

International Conference on Modern Radiotherapy:
Advances and Challenges in Radiation Protection of Patients

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Synthesis and main findings



Introduction by André-Claude Lacoste, President of French Nuclear Safety authority (NSA)

In December 2009, the French Nuclear Safety Authority (ASN) organised the 1st international conference on radiation protection of patients in radiotherapy, in collaboration with the World Health Organisation (WHO), the International Atomic Energy Agency (IAEA) and the European Commission, and in cooperation with the French Society of Radiation Oncology (SFRO), the French Society of Medical Physics (SFPM), the French Society of Radiation Protection (SFRP) and the League Against Cancer.

360 delegates from 50 countries across the world participated at the 3-day conference. 41 presentations were made and 67 posters were displayed.

I would like to emphasize the broad spectrum of expertise the conference brought together: scientists, health professionals, medical devices manufacturers, risk management specialists, radiation protection experts, representatives from Radiation Protection and Health Authorities as well as patient's associations. This diversity of attendance stemmed naturally from the originality of the programme, which covered both scientific and medical issues, such as patient sensitivity to ionising radiation and the treatment of complications. It also provided scope to discuss the benefits and risks of modern radiotherapy and to explore treatment safety issues from various perspectives, including human resources, expertise, education and training along with control and prevention strategies.

The conference concluded with a roundtable discussion on patient information. The participants included patients, doctors, and managers of medical care facilities and health authorities.

All the presentations, documents and posters are available on www.asn.fr.

This report summarises the presentations and the main findings from the Versailles conference. The lessons learned from this conference should be of benefit to any country where radiotherapy is used, as they provide a basis for improving treatment safety. It also falls to international organisations and professional societies to tackle those issues that go beyond national boundaries, such as individual radio-sensitivity or the evaluation of new technologies and practices.

Finally, on behalf of ASN, I would like to thank all members of the scientific committee and the chairman in particular, the speakers and chairpersons of the different sessions as well as and all those who helped to organise this event.

In view of the success and challenges of this conference, the Chairman of the Scientific Committee (Pr. J-M Cosset) and myself have agreed to organise a 2nd conference by the year 2012, in order to review the progress made in each of the fields explored. I already invite all of you to attend at this 2nd conference.

Main findings

1. **Justification:** no doubt on the generic justification of radiotherapy.
2. **Risk-benefit analysis:** new benefits but also new risks in the use of new technologies. Before clinical use, a clear need for an evaluation system by users (at international level), independent from manufacturers, and for guidance taking into account the different countries conditions.
3. **Responsibilities of manufacturers and suppliers:** regulators have to clearly define the responsibilities of manufacturers and suppliers on the commissioning of new devices and on the integration of the user's feedback experience. Regulatory and standardisation bodies must pay a specific attention to software associated to accelerators.
4. **Side effects and complications** (around 5% of patients undergoing radiotherapy): considerable and significant progress is still needed on registration (by medical teams) and on robust analysis and statistics at international level.
5. **Events/precursors likely to have possible effects on patients:** need to improve notification by radiotherapy centres and to develop error reporting and learning systems at national and international level (ROSI, SAFRAD) for analysis and feedback experience. Need to further international efforts to harmonize classification of events (taxonomy) to facilitate translation of reporting into learning.
6. **Accidents:** Lessons learned from past accidents are well analysed (ICRP, IAEA) and actions to progress, under the responsibility of operators, are well identified, developing:
 - Safety culture and safety tools;
 - Quality assurance program and risk analysis;
 - Adequate staffing and training.
7. **Research programs:** coordinated research programs are necessary in order to rapidly identify and carry out feasible and simple radiosensitivity tests.
8. **Responsibilities of authorities:** on the basis of best national practices, regulatory bodies and health authorities have to provide more efforts to promote actions on adequate regulations, on quality assurance, on risk analysis, on clinical audits, on good clinical practices, etc.
9. **Patient involvement:** A new challenge: to get the patient's voice in the dialogue through involvement of patients and their associations (e.g. International Network of Patients for Patient Safety) on advocacy, assessment of the quality and safety of treatments, risk acceptance and communication.

