Defining the target for radiotherapy of head and neck cancer

S. Nuyts

Department of Radiation-Oncology, Leuven Cancer Institute (LKI), University Hospital Gasthuisberg,
Herestraat 49, 3000 Leuven, Belgium

Corresponding address: Sandra Nuyts, MD, PhD, Department of Radiation-Oncology, Leuven Cancer Institute (LKI),
University Hospital Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium.
Email: sandra.nuyts@uzleuven.be

Abstract

The greatest challenge for radiation therapy is to attain the highest probability of cure with the least morbidity. Implementation of conformal radiotherapy techniques offers the possibility to target irregularly shaped volumes while optimally sparing the normal tissues. This implies however an accurate knowledge of the exact tumour extension. In order to perfectly delineate the primary tumour and to optimise the radiation dose administered to normal tissues, it is necessary for patients to undergo imaging studies. Both anatomical and functional imaging studies are currently being evaluated for treatment planning of head and neck cancer.

Keywords: *Head and neck cancer; radiotherapy; imaging.*

Introduction

Head and neck cancer is the sixth most common cancer worldwide, with 650,000 new diagnoses per year. To strive for organ preservation, even for advanced stages, radio(chemo)therapy can be applied. The greatest challenge for radiation therapy is to attain the highest probability of cure with the least toxicity. High precision 3D-conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT) are nowadays being used to optimally cover the tumoral tissues and to maximally avoid the normal structures.

To attain this goal, all cancer cells should be encompassed with sufficient dose of radiation during each fraction, while simultaneously sparing the surrounding normal tissues. Therefore, exact identification of the tumour cells is necessary. Technical improvements in the application of computed tomography scans (CT), magnetic resonance imaging (MRI) and positron emission scans (PET) have greatly improved our ability to identify tumours.

The role of imaging in staging is well recognised and several studies have provided evidence concerning the value of imaging in early response assessment to therapy, prognosis and follow up. This paper focuses on the role of imaging in defining the target for radiotherapy in head and neck cancer, both primary tumour and nodal involvement.

Target delineation

The head and neck is an ideal site for conformal radiotherapy (3D-CRT and IMRT) due to the complex geometry of this area and the severity of radiation-associated toxicity. Frequently, the distance between either gross tumour volume (GTV) or areas at high risk for microscopic disease (clinical target volume (CTV)) and critical structures such as the optic nerve, spinal cord, brainstem, salivary gland is no more then a few millimetres. In the past, it was extremely difficult delivering a high radiation dose to the tumour while limiting the dose to an organ at risk just a few millimetres away. The toxicity from head and neck radiotherapy was therefore among the worst seen in radiotherapy.

Because of the potential to escalate the dose to the tumour with the aim of improving locoregional control and to decrease the dose to normal tissue and thus reduce toxicity, 3D-CRT and IMRT have been introduced in the treatment of HNC, thanks to the progress made in

cancer imaging. To minimize the risk of geographical misses due to inadequate tumour delineation, expertise in the knowledge of the anatomy of the head and neck region, clinical examination, knowledge about the regional tumour spread, and interpretation of diagnostic imaging are of major importance. Currently, CT, MRI and fluorodeoxyglucose (FDG) PET are being used to guide the radiation oncologist in delineation of targets.

Anatomical imaging

Optimal delineation of the primary tumour and the involved lymph nodes are a prerequisite for curative radiotherapy in head and neck cancer. In the planning of radiation therapy, it is important to localise the most peripherally located tumour cells, in order to irradiate the tumour tissue as precisely as possible, while sparing the normal, adjacent tissue (organ at risk (OAR)). Improvement of target definition is therefore one of the most critical steps towards improvement in radiation therapy.

