# The value of new imaging technology for target volume delineation

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Cross sectional imaging is central to modern radiotherapy. The use of multimodality imaging can confer advantages for radiotherapy treatment planning by providing complimentary data as well as functional or biological information. The obvious use of imaging is to stage the extent of the disease and subsequently to assess response to therapy. This process is also important for radiotherapy. The intent of radiotherapy and plan design can alter substantially if there is involvement of the regional nodes or if there is local invasion into neighbouring surrounding normal structures. It is difficult to define the extent of microscopic or subclinical nodal disease spread and it cannot be visualised using morphological cross sectional imaging methods. Often it has to be estimated using clinical experience and knowledge of the disease. The use of functional and biological imaging studies can be useful in this respect and its utility is being investigated for radiotherapy. Apart from positron emission tomography (PET), which can provide functional and biological information, there are now functional studies using computed tomography (CT) and magnetic resonance imaging (MRI).

Although there are systemic modes of irradiation, such as radioisotopes, the majority of irradiation is given locally to a specified anatomical site or organ. This is administered using either external beam or brachytherapy (interstitial or intracavitary therapy). As such, the radiation source needs to be aimed or placed at the tumour or target volume. Therefore, it is crucial to appropriately identify tumour volumes or target volume(s) so that the planning of radiotherapy and its delivery can be optimised. There is a set of pre-defined nomenclature for radiotherapy planning volumes. The International Commission for Radiation Units (ICRU) Report 50 and ICRU 62 (Table 1) define a series of volumes which take into consideration factors such as the subclinical extent of disease, internal organ motion due to physiological activity, patient movement, treatment set-up variability and penumbral effects of the treating beam [1,2]. A further update for this nomenclature is expected shortly to

Table 1
Definition of radiotherapy planning volumes (ICRU 50 and ICRU 62)

| Nomenclature | Definition |
|---|---|
| Gross Target Volume (GTV) | This is the radiologically visible or clinically palpable extent of tumour and represents macroscopic disease. |
| Clinical Target Volume (CTV) | This is the GTV with a margin that includes the presumed microscopic extent of disease or subclinical nodal involvement. These microscopic extensions of disease cannot be seen on cross-sectional imaging. |
| Planning Target Volume (PTV) | This is the CTV with a margin added to account for patient movement, internal organ and target motion, uncertainties in patient set-up and treatment beam penumbra. This margin may be further subdivided into the Internal Margin and the Set-up Margin.<br>• Internal Margin: This is the volume needed to account for variation in size, shape, and position of the CTV in relation to anatomical reference set-up points.<br>• Set-up Margin: This is the volume needed to account for uncertainties in patient-beam positioning. |
| Treated Volume (TV) | This is the volume of tissue actually treated to the prescribed dose as specified by the clinician (e.g. 95% isodose volume). |
| Irradiated Volume (IV) | This is the volume of tissue irradiated to a clinically significant dose in relation to normal tissue tolerance (e.g. 50% isodose volume). |

take into account the recent introduction of image guided radiotherapy.

Cross-sectional imaging has permitted the development of conformal radiotherapy (CFRT) and intensity modulated radiotherapy (IMRT) techniques with several advantages for the patient. These include recognising the target's spatial relationship with its surrounding structures that may be dose limiting, the opportunity to shape treatment fields for CFRT and modulation of dose for IMRT to reduce toxicity, permit dose escalation and, finally, to reduce geographical miss of the tumour due to inaccurate target volume delineation. There are randomised trials in some cancers confirming the benefits of CFRT in reducing toxicity [3,4] and for dose escalation providing improved local control rates [5,6]. Using IMRT, a method of 'dose painting' may be initiated to permit boosting of the target by using different dose fractions to different volumes at the same time (i.e. a method termed simultaneous integrated boost) as an alterative method of dose escalation [7]. These sub-volumes may represent a region of rapidly proliferating tumour or perhaps a hypoxic region. By delivering a larger dose per fraction to these sub-volumes simultaneously, potential radioresistence may be overcome. The use of biological imaging can help define these sub-volumes and these approaches are still being studied. Integral to these planning advances is the need to adequately define the appropriate tumour or target volumes for boosting or sparing.

MRI has replaced CT as the imaging modality of choice for several cancer sub-types such as central nervous system cancers, pelvic cancers and muscular skeletal tumours. MRI can offer imaging advantages in identifying tumour extent for radiotherapy planning (RTP) especially where the tumour has similar x-ray attenuation to its surrounding regions and can provide complimentary information [8,9]. There are many examples of this. In meningiomas of the skull base, MRI provides complimentary information to CT and is able to detect disease extension along the skull bones [9]. In a nasopharyngeal study, CT imaging missed up to 40% of intracranial infiltration detected by MRI [10]. MRI can improve delineation for the prostatic apex and the boundaries between prostate, rectum and bladder [11–13]. Co-registered CT-MRI scans have reported that CT-defined prostate volumes are approximately one third larger than those defined by MRI suggesting that there is an overestimation with CT [14,15]. With better definition of the prostate using MRI, the treatment fields can be shaped to reduce dosage to important structures such as the rectum and penile bulb [16]. Better discrimination of the target volumes can also reduce inter- and intra-observer variability in assessing target volumes for RTP [17].

