

## REVIEW ARTICLE

# Advanced imaging applied to radiotherapy planning in head and neck cancer: a clinical review

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**ABSTRACT.** Head and neck squamous cell carcinoma represents an ideal model to investigate the application of recent advances in medical imaging to radiotherapy planning. Tumours usually remain localized, and are potentially curable with local radiation. The steep radiation dose–response relationships support the strategies of radiation dose escalation to increase local control. Two-dimensional simulator-based planning and CT planning have significant drawbacks in terms of accurate target volume definition. MRI has enhanced soft tissue delineation, but has to be fused with CT to allow dose calculation. Functional imaging using dynamic contrast enhanced CT or MRI sequences may allow improved knowledge of tumour function. Positron emission tomography (PET) may allow further physiological information to be determined. This review summarizes the current techniques in clinical development in this area.

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Head and neck cancer (HNC) is the seventh most common cancer in the UK. Whilst early stage disease has a high cure rate, stage III and IV HNC still have poor rates of local control and survival [1]. Surgery and/or radiotherapy aim to achieve locoregional control, and where it enables organ preservation with maintenance of function, radiotherapy is the modality of choice. Failure to achieve locoregional control may be due to geographical miss of primary tumour or nodes due to understaging disease, intrinsic radioresistance of the tumour, or factors such as hypoxia and proliferation known to reduce radiosensitivity of a tumour. Three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) aim to achieve better locoregional control and improve survival by radiation dose escalation, but such techniques demand more accurate localization of tumour and normal tissues with non-invasive imaging techniques.

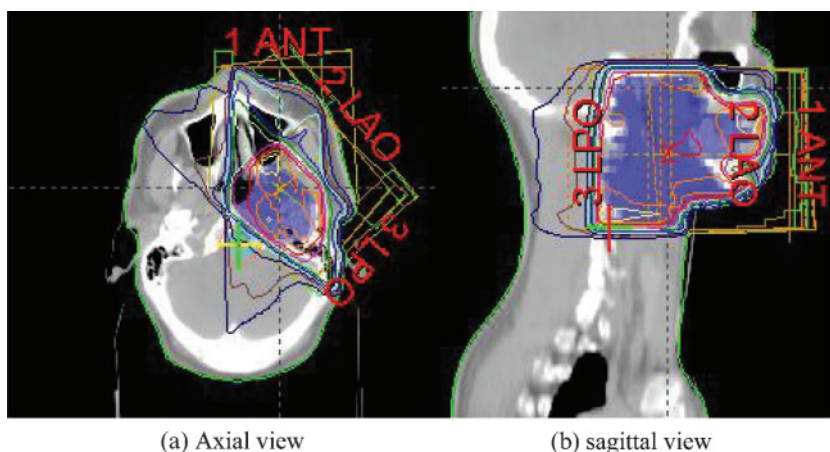
## Anatomical imaging for head and neck radiotherapy planning

### Current standard radiotherapy imaging

In the UK, the most common methods of target localization for radiotherapy planning include the use of the simulator and CT scanning. In the simulator, standard radiotherapy field borders are placed on identifiable bony landmarks, and simple outlines are taken at levels through the treatment volume. For most

patients, this approach gives the radiation oncologist a “one size fits all” treatment. There is limited opportunity for individualization of treatment volumes, although simple customization is possible with reference to bony landmarks within individual cases. It results in treatment fields with large margins around tumours to account for uncertainty of target position and conservative doses due to uncertainties in dose to organs at risk (OARs).

