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Implications of improved diagnostic imaging of small nodal metastases in head and neck cancer: Radiotherapy target volume transformation and dose de-escalation

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ABSTRACT

Diagnostic imaging continues to evolve, and now has unprecedented accuracy for detecting small nodal metastasis. This influences the tumor load in elective target volumes and subsequently has consequences for the radiotherapy dose required to control disease in these volumes.

Small metastases that used to remain subclinical and were included in elective volumes, will nowadays be detected and included in high-dose volumes. Consequentially, high-dose volumes will more often contain low-volume disease. These target volume transformations lead to changes in the tumor burden in elective and "gross" tumor volumes with implications for the radiotherapy dose prescribed to these volumes.

For head and neck tumors, nodal staging has evolved from mere palpation to combinations of high-resolution imaging modalities. A traditional nodal gross tumor volume in the neck typically had a minimum diameter of 10–15 mm, while nowadays much smaller tumor deposits are detected in lymph nodes. However, the current dose levels for elective nodal irradiation were empirically determined in the 1950s, and have not changed since.

In this report the radiobiological consequences of target volume transformation caused by modern imaging of the neck are evaluated, and theoretically derived reductions of dose in radiotherapy for head and neck cancer are proposed. The concept of target volume transformation and subsequent strategies for dose adaptation applies to many other tumor types as well. Awareness of this concept may result in new strategies for target definition and selection of dose levels with the aim to provide optimal tumor control with less toxicity.

In the past, the prognosis of patients with squamous cell carcinomas of the upper aerodigestive tract has been improved by intensifications of radiotherapy. Concomitant treatment with platinum-based chemotherapy and altered fractionation schedules improved 5-year local control up to 9.3% and 5-year overall survival up to 6.5% [1,2]. Adversely, these intensified treatments come at the expense of increased treatment-induced toxicity. Patients are more frequently confronted with severe acute toxicities such as mucositis and feeding tube dependency during treatment but also with severe long-term morbidity such as persistent xerostomia and dysphagia [1–5]. Both xerostomia and dysphagia are important negative predictors of quality of life [6,7].

As a consequence of improved prognosis, patients will live longer with the burden of permanent radiation sequelae and the consequential deterioration of quality of life. Because quality of life is a highly relevant issue in clinical practice, de-intensification of treatment in order to decrease morbidity without compromising efficacy is increasingly becoming a topic of interest in clinical research. These considerations unabatedly apply to the treatment of nodal disease in the neck, because the dose and extent of neck irradiation can have a significant impact on quality of life [8,9].

In recent years, technological advancements have improved diagnostic imaging modalities continuously, with important implications for evaluation of the neck. Combinations of multiple modalities like computed tomography (CT), magnetic resonance

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imaging (MRI) with various sequences, positron emission tomography with Fluor-18-fluorodeoxyglucose (FDG-PET), ultrasound (US) and ultrasound-guided fine-needle aspiration cytology (US-FNAC) now provide unprecedented accuracy for the detection of small nodal metastases. This influences the definition and contents of nodal target volumes for radiotherapy, and imposes changes in the radiotherapy dose levels that need to be prescribed to these volumes. Consequently, this provides a new window of opportunity for treatment de-intensification of the neck, in order to decrease treatment-related morbidity without compromising efficacy.

This review discusses the backgrounds, implementation methods, and anticipated patient outcomes for target volume transformation and dose reductions in radiotherapy of head and neck cancer.

Target volumes and dose: a binary concept

Head and neck squamous cell carcinoma has a high risk of regional lymph node metastases [10]. It is not uncommon that small nodal metastases remain undetected as they are below the detection threshold of physical examination and diagnostic imaging [11]. Clinically undetectable metastases are also known as 'microscopic', 'subclinical' or 'occult' disease.

Already since the 1950s, it was shown that radiotherapy has the potential to achieve high rates of control in surgically undisturbed cervical lymph node levels with high risk of subclinical disease [12]. It became general practice to irradiate the neck electively in case the estimated prevalence of occult nodal metastasis exceeded 20% [13]. This treatment paradigm was mainly based on the work of Lindberg et al. in the 1960s, describing the topographical distribution and prevalence of nodal metastases [14]. Since then, a binary concept was introduced, distinguishing separate target volumes for macroscopic disease and for subclinical disease. The target volume for macroscopic disease is the gross tumor volume (GTV) and will encompass the tumor and the detectable lymph node metastases using information from clinical examination and diagnostic imaging [15]. The clinical target volume (CTV) is created by expansion of the GTV in order to cover potential microscopic disease spread in the surrounding normal tissue [16]. The target volume for subclinical lymph node metastases is the elective CTV and will cover all routes of potential lymphatic spread of disease [15]. The elective CTV will encompass large anatomical volumes of the neck, containing a subset of nodal levels based on the tumor site and macroscopic nodal metastases [17].

