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Head and neck cancer

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

Sven van den Bosch [a,*], Wouter V. Vogel [b,c], Cornelis P. Raaijmakers [d], Tim Dijkema [a], Chris H.J. Terhaard [d], Abrahim Al-Mamgani [b], Johannes H.A.M. Kaanders [a]

[a] Department of Radiation Oncology, Radboud University Medical Center, Nijmegen, The Netherlands; [b] Department of Radiation Oncology, Netherlands Cancer Institute/Antoni van Leeuwenhoek; [c] Department of Nuclear Medicine, Netherlands Cancer Institute/Antoni van Leeuwenhoek, Amsterdam; and [d] Department of Radiation Oncology, University Medical Center Utrecht, The Netherlands

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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

* Corresponding author at: Radboud University Medical Center, Department of Radiation Oncology, Huispost 874, P.O. Box 9101, Nijmegen 6500 HB, The Netherlands.
E-mail address: sven.vandenbosch@radboudumc.nl (S. van den Bosch).

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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 stand-alone 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

the impact will vary. Bulk tumor that requires a high (boost) radiation dose will not be affected significantly by imaging with better spatial resolution and sensitivity. Therefore, the boost volume will remain largely unchanged. The highest impact can be expected in the area of small nodal metastases and subclinical disease.

Many small metastases that used to remain undetected and were included in elective areas (elective CTV), will now be detected and consequently included in high-dose volumes (GTV). Consequentially, the GTV covers a larger area and will more often contain small lymph nodes with relatively low-volume disease (Fig. 1A).

Metastases that migrated to GTV are no longer included in the elective CTV. As a result, the new elective CTV now contains less lymph nodes with less and smaller metastatic deposits and thus, overall the new elective CTV has less subclinical tumor load (Fig. 1A).

This so-called nodal target volume transformation is defined as "upgrading" small lymph node metastasis from the elective CTV to the GTV as a result of better imaging sensitivity (Fig. 1A). As a consequence, not only the overall tumor load in the elective CTV decreases, but also GTV areas now contain low-volume tumor deposits. This requires reconsideration of the radiotherapy dose levels prescribed to these volumes (Fig. 1B).

Radiobiological considerations

Withers and colleagues postulated that in a population of patients that harbor occult metastases, the logarithm of the number of metastatic tumor cells per patient is uniformly distributed because of a near exponential growth of small tumor deposits [36,37]. In such a population, the effective dose–response relation for control of occult metastases equals the weighted average of multiple dose–response curves for the subclinical tumor burden of all individual patients of the population. Tumor control is an exponential function of the number of surviving tumor cells, which is an exponential function of the dose. The resulting effective dose–response relation for control of occult metastases in a population of patients is near-linear (Fig. 2A) [36,37]. An extensive survey of 24 datasets on elective neck irradiation in head and neck squamous cell carcinoma indeed demonstrated a near-linear dose–response relationship for control of occult metastases in the population [38].

Two important factors that affect the dose required to achieve control of occult nodal metastases in a patient population are the pre-treatment occult tumor load (i.e. the number of undetected tumor cells) and the prevalence of occult metastases within the population.

First, the pre-treatment occult nodal tumor load directly affects the slope of the effective dose–response curve as lower numbers of tumor cells require less dose to all be sterilized. The pre-treatment occult nodal tumor load is dependent on the maximum size of metastases that remain undetected and is therefore directly dependent on the detection threshold of diagnostic imaging. It must be emphasized that with the maximum size of nodal metastases, the actual size of the metastatic tumor within the lymph node is meant and not the size of the lymph node itself. Assuming a spherical shape of occult nodal metastases, a tumor cell density of 10^8 cells per ml and a surviving fraction at 2 Gy (SF_{2Gy}) of 0.5, the effective dose–response curve can be calculated for a range of maximum sizes of occult metastasis that may be present in a population of patients assuming that all patients harbor occult metastases (Fig. 2B) [39]. For example, if in such a population the maximum diameter of undetected nodal metastases is less than 5 mm, the tumor control probability of occult disease would be approximately 70% after elective irradiation using an equivalent dose of 36 Gy in 2 Gy fractions (EQD2).

