Radiotherapy and radiology: Joint efforts for modern radiation planning and practice

J. Thariat\textsuperscript{a,}\textsuperscript{*}, P.-Y. Marcy\textsuperscript{b}, A. Lacout\textsuperscript{c}, L. Ramus\textsuperscript{d,e}, T. Girinsky\textsuperscript{f}, Y. Pointreau\textsuperscript{g}, G. Malandain\textsuperscript{e}

\textsuperscript{a} Department of radiation oncology, centre Antoine-Lacassagne, université Nice Sophia-Antipolis, 33, avenue Valombrose, 06189 Nice cedex 2, France
\textsuperscript{b} Department of radiology, centre Antoine-Lacassagne, université Nice Sophia-Antipolis, 33, avenue Valombrose, 06189 Nice cedex 2, France
\textsuperscript{c} Imaging Center, 47, Boulevard du Pont-Rouge, 15000 Aurillac, France
\textsuperscript{d} DOSisoft, 45/47, avenue Carnot, 94230 Cachan, France
\textsuperscript{e} Inria Sophia Antipolis, Asclepios Research Project, 2004, route des Lucioles, BP 93, 06902 Sophia-Antipolis cedex, France
\textsuperscript{f} Department of radiation oncology, Institute Gustave-Roussy, 33, Rue Camille-Desmoulins, 94000 Villejuif, France
\textsuperscript{g} Department of radiation oncology, service Corad, Henry S Kaplan Center, CHU de Bretonneau-2, boulevard Tonnellé, 37044 Tours, France

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Abstract With new irradiation techniques, the dose can be better matched to the contours of the tumour. The corollary is that greater precision is required. Recent intercomparison studies of treatment plans have emphasized the need to harmonise contouring practices. More of a consensus approach is based on using adaptive imaging modalities, expert group recommendations and automatic segmentation atlases, on harmonisation of dosimetric decisions through employing exhaustive nomograms for organs at risk, and on indexes for choosing optimal treatment plans. On another level, quality assurance and data pooling programmes have been set up, making use of DICOM-RT data transfer (image networks). The combination of several irradiation techniques (for example, intensity-modulated conformal radiotherapy plus CyberKnife\textsuperscript{\textregistered} boost and re-irradiation), making it possible to irradiate tumours better, requires the cumulative doses to be recorded by dose summation software. Real awareness has been achieved in recent years as regards improving the quality of treatment, pooling data and harmonising practices.

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New techniques, such as intensity-modulated conformal radiotherapy (IMCRT) and its development, modulated arc therapy (RapidArc\textsuperscript{\textregistered} VMAT, and tomotherapy), or even stereotactic radiotherapy, have better conformation capacity. Less volume of healthy tissue is irradiated with high doses, but the down side is that, since at several millimetres from the

\textsuperscript{*} Corresponding author.
\textit{E-mail address: jthariat@hotmail.com} (J. Thariat).

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tumour dose gradients are abrupt, the dose may be sub-tumoricidal. These new techniques therefore go hand in hand with a greater requirement for treatment quality in terms of contouring. Better documentation of the effects on organs at risk, including structures, which were not previously explored for lack of the means of sparing them, is now possible. For critical organs delineated, the doses delivered (in particular, maximal doses and doses delivered per unit or per percentage of the volume of the organs at risk), can now be compared with the theoretical or empirical doses according, for example, to Emami’s nomograms, or to newly constructed nomograms for previously non-contoured structures. This accurate and exhaustive contouring requirement is time-consuming and demands continuous training for radiotherapists to keep up to date, necessitating training programmes, the development of computer tools and data exchange, particularly via image networks. These tools will result in greater precision and ideally should contribute to better reproducibility and the standardisation of irradiation practices. We shall now briefly describe current practices and the resources used.

