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Target delineation for postoperative treatment of head and neck cancer

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ABSTRACT

Patients who undergo primary surgical resection for a Head and Neck Squamous Cell Carcinoma (HNSCC) are stratified post-operatively, based on the presence or absence of pathological risk factors for recurrence, to estimate their risk of treatment failure. Post-operative radiotherapy, with or without concurrent chemotherapy, is offered if there is a significant risk of recurrence, in order to eradicate potential microscopic residual cancer cells and ultimately improve loco-regional control and survival.

This review will offer practical guidelines for delineation of the post-operative primary and nodal Clinical Target Volumes (CTVs) based on a geometric expansion of the pre-operative primary and nodal Gross Tumour Volumes (GTVs), as already implemented in the definitive radiotherapy setting. Nodal levels requiring elective treatment are defined for inclusion in the prophylactic CTV. Optimising patient selection for post-operative treatment is discussed as well as areas of controversy, relating to the dose prescription and extent of nodal volumes to be included in the CTV. Finally, clinical trials exploring the prospect of adjuvant treatment de-intensification after transoral surgery for HPV-positive oropharyngeal cancer are outlined. The aim is to improve consensus amongst clinicians and contribute towards improving outcomes for surgically treated patients with HNSCC.

Introduction

Post-operative radiotherapy (PORT) and chemo-radiotherapy (POCRT) are commonly prescribed treatments for patients with Head and Neck Squamous Cell Carcinoma (HNSCC). However, discrepancies exist in the way that these treatments are applied, for the following reasons:

(i) There are a lack of comprehensive, contemporary, internationally agreed guidelines, to aid the delineation of the primary and nodal Clinical Target Volumes (CTV) in the post-operative (or adjuvant) setting, in contrast to the definitive radiotherapy (RT) setting [1,2].
(ii) There has been a substantial increase in the incidence of oropharyngeal squamous cell cancer (OPSCC) caused by Human Papillomavirus (HPV) infection (so called 'HPV-positive cancers') across the developed world [3]. It is well documented that HPV-positive OPSCCs have a better prognosis compared to HPV-negative OPSCCs [4], raising the possibility that they could be managed differently, in the post-operative as well as the definitive RT setting.
(iii) Clinical trials prior to the last 10–15 years have looked at patients treated with open surgery. However, Transoral Surgery (TOS), primarily using a laser (Transoral Laser Microsurgery [TLM]) or robot (Transoral Robotic Surgery [TORS]), has largely replaced open surgery for subsites including the oropharynx and larynx. TLM and TORS are minimally invasive surgical techniques, which have the potential to excise early T stage tumours with considerably less long-term functional deficit than open surgery [5]. However, a majority of patients will also undergo post-operative therapy, either with PORT (21–58% of cases) or POCRT (16–62% of cases) [5–8] and little is known about the optimal adjuvant treatment after TOS. Post-operative treatment significantly increases acute and late toxicity rates after TOS [5,6] and optimising adjuvant treatment schedules is an important goal to improve long-term quality of life.

This manuscript will review the indications for PORT and POCRT, propose guidelines to aid delineation of the post-operative CTV and consider some areas of controversy and uncertainty in this setting.

Indications for post-operative treatment

Pathological risk factors have been identified which predict for recurrence after surgery for HNSCC. The presence of microscopic disease

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at the margins of resection [9,10] and/or the presence of extracapsular spread (ECS) of nodal disease in the neck [10,11] have been clearly defined as independent poor prognostic features. Indeed, the profound effect of ECS on prognosis for non-viral HNSCC has resulted in its inclusion in the UICC/AJCC TNM (8th edition) N staging classification [12]. The benefit of PORT, in terms of improving loco-regional control, as well as disease-free and overall survival, has been demonstrated in patients with these risk factors [10]. Furthermore, addition of concurrent chemotherapy with Cisplatin to PORT is recommended for patients with these pathological risk factors [13], based on the results of two landmark studies, RTOG 9501 and EORTC 22931 [14,15]. In both studies, POCRT improved local control and disease-free survival rates compared with PORT alone, although overall survival was only significantly improved in one study, possibly due to the different eligibility criteria in both. When the results of both studies were pooled [16], POCRT significantly improved overall survival in patients with involved resection margins around the primary tumour and/or presence of ECS in the neck. An involved or positive resection margin is variably defined in the literature, but is traditionally regarded as being at or within 1 mm of the primary tumour margin [17]. Patients with initial positive margins, either mucosal or deep, which are converted to negative margins by a further resection, have similar loco-regional control and overall survival rates as those with initial negative margins [29]. However, it is important to point out that patients with known macroscopic residual disease in the tumour bed (R2 resections) are not candidates for PORT or POCRT and should undergo re-resection or definitive RT/CRT.

