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Review Article

Post-operative radiotherapy for oral cavity squamous cell carcinoma: Review of the data guiding the selection and the delineation of post-operative target volumes

Mererid Evans [a,*], Pierluigi Bonomo [b], Po Chung Chan [c], Melvin L.K. Chua [d], Jesper Grau Eriksen [e], Keith Hunter [f], T.M. Jones [f], Sarbani Ghosh Laskar [g], Roberto Maroldi [h], Brian O'Sullivan [i], Claire Paterson [j], Luca Tagliaferri [k], Silke Tribius [l], Sue S. Yom [m], Vincent Gregoire [n]

[a] Division of Cancer and Genetics, Cardiff University and Dept. of Clinical Oncology, Velindre University NHS Trust, Wales, UK
[b] Dept. of Radiation Oncology, Azienda Ospedaliero-Universitaria Careggi, University of Florence, Italy
[c] Dept of Clinical Oncology, Velindre University NHS Trust, Wales, UK
[d] Division of Radiation Oncology, National Cancer Centre Singapore, Singapore
[e] Dept of Experimental Clinical Oncology, Aarhus University Hospital, Denmark
[f] Liverpool Head and Neck Centre, Molecular and Clinical Cancer Medicine, University of Liverpool, UK
[g] Dept. of Radiation Oncology, Tata Memorial Hospital, Mumbai, India
[h] Dept. of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Italy
[i] Dept. of Radiation Oncology, Princess Margaret Cancer Center, University of Toronto, Canada
[j] Beatson West of Scotland Cancer Centre, Glasgow, UK
[k] Dept of Diagnostic Imaging and Oncology, Fondazione Policlinico, Gemelli University Hospital, Rome, Italy
[l] Dept of Radiation Oncology, Asklepios Klinik St.Georg. Hamburg, Germany
[m] Dept. of Radiation Oncology, University of California San Francisco, United States
[n] Dept of Radiation Oncology, Centre Léon Bérard, Lyon, France

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ABSTRACT

Background and Purpose: To date, no consensus guidelines have been published that systematically guide delineation of primary and nodal Clinical Target Volumes (CTVs) in patients who require post-operative radiotherapy (PORT) for head and neck squamous cell carcinoma (HNSCC). As a result, significant individual, institutional and national variation exists in the way that CTVs are delineated in the post-operative setting, leading to considerable heterogeneity in radiotherapy treatment.

Methods: A multi-disciplinary group of experts was convened by the European Society for Radiotherapy and Oncology (ESTRO), including radiation oncologists from Europe, North America and Asia, as well as surgery, radiology and pathology representatives. Oral cavity squamous cell carcinoma (OCSCC), where surgery followed by PORT is the standard of care, was first selected for focus. The indications for PORT, and the influence of tumour subsite and stage on post-operative treatment volumes, were considered with reference to current evidence, and clinical experience within the group.

Results: We present clear recommendations regarding the indications for PORT in OCSCC, and propose a new classification of lateralised and non-lateralised OCSCC, to help guide the delineation of post-operative nodal CTVs.

Conclusions: The evidence and expert opinion summarised in this manuscript provides the background and context required to underpin new international consensus guidelines for the delineation of primary and nodal CTVs for OCSCC in the post-operative setting.

* Corresponding author.
E-mail address: Mererid.Evans@wales.nhs.uk (M. Evans).

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Introduction

Inter-observer variability has been reported in the delineation of radiotherapy target volumes for head and neck squamous cell carcinoma (HNSCC), constituting a significant source of uncertainty in the radiotherapy treatment pathway for head and neck cancer patients [1,2]. The advent of increasingly conformal radiotherapy planning techniques, including Intensity Modulated Radiotherapy (IMRT), Volumetric Modulated Arc Therapy (VMAT) and Proton Beam Therapy (PBT), have increased the potential clinical impact of relatively small differences in target volume delineation, both in terms of tumour control and toxicity. While most post-radiotherapy HNSCC recurrences occur within the Gross Tumour Volume (GTV), marginal recurrence rates of 6 % and 18 % have been reported after post-operative [3] and definitive IMRT [4,5] respectively. Optimising radiotherapy delineation protocols to minimise the risk of marginal and out-of-field failures, while sparing Organs at Risk (OARs) to achieve evidence-based reductions in late toxicity, including xerostomia [6] and dysphagia [7], is a crucial goal.