CT planning provides a 3D representation of the target volume and OARs allowing improved target definition and also accurate OAR delineation. The use of iodinated contrast agents increases sensitivity, and CT with contrast remains the best modality for defining nodal disease, cartilage invasion, or bone destruction [2, 3]. Reconstruction of high resolution coronal and sagittal sections may aid RT planning. CT images are most accurate when tumour interfaces are with air cavity, fat, or bone such as in the paranasal sinuses or neck, but are less accurate when the tumour interfaces with normal soft tissue such as in the tongue, or when there may be mucosal spread for example in the larynx and hypopharynx [4]. CT planning generates electron density data for photon dose calculation, and calculation of dose–volume histograms. CT planning allows accurate conformal shaping of the radiotherapy portals around the target and shielding of the OARs (Figure 1). CT planning removes many of the uncertainties of position of tumour and OAR. However, CT planning *per se* does not necessarily allow radiation dose escalation, especially if the adjacent OARs are neurological. The spinal cord, brain stem and optic nerves are assumed to have a serial



**Figure 1.** Three-dimensional conformal radiotherapy planning. CT plan of a left sided oropharyngeal tumour. Blue colourwash: planning target volume (PTV), isodose levels indicated by coloured linear boundaries. ANT: anterior beam, LAO: left anterior oblique, LPO: left posterior oblique.

organization of functional subunits, where inactivation of a single subunit causes loss of function of the whole organ. In this setting, the risk of late toxicity is determined by the maximum dose received by the OAR, and therefore partial reductions of the volume of tissue irradiated, such as those offered by 3D-CRT, do not reduce the risk of late toxicity. In such cases the more advanced radiation delivery techniques such as IMRT, which can produce dose distributions with concave isodose surfaces, may be required [5, 6].

#### Use of MRI for treatment planning in head and neck cancer

The main advantage of MRI over CT is significantly greater soft tissue contrast, permitting better definition of disease extent and OAR [7].  $T_1$  weighted images give good anatomical detail whilst  $T_2$  weighted images can differentiate between normal and pathological tissues. Image contrast can be enhanced by intravenous gadolinium. Artefacts arising from dental amalgam can be made significantly less conspicuous on MRI than CT. MRI is the modality of choice for imaging tumours of the base of tongue and lesions arising at the skull base [8, 9], also visualization of important OAR such as the orbit, optic nerves and chiasm and central nervous system. Emami et al showed that the co-registration of two anatomical modalities, MRI and CT improved the target definition of cancer of the nasopharynx [10].

The use of MRI in radiotherapy treatment planning is limited by the presence of geometrical distortions, including inhomogeneities within the magnetic field and non-linearities in the spatial-encoding gradients. These distortions increase as the distance from the isocentre increases and have been reported to be 5 mm at 12 cm from isocentre [11]. These therefore are of clinical significance for head and neck planning, and need to be either removed by a post-processing technique [12, 13], or by CT/MR fusion and image correction. Electron density information necessary for treatment dosimetry cannot be obtained from MRI, and the images have to be fused with CT data if this information is to be used in treatment planning calculations. Therefore fusion of distortion-corrected MRI and CT images could provide both the improved target definition and dosimetric accuracy required for treatment planning.

Intrinsic susceptibility-weighted or blood oxygenation level dependent (BOLD) MRI exploits the differences in magnetic susceptibility of oxyhaemoglobin and deoxyhaemoglobin. Changes in blood oxygenation can therefore be characterized by looking at differences between  $T_2^*$  weighted images during a change in oxygenation, and may help to identify hypoxia in tumours. No intravenous contrast agents are required; however, BOLD effects are very short lived, and require rapid sequences. Some of the changes in signal can be small and are difficult to reproduce.

