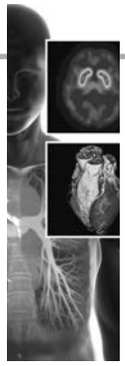

Role of the radiologist in radiotherapy planning

"It is obvious that the input of the radiologist with a clear understanding of the development of these new modalities is essential if the potential of the newer forms of radiotherapy treatment delivery is to be optimized."

Sidath H Liyanage
Department of Diagnostic Imaging, Barts and The London Hospitals NHS Trust, London, UK

Rodney H Reznek
Author for correspondence: Centre for Molecular Oncology & Imaging, Institute of Cancer, St Bartholomew's Hospital, London, UK
Tel.: +44 207 601 8864;
Fax: +44 207 601 8868;
r.h.reznek@qmul.ac.uk

A key issue in radiotherapy treatment planning (RTP) is how to deliver the prescribed radiation dose to cancer cells, whilst keeping the dose to normal tissue as low as possible. Conventional radiotherapy fields are usually square or rectangular and invariably include unnecessary normal tissue during irradiation. Over the past few decades, innovations in cross-sectional imaging and advances in radiotherapy equipment have resulted in high-precision radiotherapy techniques such as conformal and intensity-modulated radiotherapy (IMRT). These techniques utilize imaging to plan an ideal radiotherapy treatment, the goal of which is to improve the therapeutic ratio, which is the relationship between the dose required to achieve local control and the expected treatment-related complications.

Conformal radiotherapy involves the geometric modulation of the radiation beam to the shape of the tumor. This has resulted in improvements in the therapeutic ratio by minimizing normal tissue complications and allowing increased dose and improved local control [1]. IMRT is an advanced form of 3D conformal radiotherapy. Its value is in treating areas with complex shapes and where the tumor lies in close proximity to radiosensitive normal structures. In addition to the geometrically contoured beam, the ability of IMRT to deliver nonuniform dose patterns by design has led to the concept of 'dose painting' [2], where a subvolume with a potential resistance to irradiation can receive an additional dose. Planning studies have outlined potential dosimetric benefits for using IMRT in several radiotherapy treatment sites including head and neck, breast, prostate and the CNS [3–6].

The concept of gross, clinical and planning target volumes (GTV, CTV and PTV), as proposed by the International Commission on Radiation Units and Measurements in Reports 50, 62 and 71 [7], is now well accepted and widely used in RTP. The use of this nomenclature allows for uniformity in designing treatment volumes and is a prerequisite for progress in the development of radiation therapy.

The increased conformality of modern radiotherapy planning techniques necessitates improved means of defining target volumes for treatment. Target volume definition (TVD) is recognized to be one of the most significant geometric uncertainties in radiotherapy planning. Much of this uncertainty can be reduced by optimizing the imaging, by selecting the appropriate imaging modality, by multimodality imaging and by involving the trained radiologist familiar with TVD. The rapidity of technical developments over the last several years has meant that the processes of radiotherapy planning and delivery need a radical redesign.

Computed tomography (CT) is the current standard imaging modality for radiotherapy planning. It is widely available, geometrically accurate and provides electron density information that is necessary for planning algorithms. However, CT is not always the best modality to identify the GTV for a number of anatomical regions. This is owing to its limited ability to discriminate between the tumor and adjoining soft tissues if they possess similar attenuation values unless there is a fat, air or bone interface between these structures. This limitation has led to significant inter- and intra-observer variability in defining target volumes in a variety of cancer subsites [8,9]. Therefore, in the clinical practice of radiotherapy, MRI is often added to CT-based planning to improve TVD.

The fundamental step in the radiotherapy planning process is optimal delineation of the target volumes for treatment. Any inaccuracy in TVD may lead to inadequate tumor coverage, thus resulting in locoregional recurrence and death. The task of identifying the tumor target volume has become increasingly complex owing to interpretation of multiple sources of imaging

part of future medicine fsg

and sites increasingly requiring detailed nodal outline. One of the characteristics of IMRT is that the high-dose volume is generally smaller than the traditional non-IMRT-based methods. This has the benefit of limiting the high dose to the tumor but also increases the possibility of a geographical miss if the target volume is not accurately defined. As the ability to deliver radiotherapy becomes increasingly more precise, it is likely that target volume delineation may become the biggest source of variation in radiotherapy planning. Several studies have shown the marked variation in GTV delineation between clinical oncologists and radiologists [10–13]. Differences arise owing to a lack of understanding of normal anatomical structures and variants, and inclusion of unrelated nonmalignant pathology in the GTV. Consistently, the GTV defined by the radiologist is the smallest, has the smallest observer variation and most closely resembles the pathology.