In 2018, international consensus guidelines were published to guide the delineation of the primary tumour Clinical Target Volume (CTV-P) in HNSCC patients receiving definitive radiotherapy or chemoradiotherapy [8]. The aim of these guidelines was to reduce the occurrence, and potential clinical impact, of variability in primary tumour target volume delineation. In contrast to the definitive setting, comprehensive guidelines for delineating target volumes in the post-operative setting do not exist, and arguably are even more necessary in view of the significant changes in anatomy that can occur following surgery, and the inherent differences that exist in the interpretation of the constellation of risk factors for recurrence that are ordinarily addressed in the post-operative histology report. In order to address the need to develop guidelines for the post-operative setting, a multidisciplinary group was convened by the European Society for Radiotherapy and Oncology (ESTRO) representing the head and neck community, including international leaders in the field of radiation oncology from outside Europe, to increase the global reach and relevance of the guidelines produced, and enable them to be endorsed by international groups from across the globe. In order to represent the multi-disciplinary management of HNSCC patients, representatives of surgery (TMJ), pathology (KH) and radiology (RM) were also invited into the group. Through a series of virtual and face-to-face meetings, consensus was reached on how the guidelines would be developed, and what they would contain. In view of the complexities associated with delineation in the post-operative setting, and the predominance of surgery as primary treatment for oral cavity squamous cell carcinoma (OCSCC), the group agreed to focus initially on the post-operative management of OCSCC; these guidelines will subsequently be adapted for the post-operative management of tumours resected from the oropharynx, hypopharynx and larynx. The guidelines focus on conventionally fractionated external beam radiotherapy and not stereotactic body radiotherapy (SBRT) or brachytherapy. In suitable cases, the use of brachytherapy may be considered as a monotherapy or boost technique for OCSCC in the post-operative setting in centres that offer it [9]. In this manuscript, the general principles for the treatment of oral cavity tumours and the risk factors that warrant PORT are reviewed. These principles underpin recommendations in an accompanying manuscript that sets out new guidelines for the selection and delineation of primary and nodal target volumes in the post-operative setting for OCSCC.

General principles for the management of oral cavity carcinoma

Surgical resection of the primary, followed by risk-stratified adjuvant treatment, is recommended for patients with operable oral cavity squamous cell carcinoma (OCSCC). Non-surgical treatment may be considered for patients with inoperable OCSCC and/or patients who are ineligible for, or decline, surgery. In these cases, CTV-P delineation should follow previously published guidelines [8]. The present guidelines will focus on delineation of CTVs for OCSCCs in the post-operative setting, after adequate surgery +/- reconstruction has been undertaken.

Making detailed recommendations about the optimal surgical approach used to resect a primary OCSCC is not within the scope of these guidelines. In general terms, a surgical approach designed to minimise the possibility of a positive (<1 mm) or close (1 to ≤ 5 mm) margin at the primary site on initial resection is recommended, because close and positive margins are significantly associated with increased local recurrence and overall recurrence in OCSCC in large retrospective studies [10] and with worse survival outcomes on secondary analysis of a randomised controlled trial (RCT) of post-operative chemo-radiotherapy (POCRT) +/- lapatinib where greater margin distance was associated with improved survival [11]. A *meta*-analysis of individual patient local recurrence-free survival data (LRFS) from 8 studies in early T1-T2 OCSCC showed that additional resection of cases with initial positive/close margins on frozen section to achieve clear (or negative, >5 mm) margins on final histology does not significantly improve local control, suggesting that positive margins may reflect more infiltrative tumours/more aggressive biology [12]. Thus when definitive histology shows a pT1/T2 tumour with positive/close margins, re-excision may be considered if feasible, but it remains unclear whether this affects prognosis and/or obviates the need for PORT or POCRT. Such decisions need to be taken cautiously and the need for clear margins must be balanced with long-term function and quality of life for each patient.

Involvement of the T-N tract (soft tissue connecting the primary tumour to neck lymph nodes) appears to confer a worse prognosis in advanced OCSCC and an *en-bloc* resection with in-continuity neck dissection may result in better oncological outcomes in cases of advanced disease [13]. In early OCSCC, where there is a move towards minimally invasive surgery and discontinuous neck dissection/sentinel node biopsy (SNB), the T-N tract remains *in situ* and whilst the available data suggests that the frequency of microscopic involvement of the T-N tract is modest in early stage disease (12 % in pN0 disease; 18 % in pT1-2 N + disease) there may be implications for post-operative treatment [14].