Ultrasmall Superparamagnetic Iron Oxide (USPIO) particles have been reported to have high sensitivity and specificity in discriminating microscopic tumour involvement in nodal tissue [18]. Nodal volumes are often included in the CTV for radiotherapy and defining its involvement is important. Inadequate nodal coverage can compromise local control or unnecessarily irradiate normal structures [19].

Functional MRI may provide further characterisation of tissue that can aid identification of tumour regions for irradiation boosts using methods such as IMRT or image guided radiotherapy (IGRT). Functional MRI may also be used to delineate regions of the brain that would result in significant patient morbidity if excessively irradiated and avoidance of these regions during stereotactic radiosurgery can improve patient outcomes. Diffusion tensor MRI (DTI) can demonstrate white matter abnormalities based on cerebral tissue anisotrophy and provide information on white matter infiltration by occult tumour [20]. This information can then be used to optimise and individualise target volumes [21].

Tumour features of vascular angiogenesis and increased cellular growth are factors assessed by dynamic contrast enhanced MRI (dcMRI) and diffusion weighted-MRI (dwMRI) respectively. Assessing the sequential vascular perfusion changes in tissue can characterise normal, tumour and irradiated tissues [22] whereas dwMRI relies on the tumour regions having increased cellular density, due to tumour proliferation, with a corresponding reduction of water diffusion in this region that is quantified through apparent diffusion coefficient (ADC) maps [23]. Tissues regions with lower ADC are more likely to contain tumours. These findings may be used to delineate preferential targeting or boosts with radiation. Similarly, blood-oxygen-level dependent (BOLD) MRI can map regions of tumour hypoxia for image guided IMRT or brachytherapy [24].

Magnetic resonance spectroscopy (MRS) can detect low molecular weight metabolites that reflect cellular processes. MRS may indicate the presence of tumours and infiltration not noted by standard MRI sequences using spectra profiles of Lipids/Creatine and Lactate/Creatine. Raised profiles have been noted in the peritumoural region of high grade tumours suggesting this region remains at high risk for recurrence and should be included in the CTV [25]. Using MRS data in prostate cancer, investigators have delineated apparent dominant intra-prostatic lesions

for dose boosting using either IMRT or high dose rate brachytherapy [26].

PET can provide important tumour and normal tissue physiological and biological data. The most commonly used PET tracer is $^{18}$F-FDG and relates glucose metabolism to the increased metabolic activity usually seen in cancers. PET tracers are now available to assess different aspects of tumour metabolism such as hypoxia and proliferation. By quantifying different aspects of tissue metabolism with different PET tracers, regions of hypoxia and altered tissue activity may be used to aid target volume delineation. One example is that FDG-PET in the brain is limited due to the normally high glucose uptake in the brain, so more specific PET tracers are needed. Radiolabelled amino acids, methionine (MET), alanine and tyrosine, are used on the basis that cellular turnover is much greater in tumours than in cerebral tissues. MET-PET has use for target volume delineation as it is reported to have higher sensitivity and specificity for tumour tissue [27]. In addition, molecular imaging may be used to identify different tumour related phenotypes and genotypes that may also be useful in determining subclinical target volumes or CTV for RTP [28,29].

One of the advantages of PET is the exclusion or confirmation of nodal or metastatic involvement. PET may visualise disease in radiological normal size nodes. Its use in lung staging has changed practice. In lung radiotherapy, the use of FDG-PET resulted in a substantial change in treatment plans between 22 and 62% of cases [30–34]. The two main contributions of PET for RTP were in the identification of involved mediastinal nodes and the improved ability to better distinguish between tumour and atelectasis. Another advantage of using PET-CT information is that interobserver variability is also substantially reduced for lung planning [34,35] and this benefit is most pronounced for regions in the mediastinum and in the presence of atelectasis [36].

There are limitations in using functional imaging for RTP and recognition of these limitations is useful when considering the added value of using functional imaging for target volume delineation, especially when determining where to draw the 'line' between normal and tumour tissue for the CTV. In an important study of head and neck tumours, surgical pathological data was correlated with imaging using CT, MRI and FDG-PET [37]. This small but robust study reported that all imaging modalities overestimated the tumour volume with the largest difference coming from CT followed by MRI and FDG-PET. There is also uncertainty as to what is the most reliable parameter to be used to define PET disease involvement, as numerical values of the PET intensity levels selected, such as standardised uptake value (SUV), are quite arbitrary. Furthermore, many different parameters can affect PET intensity levels such as patient characteristics, scanner and scanning technique, organ motion and deformation. It remains crucial to undertake careful histopathological correlation with multimodality imaging in order to verify the 'true' value of the imaging modality in question in defining the microscopic extent or biological parameters of the disease.

## Conflict of interest statement

There are no conflicts of interest.

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