#### Functional imaging

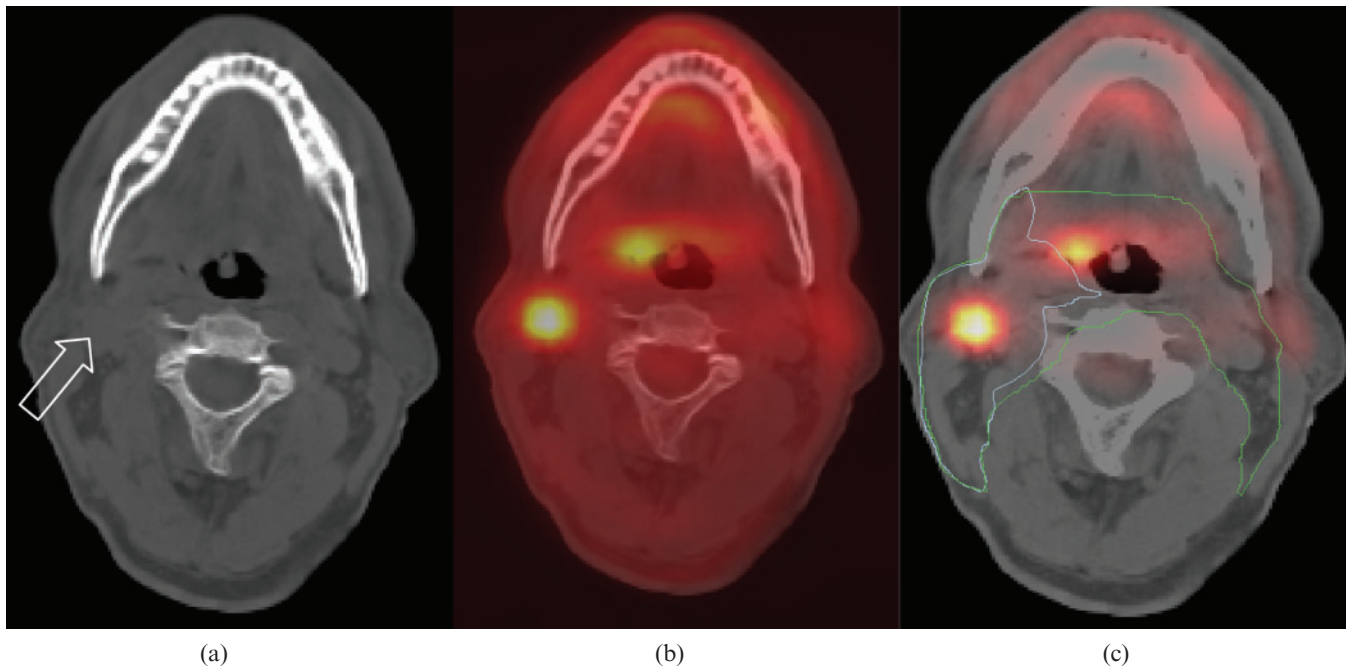
Functional imaging is defined as characterizing tumours radiologically in terms of their biochemistry or physiology. Such imaging modalities include positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance spectroscopy (MRS), and dynamic contrast-enhanced MRI and CT. Functional imaging may improve staging of disease by detecting occult carcinoma, or give clearer delineation of areas of previously known tumour (Figure 2). Furthermore, it may provide information on tumour parameters such as blood flow, vascular permeability, proliferation rate and oxygenation. The introduction of functional imaging to radiotherapy planning adds a new concept, termed the biological target volume (BTv) [14].

#### PET

( $^{18}$ F)-Fluoro-2-deoxy-D-glucose ( $^{18}$ FDG) is the most commonly used imaging tracer in the diagnosis and staging of HNC. Table 1 summarizes studies showing the sensitivity and specificity in diagnosis of HNC which is superior to CT and MR in assessing lymph nodes, distant metastases and second primaries in a single study [15–23], although the number of false positives makes the specificity suboptimal.

#### PET-CT

PET alone has been of limited value in radiotherapy planning because of its limited spatial resolution



**Figure 2.** <sup>18</sup>F-FDG PET/CT case study. This patient presented with a right sided level II node containing metastatic squamous cell carcinoma. Conventional imaging with a diagnostic contrast enhanced CT scan showed the right neck node but the primary tumour was occult. (a) The non-contrast enhanced CT component of the PET/CT scan illustrates this (arrow points at node). (b) <sup>18</sup>F-FDG PET/CT demonstrated the right neck node and but also identified an area of <sup>18</sup>F-FDG uptake in the right tongue base which on biopsy was proven to be the primary site. (c) The planning target volume (PTV) defined in blue shows the target volume planned with conventional data only whereas the PTV defined in green shows the expansion of this when the PET/CT identifies the tongue base tumour and therefore includes the oropharynx and contralateral neck. The PTV increased by 467 cm<sup>3</sup> with the addition of data from the PET/CT.