Second, the prevalence of occult nodal metastases directly affects the dose required to achieve a certain control rate of occult nodal metastases in the population. In head and neck squamous

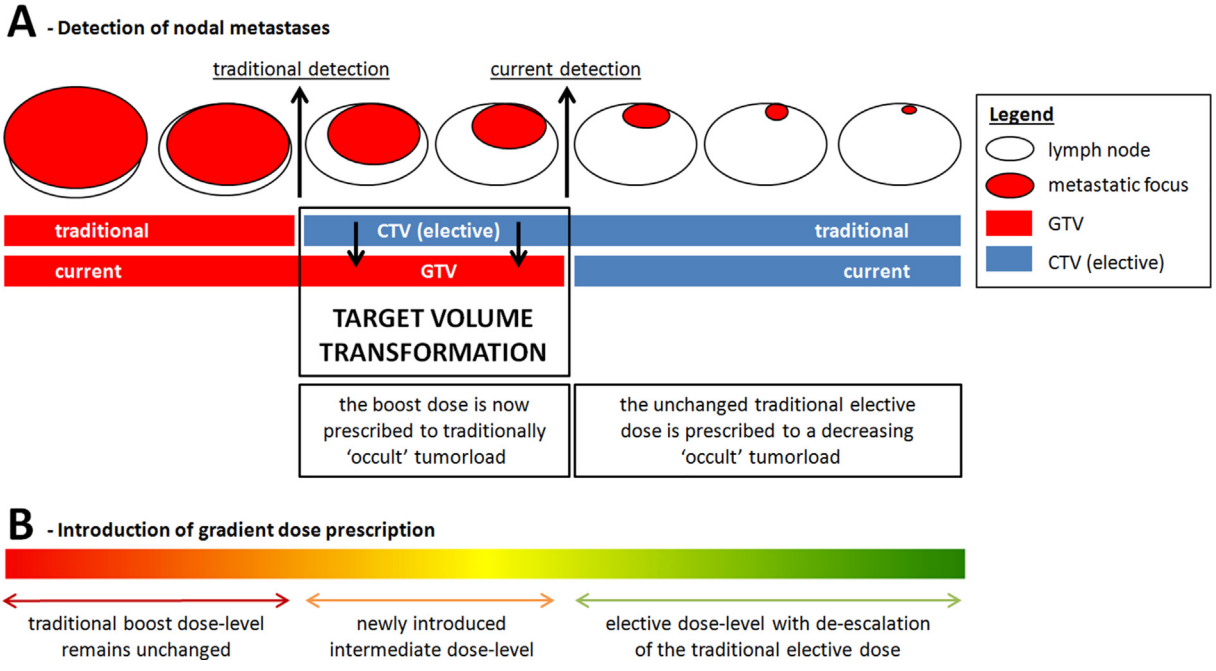

Fig. 1. Target volume transformation. (A) Nodal target volume transformation is defined as "upgrading" lymph node metastasis from the elective CTV to GTV based on their increased detectability resulting from improved diagnostic imaging techniques. Target volume transformation may result in overtreatment of both volumes. First, the boost-dose is now prescribed to small lymph node metastases that would have traditionally been treated with the elective dose. Second, the traditional elective dose is prescribed to the elective CTV while the occult tumor volume within the elective CTV is decreased as a result of improved diagnostic imaging. (B) By refining traditional binary dose prescription to a gradient dose prescription that is proportional to (occult) tumor volume, the current overtreatment can be addressed in order to decrease treatment-related morbidity without compromising efficacy. *Abbreviations:* CTV = clinical target volume; GTV = gross tumor volume.