Along with surgery to the primary, therapeutic neck dissection is recommended for the treatment of patients with OCSCC and clinical regional lymph node metastases (N + disease), regardless of subsite within the oral cavity. For patients with a clinically node negative neck (cN0), elective neck dissection (END) at the time of primary surgery is recommended based on the results of a phase III randomised controlled trial (RCT) of 596 patients with T1-T2N0 OCSCC which demonstrated a statistically superior 3 year overall survival rate following up-front END compared to therapeutic node dissection on relapse (80.0 % vs 67.5 % respectively, hazard ratio for death 0.64 in the END group, P = 0.01) [15]. These results were confirmed in the SEND study that included 250 randomised and 346 observational cohort patients with T1-T2N0 OCSCC [16]. Occult neck disease was found in 19.1 % (T1) and 34.7 % (T2) of patients in this study, highlighting the importance of pathologically staging the neck in clinically N0 disease. Primary tumour specific factors including depth of invasion (DOI) are associated with risk of occult lymph node metastases in OCSCC and some authors have suggested criteria (e.g. DOI < 4 mm) by which patients may be selected for avoidance of elective neck dissection [17] – there is however a lack of randomised evidence to support this approach.

The decision about whether to perform unilateral (ipsilateral to the primary) or bilateral neck dissection should be discussed at the multidisciplinary tumour board prior to surgery. In general, unilateral neck dissection is recommended for patients with lateralised OCSCC, whilst a bilateral neck dissection is recommended in cases of non-lateralised OCSCC which are close to, or crossing, the midline. The varying definition of lateralised and non-lateralised OCSCC used in the literature to date is confusing, and a standard definition is required to facilitate future decision-making, as proposed later in this manuscript.

Lymph node yield, widely regarded as a surrogate for neck dissection

quality, is an independent prognostic factor for survival in patients with clinically localised (cN0) OCSCC. A total node yield of < 18 has been associated with reduced overall survival rates in two retrospective, multi-institutional cohort studies [18,19] and in a study of > 4500 clinically node negative (cN0) OCSCC patients from the National Cancer Database [20]. Removal of ≥ 18 nodes was also associated with improved outcomes in 572 HNSCC patients treated on two NRG Oncology RTOG trials, 98 % of whom were pathologically N + and approximately a third of whom had OCSCC [21]. These studies recommend that an adequate neck dissection should include at least 18 nodes, even in a cN0 neck and when a selective neck dissection is undertaken, in keeping with ASCO guidelines [22]. In contrast, another retrospective series of > 570 OCSCC patients from Canada (36 % were clinically node positive) suggests that a nodal yield of > 15 nodes may be sufficient to improve disease-free survival and loco-regional control [23]; thus, further work is required to define the optimal cut-off. An ongoing prospective, multi-centre, observational study of OCSCC and oropharyngeal cancer patients in Europe and North America is aiming to define reliable cut-off values for lymph node yield and lymph node ratio (see later) that predict survival [24].

Sentinel Node Biopsy (SNB) is an alternative to elective neck dissection in cT1-T2N0 OCSCC. A prospective, observational cohort study (Sentinel European Node Trial [SENT]) of 415 patients with cT1-T2N0 OCSCC reported a microscopic sentinel lymph node metastasis rate of 23 %; a positive SNB led to a neck dissection within 3 weeks, resulting in 3-year disease-specific survival of 94 % [25]. Two phase III RCTs, from France and Japan, have subsequently shown equivalent survival rates and improved functional outcomes following SNB compared to END [26,27], although the large non-inferiority margins in these trials means that smaller yet clinically meaningful differences cannot be ruled out [28]. The results of the ongoing phase II/III NRG-HN006 RCT (https://clinicaltrials.gov/study/NCT04333537) comparing SNB vs END for T1-T2N0 OCSCC are awaited with interest. In the meantime, SNB has been adopted by many specialist centres as an alternative to END in patients with early (cT1-T2N0) OCSCC. Post-operative management of OCSCCs should follow similar principles, whether upfront neck dissection, or SNB followed (in positive cases) by neck dissection, has been carried out. A strategy that omits completion neck dissection in SNB positive cases and proceeds to immediate adjuvant treatment may seem rational but is not routinely recommended and should be tested in randomised trials.