> *"...it is essential that radiologists ... become familiar with the oncologists' requirements for radiotherapy planning because only then will optimal use be made of newer developments in imaging and the great potential of targeted treatments realized."*

For several tumor types MRI has now replaced CT as the imaging modality of choice. This applies to tumors of the CNS, soft-tissue sarcomas and pelvic cancers. The major advantage of MRI compared with CT is in its ability to characterize soft tissues that have similar electron densities [14]. Tissue contrast can be altered by manipulating the imaging parameters, which include proton density information and T_2- or T_1-weighted parameters. In this manner, MRI provides not only better TVDs but also better delineation of organs at risk (OAR) for dose avoidance in RTP. Other benefits of MRI include its multiplanar capability, the ability to distinguish between post-treatment fibrosis and tumor recurrence, and avoidance of metal and bony artifacts that may obscure visualization of organs and tumor on CT.

Despite these obvious advantages in the use of MRI for TVD, the use of MRI alone has not yet seriously challenged the utilization of CT for RTP in most sites. The main reasons for this include MR image-related distortions and the lack of electron density information, which is needed to account for tissue inhomogeneities and to calculate radiotherapy dose distributions [15]. However, efficient MR distortion assessment and CT co-registration programs have been investigated in recent years with good results [15].

There are several further developments in MRI that will have a positive impact on RTP [15]. Lymph node-specific contrast agents (ultrasmall particles of iron oxide) have improved detection of microscopic nodal metastases in pelvic cancer enabling pelvic and para-aortic nodes to be included in the CTV [16]. Diffusion-weighted imaging and diffusion-tensor imaging, cine MRI and ultra-fast MR sequences that can identify OAR and PTV prior to delivery of each radiotherapy treatment can help implement image-guided radiotherapy. High field strength scanners and open MR simulators substituting CT simulators will help improve the definition of both tumor and OAR. It is the radiologist who is trained in the use of cross-sectional imaging and therefore best placed to choose the most appropriate imaging modality to define the GTV.

The recent technological revolution in imaging has paved the way for assessment of the biological characteristics of tumors. These so-called 'functional' or 'molecular' imaging modalities provide noninvasive information including metabolic, biochemical and physiological information, in addition to the anatomical data [17]. Ling *et al.* have suggested calling this 'biological imaging' [18]. They have also proposed the concept of a 'biological tumor volume'. This separates the tumor according to its biological activity. The added information from functional imaging on active or radio-resistant tumor regions can be exploited for radiotherapy boost volumes, dose escalation, combined therapy with chemotherapy or radiosensitisers, or to select nonresponders during a course of radiotherapy for more aggressive therapies.

> *"...conformal and intensity-modulated radiotherapy ... utilize imaging to plan an ideal radiotherapy treatment, the goal of which is to improve the therapeutic ratio..."*

MRI promises to be a leading imaging modality in the field of biological imaging [15]. A number of advanced MR techniques including MR spectroscopy, dynamic contrast-enhanced MR, diffusion-weighted MRI, blood-oxygen-level-dependent MRI and diffusion-tensor MRI have been the subject of intense research in recent years.

For example, work completed in the use of MR spectroscopy in the brain and in the prostate have identified dominant lesions for delivery

of higher doses [19], and angiogenesis can be depicted by dynamic contrast-enhanced MR. Diffusion-weighted MRI provides the opportunity to select regions of poor response during radiotherapy for additional boosts. It has been known for some time that tumor hypoxia increases resistance to radiotherapy and blood-oxygen-level-dependent MRI can map areas of hypoxia in tumors [20]. The addition of hypoxia maps of tumors could assist IMRT to deliver a boosted dose to areas of hypoxia without increasing the total PTV. Diffusion-tensor MRI in the CNS can provide information on white matter infiltration by occult tumor that can be used to optimize and individualize target volumes.

The use of FDG-PET has had a substantial impact in RTP at a number of cancer subsites by clarifying TVD. Studies have shown modification in TVD on the basis of information obtained with FDG-PET in 10–100% of patients with head and neck cancer, in 22–62% of patients with lung cancer and in 20% of patients with cervical cancer [21]. Other tracers are being developed to quantitate and image cellular proliferation, hypoxia, apoptosis and angiogenesis, and may prove helpful in accurate TVD [21]. FDG-PET may also permit functional avoidance of normal tissue and reduce interobserver variability. An example of this involves the use of PET to distinguish between tumor and atelectasis in lung radiotherapy.

It is obvious that the input of the radiologist with a clear understanding of the development of these new modalities is essential if the potential of the newer forms of radiotherapy treatment delivery is to be optimized.