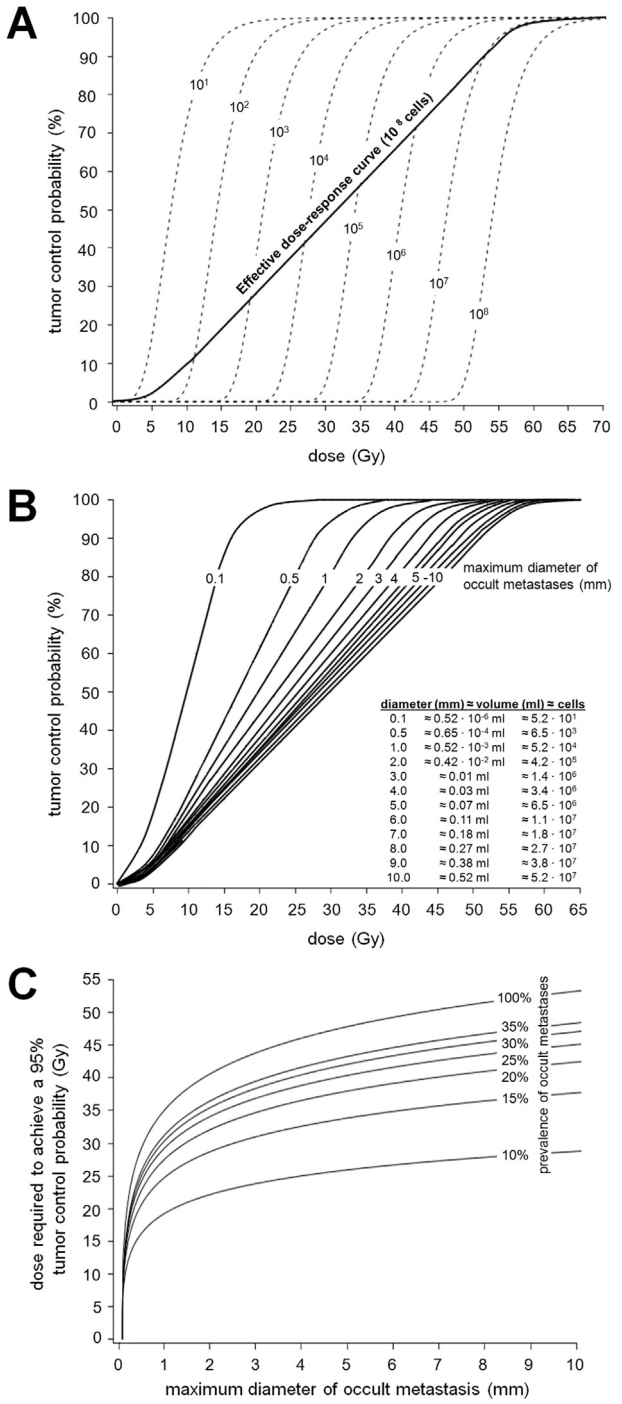

Fig. 2. Dose response of subclinical disease. (A) Assuming a uniform distribution of the logarithm of the number of metastatic tumor cells in a population of patients harboring occult metastases, the effective dose–response curve for control of occult disease is near-linear in such population [36,37]. An SF_{2Gy} value of 0.5 was used. (B) The slope of the effective dose–response curve is dependent on the maximum size of undetected metastases (i.e. the number of occult tumor cells) and is therefore dependent on the detection threshold of diagnostic imaging. A tumor cell density of 10^8 cells per ml was used and a spherical shape of occult metastases was assumed. (C) The effect of prevalence and maximum diameter of undetected metastases on the dose required to achieve a 95% control rate of occult disease. Between a maximum diameter of 3–10 mm, the curves approach linearity. Therefore, these radiobiological models suggest that for every 1 mm improvement of the detection threshold of diagnostic imaging (within the range 3–10 mm), the elective dose may be reduced by 1.0–1.2 Gy without compromising the 95% control rate of occult disease (Fig. 2C). *Abbreviations:* SF_{2Gy} = surviving fraction at 2 Gy.

cell carcinoma, the prevalence of occult cervical nodal metastases ranges between 10% and 35% in a clinically negative neck (cN0), dependent on the site of the primary tumor and the T-stage [11].

In the previous example, it was assumed that all patients in the population would harbor occult nodal metastases. However, in case of a lower prevalence the control probability of occult disease for the whole population would increase while using the same dose. For example, when a population with a maximum diameter of undetected nodal metastases of less than 5 mm and a 20% prevalence of occult disease is electively irradiated with 36 Gy (EQD2), the tumor control probability of occult disease in the whole population would be approximately 94%. This equals the 70% control of occult disease due to elective irradiation in the 20% of patients that do harbor occult nodal disease, plus 100% control in the 80% of patients without occult disease.

In head and neck squamous cell carcinoma, the control rate of electively irradiated lymph node areas at 2 years after treatment is approximately 95% [40]. The dose required to achieve a 95% control rate of occult disease can be calculated for different prevalences of occult disease and for a range of maximum sizes of occult metastasis that may be present within the population (Fig. 2C). Interestingly, if the maximum diameter of undetected metastasis is between 3 and 10 mm, the curves are more or less linear (Fig. 2C). Therefore, these radiobiological models suggest that for every 1 mm improvement of the detection threshold of diagnostic imaging (within the range 3–10 mm), the elective dose may theoretically be reduced by 1.0–1.2 Gy without compromising the 95% control rate of occult disease (Fig. 2C). Because no imaging modality supports the detection of tumor deposits at the sub-millimeter level, de-escalation of the elective dose below 30 Gy without compromising control of subclinical disease seems to be unrealistic in the near future (Fig. 2C).