Microvascular free-flap reconstruction is an established technique used to fill soft tissue and/or bone defects resulting from surgical resection of OCSCCs that are unsuitable for primary closure. Use of large pedicled flaps, such as pectoralis-major flaps, is less common and usually reserved for patients in whom free-flap reconstruction is not an option. Accurate localisation of the anastomosis area between the flap and native tissues which represent the tumour resection border is key for adjuvant treatment planning but can be challenging, as has been highlighted by the Groupe d'Oncologie Radiothérapie Tête Et Cou (GORTEC) [29]. Accurate localisation requires good dialogue with the operating surgeon and/or review of the operation notes that give details of the reconstruction; localisation may also be aided by placement of titanium ligature clips implanted in the walls of the surgical cavity [30], and/or the use of a planning/post-operative MRI scan.

Risk factors for recurrence after surgery for oral cavity carcinoma

Pathological risk factors have been identified which predict for recurrence after surgery for HNSCC. The presence of microscopic disease at the margins of resection [31,32] and/or the presence of extracapsular extension (ENE) of nodal disease in the neck [32] have been long been recognised as independent poor prognostic features for surgically resected HNSCC. Indeed, the profound effect of ENE on prognosis for non-viral HNSCC, including OCSCC, resulted in the upstaging of patients with ENE to N3b disease in the UICC/AJCC TNM 8th edition clinical staging classification [33]. 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 [32]. 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, particularly when clusters of 2 or more of these risk factors occur together; four such factors confer a prognosis similar to that of ENE [34] (see Table 1).

A detailed description of the optimal datasets for histopathological reporting of OCSCC and the challenges in staging OCSCC are beyond the scope of this manuscript but are summarised in nationally accredited guidelines [35,36] and proceedings of national society meetings [37]. The histological risk factors that predict for recurrence in the context of OCSCC are considered below.

Nodal factors

Extranodal Extension. Pathological extranodal extension (pENE) is defined by the College of American Pathologists as "extension of metastatic tumour, present within the confines of the lymph node, through the lymph node capsule into the surrounding connective tissue, with or without associated stromal reaction" and is measured from the external aspect of the lymph node capsule to the most distant tumour focus. ENE is a poor prognostic factor in cervical node-positive OCSCC [38,39] and correlates with increased risk of regional and distant recurrence, and poorer disease-free and overall survival.

Classification of pENE into minor or microscopic ENE (≤2 mm) or major (>2 mm) ENE is recommended by the AJCC for data collection and future analysis [40]. Whilst most studies demonstrate worse survival outcomes for patients with ENE-positive vs ENE-negative disease, the prognostic significance of minor vs major ENE is unclear and is complicated by the varying classifications used in the literature, the subjective nature of its assessment, and the effect of adjuvant treatment. A retrospective study of 186 OCSCC patients from Michigan found no significant difference in disease-free or overall survival between patients with major and minor pENE at a 2 mm threshold [41], and another reported poorer overall survival only in cases with soft tissue metastasis defined as complete replacement of a lymph node with no residual nodal architecture [42]. In contrast, pathologic review of 245 surgically resected pN + OCSCCs undertaken at Memorial Sloan Kettering Cancer Centre found that disease specific survival, on multivariate analysis, was significantly lower in patients with major ENE compared with patients with minor ENE, but not significantly different between patients with minor ENE and patients with no ENE [43]. A cut-off of 1.7 mm of pENE

Table 1
Pathological T and N risk factors for recurrence in Oral Squamous Cell Carcinoma (OCSCC).

	Established risk factors for recurrence and indications for PORT	Possible risk factors
Primary tumour factors	Positive margin (<1 mm)* Close margin (1 to ≤ 5 mm) pT3 and pT4 category** Perineural Invasion (PNI)*** Lymphovascular Invasion (LVI)***	Moderate-high grade Worst pattern of invasion (WPOI) grade 5 Tumour Infiltrating Lymphocytes (TIL) low
Nodal factors	Extranodal Extension (pENE)* pN2 and pN3 category	pN1 single node > 10 mm