Contouring quality, the contribution of imaging and the clinical implications

If contouring the tumour is inadequate, coverage of its target volume may be reduced. The relative vagueness that there used to be in defining target volumes with 2D is no longer possible with irradiation techniques that have a high conformity index for maintaining at least equivalent locoregional control of tumours. The reports 50 and 62 of the International Commission on Radiation Units & Measurements (ICRU) (www.icru.org) defined target volume concepts: Gross Tumour Volume (GTV), the probability of its microscopic extension corresponding to the Clinical Target Volume (CTV), margins to be applied depending on movement of the organ (Internal Target Volume [ITV]), margins to be applied to take account of patient repositioning uncertainties [1]. These reports did not evoke the problem of radioanatomical GTV delineation uncertainties nor of variability in defining the clinical history of the CTV. The uncertainties are largely related to a human factor and can influence irradiation results. Intra- and interobserver variations in delineation can sometimes be more significant than patient repositioning uncertainties. Many teams are beginning to propose recommendations or atlas so as to standardise practices and reduce the range of contouring uncertainties [2], which along with contouring variability, are multifactorial. They depend, for target volumes, on the operator’s (the radiotherapist’s) knowledge, on the natural history of the disease, and on the specific points noted in the patient’s medical records (the clinical description of extensions of the disease, the precision of the postoperative report, with a detailed description of the lesions and the quality of peroperative margins by the surgeon, and the documentary level of the histology report based on the surgeon’s focused description). In many cases this step requires close consultation between the various specialties—the radiotherapist, the radiologist and the surgeon—in particular when the patient has not been seen clinically preoperatively. These uncertainties and the contouring variability also depend on the imaging modalities used for contouring and the frames used. Artefacts, such as artefacts related to dental material close to a tumour of the buccal cavity (Figs. 1 and 2) or to a hip prosthesis in relation to a pelvic tumour, can increase contouring uncertainties on a target volume scan. On tomoscopy scans (megavoltage in contrast to the kilovoltage used during the dosimetry scan) these artefacts are reduced. A contrast-enhanced scan provides essential information in certain locations such the head and neck, with a carcinoma in situ (Fig. 3): there is better contrast between the tumour and adjacent tissues, better discrimination of the lymph node relative to the vessels and to adenopathies [3], or, in the case of pelvic tumours, the urinary tract can be viewed (Fig. 4) on a late “urological” sequence to see the ureter and excretion from it. The benefit is greater than the constraints connected with the injection [4], which include the need to train radiotherapy operators (in infusions), to acquire a

Figure 1. Artefacts of dental origin preventing any satisfactory interpretation using CT (a). Axial T2 MRI perfectly showing adipose metaplasia of the cervical platysma myocutaneous flap (T2 hypersignal, arrow) following pelvisoscopy, bilateral functional lymph node dissection and irradiation (b). Absence of locoregional recurrence of the known, moderately differentiated, epidermoid carcinoma of the mobile tongue.
Figure 2. CT/MRI fusion in ENT identification imaging. When MRI can be performed (taking account of any contraindications) and interpreted (absence of movement artefacts), it is superior to a CT scan, even with injection. (a): CT without injection not contributing anything useful. Metal hardening artefacts of the X-ray beam (dental amalgam) that do not interfere in contrast-enhanced MRI (b). MRI detects a subangulomandibular adenopathy (oblique arrow), enhancement of the masseter (horizontal arrow) and of the retrostyloid space (vertical arrow) to be taken into account in radiotherapy management of this cystic adenoid carcinoma of an accessory salivary gland of the oropharynx.

Figure 3. CT/MRI fusion. Axial plane of a recurring epidermoid cancer of the right palatine tonsil extending to the base of the tongue, the soft palate and to the infratemporal fossa. Contralateral location. (a): Contrast-enhanced CT shows extension of the lesion better than CT and T1-weighted MRI without injection (b), but is less precise than MRI with injection as regards the extension to the infratemporal fossa, the soft palate and the bone marrow (c) (mandible-arrow). (d): T2-weighted axial slice with fat saturation (CSF white), blur due to movement by the patient (a major disadvantage of MRI).
Radiotherapy

This treatment fusion, iodine from steep scan lesser agent questionnaire of contouring inexact ence. The risk in injecting iodine is twofold. The risk of anaphylactic shock means the presence of medical staff is necessary during injection, in the room containing the scanner for radiotherapy, with premedication possibly, if allergy is suspected [4,5]. The second, lesser known risk is of nephropathy induced by the contrast agent (contrast-induced nephropathy — CIN), which is all the higher if the patient is diabetic, elderly, dehydrated, and if the product injected is ionic and hyperosmolar [6]. This means systematic control of creatinine clearance in any patient at risk, i.e. meeting one of the items on the Choyke questionnaire positively [7].