Part 1. Technical and regulatory considerations (overview)

A. Paradigms of external radiotherapy and brachytherapy : “New techniques, new benefits and new risks”

In recent years, radiation therapy has seen many technological advances and innovations, with the introduction of improved imaging (fast CT scanners, anatomical and functional MRI, PET) and new treatment devices as helical tomotherapy, robotic radiotherapy, proton therapy and new types of brachytherapy techniques (HDR, PDR).

These technological advances allow concentrating high dose irradiation onto the tumour, to shape the radiation field to avoid specific critical normal structures in the vicinity of the tumour and consequently to limit the dose delivered to surrounding normal tissues.

These advances have thus the potential to improve the patient safety by increasing tumour control and decreasing the adverse events.

But :

- These advanced techniques are often commercialised and marketed without evidence of cost-effective and clinical benefit (improved survival and quality of life of cancer patients); they only need to demonstrate safety of the new equipment, while the introduction of new pharmacological agents needs to demonstrate improved efficacy;
- Regulatory requirements to approve the use of a new techniques in radiotherapy are much weaker than the requirements to adopt a new therapeutic drug for clinical purposes ;The pace of innovation is so high that it could be in conflict with the development of quality approach.

Consequently these innovations require:

- The development of clinical trials similar to drug testing for evidence based radiotherapy ;
- Adequate training and verification of the knowledge of staff in planning, implementation and quality assurance of advanced technology.

B. Equipment safety, staffing, education and training”

Modern and conventional radiotherapy equipments must be selected, purchased, installed, commissioned and calibrated, following meticulous procedures.

Commissioning and calibration are required to ensure mechanical and dosimetric performances of linear accelerators and to guarantee technical safety during their lifetime, in conjunction with the contractual maintenance programme.

The role of the radiation technologists within the radiation therapy teams allows them to detect a majority of events. Consequently, radiation technologists should receive proper training on equipments and software use and should have an adequate learning period for the implementation of new methods or use of new acquired technology. Newly hired staff must also be properly trained in accordance with their experience.

A wide variety of approaches exists in education and training of medical physicists. In EFOMP’s view a harmonized qualification to be registered as qualified medical physicist (QMP) or specialist medical physics (SMP) is necessary. EFOMP thus recommends a five-year university education followed by a minimum of two year postgraduate training in Medical Physics to be registered as QMP. EFOMP also recommends all National Member Organizations to incorporate, in the

education of all trainees in Medical Physics, courses on safety and risk analysis as initiated by The Netherlands in Eindhoven in 2001.

When addressing radiation safety in radiotherapy through education and training, the actions of the IAEA have included developing standardised training materials, organising training courses and providing this information on the Radiation Protection of Patients website (<http://rpop.iaea.org>). Regarding medical physics, the long-term strategy of the IAEA is to contribute to the establishment and harmonization of education programmes, including clinical training and professional accreditation, knowing that this strategy can be achievable and sustainable only in countries where a critical mass of applications exists in medical use of ionizing radiation (treatment and imaging).

The evolution of radiotherapy technology require a need for strategic management of the limited financial and human resources to ensure safe and high quality treatment of cancer patients with highly educated staff at all levels. Education and training are an essential part of this quality and safety management system. This requires a systematic approach, in which education and training needs are clearly identified together as a key of success.

C. “Controls/Quality assurance/Audits”

Quality control has always been recognised as an essential factor in guaranteeing the necessary degree of dosimetric accuracy and optimum treatment results. External dosimetry controls provided by external organisms, such as IAEA at the international level or EQUAL-ESTRO at the French and European level, have proven to be useful for the improvement of dosimetry practices.

To improve patient safety, quality control is necessary but not sufficient and should be complemented by quality assurance evaluated through clinical audits done by multi-disciplinary expert teams (oncologists, medical physicists and radiation technologists) assessing radiation therapy practices and procedures. Clinical audits are promoted and developed at national level in different countries and by the IAEA (Quality Assurance Team for Radiation Oncology – QUATRO) through independent peer review evaluation of practices, adequacy of infrastructure, equipment, human resources and procedures.

