning was dependent on different criteria including dosimetric criteria on the target volume (70, 74 and 78 Gy dose escalation), anatomic criteria [planned target volume (PTV), depending on tumor aggressiveness, was restricted to the prostate, or the prostate and seminal vesicle in case of tumor invasion or to the prostate and pelvis in case of bone metastasis] and dose tolerance of the organ at risk, including mainly the rectum and the bladder. Treatment planning included a simulation of the different treatment sequences with a dedicated TPS (Cadplan, Ightham, UK). Monitor units were determined to configure the accelerator for each radiotherapy fraction depending on the dose prescribed by the radiation oncologist, the type of wedges (static or dynamic) and the characteristics of the beam.

Doses were recalculated for each patient using the same TPS and considering the different sources of errors identified during the treatment process (Fig. 1). It was possible to recalculate the mean, maximum and minimal doses to the PTV, the maximum dose to the rectum and the percentage of rectal volume receiving a dose higher than 70 Gy, and maximal dose to the bladder and the bladder volume that received a dose higher than 70 Gy based on the reconstructed dose-volume histograms. Dose recalculation was compared to dose reconstruction using anthropomorphic phantoms irradiated in the same conditions as the patients treated with the Clinac 2100 C. The tissue-equivalent anthropomorphic phantom was equipped with passive dosimeters (L0-α-alanine and thermoluminescent dosimeter). Treatment protocol was delivered to the anthropomorphic phantom using the machine equipped with the static wedge and implemented with the number of MUs calculated for the implementation of the machine with dynamic wedge. Finally, the overdose was evaluated by comparing the planned dose to the reconstructed delivered dose (Fig. 1).

MEDICAL MANAGEMENT

As reported by Voswinkel *et al*., three patients with refractory radiation-induced hemorrhagic colitis were treated with mesenchymal stem cell (MSC) therapy (*10*). The radiation overdose led to severe refractory hemorrhagic colitis and recto-vesicular as well as recto-prostatic fistula. Mesenchymal stem cells can be easily recovered from bone marrow and enriched through their property of adhering to tissue culture surfaces (*14*). The three patients received MSCs by intravenous infusion. Different clinical parame-

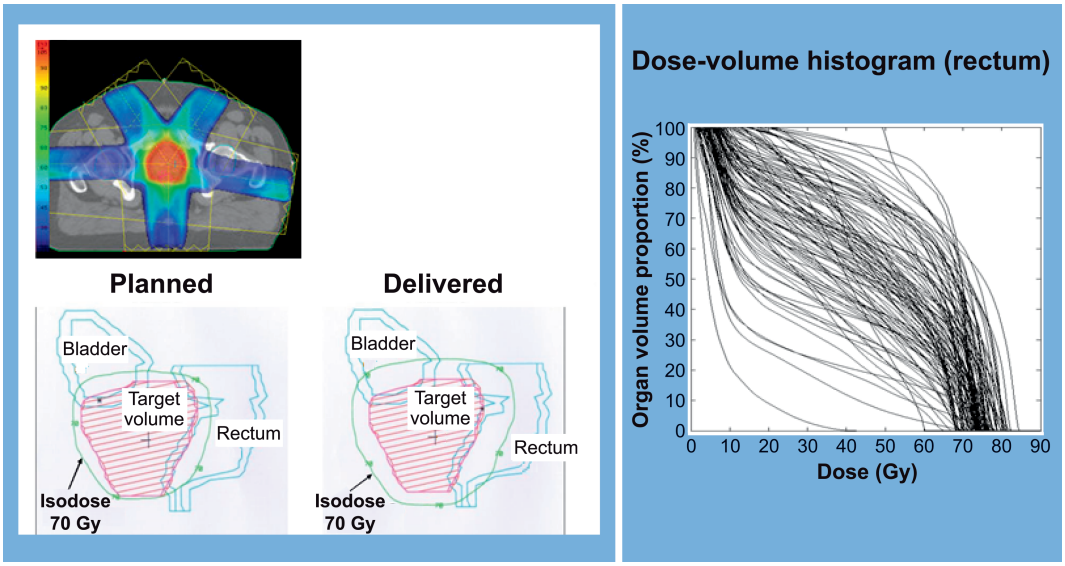

FIG. 1. Dose reconstruction of cohorts of patients who accidentally received an overdose for their prostate adenocarcinoma. The rectum and the bladder are the two main organs at risk. Dose volume histogram for the rectum is shown.

ters, i.e., pain, hemorrhage and fistulization (MRI, colonoscopy), were assessed before MSC administration, then again at 1 and 6 months after MSC therapy.