*Indications for post-operative chemo-radiotherapy.
** pT category (UICC/AJCC TNM 8th ed.) includes tumour size and Depth of Invasion (DOI): pT1 < 2 cm and DOI ≤ 5 mm; pT2 ≤ 2 cm and DOI > 5 mm or > 2 cm and ≤ 4 cm and DOI ≤ 10 mm; pT3 > 2 cm and ≤ 4 cm and DOI > 10 mm or > 4 cm but DOI ≤ 10 mm; pT4 invades adjacent structures (e.g. bone of mandible or maxilla or adjacent skin) and/or > 4 cm and DOI > 10 mm.
*** PNI and LVI are possible risk factors for recurrence and are commonly considered together and/or with other risk factors to guide adjuvant decision making.

was the optimal prognostic threshold for predicting disease specific survival in this study. A more recent study from Princess Margaret Cancer Centre, Toronto of 384 surgically resected pN + OCSCCs who were re-reviewed and classified as having minor (≤2 mm) or major (>2 mm) ENE reported that patients with minor ENE had similar 5-year loco-regional control and distant control, but lower disease-free survival (38 % vs 51 %, p = 0.02) compared with patients with no ENE, while patients with major ENE had a trend for lower loco-regional control (59 % vs 74 %, p = 0·07) and significantly lower distant control (58 % vs 82 %, p = 0·005) and disease-free survival (13 % vs. 38 %, p=·001) compared with those with minor ENE [44]. Adjuvant treatment is recommended for patients with ENE as discussed later in the manuscript.

Lymph node burden

Node negative (pN0) disease. In retrospective series of OCSCC, the rate of recurrence in node negative (pN0) neck treated with surgery alone varies between 8–15 % [45,46]. If the neck is pN0 after an adequate neck dissection (≥18 nodes) then that is not in itself an indication for PORT. However, some levels of the pN0 neck are often included in the radiotherapy treatment volumes for OCSCC where there are indications for PORT at the primary site. Despite being widely practised, the benefit of treating the nodal regions in the pN0 neck is unknown. A non-randomised phase II trial of 77 patients with HNSCC, including only a few OCSCC patients, omitted PORT to the pN0 neck and reported a regional control rate of 97 % in the unirradiated pN0 neck [47]. A recently completed prospective randomised phase II multi-centre study (PRESERVE, Clinicaltrials.gov identifier: NCT03997643) randomised OCSCC patients with pT1-4 N0-2 OCSCC with at least one pN0 neck to standard PORT or pN0-neck avoiding PORT, and will report regional failure as its primary endpoint; the results are awaited with interest [48].

Single positive node

Single larger nodal metastases portend a worse prognosis for HNSCC in general as reflected in the TNM staging system (>3 cm N2a, >6 cm N3a). A single node > 3 cm has long been associated with an increased risk of loco-regional recurrence after surgery and is an indicator for recommending PORT [34].

Retrospective studies have shown that larger metastatic deposits predispose to pENE. In one study of 212 OCSCC patients with regional nodal metastases, a cut-off point of 11.5 mm had a sensitivity of 79.8 % and specificity of 72.8 % for pENE prediction [49]. A further study reported pathological analysis of 231 nodes with pENE, and 200 nodes without ENE, from 94 OCSCC patients who had undergone neck dissection [50]. Incidence of pENE was associated with larger LN size (p < 0.001), yet even smaller nodes carried a risk of pENE which was found in 48 % of nodes with diameter < 10 mm and 29 % nodes < 5 mm.

Whether the size of a metastatic deposit influences outcome in patients with pN1 disease is not clear. In a retrospective analysis of 707 OCSCC patients, including 121 patients with a single neck node (pN1), a nodal metastatic deposit measuring ≥ 12 mm was associated with a non-significant trend to worse overall survival on multivariate analysis (p = 0.09) [51]. What is more convincing is that the size of the nodal metastasis in OCSCC patients with pN1 disease may predict benefit from PORT. A cohort study of 1909 patients with pN1 OCSCC in the National Cancer Database, 898 of whom received PORT, showed that patients with nodal metastasis measuring > 10 mm derived greater benefit from PORT compared to patients with smaller metastases [52].

Overall, the recommendation of PORT can be streamlined for patients with pN1 disease. PORT may be considered for some cases with a single pathological node > 1 cm in size, particularly where there are strong indications for PORT at the primary site. If the node is < 1 cm in size, and an adequate neck dissection (≥18 nodes) has been carried out, then PORT to the neck may not be required. Where PORT is given, the type of surgical approach to the primary tumour (transoral vs pull-through) and the ensuing clearance (or not) of the T-N tract may also be important factors to consider, to provide adequate coverage of the T-N tract.