Computed tomography

CT is at present routinely used for initial delineation of tumour volumes and is considered to be the gold standard. The use of iodinated contrast agents increases sensitivity. CT planning provides a 3D representation of the target volume and OARs as shown in Fig. 1. CT scanning offers inherent information on electron density mapping, used by algorithms for photon dose calculation. However, both inter- and intraobserver variability in both GTV and CTV delineation exists. Hermans *et al.*[1] investigated the inter- and intraobserver variability of CT based volume measurement of 13 laryngeal tumours by five different observers. Both interobserver variability and, to a lesser extent, intraobserver variability had a statistically significant effect on volume measurement and the most experienced observer obtained the most stable mean tumour volume over all sessions. Several groups have therefore published guidelines on both delineation of primary tumour CTV and nodal regions, based on CT images[2–4].
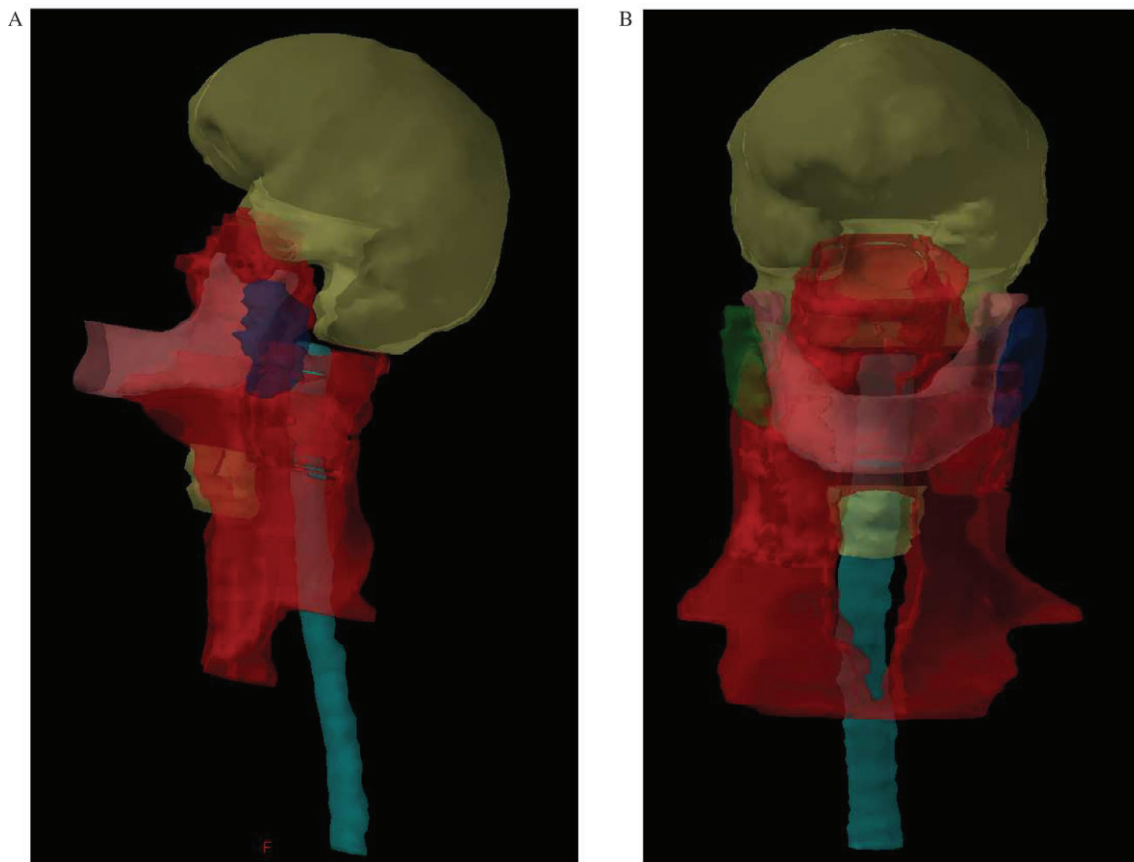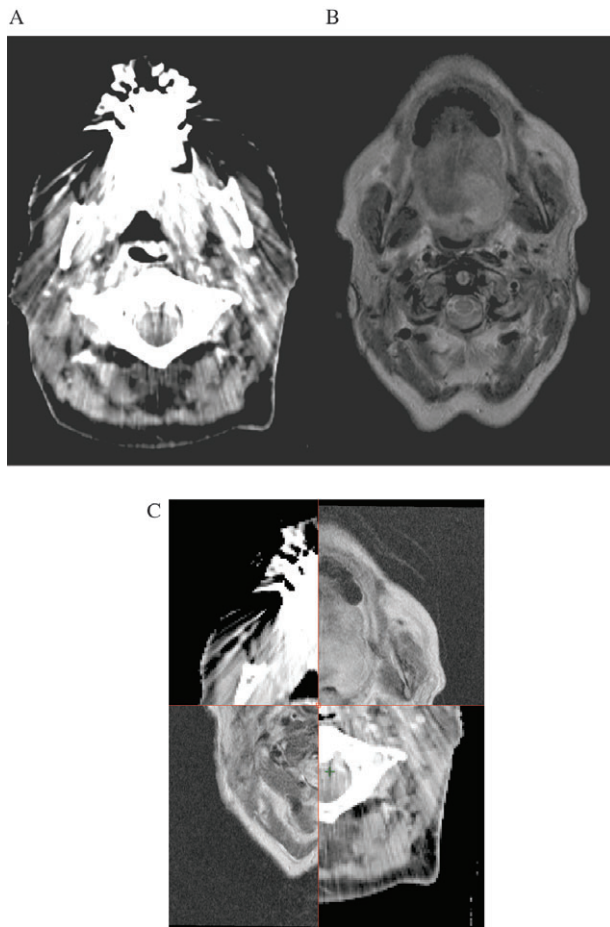