Épinal I Cohort: The 24 Patients Injured from May 2004 to August 2005

Most of patients who received a radiation overdose of 20% from the wedge error, and the 10% additional dose related to the portal images, suffered from severe rectitis and cystitis and experienced intense pain (resistant to morphine). The conventional treatment included cortico-therapy, chlodronate and hyperbaric oxygen-therapy (HBO). Few patients needed colostomy or ureterostomy. Some patients were bedridden and five of them died, including four from the consequences of the accident. Others suffered from severe anal or bladder incontinence requiring the use of incontinence products in large numbers. No patients went unharmed. Stem cell therapy was proposed as an alternative strategy for those who did not respond to conventional treatments. At that time, three patients, comprising the most severe cases, received MSC injection on compassionate grounds. The other patients received coordinated and multidisciplinary care and follow-up.

Numerous published clinical trials have demonstrated that cell-based therapy appears to be a novel approach for enhancing regeneration or repair of damaged tissues (*9, 11*). As stem cell-based treatments have constituted a promising therapy in fistula management worldwide this last decade (*8*), it was proposed that 3 of the 24 patients, who had high-grade severity, receive MSCs. Furthermore, injections of adult stem cells mainly reduced local and systemic inflammation that, in the untreated course of disease, would lead to progressive and irreversible necrotizing damage. The beneficial effects of MSCs in tissue are attributed to their anti-inflammatory properties (*13*). The paracrine factors secreted by MSCs (extracellular vesicles, proangiogenic factors and anti-inflammatory cytokines) are delivered into the target organ. For these patients, the systemic administration of MSCs was beneficial, with anti-inflammatory effects as well as hemorrhage reduction (*10*).

After MSC therapy, two patients experienced a beneficial effect with regard to pain and hemorrhage. In one patient, pain reappeared 6 months after MSC injection. Reduction of pain was observed after a second injection of stem cells. In addition, prostate cancer remained in stable complete remission in all patients, and no toxicity occurred. Moreover, evaluation of lymphocyte subsets after stem cell therapy revealed a significant reduction of activated effector T lymphocytes associated with a significant increase in $CD4^+$ $CD25^+$ T lymphocytes (potentially regulatory T cells), demonstrating an immune modulation towards a lymphocyte pattern of regulatory cells with an anti-inflammatory potential (*10*).

More importantly, pain was the first symptom and principle criterion for patient self-assessment. Pain was evaluated in a multidimensional approach (*15–17*): functional and emotional aspects as well as cognitive and behavioral aspects are integral to pain evolution. For pain assessment a general questionnaire was used; this questionnaire is most frequently used and best represents an internationally recognized questionnaire for assessing quality of life (*18*).

Case 1. This patient suffered from an overdose of more than 70 Gy of 37% of the rectum and 40% of the bladder, respectively. Tissue injury affected the prostate cavity, rectum and bladder, and was accompanied by a recto-urethral fistula that resulted in the following clinical

manifestations: urine loss in the rectum; pollakisuria; and mictional pain and bleeding. Magnetic resonance imaging (MRI) showed a large necrotic zone and a fistula within the prostate cavity. First-line therapy of these accidental complications consisted of colostomy and suprapubic catheterization. Rectal endoscopy before MSC injection revealed an extremely large recto-urethral fistula. The lasting symptoms consisted of severe and permanent rectal and cystitis pain (*10*). The MSCs were obtained by two collections from the patient's two nieces, consecutively. The first bone marrow collection was insufficient and withdrawn. The second collection of MSCs from the second niece was administered to the patient, and resulted in a complete reduction of pain 10 days after injection (*10*).