Multiple positive nodes (pN2b, AJCC/UICC 8th ed.)

The RTOG 85–03 and 88–24 clinical trials [34,53] showed that involvement of ≥ 2 lymph nodes increases the risk for loco-regional failure in HNSCC. A study of 14,554 surgically treated OCSCC patients identified from the National Cancer Database, demonstrated increasing mortality with an increasing number of positive nodes without plateau: estimated 5-year overall survival rates were 65.3 %, 49.9 %, 41.1 %, 29.7 %, 27.5 %, 18.5 %, and 9.7 % for those with zero, one, two, three, four to six, seven to nine and ≥ 10 positive nodes [54]. Patients with ≥ 4 positive nodes have worse outcomes in most studies [55]. High lymph node ratio (or density), defined as the number of positive lymph nodes divided by the total number of resected nodes, has been associated with higher loco-regional failure rate, and poorer overall and disease-specific survival in OCSCC. In an international, multicentre study of 4254 patients with OCSCC, 5 year overall survival rate was 49 % for patients with LNR ⩽0.07 compared with 35 % for patients with LNR > 0.07 ($P < 0.001$) [56]. Meaningful and comparative LNR data relies on ensuring adequate nodal yield at neck dissection.

Level I, followed by levels II and III, are the most commonly involved nodal basins as shown in an analysis of 8281 OCSCC cases in the SEER database who underwent neck dissection 2004–2011 [57]. Involvement of level IV (11 %) and V (5.5 %) is less common [58]. In a study of 510 patients, the frequency of level IV and V metastases varied significantly between elective (level IV 3 %, level V 1 %) and therapeutic (17 % level IV [p < 0.001], 6 % level V [p < 0.03]) neck dissections in patients with floor of mouth and gum primaries, but were not seen in any group with tongue, retromolar trigone, and cheek primaries [59]. In a *meta*-analysis of > 300 patients with previously untreated OCSCC in 9 studies, the overall percentage of patients with level IIb metastases was 6 % (95 % CI:3.5–8.6); most (85 %) patients with level IIb nodal involvement had additional nodal disease, predominantly in level IIa [60]. The 5-year disease-specific survival is higher for patients with level I, II and/or III involvement only (42 %), compared with patients with level IV (30.6 %, p < 0.0001) or V (26.4 %, P < 0.0001) involvement [57].

Skip metastases, occurring when a metastasis is found in a higher level without involvement of the 1st echelon or intermediary node, can occur in OCSCC, predominantly to levels IIb and III, and more rarely to level V [58]. The rate of skip metastases to level IV in a clinically node negative (N0) neck has been debated [61]. In a systematic review and *meta*-analysis of 11 retrospective and 2 prospective RCTs the overall rate of skip metastases to level IV was low (<5% with a fixed-effects model of 0.50 %) [62].

The lingual lymph nodes (LLN), a group of in-transit nodes located on the route of lymph drainage from the oral (particularly tongue) mucosa to the regional nodes in neck levels I and II, may harbour metastatic disease, with a frequency of 3.5 %-7.1 % reported in retrospective studies of surgically treated OCSCC [63,64]. These studies have reported an association between LLN metastasis and cervical regional nodal metastases and poorer outcomes. Four topographic groups of LLN have been defined: median (between genioglossus and geniohyoid muscles), intermediate parahyoid (medial to the hyoglossus muscle, at the greater cornu of the hyoid bone), lateral sublingual (at the sublingual salivary gland) and lateral submandibular (lateral to the hyoglossus muscle, at the deep surface of the submandibular salivary gland) [65] which could aid further study to define their relevance for surgery and post-operative treatment in OCSCC.

Primary tumour factors

Margins. The impact of positive margin status on outcomes in OCSCC

has been previously discussed. As with positive margins, close resection margins around the primary tumour are variably defined in the literature, but in the oral cavity from a surgical point of view > 5 mm is clear, 1–5 mm is close, and < 1 mm is a microscopically involved/positive resection margin [35]. For practitioners who use the residual tumour (R) classification, R1 refers to microscopic residual tumour at the margin, and R0 to no residual tumour at the margin [66]. An R2 resection has macroscopic (either by imaging or intraoperative assessment) residual tumour at the margin and requires treatment with definitive chemo-RT which is not covered by these guidelines. Acknowledgement is made of fixation and processing distortion on measurements which may cause shrinkage including the surgical margin, and on the effect of laser and/or electrocautery associated tissue distortion at the margin. Microscopically positive and close margins are associated with increased risk of local recurrence and are indications for PORT [34].