Figure 1 **Lateral (A) and frontal (B) view of 3D reconstructed volumes, based on volumes contoured on CT images. A young male patient with a nasopharyngeal carcinoma, being treated with high dose radiotherapy to the nasopharynx and bilateral neck nodes (level Ib to V). Red, target volumes (tumoral and nodal volumes); pink, mandible; blue, spinal cord; blue and green, parotid glands; yellow, brains; yellow, laryngeal structures.**

Magnetic resonance imaging

Evidence is growing that complementary information from alternative imaging modalities could help decrease the variability encountered for GTV delineation. MRI shows several potential advantages over CT, such as better discrimination between tumour and normal tissues in many organs and less artefacts caused by for example dental fillings. The use of MRI in treatment planning might be limited by the presence of geometrical distortions. Electron density information necessary for treatment dosimetry cannot be obtained from MRI. Therefore fusion of distortion-corrected MRI and CT images could provide improvement in target delineation (Fig. 2).

Rash et al.[5] outlined the GTV in six patients with advanced cancers with extension to the base of the skull on CT, axial MRI, and coronal or sagittal MRI. MRI-derived GTVs were 30% smaller and had less inter-observer variation than CT-derived GTVs. The ability to obtain images in any anatomical plane and the superior soft tissue contrast of MRI has led to its use in target delineation in nasopharyngeal carcinoma (NPC). Enami et al.[6] examined the use of MRI and CT in 8 NPC patients. Compared with CT, the MRI-based targets were 74% larger and did not always include the CTV targets. On average, the composite CT+MRI GTV was 10% larger than the GTV drawn from MRI alone. Therefore, the use of CT-based targets may lead to under-dosing of some regions of the tumour. The authors concluded that fusion of MRI and CT images is recommended in treatment planning for NPC, because it significantly reduces the possibility of missing parts of the tumour volume. This was confirmed by Chung et al.[7] who studied the impact of MRI versus CT on NPC in 258 patients. They found that MRI was superior to detect intracranial infiltration since in 40.3% of patients this was detected by MRI, whereas CT showed negative findings. Detection of pterygopalatine fossa involvement accompanying intracranial invasion was higher with MRI than CT (96.1% versus 56.9%). Currently, MRI is considered the imaging modality of choice for tumours of the base of the tongue and lesions arising at the base of the skull.