Case 2. This patient suffered from an overdose of more than 70 Gy of 53% of the rectum and 43% of the bladder, respectively. Radiation-induced tissue injury affected the prostate cavity, bladder and rectum. Specific therapy of radiation injury consisted of discharging colostomy. The radiation-induced effects led to chronic pain and permanent rectal bleeding in addition to the discharging colostomy and urinary tube. The MRI revealed necrosis of the prostate cavity, a retracted urinary bladder, active cystitis and rectitis and a decomposition of the bladder-prostate bond, as well as a recto-prostatic fistula. The urethro-cystoscopy displayed a stenosis of the upper rectum. A large ulceration appeared on the anterior side of the rectum communicating with the prostate cavity (*10*). MSCs were obtained via two bone marrow collections from the patient's son. The first estimation of a beneficial effect of MSC therapy was observed through significant decrease of bleeding four weeks after cell administration and significant reduction of pain by two weeks after MSC injection. Quality of life improved and was estimated at 80% by the patient. Thus, the efficacy of MSCs on bleeding was confirmed here (no transfusions were required after first MSC therapy). However, six months later, pain recurred and a second MSC injection was performed, with a significant positive effect on pain (*10*).

Case 3. This patient suffered from on overdose with more than 70 Gy on 29% of the rectum and 24% of the bladder, respectively. One year after radiotherapy, the patient obtained a discharging colostomy followed by 20 sessions of hyperbaric oxygen therapy. The tissue damage by overexposure affected the prostate cavity, rectum and bladder resulting in urine incontinence and pain. The MRI showed cystitis and a reduced capacity of the bladder due to strongly enlarged walls. MSCs were collected from his daughter's bone marrow. Six months later, a good tolerance with reduction of analgesic therapy was noted. No further MSC injections were performed (*10*).

Although this medical management of the patients, using on stem cell therapy, did not have the statistical power to confirm efficacy objectively, and despite the lack of a control arm, the efficacy outcomes were nevertheless interesting. The additional goal of this study was to obtain preliminary data on efficacy necessary for subsequent phase II trial design. The novel therapy described here could provide significant benefits relative to current approaches in clinical management.

Épinal II Cohort: Patients that Received Radiation Overdose from Portal Imaging, 2001 to November 2006

From 2001 to 2006, 397 patients received a radiation overdose of 10% on average, in addition to the initially prescribed dose of 70–78 Gy, depending on the clinical situation. The overdose received induced complications (rectitis) more intense than those described in the literature. These mainly involved hemorrhagic proctitis that resisted conventional treatment and required repeated argon plasma coagulation sessions or hyperbaric oxygen therapy, which can sometimes lead to incontinence. Some of the patients had no complications (*4*). All the patients were informed about the overdose they received and were seen by a radiation oncologist. Endoscopic monitoring was organized to conduct an objective assessment of the rectitis cases and specially to provide care in a specialized environment (*4*). Twelve additional cases were declared, involving patients who received a significant overdose from portal imaging.

Épinal III Cohort: Patients that Received Radiation Overdose due to Calculation Errors, 1989–2000

An examination of patients who had presented with complications from radiotherapy and who were then treated, prior to the period identified as presenting a risk of radiation overexposure, led to the discovery of a systematic configuration error with the software used to operate the radiotherapy machines, which occurred between 1989 and 2000. The radiation overdose depended on the energy of the photons used: 3% for 6-MV X-ray photons (1,100 patients treated between 1993 and 2000), 5.5% for 12-MV X-ray photons (3,500 patients treated between 1989 and 1999) and 7.1% for 25-MV X-ray photons (300 patients treated between 1999 and 2000). In a press release on September 7, 2007, the Minister requested that patients who received an overdose of 7% be contacted individually and offered a medical consultation, care and monitoring (*5*).

MEDICAL FOLLOW-UP

While medical care and monitoring were being provided, a research program was developed to improve scientific knowledge on the iatrogenic effects of overexposure to therapeutic ionizing radiation, to jointly study the dosimetric, clinical, biological and genetic characteristics of these patients. The observational clinical trial ''Épinal: Patients Overexposed for a Prostate Adenocarcinoma'' (EPOPA) (ClinicalTrials.gov: Identifier: NCT00773656) was initiated in 2007 with the goal of organizing a long-term medical