A number of other pathological risk factors have also been associated with an increased risk of loco-regional recurrence after surgery and are indicators for recommending PORT: ≥ 2 or involved lymph nodes [11,18], a single node > 3 cm [11], perineural invasion [11,19], close mucosal margins [11] and T3-4 stage [20], particularly when clusters of 2 or more of these risk factors occur together [11]. Grade of the primary tumour and presence of lympho-vascular invasion have also been identified as possible risk factors for recurrence [21], but their individual significance remains unclear. Furthermore, for oral cavity cancers, increasing depth of invasion is associated with a worse disease-free and overall survival and has been incorporated into the UICC/AJCC TNM (8th edition) pT classification [12,22]. As with positive margins, close resection margins are variably defined in the literature, but are traditionally regarded as being 1–5 mm from the primary tumour margin [17]. Obtaining margins of > 5 mm is often not feasible in the larynx and pharynx with a transoral approach, particularly TLM. Therefore in contrast to most study protocols which define margins < 5 mm as close, some current studies have set a lower cut off of 3 mm (e.g. ECOG 3311 [NCT01898494]).

A number of studies have attempted to stratify patients into risk groups, based on the presence or absence of clusters of pathological risk factors for recurrence [11,21,23]. Despite differing nomenclature, these risk groupings are similar in principle and can aid adjuvant treatment decision making. Low risk groups, with no adverse pathological features, have excellent loco-regional control and survival outcomes (90% and 83% respectively at 5 years [23]) and do not require PORT. High risk groups, most commonly defined as patients with positive surgical margins and/or ECS, should be offered POCRT as long as there are no contraindications to this. Although patients with a multiplicity of other risk factors have been deemed 'high risk' in some studies [21,23], there is no conclusive evidence that POCRT improves outcomes compared to PORT alone in these patients. Intermediate risk groups should be offered PORT. As always, there are areas of uncertainty which require individualized treatment decision-making e.g. it is difficult to estimate the risk of loco-regional recurrence in patients for whom PNI and/or LVI is the only adverse pathological factor, because these characteristics are often found in patients with other known factors for recurrence. However, because these characteristics may represent more aggressive loco-regional disease, PORT should be considered, particularly where other risk factors exist [13].

Target volume delineation in the post-operative setting

There are limited data on which to base target volume delineation guidelines in the post-operative setting. Furthermore, outlining after surgery can be difficult due to changes in anatomy, secondary to loss of tissue, post-operative collections and deformation of adjacent normal structures.

The recommendations in this manuscript are based on the following:

(i) Internationally agreed consensus guidelines which aid the delineation of neck node levels in the node negative (N0) neck (initially published in 2003 [24] and updated in 2013 [1]) which have been widely adopted into clinical practice and trial protocols worldwide.
(ii) Guidelines (published by the same authors in 2006) which aid the delineation of nodal Clinical Target Volumes (CTV-N) in the node positive and post-operative neck [25]. These guidelines have also been widely implemented, adapted and incorporated into institutional and clinical trial protocols.
(iii) Internationally agreed consensus guidelines which aid the delineation of the primary Clinical Target Volume (CTV-P) in patients receiving definitive RT/CRT for laryngeal, hypopharyngeal, oropharyngeal and oral cavity cancers [2]. These guidelines are based on a geometric approach to defining the CTV-P and, whilst they cannot be applied directly to the post-operative setting, the same geometric principles may be utilized, providing that pre-operative scans, as well as operative findings and histopathology reports, are available to guide delineation.
(iv) Radiotherapy guidelines implemented in PATHOS (ClinicalTrials.gov NCT02215265), an ongoing phase III clinical trial of PORT/POCRT in patients with HPV-positive OPSCC [26].

Pre-operative imaging, pan-endoscopy reports, intra-operative findings and the final pathology result should be available to inform treatment volume delineation. The following steps are aimed at identifying the at risk post-operative bed using a systematic approach, based on the fundamental principles of CTV delineation for definitive RT. An example case, illustrating the steps laid out below, is included in Fig. 1.

Patients should undergo a planning CT scan (e.g. at 2 mm slices) with IV contrast in a 4–5 point fixation immobilization mask. Co-registration of the pre-operative diagnostic CT and/or MRI scan with the treatment planning CT scan is recommended.

(i) Re-creating the pre-operative primary and nodal Gross Tumour Volumes (GTV):

The position of the pre-operative primary tumour and involved node (s) (referred to as GTV-P and GTV-N respectively) should be re-created on the planning CT scan, preferably with the aid of co-registered diagnostic CT and/or MRI scans. When co-registration is not accurate or cannot be done, the pre-operative anatomical position should be used to re-create both. For tonsillar tumours identified only on tonsillectomy, the GTV-P should be the site of the entire tonsil. The GTV-P and GTV-N should be edited as necessary, based on anatomical changes following surgery.

(ii) Creating the Clinical Target Volume (CTV):

According to the ICRU definition, the CTV includes the GTV plus a volume of normal tissue at risk for microscopic tumour infiltration with a probability of occurrence considered relevant for therapy [27]. In the post-operative setting, the CTV should include the primary and nodal tumour bed, with a suitable margin to account for microscopic spread, all pathologically involved nodal levels, as well as other at risk, undissected nodal levels.