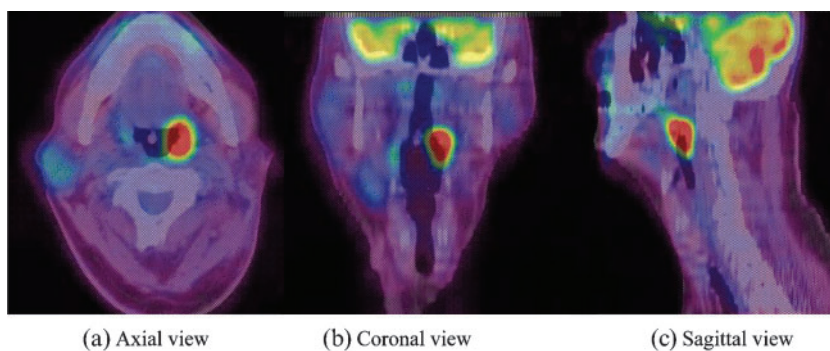
(4–5 mm for <sup>18</sup>F-FDG-PET) and a lack of anatomical landmarks. Software image co-registration of non-contemporaneous PET images and CT or MRI is possible, but may generate significant matching errors which make it unsatisfactory for radiotherapy planning. Integrated PET/CT scanners produced hardware fused images (Figure 3) which reduces these errors and increases accuracy compared with PET alone in head and neck cancer (96% vs 90%, *p* = 0.03, [15]). The CT component of a standard PET/CT scan is not usually of diagnostic resolution in order to minimize the radiation dose received by the patient. Optimal CT scanning, for example with multislice scanners, are sometimes advised to supplement the PET/CT examination. PET/CT is likely to have a maximum impact in the head and neck region because accurate co-registration enables differentiation between pathological and physiological areas

of <sup>18</sup>F-FDG uptake. Common causes of false positives are Waldeyers ring, salivary glands, brown fat and fast twitch muscles, which have the potential to cloud the diagnostic picture.

Using PET, an area of tracer uptake may be seen which is distinct from, or overlap the conventionally defined gross target volume (GTV). In lung cancer planning, the addition of PET led to 26–100% of patients having a change in radiotherapy management when compared with CT plans alone [24]. The changes were not consistent. 15–64% of patients showed an increase in the planning target volume (PTV) and 21–36% had a decrease. Ciernik et al [25] took 39 patients with mixed primaries (12 with HNC) and compared GTV and PTV when localizing using CT alone compared with <sup>18</sup>F-FDG-PET/CT. They observed that the GTV in HNC changed in 32% with the PET data (either an increase or decrease)

**Table 1.** <sup>18</sup>F-FDG-PET in staging head and neck cancer (HNC)

Author	Year	Number of patients	T stage		N stage		Management change (%)
			Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	
Schmid [16]	2003	48					8
Dizendorf [17]	2003	202					27
		all sites					
Kresnick [18]	2001	24					21
Hanasano [19]	1999	146	50	83	86	73	
Kau [20]	1999	70			87	94	
Nowak [21]	1999	71	87	67	80	92	
Wong [22]	1997	54			67	100	



**Figure 3.** Hardware-fused  $^{18}\text{F}$ FDG-PET/CT showing primary tumour in the left oropharynx. The position of the  $^{18}\text{F}$ FDG uptake can be seen in relation to the CT derived anatomy in three dimensions.

and the mean PTV change was 20%. Interestingly, the interobserver variability was reduced when the PET data were included compared with CT alone. Nishioka [26] looked at image fusion between  $^{18}\text{F}$ FDG-PET and MRI/CT for radiotherapy planning in 12 patients with oropharyngeal carcinoma and nine patients with nasopharyngeal carcinoma. They concluded that the fusion was useful in GTV and CTV determination, and enabled sparing of normal tissues. Scarfone et al observed an average increase in GTV of 15% when defined by PET/CT versus CT alone [27]. Table 2 summarizes radiotherapy planning studies with PET imaging.