TABLE 1
Patient Grading at 5 Years Postirradiation

	Grading of rectal bleeding (5 years after radiotherapy)			
	Grade 0	Grade 1	Grade 2	Grade 3/4
Size	84	91	25	8
Épinal 1 cohort	1	3	1	0
Épinal 2 cohort	76	85	23	7
Épinal 3 cohort	7	3	1	1
Median age	74	74	75	76
Delay after radiotherapy	62	54	58	44

TABLE 2
Evolution of the Patient Grading from 5 to 10 Years Postirradiation

	Grading evolution from year 5 to 10			
	Grade 0	Grade 1	Grade 2	Grade 3/4
Toward less severe grade	0	9	9	2
Preserving the same grade	53	56	11	5
Toward more severe grade	20	16	2	0

follow-up of the Épinal patient cohort and improving scientific knowledge on iatrogenic effects.

Clinical Scoring

Patients suffering from severe adverse effects (proctitis, cystitis and tissue necrosis) for most of the overexposed patients were included in this follow-up. The objective was to increase the medical and scientific knowledge on adverse effects related to radiation overexposure by studying its effect on dosimetric, clinical and biological parameters. Side effects related to radiotherapy were quoted according to the severity of the radiation-induced lesions as estimated by the SOMA LENT scale (*19, 20*). In addition, biobanking of serum and tissue biopsies was established for further biological investigation. Biomarkers needed to be identified for the diagnosis and prediction of risk of complication. Five years after radiotherapy, 16% of the patients continued to experience severe side effects (grade >2) resulting from their overexposure (Table 1).

Radiation-induced complications occur as a dynamic process that evolves over months and even years after radiotherapy is completed. Medical follow-up is imperative and required for at least 10 years.

The evolution of the patient grading score showed that 5 years after completion of radiotherapy, the patients graded 0 and 1 evolved to a more severe grade, whereas those graded higher (i.e., 2, 3 or 4) experienced a decrease to a lower severity grade (Table 2).

Identification of Biomarkers of Radiosensitivity and Risk of Toxicity

Gastrointestinal radiation-induced injury is unpredictable; while a number of biomarkers were studied, it was found that they did not correlate with the clinical scores for complications, making them highly impractical. Thus, further work is needed to identify other potential biological markers as important diagnostic and prognostic tools to predict complications resulting from abdomino-pelvic radiotherapy.

In these different cohorts of patients, the severity of tissue damage observed after radiation overexposure with significant symptoms was not necessarily proportional to dose received (*23*). Several biomarkers of individual radiation sensitivity have been proposed as predictive assays of late toxicity such as radiation-induced CD8 T-lymphocyte apoptosis (RILA) (*21, 22*). Previously reported multicenter studies have demonstrated a good predictive value in patients with high RILA values and low-grade late toxicity (*22*). Therefore, the correlation between individual radiosensitivity and the severity of radiation-induced effects related to the magnitude of radiation overexposure was investigated. It was shown in this study that RILA did not correlate with the inter-individual variation in maximal digestive toxicity and maximal urinary toxicity. In this study, the assessment of RILA was performed after occurrence of the accident and establishment of the EPOPA cohort, although the samples were collected after a median of 4.8 years postirradiation (*23*).

Similarly, in this large prospective study, our group sought to identify innovative molecular risk factors associated with severe complications of radiotherapy in these patients with prostate adenocarcinoma who were overexposed to radiation. More recently, extracellular vesicles (EVs) have emerged as novel potential biomarkers for different pathologies (*24*). Extracellular vesicles constitute a heterogeneous group of cell-derived vesicles that are enclosed by a lipid bilayer containing various proteins, receptors, nucleic acids, chemicals and structural molecules derived from the cell of origin. Thus, EVs appear to serve as both markers and mediators of pathologies (*25*). Nonetheless, two main EV subpopulations have been consistently identified in this study and were classified according to their size and biogenesis: microvesicles (MVs) and exosomes (*24, 25*). Here, we observed that the number of MVs tended to increase in the blood of patients with a high grade of severity (grade 3/4) compared to patients with lower grades of severity.[2] These MVs were mainly derived from platelets. However, no modification in the number of exosomes associated with the different grades of severity was observed. More importantly, the number of platelet-derived MVs and the ratio of monocyte-derived MVs on endothelial cell-derived MVs jointly increased the risk of higher toxicity for these patients. Proteomics analysis of MVs revealed a group of proteins under-represented in grades ≥ 2

[2] Ribault A, Benadjaoud M, Squiban C, Arnaud L, Judicone C, Leroyer AS, et al. Circulating microvesicles predict complication of radiotherapy associated to severe radiation proctitis consecutive to abdominopelvic radiotherapy (manuscript submitted).