Figure 2 **Example of CT/MRI fusion image. A 63-year-old female with a squamous cell carcinoma of the left base of the tongue. CT scan (A) shows artefacts caused by dental fillings. T2-MRI images (B) show excellent soft tissue–tumour contrast. MRI and CT are co-registered via the treatment planning software to allow accurate tumour delineation (C).**

Functional imaging

Besides the location, size and extent of the tumour, knowledge about biological features of the tumour might be useful in radiotherapy of head and neck cancer. Functional images show metabolic, physiologic, genotypic, and phenotypic data that may improve target definition for radiation therapy.

Positron emission tomography

The impact of PET imaging on target delineation in radiotherapy for HNC has recently been investigated. The utility of PET has been further improved by the introduction of combination PET/CT scanners. Syed et al.[8] examined the impact of combined FDG PET/CT in HNC in 24 patients and concluded that PET/CT significantly increased interobserver agreement and improved the confidence in disease localisation of FGD-avid lesions by 51%. However one crucial remark must be made concerning the interpretation of the PET images. If we want to use PET to delineate volumes, we must define the way the PET images are viewed. For example, changing the window setting changes the interpretation of lesion margins; the optimal window setting for radiotherapy contouring applications has yet to be determined. Currently, every study uses its own threshold, or even does not comment on what threshold was used, which makes it difficult to compare the data.

Scarfone et al.[9] evaluated the influence and accuracy of FDG PET in target volume definition as a complementary study to CT in six HNC patients. Tumours were delineated on CT and modified based on the PET data.

The resulting PET/CT tumour and lymph node volume was larger than the original CT volume by an average of 15% and 17% respectively. The authors concluded that PET can act as a complementary modality, providing information on target viability not visible by CT. Koshy et al.[10] also examined the use of FDG PET in radiotherapy planning in 36 patients with HNC. Radiotherapy volumes and dose were altered in five patients (14%) and four patients (11%) respectively. Paulino et al.[11] found that the PET GTV was smaller, the same size, and larger than the CT GTV in 75%, 8% and 18% of HNC patients, respectively. In approximately 25% of patients, the primary GTV would have been underdosed when the CT GTV was used for IMRT planning. Ciernik et al.[12] used integrated PET-CT for target volume definition in 39 patients with various solid tumours; 12 were HNC. They detected an increase in PET GTV of $\geq$25% compared to CT GTV in 17% of patients; the GTV was reduced $\geq$25% in 33% of patients. In patients with nasopharyngeal (9) and oropharyngeal (12) tumours, Nishioka et al.[13] found that PET-CT detected 39 positive nodes in contrast to only 28 nodes detected by clinical examination and CT/MRI. In four patients, the nodal status was increased, which impacted on target delineation. In general, all studies conclude that PET adds extra information to both CT and MRI concerning target delineation.

However, we must keep in mind that the majority of FDG PET findings lack corresponding pathology data. A small study by Schwartz et al.[14] compared FDG PET findings with the pathology findings in 20 patients undergoing neck dissection. FDG PET/CT showed a high nodal staging sensitivity and specificity of 96% and 98.5% respectively. FDG PET/CT detected nodal disease in two patients considered to have node-negative disease by CT alone. Daisne et al.[15] compared CT, MR and FDG PET in 29 patients with stages II–IV HNC. Nine patients underwent total laryngectomy. PET volumes were delineated based on a specific tumour to background ratio. The key finding of this study was that, in comparison with the surgical specimen used as reference, all the imaging modalities tended to result in overestimation of the tumour extension. For anatomical imaging, average GTVs were up to 107% larger, whereas for functional imaging, a 46% overestimation was still observed. Despite this finding, all three imaging modalities failed to depict a small fraction of the subclinical tumour extension, which thereby revealed their insufficient resolution.

Dose-painting based on functional imaging

Biological information gathered from functional images can be used to guide radiotherapy. Recent interest has been developed to create non-uniformity within the targets, more specifically to increase the dose to certain tumour subregions in order to increase local control (so-called dose-painting). IMRT has the ability to deliver non-uniform dose distributions, but the question remains how to track the regions of interest. Therefore, a lot of effort has been put into developing imaging modalities to deliver molecular and biological information regarding hypoxia, proliferation, apoptosis, angiogenesis and receptor status of tumours.