#### Other PET tracers for functional imaging

DNA precursors, such as  $^{11}\text{C}$  or  $^{124}\text{I}$  labelled thymidine or deoxyuridine, are incorporated into DNA during repair or S phase and can be imaged to non-invasively identify regions of cell proliferation.  $^{11}\text{C}$ -labelled methionine or choline are substrates for protein synthesis and have been tested in prostate cancer [28]. Imaging of tumour hypoxia with tracers is now possible. An example is the group of imidazole containing agents (*e.g.*  $^{18}\text{F}$ -misonidazole) which are bioreductive molecules that accept an electron to form a free radical that is incorporated into the cell constituents under hypoxic conditions.  $^{62}\text{Cu}$ -diacetylbis (N-4-methyl-thiosemicarbazone, Cu-ATSM) is a non-imidazole bioreducible radiopharmaceutical which has been used clinically to image hypoxia and to define a potential target for therapy [29].

#### SPECT

SPECT produces a three-dimensional tomographic image of the distribution of an injected radioisotope, and therefore is of potential interest for radiotherapy

planning. However, the detection of single photons, rather than two coincident rays, reduces the spatial resolution compared with PET. In view of this, SPECT has remained in the research arena in the head and neck region.

#### Magnetic resonance spectroscopy (MRS)

MRS provides a non-invasive method with which to identify and quantify the presence of specific chemicals within a tissue, *e.g.* tissue metabolites or the presence of a specific drug. It could feasibly be used to identify chemicals associated with hypoxic tissue. Current limitations of MRS include sensitivity, limited spatial localization and organ motion, but advances in data acquisition techniques have the potential to make spectroscopy an increasingly important clinical tool [30, 31].

#### Dynamic contrast-enhanced imaging of tumour vascularity, blood flow and permeability

Rapid scanning sequences during the administration of contrast agents for CT and MRI have allowed dynamic scans that can impart information regarding the biology of the tumour and its microenvironment, such as blood flow, vascular permeability, hypoxia and pH. Two techniques are currently in clinical research.

#### Dynamic contrast enhanced (DCE) MRI

DCE-MRI involves the acquisition of multiple sequential MRI scans of an area of interest following injection of a contrast agent. This enables study of pharmacokinetics

**Table 2.**  $^{18}\text{F}$ FDG-PET and radiotherapy planning

Author	Year	n	Tumour type	Fusion	Results
Scarfone [27]	2004	6	HNC	Software fusion $^{18}\text{F}$ FDG-PET and CT	Modified GTV by a mean 15% increase
Ciernik [25]	2003	39	Various	Hardware fusion $^{18}\text{F}$ FDG-PET/CT	GTV Change-56%, Reduced inter-observer variability
Nishioka [26]	2002	21	HNC	Software fusion $^{18}\text{F}$ FDG-PET with MRI/CT	Useful in GTV and CTV, and normal tissue sparing

n, number of patients; HNC, head and neck cancer; NSCLC, non small cell lung cancer; GTV, gross tumour volume; CTV, clinical target volume; PTV, planning target volume.

of para-magnetic contrast agents and provides information on tumour vascularity, blood volume and vessel permeability. MRI sequences can be designed to be sensitive to the initial, largely intravascular phase of contrast delivery [32, 33]. Cooper et al [34] examined the relationship between DCE-MRI parameters and Eppendorf  $pO_2$  histographic measurements in 30 patients with cervical carcinoma and found a correlation between maximum enhancement over baseline and rate of enhancement, using  $T_1$  weighted sequences, with both median  $pO_2$  and proportion of  $pO_2$  with values less than 5 mmHg. They concluded that DCE-MRI could be used to measure hypoxia in human tumours *in vivo*. Hoskin et al [35] examined tumour perfusion in patients with advanced HNC using DCE-MRI ( $T_1$  weighted sequences) and found a correlation between local tumour control and maximum tumour enhancement following accelerated radiotherapy.

### Perfusion CT

Similarly, rapid acquisition of images by spiral or multislice CT, as contrast is given, can estimate tissue perfusion based on the contrast density changes over time [36]. Histological assessment of tumour neovascularization such as microvessel density correlates with contrast enhancement parameters in lung and renal cancer [37, 38]. Hermans et al [39] used this method in patients with HNC who had undergone radical radiotherapy or chemotherapy and concluded that tumour perfusion was an independent predictor of local control, with decreased perfusion levels associated with a higher local failure rate. Possibly these tumours had a reduced blood supply rendering them relatively hypoxic and therefore radioresistant.