(keratins) and a group of proteins more abundant in grades ≥ 2 (angiogenesis and inflammation). More importantly, a significant correlation was found between the number of platelet-derived MVs and monocyte-derived MVs with the range of doses up to the median exposure of bladder/rectum and anterior prostate, respectively. We can conclude that the addition of MV variables to clinical pathological variables improve the identification of patients with high-grade severity. Microvesicles could be considered as a biomarker and may be valuable for prognosticating radiotherapy complications (*15*). A limitation of our prospective study was that model development and validation cohorts were from a highly selective group of patients overexposed to radiation, with a specific protein signature. These data need to be validated with the use of a cohort of radiotherapy patients at different time points, including before, at the conclusion of and months after, radiotherapy, thus providing information on the evolution and progression of the biomarker associated with clinical symptoms (*26*).

LESSONS TO BE LEARNED

The Radiation Oncology Department of Épinal Hospital has been upgraded by reinforcing quality and safety (collection of undesirable events, feedback committee, document management, etc.). The central concern was to create a high-quality level for the new organizational structure. The actions performed were under optimal quality and safety conditions following the approval of the ASN after a rigorous inspection. The lessons to be learned from this accident were to provide better risk prevention, improve knowledge of incidents and accidents, and early implementation of corrective measures.

National regulation was reinforced, with requirements set in terms of quality assurance and security applicable to the technical facilities in radiation oncology. ASN and SFRO proposed a new high-quality assurance and risk management approach of the practices in radiation oncology (*1*). Recommendations were proposed including consideration of organizational and human factors, improvement of training and qualification of professional practitioners, recommendations to manufacturers, obligations to incident or accident reporting, patient follow-up or practice evaluation by a clinical peer review.

In addition, long-term medical and scientific follow-up was set up for the Épinal patient cohorts. Additionally, three of the 24 patients with high grade severity received MSC therapy. This compassionate trial demonstrated the feasibility of cell therapy for patients overdosed during radiation therapy for prostate cancer. Consequently, a new protocol was undertaken in 2013 for the treatment of late severe damages of abdominal radiotherapy (‘‘Evaluation of the efficacy of MSC injection on the symptomatology of chronic and severe side effects of abdomino-pelvic radiotherapy after conventional treatment failure’’, Phase II interventional clinical trial PRISM) [European Clinical Trials Database (EudraCT) 2014-001462-99, NCT 02814864 https://clinicaltrials.gov/].

ACKNOWLEDGMENTS

The data found in this article was presented at the CONTREC Conference, May 14–18, 2018, Winthrop Rockefeller Institute, Petit Jean Mountain, Morrilton, AR. Special thank you to Prof. Martin Hauer-Jansen for his invitation. Patrick Gourmelon contributed to the medical management of the Épinal accident, Prof. Norbert Claude Gorin and Dr. Jan Voswinkel were in charge of the patients treated with MSC, Dr. Jean Marc Simon contributed to the patient grading, Jean François Bottollier-Depois, Isabelle Clairand, François Trompier and Chrystelle Huet contributed to the dose reconstruction, Mohammedamine Benadjaoud contributed to the statistical analysis, and Agnès François and Alain Chapel contributed to radiopathology and stem cell therapy expertise.