Toward a gradient dose prescription

Head and neck cancer

Target volume transformation due to improved diagnostic imaging results in unintentional overtreatment of the neck in radiotherapy for head and neck cancer (Fig. 1A).

Three situations of overtreatment can be distinguished:

(1) The boost-dose is nowadays prescribed to relatively small lymph node metastases, that were treated with the elective dose in the past.
(2) The traditional elective dose is prescribed to an elective CTV that currently has a much lower tumor load.
(3) The traditional nodal levels selected for elective irradiation are still based on historical data of neck surgery or recurrence after radiotherapy, while the prevalence of subclinical disease nowadays is lower.

This current overtreatment of the neck provides a new window of opportunity for treatment de-intensification, in order to decrease treatment-related morbidity without compromising efficacy. The traditional binary dose prescription should be refined into a gradual prescription with dose being proportional to tumor load and the estimated prevalence of occult disease (Fig. 1B).

A combination of the following approaches can be considered:

1) *Introduction of an intermediate dose level* can address the current overtreatment of relatively small lymph node metastases that are nowadays treated with the boost dose but were treated with the elective dose in the past.

Studies assessing recurrence in the electively irradiated neck may identify selection criteria for lymph nodes that can be treated with intermediate dose. A recent analysis on recurrence in electively irradiated lymph nodes in 264 head and neck cancer patients identified nodal volume and size (summed long- and short-axis diameter $\geq$17 mm) as important risk factors for nodal failure after elective irradiation with an equivalent dose of 45 Gy in 2 Gy fractions (EQD2) [40]. Because of a limited positive predictive value, it was concluded that nodal size could not be the sole selection criterion [40]. It was suggested that the combination of nodal size and FDG-uptake as a surrogate parameter for tumor cell density may provide an estimate of tumor load and subsequently, the radiation dose required for control [41]. For well selected small metastases, an intermediate dose level of 60 Gy (EQD2) may be sufficient as no recurrences in electively irradiated lymph nodes were observed above this dose in the previously mentioned retrospective analysis [40]. Radiobiological evaluations in this manuscript also show a high tumor control probability at the 60 Gy dose level (Fig. 2A) [36,37].

To date, there is only one ongoing multi center randomized controlled trial that investigates the safety and long-term morbidity of a gradient dose prescription with the introduction of an intermediate dose level and de-escalation of the elective dose in the treatment of oropharyngeal, laryngeal and hypopharyngeal squamous cell carcinoma (NCT02442375) [42]. In this study, named the UGPRADE-RT trail, 300 patients will be accrued in 6 head and neck cancer centers in the Netherlands and will be randomized (ratio 2:1) to gradient dose prescription or to traditional binary dose prescription [42]. Treatment arms will be balanced for tumor site, human papillomavirus (HPV)-status (in case of oropharyngeal cancers) and stage using minimization with a random element. A radiotherapy planning FDG-PET/CT-scan in treatment position using an individual head, neck and shoulders immobilization mask will be acquired in all patients. In the intervention arm, based on a risk-assessment algorithm using nodal size and nodal FDG-uptake, lymph nodes are selected for treatment with an intermediate dose level of 60 Gy (EQD2). Irrespective of tumor site or HPV-status, dose to the elective neck is being de-escalated to 35 Gy (EQD2) versus 45 Gy (EQD2) in the control arm. Dose prescription to gross tumor will be equal in both treatment arms, 73 Gy (EQD2) to the metabolic tumor volume (MTV) and 67 Gy (EQD2) to the CTV. An accelerated fractionation scheme will be used delivering 34 fractions of 2 Gy in 5.5 weeks (6 fractions per week).

2) *De-escalation of the elective dose* can address the current overtreatment of the elective CTV resulting from a decreased occult tumor load. With current state-of-the-art diagnostic strategies, the number of patients with missed nodal deposits of 5 mm or larger in diameter is rapidly declining. Radiobiological evaluations described in this manuscript theoretically support reduction of the elective dose to approximately 35–40 Gy (EQD2) to achieve a control probability of approximately 95% (Fig. 2C).