European Commission guidelines on clinical audits, applying to all medical radiological practices, have been published in order to implement the requirement of Directive 97/43/Euratom (RP159 -2009). Clinical audits, as proposed by the guidelines, are neither regulatory inspections nor quality assessments or controls but have to go further and to provide recommendations on good practices (structure, process and outcome such as, quality assurance, dosimetry and methods of follow-up of treatments).

The ways forward to improve quality assurance are to:

- Develop new methodologies for external dosimetry controls in order to take into account new technologies and to assess the entire radiotherapy workflow from patient data acquisition and treatment planning to dose delivery;
- Emphasise that internal and external dosimetry controls and clinical audits are complementary;
- Adopt, in each member state of EU, the model of clinical audit with respect to their national legislation and administrative provisions. The IAEA and WHO guidance should be also taken into account for the implementation.

D. Accidents : ‘Events recording, reporting and evaluation’

In addition to the development of clinical trials, better staff training, quality control and audits, in order to improve patient safety, the risks related to each stage should be managed based on:

- Proactive methods to identify vulnerable aspects of the radiotherapy treatment, using risk matrix or probabilistic safety assessment, both methods being complementary;
- The feedback from experience by sharing information on the incidents and near incidents within the radiation oncology community. Actions have been undertaken at national and international levels, i.e. the development of a reporting and learning web based system (ROSI) at international level and, the implementation, in many French cancer centres, of a methodology coming from the aviation world based on the recording and analysis of the precursor events.

One of the safety issues in radiation therapy is linked to the use of computers at all the steps of the treatment planning and delivery, with the use of “treatment planning systems” (TPS) and “record and verify systems” associated to a multiplicity of data exchanges between the various pieces of equipment.

Both manufacturers and users have a major responsibility regarding safety issues:

- Manufacturers, by providing computer aided solutions oriented specifically towards safety management (fully integrated systems, safety tools);
- Users, by ensuring a good understanding of the TPS functions mainly.

E. Accidents : “Lessons of the past”

In radiation therapy, sources of errors possibly leading to events or accidents are multiple. Lessons from accidents in conventional external radiotherapy, in modern external radiotherapy and in brachytherapy have allowed identifying some key common areas of improvement:

- Responsibilities: ensure there are clear and unambiguous in all aspects of the process.
- Quality assurance program: ensure very strict adherence from all staff to quality assurance program and ensure procedures are written and comprehensive, relating to all steps in the radiotherapy process.
- Training and understanding: ensure appropriate education and training of professionals and adequate level of standing.
- Working with awareness and alertness: to reduce the possibility of human errors in a context of lack of organisation.
- Communication and recording: regular feedback on safety from staff to develop and maintain safety culture.
- Proactive methods of safety assessment are necessary (i.e.: risk analysis methodology).

Furthermore, several events involving new technologies stress the need for:

- Reviewing the training in radiotherapy physics before introducing new technologies.
- Understanding by staff of new technologies.
- Communication and recording.
- Updating quality assurance protocols and developing specific dosimetry protocols.

F. National strategies and regulations

National strategies to improve patient safety and process efficiency in radiotherapy are managed by one or several authorities or agencies, more or less independent from the government. The complexity of radiotherapy represents a challenging issue that has led them to develop different actions:

- Issue of publications, guides and recommendations to develop a safety culture and to report events. Those documents result from the collaboration with professional bodies
- Management of radiotherapy incidents through :
 - issue of recommendations for classification, investigation and notification of radiological events
 - analysis and dissemination of experience across the professional community and health organizations
 - distribution of appropriate and correct information to patients and the public, including a scale to rate the events severity and the publication of inspection reports
- Periodic visits or inspections of radiotherapy departments with a specialised inspector team. The control can be planned or unexpected if related with an event
- Development of inspection protocols
- Supporting departments in different situations and providing advice
- Training in general knowledge on radioactive materials or specific activities
- Development of regulations that are comprehensive, updated with new technologies and discussed with stakeholders