Received: October 8, 2018; accepted: May 8, 2019; published online: July 2, 2019

REFERENCES

1. ASN Report: Scale used to classify nuclear incidents and accident and radiation protection events in the context of radiotherapy procedures. https://www.asn.fr.
2. Ash D. Lessons from Epinal. Clin Oncol 2007; 19:614–5.
3. IRSN. Expert assessment of radiotherapy practices at Jean-Monnet Hospital in Epinal between 1987 and 2000. 2007. www.irsn.org.
4. Marchesi V, Aigle D, Peiffert D, Noel A, Simon JM. Securitization of the bi-site radiotherapy activity as part of the resumption of treatments in the Hospital of Epinal by the team of Alexis Vautrin Nancy Cancer Center. Cancer Radiother 2009; 13:740–3.
5. Peiffert D, Simon JM, Eschwege F. L’accident d’Epinal: passe, present, avenir. Cancer Radiother 2007; 11:309–12.
6. Guide des procedures de Radiotherapie externe 2007. https://www.has-sante.fr.
7. Derreumaux S, Etard C, Huet C, Trompier F, Clairand I, Bottollier-Depois JF, et al. Lessons from recent accidents in radiation therapy in France. Radiat Prot Dosimetry 2008; 131:130–5.
8. Mizuno H. Adipose-derived stem and stromal cells for cell-based therapy: current status of preclinical studies and clinical trials. Curr Opin Mol Ther 2010; 12:442–9.
9. Garcia-Arranz M, Herreros MD, Gonzalez-Gomez C, de la Quintana P, Guadalajara H, Georgiev-Hristov T, et al. Treatment of Crohn’s-related rectovaginal fistula with allogeneic expanded-adipose derived stem cells: A phase I-IIa clinical trial. Stem Cells Transl Med 2016; 5: 1441–6.
10. Voswinkel J, Francois S, Simon JM, Benderitter M, Gorin NC, Mohty M, et al. Use of mesenchymal stem cells (MSC) in chronic inflammatory fistulizing and fibrotic diseases: a comprehensive review. Clin Rev Allergy Immunol 2013; 45:180–92.
11. Georgiev-Hristov T, Guadalajara H, Herreros MD, Lightner AL, Dozois EJ, Garcia-Arranz M, et al. A step-by-step surgical protocol for the treatment of perianal fistula with adipose-derived mesenchymal stem cells. J Gastrointest Surg 2018; 22:2003–12.
12. Semont A1, Mouiseddine M, Francois A, Demarquay C, Mathieu N, Chapel A, et al. Mesenchymal stem cells improve small intestinal integrity through regulation of endogenous epithelial cell homeostasis. Cell Death Differ 2010; 17:952–61.
13. Bessout R, Demarquay C, Moussa L, Rene A, Doix B, Benderitter M, et al. TH17 predominant T-cell responses in radiation-induced bowel disease are modulated by treatment with adipose-derived mesenchymal stromal cells. J Pathol 2015; 237:435–46.
14. Benderitter M, Gourmelon P, Bey E, Chapel A, Clairand I, Prat M, et al. New emerging concepts in the medical management of local radiation injury. Health Phys 2010; 98:851–7.

15. Von Korff M, Jensen MP, Karoly P. Assessing global pain severity by self-report in clinical and health services research. Spine (Phila Pa 1976) 2000; 25:3140–51.
16. Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic nonmalignant pain. J Pain 2004; 5:133–7.
17. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67:361–70.
18. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30:473–83.
19. Ling CC, Kutcher GJ, Mohan. LENT SOMA scales for all anatomic sites. Int J Radiat Oncol Biol Phys 1995; 31:1049–91.
20. LENT SOMA tables. Radiother Oncol 1995; 35:17–60.
21. Ozsahin M, Crompton NE, 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; 11:7426–33.
22. Azria D, Riou O, Castan F, Nguyen TD, Peignaux K, Lemanski C, et al. Radiation-induced CD8 T-lymphocyte apoptosis as a predictor of breast fibrosis after radiotherapy: Results of the prospective multicenter French trial. EBioMedicine 2015; 2:1965–73.
23. Vogin G, Merlin JL, Rousseau A, Peiffert D, Harle A, Husson M, et al. Absence of correlation between radiation-induced CD8 T-lymphocyte apoptosis and sequelae in patients with prostate cancer accidentally overexposed to radiation. Oncotarget 2018; 9:32680–9.
24. Burger D, Schock S, Thompson CS, Montezano AC, Hakim AM, Touyz RM. Microparticles: biomarkers and beyond. Clin Sci (Lond) 2013; 124:423–41.
25. Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol 2013; 200:373–83.
26. Flamant S, Tamarat R. Extracellular vesicles and vascular injury: new insights for radiation exposure. Radiat Res 2016; 186:203–18.