Because the drainage patterns of the cervical lymphatic system follow predictable routes, detailed descriptions of the topographical distribution and prevalence of (occult) nodal metastases are available [14,43,44]. As such, it is even conceivable to envision a graded dose prescription within the elective CTV based on the prevalence of occult metastases per anatomical nodal level. For example, nodes at the first draining station may receive a dose of 40 Gy (EQD2) whereas secondary and tertiary stations may receive further stepwise de-escalated doses because they have a lower probability of occult disease.

De-escalation of the elective dose was investigated in a multicenter randomized clinical trial [45]. A total of 200 head and neck cancer patients were randomized to elective treatment of the neck using a 50 Gy or 40 Gy dose levels. After a 2-year follow-up period, there was no statistically significant difference in survival or regional recurrence. Two patients had recurrence in electively irradiated lymph nodes using the 40 Gy dose level, versus one patient with the 50 Gy dose level. A significant reduction of xerostomia and a trend toward less dysphagia was found in the 40 Gy elective treatment arm [45]. The same research group also analyzed a prospective cohort consisting of 233 head and neck cancer patients, all treated with a 40 Gy elective dose level [46]. The 2-year actuarial rate of recurrence in electively irradiated lymph nodes was 3.9% (95% CI: 1.8–6.0) [46]. A recent retrospective analysis, demonstrated a comparable rate of recurrence in electively irradiated lymph nodes of 5.1% (95% CI: 2.4–7.8%) using a 45 Gy (EQD2) elective dose level [40]. De-escalation of the elective dose to 36 Gy (EQD2) in combination with concomitant platinum-based chemotherapy was investigated in a prospective single-arm trial enrolling 54 head and neck cancer patients (57% of whom had HPV positive disease) [47]. After a median follow-up period for surviving patients of 36 months, no recurrences in electively irradiated lymph nodes were observed [47].

Currently, there are few ongoing trials investigating the safety and toxicity of de-escalation of the elective dose. The previously mentioned UPGRADE-RT trial investigates a 35 Gy (EQD2) versus 45 (EQD2) elective dose level (NCT02442375) [42]. Another prospective single-arm trial investigates de-escalation of the elective dose to 40 Gy (NCT03067610).

3) *The selection of neck levels for elective treatment* needs to be adapted as a consequence of the increased accuracy of diagnostic imaging. As a result of a decreasing prevalence of occult metastases in radiologically uninvolved lymph node levels, it is conceivable that elective irradiation can be omitted in those areas having the lowest prevalence of occult nodal metastases. For example, if the primary and secondary draining nodal levels are negative by current modern imaging, the tertiary draining level is at very low risk and may not need elective treatment.

The single-arm INFIELD trial investigates the safety and toxicity of de-escalation of the elective dose 40 Gy (EQD2) in combination with an altered selection of elective CTV areas in head and neck cancer (NCT03067610). Following an 'involved node' approach, elective irradiation of nodal levels III and IV will only be done in case of pathologic lymph nodes in the directly adjacent proximal level. Irradiation of level IB or V will only be done in case of suspicious or pathologic lymph nodes in these levels.

As a consequence of better diagnostic imaging, the risk assessment for contralateral nodal involvement probably also changes. Tumors approaching the midline, advanced T-stage and (multiple) ipsilateral nodal metastases are known risk-factors for contralateral nodal involvement in head and neck cancer [48–54]. Due to increased diagnostic accuracy, also the indications for elective irradiation of contralateral nodal areas need refinement with the likely result that more patients can be spared the morbidity of bilateral neck treatment. The single-arm SUSPECT trial evaluates the feasibility, safety and toxicity of a non-invasive sentinel node mapping procedure in order to facilitate selection of elective CTV in patients with unilateral cT1-3N0-2b head and neck cancer (NCT02572661). Sentinel node mapping using SPECT-CT will be performed and based on the absence or presence of contralateral tracer accumulation, elective irradiation of the ipsilateral or bilateral neck will be administered.