As a consequence of separate target volumes for macroscopic disease (GTV) and subclinical disease (CTV), it became general practice to deliver 2 dose-levels in radiotherapy for head and neck cancer. The current prevailing dose levels for macroscopic disease (70 Gy in 2 Gy fractions) and for elective treatment (45–50 Gy in 2 Gy fractions) were empirically determined in the 1950s and have not changed ever since [12].

Technological improvement of diagnostic imaging

In the 1950s, when the prevailing radiotherapy dose levels for head and neck tumors were developed, detection of nodal involvement in the neck relied on mere visual inspection and palpation [12,14]. Since then, several diagnostic imaging modalities have been introduced.

From the 1980s CT and later MRI and US were able to detect nodal involvement earlier and in more patients as compared to palpation [18,19]. However, it was soon clear that no single imaging modality was clearly superior to the other, and that imaging findings suffered from limited specificity and generally needed to be confirmed by (image-guided) biopsy. Many subsequent efforts were put in comparing MRI, CT, US and US-FNAC [18]. The highest accuracy was generally reported for US-FNAC, mainly based on the inherent specificity of positive pathological findings, but with limited sensitivity and practical limitations in the number of evaluable nodes. In subsequent decades CT and MRI advanced to better image quality, but these non-invasive modalities continued to rely on non-specific anatomic criteria and could not provide a large impact on clinical decision making in nodes sized less than 10–12 mm [20]. From the 2000s, FDG-PET(/CT) was introduced as another non-invasive image modality, based on functional evaluation of glucose metabolism. It was shown that the acquisition and reconstruction of PET images could be optimized to the anatomical situation of the neck with low attenuation and scatter, to provide the best possible sensitivity [21]. Two meta-analyses of standalone FDG PET in 2008 showed a good accuracy for staging of the neck, better than conventional anatomical imaging, and with impact on treatment decisions [22,23]. The image quality of PET further increased over time and in 2013 and 2015 large meta-analyses showed superiority of PET/CT over conventional anatomical imaging for nodal staging [24,25].

The improved sensitivity of imaging procedures has resulted in higher detection rates of small metastatic deposits. With palpation, nodes below 10–15 mm are generally missed, except in very slender patients. With increasing image quality, size criteria lower than 10 mm for anatomical imaging have been suggested, but this resulted in lower specificity [26]. For FDG-PET/CT, one study from 2014 involving 91 head and neck cancer patients with a negative neck on palpation reported overall mean size of true positive nodes of 12.4 mm (95% CI: 5.7–19.1 mm) versus 5.7 mm (95% CI: 1.2–10.2 mm) of false negative nodes, suggesting a detection threshold between 5 and 10 mm [27]. Similar observations were previously reported by another group in 2008 [28]. For US, size is not the only relevant parameter, but reasonable sensitivity and accuracy was demonstrated from 5 mm shortest axis diameter [29]. Accuracy may be further improved by adding features like shape, vascularity patterns and necrosis [30]. For MRI, the ability to detect nodal metastases between 7 and 10 mm was demonstrated with good sensitivity and specificity [31]. This could be improved further by adding features like border irregularity and homogeneity of signal intensity [31]. CT remains suboptimal for detection of small lymph nodes [32].

Despite all advances, no imaging modality is clearly superior and best reported accuracies are around 75% [33]. The applied modalities are considered complementary to some extent. Integrated approaches with combined information from MRI, FDG-PET/CT and US, complemented with additional targeted evaluation of suspect nodes with US-FNAC, are believed to provide good staging accuracy in most patients [34,35]. The exact sensitivity and specificity of many currently applied clinical strategies have not been investigated in detail but will certainly surpass the value of palpation alone. With current state-of-the-art diagnostic strategies, the number of patients with missed nodal tumor deposits of 5 mm or larger in diameter is rapidly declining.

Based on current and anticipated developments in all imaging modalities, with ever increasing spatial resolution and continuously developing criteria for interpretation, it can be assumed that the accuracy of detecting small nodal metastases will further improve over the coming decades.

Target volume transformation

The improvements in diagnostic imaging of nodal metastases will influence the definition and contents in terms of tumor load of various target volumes for external beam radiotherapy, although

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