## Application of functional imaging to head and neck cancer treatment planning

### Hypoxia targeting

Low oxygen levels are associated with reduced apoptotic potential, increased angiogenesis and increased frequency of mutations [40], and are associated with poor local control and survival. Hypoxic radioresistance may be overcome to some extent by increasing tumour oxygenation, hypoxic cell sensitizers, or increasing the radiation dose [41, 42]. Some studies both *in vitro* and *in vivo* suggest that a radiation dose 2.5–3 times current dose levels are required to overcome the effects of hypoxia [43]. However, others suggest that more modest dose increases of 1.2–1.5 times the primary dose may result in equivalent tumour control [44]. These doses, in the region of 90–100 Gy, are potentially achievable to areas within tumours with concomitant boost techniques deliverable with IMRT [45]. The spatial and temporal stability of the hypoxic volume during radiotherapy is critical for such approaches and is the subject of ongoing studies. Chronic, or diffusion limited hypoxia is defined by reduced  $pO_2$  over hours to days, thought to be due to the distance from a capillary, the oxygen content, the rate of blood flow and the oxygen

metabolism of that capillary. Acute, or perfusion limited hypoxia is defined when the variation is over minutes and is thought to be due to intermittent reductions in capillary flow. Dose escalation strategies based on targeting areas of chronic hypoxia are only likely to succeed if this is the dominant cause of treatment failure. PET imaging with  $^{18}F$ -Miso, or CuATSM have been used in this context to quantify hypoxia in head and neck cancer [46, 47]. In a study by Taylor et al [48], BOLD MRI, in conjunction with carbogen-breathing in patients with head and neck carcinoma, suggested improved tissue oxygenation and blood flow; however, difficulties with measurement and reproducibility of BOLD signals have made it impractical for radiotherapy planning.

### Validating hypoxia imaging using histological markers

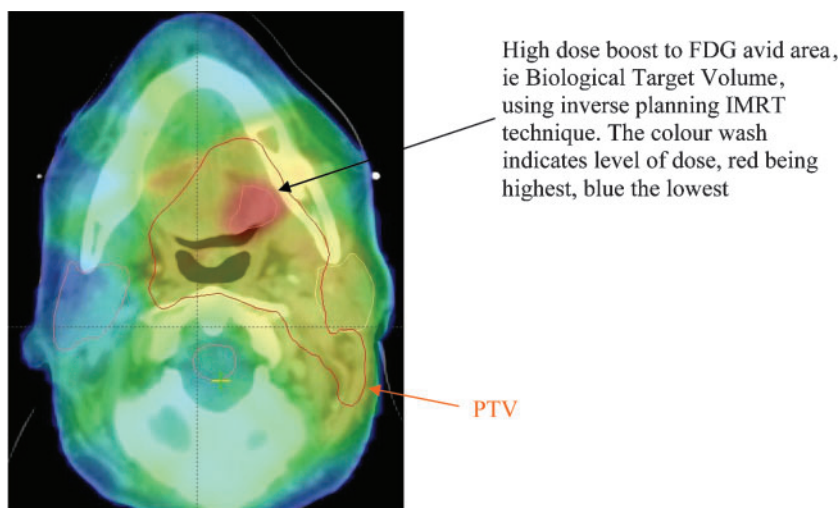
Direct measurement of tissue oxygen tension is possible using the Eppendorf polarographic electrode. This technique is not ideal for validating hypoxia because it is invasive, requires accessible tumours and is highly user dependent. 50–150 readings are required per sample, and spatial heterogeneity remains a problem [49]. Sequential readings in assessment of temporal changes are unreliable due to tissue damage following initial formation of tracks [50]. Despite this, DCE-MRI parameters have been correlated to Eppendorf measurements in carcinoma of the cervix [34].