The organisations have identified several objectives for the future:

- Standardization of the practices at national level
- Development of taxonomy for reportable incidents to optimise the data bases (causative factors and error detection)
- Contribution to international reporting and learning
- Exchange at international and European levels on quality assurance program, on risk analysis and on information of public and patient
- Strengthening regulatory overview for radiation therapy devices to harmonize practices within the national territory

Part 2. Biological and clinical considerations (overview)

G. Challenges in radiotherapy : “Individual radiosensitivity”

Individual hypersensitivity to high doses of ionising radiations has been well documented by radiotherapists and radiobiologists. Pathologies related to severe hypersensitivity to radiations concern homozygous genetic disorders in DNA repair and cell signalling (e.g., ATM, NBS1, LIG4). Approximately 5% (1%-10%) of patients show severe normal tissue reactions, i.e., deterministic effects, as a consequence of radiotherapy.

On the contrary, 5 % of patients could be considered less sensitive to radiation than the average, based on a normal distribution assumption. In such cases, a standard radiotherapy dose may be too low to sterilize tumours. How can the dose be increased to guarantee effective treatment? This is a tremendous challenge for radiotherapists and cancer specialists. Syndromes exhibiting sensitivity to radiation carcinogenesis also exist. They represent another form of individual sensitivity to radiations although the frequency of such sensitivity has not been evaluated so far.

Escalation of dose

Modern conformal radiotherapy is performed with accelerators equipped with multileaf collimators used to change the radiation beam size in real time. In combination with 3D medical imaging, it is thus possible to multiply the beam angles and to target more precisely the tumour, allowing a higher dose to be delivered to the tumour. Although it is established that conformal therapy has decreased the occurrence of side effects for standard practices (same dose delivered), dose escalation may be responsible in the future of an increase in the frequency and/or the severity of side effects or complications.

On another hand, the volume of healthy surrounding tissues exposed to radiation during conformal therapy increases. Consequently, radiation carcinogenesis might be on the rise and it will take years before it can be formerly established.

Detection of individual sensitivity

Since modern 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, progress in the knowledge of individual radiosensitivity is mandatory.

Predictive tests of radiation sensitivity (i.e., clonogenic, micronuclei, cytogenetic and DNA repair assays) have been carried out for a long time and were not so successful in practice due to either the complexity of the tests or to their rather poor positive predictive value and/or a limited access to cases of interest.

More recent approaches are more successful and possibly combine:

- Evaluation of CD8 T Lymphocyte apoptosis, reduced in case of hypersensitivity;
- Evidence of 4 or more single nucleotide polymorphism (SNP) alterations in ATM, SOD2, TGFb1, XRCC1, XRCC3 and RAD21 in T lymphocytes;
- Evaluation of DNA double strand break repair gene function on fibroblast from skin biopsies by pH2AX and MRE11 immunofluorescence assays.

An overall agreement on the following issues has been reached:

- Patients exhibiting durable side effects and complications after standard radiotherapy raise the world’s most serious radiation protection problem (a few hundred thousand patients annually).
- Time has come to monitor individual radiosensitivity of patients before radiotherapy. The methods outlined above should be used in practice for evaluation on a large scale.

Correlations with clinical outcome, i.e., the existence of side effects and complications to be performed;

- Formal studies of side effects and complications after radiotherapy with no errors in the dose delivered or in the volume of irradiation should be performed on both national and international levels in order to objectivise them. Data bases to be built;
- More research is needed to evaluate tumour sensitivity/normal tissue sensitivity over a large range of doses and to correlate with the clinical radiocurability of tumours and radiation induced over-reactions in normal tissues.

H. Treatment of complication and late morbidity

The burns treatment center at Percy Military Hospital recently had occasion to treat victims of radiation burns who exhibited acute, radiation-induced skin syndromes. The cell therapy approach was developed for these patients. The medical treatment of this type of pathology remains extremely complex and delicate. Feedback from the clinicians highlights the need for new therapeutic strategies. Cell therapy could bring about significant progress in this area. In the past two years, several patients have benefited from cell therapy, in conjunction with surgical treatment involving exegesis and epidermal autograft.