The presence of high-grade dysplasia/carcinoma in situ at the margin is associated with an increased risk of local recurrence and should be recorded in the pathology report [35]. Whenever possible, resection of the dysplastic area should be attempted to reduce the risk of future recurrence.

While tumours arising in the oral tongue are relatively distant from bone structures, even small lesions arising from other oral subsites may be close (buccal mucosa) or directly adjacent (alveolar ridge, floor of mouth, retromolar trigone) to bone structures (alveolar process, mandible, maxillary bone). Achieving 'clear' (>5 mm) margins in these cases is challenging and this should be considered in adjuvant decision-making, particularly for early T1 tumours where there are no other risk-factor for recurrence; in these cases, 'close' margins without involvement of the periosteum may be considered sufficient with no need for adjuvant treatment.

T-category. Advanced T category, defined as T3-T4 disease, is associated with higher local recurrence rates in surgically resected HNSCC compared to T1-T2 disease [67] and is an indication for PORT. A National Cancer Database (NCDB) analysis of 3268 patients with pT4aN0 OCSCC treated with mandibulectomy demonstrated that PORT was associated with improved overall survival, and that the relative survival advantage from PORT improved with increasing tumour size (adjusted HR in favour of PORT: 0.63 for tumours > 4 cm [95 % CI: 0.48–0.82] vs 0.76 for tumours > 2 cm but ≤ 4 cm [95 % CI: 0.62–0.93] vs 0.81 for tumours < 2 cm [95 % CI: 0.57–1.15]) [68].

Pathological T1-2 disease is not an indication for PORT *per se*, unless coupled with other risk factors for recurrence. The impact of PORT in patients with pT1-T2N1 OCSCC without adverse nodal features has been studied in > 2000 surgically treated patients from the SEER database 1983 –2013 [69,70]. Patients with pT2N1 disease were more likely to receive PORT, and PORT appeared to have a greater impact on overall and disease specific survival in T2 compared to T1 disease. A recent cohort study of 209 patients from 27 centres in Germany reported no impact on survival, but a decrease in loco-regional recurrences following PORT in T1-T2N0 OCSCC [71]. Consideration of PORT in these patients requires the clinician to balance the presence of other risk factors for recurrence and the toxicity/impact on QOL of post-operative treatment. Furthermore, where an *en bloc* resection has not been carried out, consideration may be given to PORT to cover the path of microscopic disease spread from the primary to the neck (the T-N tract). Irradiation of the path of microscopic disease is not normally required in an N0 neck with a small primary tumour and is typically only considered in the presence of other risk factors such as lymphovascular invasion (LVI).

Depth of Invasion. Increasing depth of invasion (DOI), measured perpendicular to the surface mucosa, from the level of the basement membrane of the closest adjacent normal mucosa to the deepest point of tumour invasion, predicts for lymph node metastasis [17] and for worse disease-free survival and overall survival in patients with OCSCC. As a result, DOI has been incorporated into the UICC/AJCC TNM (8th edition) T classification [33]. Including DOI in the pT classification upstaged 22.8 % of patients in a retrospectively analysed cohort of 298 OCSCC patients who had a worse disease-free and overall survival compared to patients who were not upstaged, indicating that the 8th edition T category classification enables better stratification of patients with OCSCC [72].

Intriguingly, one small (n = 123) retrospective study has suggested that the margin to DOI ratio (MDR) is an independent predictor of disease-free survival, and that the minimum safe surgical margin can be calculated by multiplying DOI by 0.5 [73]. Larger studies are required to explore this further.

The impact of PORT based on DOI was explored in a multi-institutional international collaborative study involving a retrospective cohort of 1,409 patients with OCSCC ≤ 4 cm in size treated between 1990–2011 [74]. In this study, DOI was strongly correlated with other adverse pathological features including positive/close margins, primary tumour size, pN + status and ENE. In patients without other adverse risk factors (pN0, clear margins), no significant association was seen between disease-specific survival and DOI, even in the absence of PORT. The authors concluded that the deterioration in prognosis associated with DOI reflects an association with other adverse risk factors, and that DOI alone should not be an indication for PORT.