Hypoxia is believed to be a major determinant in tumour response to radiation and their subsequent outcome. Hypoxic cells are 2.5−3 times more resistant to ionising irradiation than well-oxygenated cells. Identifying and quantifying tumour hypoxia may predict outcome and identify patients who can benefit from more aggressive radiotherapy to overcome the hypoxic effect. In future, escalating the dose to these tumour regions might improve outcome.

PET scanning can be used to identify and quantify hypoxia in solid tumours. Several tracers have been tested so far, both imidazole and non-imidazole containing agents. [18]F fluorinated misonidazole (FMISO) was administered to 45 patients with locally advanced HNC enrolled in a trial with the hypoxia-activated prodrug Tirapazamine[16]. Seventy-one percent of patients had detectable hypoxia on PET scan and the risk of locoregional failure was significantly higher in hypoxic patients. Chao et al.[17] examined the feasibility of dose-escalation to hypoxic areas using IMRT by co-registration of Cu-ATSM PET to CT images for treatment planning. This planning study showed that 80 Gy could be delivered in 35 fractions to the hypoxic target volume, with 70 Gy in 35 fractions delivered to the rest of the clinical target volume. Clinical value has still to be proven.

Temporal stability might be a concern for hypoxia imaging. Intermittent opening and closure of vessels can cause microscopic changes in oxygenation, so-called acute hypoxia. In addition, reoxygenation of hypoxic regions occurs during the 6−7 weeks period of fractionated radiotherapy. Studies on the temporal stability of tumour hypoxia mapping are therefore necessary (Fig. 3).

Although these new tracers have promise, much more work remains to be done before they can be used to influence treatment decisions for these patients. The difficult challenge is to validate the correlation with marker uptake and the presence of viable hypoxic cells. This validation is however difficult, because no gold standard for measuring these tumour properties exists.