A recent review conducted by The Royal College of Radiologists in the UK showed a surprising lack of involvement of radiologists in the process of defining the tumor volume [22]. Yet, the lack of routine radiology involvement carries the risk of systematic errors being introduced in tumor outlining potentially compromising local control and increasing radiation-induced morbidity. In many centers this is one of the few processes within radiotherapy planning not subject to formal checks. Conversely, it is essential that radiologists with an interest in cancer imaging become familiar with the oncologists' requirements for radiotherapy planning because only then will optimal use be made of newer developments in imaging and the great potential of targeted treatments realized.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Bibliography

1 Dearnaley DP, Khoo VS, Norman AR *et al.*: Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. *Lancet* 353(9149), 267–272 (1999).

2 Taylor A, Powell MEB: Intensity-modulated radiotherapy – what is it? *Cancer Imaging* 4, 68–73 (2004).

3 Guerrero Urbano MT, Clark CH, Kong C *et al.*: Target volume definition for head and neck intensity modulated radiotherapy: pre-clinical evaluation of PARSPORT trial guidelines. *Clin. Oncol.* 19, 604–613 (2007).

4 Donovan E, Bleakley N, Denholm E *et al.*: Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. *Radiother. Oncol.* 82, 254–264 (2007).

5 Zelefsky MJ, Levin EJ, Hunt M *et al.*: Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localised prostate cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 70, 1124–1129 (2008).

6 Pirzkall A, Debus J, Haering P *et al.*: Intensity modulated radiotherapy (IMRT) for recurrent, residual, or untreated skull-base meningiomas: preliminary clinical experience. *Int. J. Radiat. Oncol. Biol. Phys.* 55, 362–372 (2003).

7 Berthelsen AK, Dobbs J, Kjellén E *et al.*: What's new in target volume definition for radiologists in ICRU Report 71? How can the ICRU volume definitions be integrated in clinical practice? *Cancer Imaging* 11(7), 104–116 (2007).

8 Cattaneo GM, Reni M, Rizzo G *et al.*: Target volume delineation in post-operative radiotherapy of brain gliomas: interobserver variability and impact of image registration of MR (pre-operative) images on treatment planning CT scans. *Radiother. Oncol.* 75, 217–223 (2005).

9 Giraud P, Elles S, Helfre S *et al.*: Conformal radiotherapy for lung cancer: different delineation of the gross tumour volume (GTV) by radiologists and radiation oncologists. *Radiother. Oncol.* 62, 27–36 (2002).

10 Steenbakkers RJ, Duppen JC, Fitton I *et al.*: Observer variation in target volume delineation of lung cancer related to radiation oncologist-computer interaction: a 'Big Brother' evaluation. *Radiother. Oncol.* 77, 182–190 (2005).

11 Van de Steene J, Linthout N, de Mey J *et al.*: Definition of gross tumour volume in lung cancer: inter-observer variability. *Radiother. Oncol.* 62, 37–49 (2002).

12 Senan S, van Sörnsen de Koste J, Samson M *et al.* Evaluation of a target contouring protocol for 3D conformal radiotherapy in non-small cell lung cancer. *Radiother. Oncol.* 53, 247–255 (1999).

13 Cazzaniga LF, Marinoni MA, Bossi A *et al.*: Interphysician variability in defining the planning target volume in the irradiation of prostate and seminal vesicles. *Radiother. Oncol.* 47, 293–296 (1998).

14 Khoo VS: MRI – "magic radiotherapy imaging" for treatment planning? *Br. J. Radiol.* 73, 229–233 (2000).

15 Khoo VS, Joon DL: New developments in MRI for target volume delineation in radiotherapy. *Br. J. Radiol.* 79(Spec No. 1), S2–S15 (2006).

16 Taylor A, Rockall AG, Reznek RH, Powell ME: Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* 63, 1604–1612 (2005).

17 Price P: Molecular imaging to improve radiotherapy. *Radiother. Oncol.* 78, 233–235 (2006).

18 Ling CC, Humm J, Larson S *et al.*: Towards multidimensional radiotherapy (MD-CRT): biological imaging and biological conformality. *Int. J. Radiat. Oncol. Biol. Phys.* 47(3), 551–560 (2000).

19 Payne GS, Leach MO: Applications of magnetic resonance spectroscopy in radiotherapy treatment planning. *Br. J. Radiol.* 79(Spec No. 1), S16–S26 (2006).

20 Padhani A, Krohn KA, Lewis J, Alber M: Imaging oxygenation of human tumours. *Eur. Radiol.* 17, 861–872 (2007).

21 Apisarnthanarax S, Chao KS: Current imaging paradigms in radiation oncology. *Radiat. Res.* 163, 1–25 (2005).

22 Jefferies S, Taylor A, Reznek R: Radiotherapy Planning Working Party. Results of a national survey of radiotherapy planning and delivery in the UK in 2007. *Clin. Oncol.* 21, 204–217 (2009).