Exogenous and endogenous markers are more promising. Exogenous markers are chemicals that accumulate or are bioreducible in hypoxic conditions, *e.g.* nitroimidazoles [51]. These retained bioreductive products can be detected by immunohistochemistry, *e.g.* pimonidazole [52]. Pimonidazole staining has been correlated with outcome in HNC [53]. Endogenous markers are gene products that are up-regulated in the presence of hypoxia. Aebbersold et al reported 94% of a cohort of 98 oropharyngeal squamous cell carcinomas over-expressed the transcription factor, hypoxia-inducible factor 1- $\alpha$  (HIF 1- $\alpha$ ) [54]. Carbonic anhydrase-9 (CA9) has been shown to have the greatest magnitude of expression in response to hypoxia among a range of 12 genes [55]. CA9 levels rise from 4 h to 24 h of levels of  $pO_2$  at 20 mmHg and less. Expression has been concordant with pimonidazole in head and neck cancer [53], and with polarographic (electrode) measurements [56] in cervical cancer.

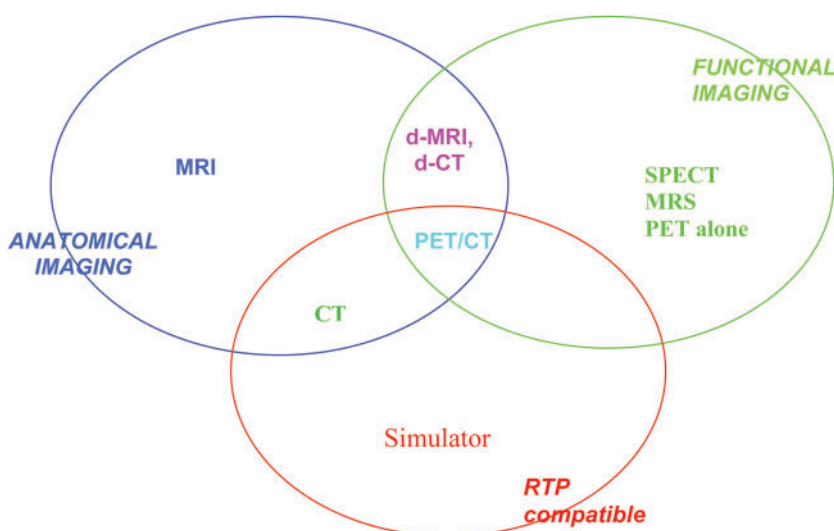
The examination of tumour specimens for hypoxia with the above markers can be used to validate imaging methods performed in the pre-operative period, as long as careful attention is paid to the orientation of the specimen at the time of surgery and histological sections are cut in the same plane as the test images.

### What is the likely impact of functional imaging on radiotherapy planning?

Functional imaging adds to anatomical imaging for radiotherapy planning in a number of ways. First, functional imaging may alter disease stage, which may have a major impact on disease management. This is



**Figure 4.** Intensity-modulated radiotherapy (IMRT) plan, illustrating dose boost to a biological target volume (BTV).



**Figure 5.** Interaction of anatomical and functional imaging modalities and their compatibility with radiotherapy planning (RTP).

more likely to be an issue in diseases such as lung cancer with a high metastatic potential, than with head and neck cancer. Second, functional imaging may improve our localization of the target volume by detection of unexpected tumour extension, or presence of occult locoregional metastases in lymph nodes. This will lead to changes in GTV and CTV definition which may be clinically significant. Finally, functional imaging may determine radioresistant sub-regions within the conventional GTV due to hypoxia or accelerated proliferation. Such biological target volumes may be suitable for radiation dose escalation delivered by techniques such as simultaneous IMRT boosts (Figure 4). These allow increase in total dose and dose-per-fraction, which radiobiologically may be of particular benefit.

## Conclusion

Several new imaging techniques, both anatomical and functional are currently being evaluated for treatment planning for head and neck cancer (Figure 5). As well as improved conventional target volume definition, new biological target volumes may be generated by these

imaging methods. Careful validation of these imaging methods against histological parameters is urgently required before they can be integrated into clinical treatment planning. Functional imaging will most likely be used in conjunction, rather than as an alternative to, conventional imaging techniques.

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