Biological information can also be gathered by MRI. Tissue perfusion can be estimated using MRI from the increase in the T1 signal after the bolus administration of a gadolinium-based contrast medium and tissue oxygen levels can be assessed non-invasively by blood-oxygen level-dependent (BOLD) techniques. These techniques have already proven to predict treatment response and prognosis[18,19], but their value in radiotherapy treatment
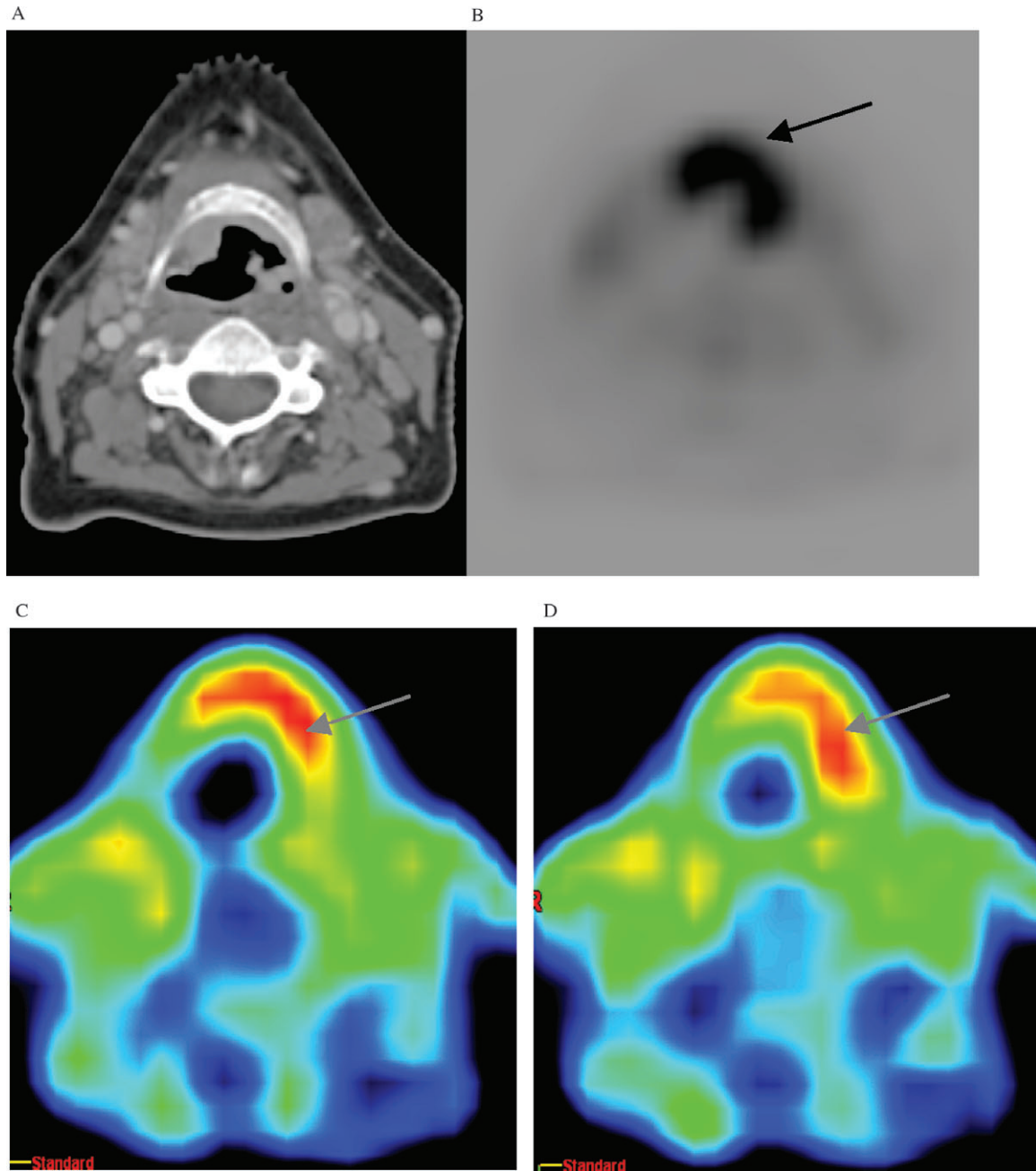
Figure 3 **Temporal change in hypoxia. (A) CT scan of a 52-year-old female patient who presented with a squamous cell carcinoma of the supraglottis, stage T4aN2c. A baseline FDG PET (B) shows uptake at the primary tumour (black arrow). A FMISO PET was acquired one day later (C1) and shows uptake in the primary tumour (grey arrow), demonstrating the presence of hypoxia. The repeat FMISO PET after 4 weeks of radiotherapy (D) shows a decrease in the FMISO uptake suggesting a temporal change in hypoxia. Hypoxic volumes only showed partial overlap, suggesting spatial changes in hypoxia.**

planning is still under investigation. The value of diffusion-weighted MRI (DW-MRI) in radiotherapy planning is also under investigation. DW-MRI is able to characterize tissue and generate image contrast based on differences in tissue water mobility. The ability to investigate the tissue micro-structure non-invasively, based on proton movement, opens a potential novel approach in target delineation[20].

Conclusion and future challenges

The use of multimodality imaging, both anatomical and functional, has already led to improved staging of disease and improved treatment planning by better dose delivery to GTV while sparing critical normal structures. The development of imaging markers associated with prediction of radioresistance and/or outcome could impact

significantly on treatment planning. Such information could be used in the (near) future to design conformal dose distributions, 'paint' additional dose to specific tumour regions, or rationally describe adjuvant therapy targeted to specific tumour phenotype and genotype.

There remain still some hurdles to be overcome, including imaging–pathological validation, and accounting for spatial and temporal tumour motion during radiation therapy. We must also keep in mind that no single imaging modality can provide us with the entire picture of tumour profiling. Anatomical and functional imaging fusion will be essential. Knowledge about the capabilities and especially limitations of all the imaging modalities remains essential in their clinical use.

Future studies should help determine whether incorporating these and other imaging modalities will improve our ability to cure head and neck cancer and/or reduce the morbidity of our treatment.

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