The use of multimodality imaging [8] may sometimes be substituted for iodine injection at the time of the dosimetry scan, but other than for strictly intracranial tumours, the use of imaging for diagnostic purposes, which is not in a position to treat and therefore has no radiotherapy restraint, implies inexact registration of the various imaging modalities. Calculation of the dose is modified by 2–3% with 2D-3D, as iodine creates a hyperdense sector, which absorbs the dose at a place where there will no longer be any iodine during the treatment sessions. While the impact of the contrast agent on dose calculation seems lower than the benefit expected from contouring, the dose delta may be more significant with the use of mini-beams (stereotactic radiotherapy) and steep gradient techniques. A simple means of correcting this is to perform two scans during simulation, one without injection for dosimetry and contouring of the organs at risk (OAR), and the other with injection, for contouring the target volumes. Irradiation related to the additional scan is low at about 5 to 20 mSv. The use of multimodality imaging can significantly improve understanding and contouring of target volumes, particularly of tumour extensions (Fig. 5). MRI, therefore, and particularly functional MRI (perfusion, permeability), has become essential for contouring oligodendrogliomas which can have margins of 2–3 cm by contouring done on a scan alone, and even with MRI if standard sequences are used [9]. With better spontaneous resolution than the scan, MRI very often requires the injection of gadolinium chelates to enhance contrast of vascular lesions and blood vessels. In neuropathology, the injection of gadolinium salts shows rupture of the blood/brain barrier perfectly, as well as the foci of possible dissemination to the contralateral hemisphere or to the subependymal region. However, one disadvantage recently discovered is the risk of nephrogenic systemic fibrosis (NSF) below a creatinine

Figure 4. Axial CT slices of the pelvis, in the delayed phase. Invasive bladder carcinoma with diffuse parietal thickening; scan performed before identification and contouring. In the excretory phase the cancerous bladder wall and the terminal ureters (arrows) are outlined. Identification should take account of the degree of bladder fullness.

Figure 5. Frontal MRI section passing through the foramina ovales and the infratemporal fossae for a cystic adenoid carcinoma of an accessory salivary gland of the left oropharynx. Besides better contrast resolution of the soft tissues, by visualising the cranial nerves the extension of the neurotropic tumour of this cystic adenoid carcinoma to the base of the skull then to the Gasser lymph node (Vth cranial pair) can be clearly identified, without visible enlargement of the left foramen ovale in CT (arrows). Contouring will therefore have to take this endocranial extension, which is still clinically asymptomatic, into account.
clearance threshold of 25 ml/min [10]. The risk of NSF varies however depending on the type of contrast product used.

For organs at risk, these uncertainties and the variability of contouring depend on the operator’s (the radiotherapist’s and sometimes the dosimetrist’s) radioanatomical knowledge, and on whether recommendations have been circulated which fix common rules. Contouring certain organs at particular risk requires specific imaging modalities. Contouring the cochlea, for example, requires a bone window and scanning in one millimetre, or even thinner, slices. A radiotherapy-planning scan is best for contouring the cochlea in two or three slices, and is usually performed with slices of 2.5 mm. To compare treatment plans and prospective documentation of doses to organs at risk, it is essential to have a common definition. When (perception/sensorineural) hearing is to be evaluated, should the inner ear be contoured and what does that include? In practice, it means contouring the cochlea alone, but some practitioners also include the semi-circular canals (involved in balance). Structures previously considered as non-specific tissues, because they are impossible to contour routinely and cannot be spared, given the irradiation technique used, will be increasingly taken into account in future treatment plans. It will thus be possible to make the signs of secondary effects of irradiation clear, and document series or parallel dose/volume/organ correlations. Considering the time already allotted to contouring, computer tools will probably make contouring these “new” organs at risk automatic.

Evaluation of intervariability in contouring target volumes, contouring tools and resources used