Other tumor sites

Obviously, the concept of target volume transformation and subsequent strategies for dose adaptation applies to many other tumor types in which routine treatment includes elective irradiation of nodal areas or other tissues. These include, but are not limited to cancers of the breast, cervix, prostate, lung, esophagus, rectum and bladder. The benefit of dose de-escalation on toxicity

may vary based on the anatomical location of target volumes and the surrounding normal tissues. Also, the degree of dose de-escalation may vary between tumor types, depending on the detection threshold of imaging modalities, radiation sensitivity of the tumor and radiation tolerance of nearby normal tissues.

Discussion

The results of this manuscript support the concept of improved diagnostic imaging resulting in "migration" of small tumor deposits to different target areas, subsequently altering the overall tumor load of target volumes. Radiobiological evaluations described in this manuscript support the implications for dose reduction to these target volumes. This is arguably relevant for high dose and elective volumes, with potential consequences for various tumor types. However, this concept is based on theoretical considerations, and should not be considered as proof of clinical relevance or benefit.

Our radiobiological evaluations suggest a linear relationship between dose and tumor control for a patient population with a variety of tumor sizes in the relevant range of 3–10 mm. There is no solid evidence to support the linearity of this dose–effect relation and neither on the chances of tumor eradication in elective areas with undetected tumor deposits below size thresholds in this range. Additional support for dose reductions in target areas with low-volume tumor deposits could be pursued with pre-clinical research.

Tumor volume, however, is not the only factor that may affect the dose–response relationship and regional control in head and neck cancer. Variations in patient related factors (e.g. gender, hemoglobin blood level, leukocytosis and smoking during radiotherapy), etiology (e.g. alcohol, smoking and HPV-associated cancers) and biological factors of the tumor (e.g. intrinsic radiosensitivity, hypoxia and proliferation) are known to affect the dose–response relationship and regional control in head and neck cancer [55,56]. Obviously, concomitant treatment with radiosensitizing therapeutic agents may also alter the dose–response relationship (e.g. platinum-based chemotherapeutics, epidermal growth factor receptor inhibitors, hypoxic sensitizers and maybe in the future immunotherapy).

A selection of these previously mentioned factors are already used to stratify patients for treatment de-intensification in prospective trials. The most extensively investigated biomarker for stratification is the HPV status in oropharyngeal squamous cell carcinoma. Strategies for treatment de-intensification in case of HPV-positive disease involve reduction of chemotherapy (reduced dose cisplatin, omitting chemotherapy or replacement of cisplatin with cetuximab) or reduction of radiotherapy dose and/or volumes in good responders after induction chemotherapy or minimally invasive surgery [57,58]. PET-tracers targeting factors that affect the dose–response relationship can also serve for stratification of patients for dose de-escalation. For example, 18F-FMISO (fluoromisonidazole), a tracer targeting hypoxia is currently prospectively being investigated to guide dose de-escalation to pathological lymph nodes without hypoxia in HPV positive oropharyngeal cancer patients (NCT00606294) [59]. Moreover, quantitative parameters derived from FDG-PET such as maximum FDG-uptake, metabolic tumor volume, and total lesion glycolysis have been shown to provide important prognostic information in head and neck cancer and can also be considered for stratification of patients for dose de-escalation (for example the earlier mentioned UPGRADE-RT trial) [42,60,61].

Ultimately, clinical trials should be designed to explore the feasibility and safety of dose reductions to relevant target areas. Some trials are already ongoing, in the areas of new intermediate dose levels for macroscopic tumor, de-escalated doses to elective nodal areas, and adapted definition of target areas based on improved imaging strategies. These studies will provide data needed to support further adaptations of target area definition and dose de-escalation in clinical practice. However, one should be aware that diagnostic imaging has been improving over the past years, and consequentially that target volume transformation already happens today. For the therapeutic consequences, the results of the studies discussed previously must be awaited. Until that moment, the authors of this manuscript advise against target area adaptation or dose de-escalation based on assumed improvements in diagnostic imaging outside clinical trials.

Conclusion

The increasing sensitivity of diagnostic imaging for small nodal metastases and the resulting target volume transformations potentially have consequences for target volume definitions and dose prescription practices in radiotherapy. Adaptations in historical dose levels and elective nodal volumes may be required for head and neck cancer, and probably for several other tumor types as well. Awareness of this concept will facilitate clinical research, which may result in new strategies for target definition and selection of dose levels, with the aim to provide optimal tumor control with less toxicity.

Conflict of interest statement

All authors declare having no conflict of interest related to the content of this manuscript.

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