It was stressed the positive role of Mesenchymal Stem Cells(MSC) regarding not only local-regional inflammation and grafting success, but also reactive fibrosis in chronic, radiation-induced lesions following radiotherapy. First identified in bone marrow, MSC have also been detected in many other types of tissues (cartilage, thymus, spleen, adipose tissue, etc...). MSC have interesting properties: self renewal, high proliferation capacity and multipotency for cell differentiation, anti-inflammatory, antiseptic, immunomodulatory and trophic effects.

I. Challenges in radiotherapy : “Risk/benefit issues”

Whatever the treatment of cancer, i.e., surgery, chemotherapy or radiotherapy, used alone or in combination, there is an overall risk of impact on quality of life mostly due to painful sequelae and sometimes of fatal outcome. Indeed the major risk is the failure of cure!

Since clinical observations show that the probability of cancer cure as well as the probability of late normal tissue damage increase with dose, a good radiotherapy is not the one which does not cause any serious side effects in any patient, nor the one which cures all patients. This is the basis of the cure/risk debate in radiotherapy.

Microvascular radiation damage is the hallmark of late normal tissue damage after radiotherapy. It can progress over at least ten to fifteen years until tissue atrophy. A recent concern is the evidence of cardiovascular radiation injury after radiotherapy with a risk of mortality from myocardial infarction or heart failure. Another concern is the risk of secondary cancers within the remaining life expectancy of a cured patient. So far, this risk has been evaluated as low, in the range of 1% at most, with a larger incidence in children and young adults. Although we are lacking of precise statistics, it seems that there are not more side effects with modern conformal radiotherapy than with conventional radiotherapy.

Thus there is a series of questions still to be investigated in order to better address the risk and to increase the benefits of radiotherapy:

- Large statistics and epidemiological studies are needed to document precisely the different side effects (reversible and resulting from a transitory down regulation of normal tissue renewal) and complications (irreversible and resulting from permanent damage after irradiation) in radiotherapy.
- The mechanisms of these side effects and complications need to be more thoroughly investigated.

- What are the conditions for an increased risk of secondary cancers in the larger volume of tissues receiving low dose in conformal radiotherapy? A new ICRP document on secondary cancer risk after modern radiotherapy including practical recommendations will be published soon.

Finally, one of the most difficult issues is the risk acceptance by the patients who rely on professionals to provide them with the latest information and the most up-to-date techniques to reduce or minimize radiation risks. Particular attention should be paid to the understanding by the patient of what has been said. Communication of benefits and risks of modern technology poses new challenges to health professionals and they have to enhance their skills to properly communicate those risks to patients. Risk acceptance largely depends on the trust in professionals, in their institutions and in their previous success and failures.

Part 3. Patient Information

A round table on patient information has been organised with the participation of several French patient associations, medical doctors, a director of hospital and heads of national authorities, and international invited experts. The round table started with a patient testimony related to Epinal accident, the positions of patient associations and the feedback experience from the administration of Toulouse hospital.

All participants agreed on the following:

- Based on WHO recommendation, a legislative framework, defining patients rights and ethical principles, is really needed; a patient centered approach as well as inclusiveness in the informed decision making process and risk benefit analysis are required ;
- Patients have to be informed of possible side effects and complications due to radiotherapy; appropriated information must be clear, easily understandable and rehearsed;
- The hospital administration must strongly tackle the topic of patient information with all professionals involved in care (physician, nurse and radiation technologist);
- Involvement of patient associations is absolutely necessary, in order to develop specific tools and places for information;
- Professionals should be trained on risk communication, learn to listen to patients and to identify signals of anomalies related to the treatment;
- The hospital administration has to prepare a specific strategy in case of serial accident in order to be able to quickly inform concerned patients and to proactively inform the public.