To contour treatment volumes (GTV and the probability of microscopic extension [CTV], as well as determination of organs at risk [OAR]), medical expertise is required to define the GTV that is based on good knowledge of radioanatomy and radiodiagnostic protocols (the injection of contrast agent for a planning scan and consultation with radiologists for MRI), and on good knowledge of the history of the tumoral disease in terms of dissemination, for each type of tumour, to define the CTV. Intra- and interobserver contouring variations may be greater than the uncertainties connected with positioning the patient or with movement of the organs [11,12]. There are variations in contouring the parotid glands and ENT lymph nodes (Fig. 1), despite validated recommendations (Fig. 6). In order to standardise practices, learned societies, cooperation groups and teams have suggested tools to help define and contour target volumes and organs at risk. The use of standard protocols and an atlas to help contouring, or an automatic segmentation atlas, helps reduce intervariability. Indeed, in pelvic pathology, the definition of presacral and iliac lymph nodes can vary by a factor of 10 [13]. For prostate cancers, volumes can vary by a factor of 5 (4 to 19 cm³) with a median deviation of 9 cm³ [14]. Contouring the mammary gland on a scan suffers from intra-observer but especially interobserver variation [15]. This can have repercussions on the therapy, which may be considerable if there is partial irradiation of the breast, with differences observed in the three planes and particularly between right and left [16]. There are other comparisons in pulmonary cancers [17] and cancer of the uterine cervix (particularly for brachytherapy) [18,19]. The impact of apprenticeship was evaluated among house officers in training and emphasizes the importance of practical and theoretical training courses. Eleven delineations of a T2N2b tumour of the base of the tongue were collected before and after a theory course at the Memorial Sloan-Kettering Cancer Center [20]. The training given by experts reduced the interobserver variability. A similar approach was undertaken in France and concerned a case of epidermoid carcinoma of the right upper lobe, staged T2N2M0 [21]. The expansions were modified after training [21]. Bearing in mind contouring variability, one guarantee of quality during attempts at therapy is to simulate

Figure 6. Interobserver variability of contouring (four observers: yellow, red, light blue, dark blue) of the parotid (a), and the upper jugular lymph nodes (b).
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treatment in a dummy run: each participating centre conducts dosimetry on a virtual patient with a reference common to the trial centres. Quality assurance studies are conducted [22, 23] allowing the conformity of practices to be verified or to be modified, if necessary. Another way of standardising contouring is by using paper or online contouring atlases. A site for self-training in contouring was set up in October 2008 (www.siria.de). AFCOR (Association de Formation Continue en Oncologie Radiothérapie [the French association for continuous training in radiotherapy oncology]) (http://www.afcorfm.org/) offers continuous training seminars and theoretical and practical courses to house officers and practitioners, to teach delineation techniques and check the quality of volumes contoured. Training programs have been designed for this step in standardised contouring, which moreover permit comparison of treatment plans for contours delineated and for the dosimetry results obtained using indexes. The quality of the treatment plan is evaluated by a visual dosimetric analysis, slice by slice, or by viewing the spatial organisation of the tumour, critical organs and isodoses in the form of quantitative three-dimensional dose distribution, represented by dose-volume histograms (DVH). These DVH give the values of the maximal, minimal, mean and modal doses delivered in each volume of interest, as well as the dose delivered per unit or per volume percentage of these structures. As a result of technological developments in radiotherapy planning systems, various treatment plans for a single patient can be relatively rapidly obtained. The choice between several options ensuring the same tumour coverage and the same protection of critical organs generally favours the option that best spares healthy tissues, with the simplest ballistics or the less expensive treatment. Any detailed comparison between several treatment plans is still difficult however, and not readily reproducible. Integration and analysis of all this information would require a tool that could collate all the dosimetric data into a score or index, which would express the relationship between the irradiated tumour tissue and non-irradiated healthy tissues, and would harmonise dosimetry validation. The conformity index, a geometrical index representing the ratio between the reference isodose volume and the target volume, was created in 1993 by the Radiation Therapy Oncology Group (RTOG) and meets this objective but does not allow all the requirements of an ideal dosimetry plan (100% of the dose to the tumour, 0% to healthy organs) to be verified, because it does not take account of healthy organs. It is the same for the coverage index and the homogeneity index. To these geometrical indexes are added dosimetry indexes (for example, the integral dose or energy delivered to the patient in joules, the dose gradient or mean of the decrease in dose in % per mm between the isodose prescribed and 50% of the isodose), or radiobiological indexes such as the biological equivalent dose (BED, or equivalent uniform dose, EUD) which, when distributed uniformly in the target volume, induces the same number of clonogenic cells as the dose in Gy prescribed. These indexes are still not in general use on a routine basis, probably again through lack of experience, and because most TPS do not provide them in a simple manner.

Radioanatomy tools are moreover accessible on line (e-anatomy) as are also proposals for contouring, based on atlases for certain target volumes and organs at risk: the lymph nodes in ENT, gynaecological cancers, anorectal cancers, the pelvic lymph nodes in prostate cancers, the brachial plexus, breast cancers (such as those suggested by the RTOG http://www.rtog.org/atlas/contour.html). Some constructors offer automatic segmentation atlases, in particular for organs at risk or for the cervical lymph nodes; most are still being clinically evaluated [24].

Similarly, great variability has been shown in decisions concerning dosimetry [25]. Variability in contouring target volumes and also in making dosimetry choices, with considerable discrepancies of several percentage points on dose-volume histograms, was noted for a case of paediatric nephroblastoma, using a program for intercomparison. This experience highlights a certain lack of knowledge of dosimetry correlations with the occurrence of late toxicity and the need for prospective data from national and/or international databases [25].

Image networks

With the development of image networks, such as the one initially set up for the European Organization for Research and Treatment of Cancer protocol, Groupe d’étude des lymphomes de l’adulte (EORTC—GELA-III H10), it has been possible to exchange data securely throughout France since 2007 (including images, contouring, irradiation fields, dosimetry, as well as histopathological examination slides, patients’ files, etc.) in the DICOM and DICOM-RT format (Fig. 7) [26]. With such networks, files can be exchanged between anti-cancer centres, as well as university and regional hospital centres. They permit prospective and retrospective quality controls. Wider implementation of these networks is currently being slowed by the human factor, despite a simple procedure and their definite advantage.

Innovative irradiation techniques/Pooled technical platforms

In view of the sophistication of radiotherapy technical platforms, several departments may share one piece of equipment, particularly when implementing innovative irradiation techniques. To plan the first stages of treatment (contouring, dosimetry), limit the mobilisation of staff (radiotherapists, physicists, dosimetrists etc.) and organisational constraints, and overcome the disadvantages of this geographical separation, departments are equipped with consoles, assigned to the planning stages, on each of the user sites. These consoles are linked to clusters that store the planning data. Treatment machines then query these servers, to start the treatment. Because of the network architecture, planning sites can be separate from treatment sites. The doctors referring patients nevertheless generally have a consultation with their patients, to monitor them during the course of treatment, on the treatment site. This organisation presupposes good coordination between teams, with a continuous physical medical presence.
Mixed techniques/Adaptive radiotherapy

As innovative techniques are sometimes complementary, such as intensity-modulated conformal radiotherapy (IMCRT) and stereotactic radiotherapy, this results in treatment plans being disseminated that combine a mix of techniques [27,28]. Using treatment planning systems that differ between these techniques requires the use of dose summation software. Similarly, the use of adaptive radiotherapy (ART), consisting of re-planning treatment when morphological modifications have been observed during irradiation, needs the ability to recalculate cumulative doses on a routine basis, simply and rapidly. This concept of adaptation is not new, since cervical thickness or the size of cervical adenopathies has been measured for decades during irradiation of the ENT region to adapt the energy if there is a reduction (Fig. 8), following Bataini’s example, in order to modify fields depending on their clearance. Nevertheless, starting in about 2005, adaptive radiotherapy is now using imaging and in particular, image-guided radiotherapy (IGRT). Dosimetry tools make it possible to accurately calculate cumulative doses depending on adaptations secondary to morphological changes (tumour reduction (Fig. 3) or loss of weight by the patient) observed in the course of treatment [29]. The clinical and medical benefit of ART has not been validated, but many prospective studies are underway.

Figure 7. Structure of the network set up in France for the H10 therapeutic trial.

Figure 8. Adaptive radiotherapy based on a replanning CT scan during the 4th week of irradiation: a: planning CT scan performed eight days before the 1st session of irradiation (dose received zero = 0 Gy); performed at the 16th session of irradiation (dose received 30 Gy); b: significant tumoral reduction observed of the adenopathies of a moderately differentiated epidermoid carcinoma of the oropharynx, justifying recontouring and calculation of the cumulative dose as a function of these changes.
A reduction in the bilateral volume of the parotid glands of 17% and of the target volume of 5% has, for example, been shown on the 17th day of irradiation by IMCRT of oropharyngeal carcinomas in situ, making it necessary to recontour the volumes and recalculate the doses accumulating from the treatment already given and from that to come [30].

**Conclusion**

Improvement in the quality of irradiation, owing, particularly, to the ballistics possibilities of new techniques, is associated with a requirement for standardisation, precision, reproducibility and safety. Training and advisory programmes have been set up over recent years due to this need for standardisation and for quality in radiotherapy practice. Implementing innovative radiotherapy techniques also relies on tools such as multimodality imaging (major role of radiologists during radiation therapy planning), image networks, dose summation programs, etc., which have indeed become indispensable for precision radiotherapy of quality.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

**References**