Perineural invasion. Perineural invasion (PNI) has long been associated with an increased risk of loco-regional recurrence after surgery [34,75]. Controversy exists about the administration of PORT when PNI is the only adverse histological feature. In a retrospective study of 1524 OCSCC patients who underwent surgery between 2012–2015 incidence of PNI was 20.3 % and was higher in oral tongue cancers [76]. Presence of PNI adversely affected overall and disease-free survival (HRs 1.7 and 1.84 respectively) across all subgroups, including in patients with node negative disease, and addition of PORT improved survival.

Lymphovascular Invasion. Lymphovascular invasion (LVI) has also been identified as a possible risk factor for recurrence after surgery [77]. In OCSCC specifically, a *meta*-analysis of 36 studies involving 17,109 patients concluded that LVI is associated with higher incidence of lymph node metastases and worse survival, even in patients with early-stage OCSCC [78]. Like PNI, recommending PORT when LVI is the only adverse histological feature is controversial and PORT is generally recommended when LVI exists with other risk factors for T- or N- category recurrence.

Tumour grade and pattern of invasion. Grade of the primary tumour has also been identified as a possible risk factor for recurrence [77], but its individual significance remains unclear. What appears more relevant for OCSCC is the type of invasive front, specifically the worst pattern of invasion (WPOI) seen at the advancing front of the tumour, which can be graded from 1 (best, cohesive) to 5 (worst, most infiltrative) [35]. In a retrospective cohort study of 772 patients, tumours displaying type 4–5 WPOI required larger surgical margins (7.8 mm), compared to tumours that were more cohesive with type 1–3 WPOI (1.7 mm) [79]. Tumours displaying type 4–5 WPOI were associated with higher local recurrences in this study. Pattern of invasion, if reported on diagnostic biopsy specimen, could inform the surgical approach to OCSCC. Currently however the evidence is weak and unclear regarding the relevance of WPOI to decision-making about PORT, over and above information on margin status.

Retrospective studies suggest that clustering risk factors including PNI, moderate/high tumour grade, close/involved margin status and pN + status can aid prognostication in OCSCC beyond TNM8 staging [80] and guide adjuvant decision making. A retrospective cohort study of > 500 patients from China with pT1-T2N0 OCSCC demonstrated improved disease-free and overall survival. Cases with moderately-

poorly differentiated squamous carcinomas, without PNI or LVI, who received PORT had better disease-free and overall survival than those who did not; similarly, cases with PNI and/or LVI also had better outcomes after PORT [81]. However, a lack of randomized, prospective evidence precludes definitive conclusions to be reached in every clinical scenario, as highlighted in work undertaken by the GORTEC and Italian Association of Radiation Oncology (AIRO) to reach consensus on indications for PORT in low to intermediate risk OCSCC [82]. Good multidisciplinary discussion, and shared decision-making with patients, is advised in view of the limited evidence available and the importance of a risk/benefit discussion for the individual patient.

Tumour-infiltrating lymphocytes (TIL) and molecular biomarkers. There is increasing evidence that TILs have prognostic and potentially predictive significance in some HNSCCs, with high TIL tumours being associated with better outcomes in HNSCC [83]. Studies have shown that scoring tumours as TIL_{high} (TIL infiltrate in > 80 % of tumour), $TIL_{moderate}$ (TIL infiltrate in 20–80 % of tumour) and TIL_{low} (TIL infiltrate in < 20 % of tumour) from H&E sections is practical. In comparison to virally-driven oropharyngeal cancers, OCSCCs are less likely to be TIL_{high}, and there is no evidence yet that TIL levels can guide treatment decision making for OCSCCs. Capturing this information on the histopathology report may help inform future guidelines [35].

There appears to be no correlation between Human Papillomavirus (HPV) infection and OCSCC [84,85]. Routine testing of P16 IHC/HPV-DNA ISH, or other molecular markers, is currently not recommended in cases of OCSCC.

Oral verrucous carcinoma. Oral verrucous carcinoma (VC) is a well-differentiated tumour rarely associated with regional or distant metastases, which constitutes ~ 3 % of OCSCCs [86]. Complete surgical resection results in excellent outcomes. The available evidence does not support the use of PORT for VC, and analysis of 581 oral VC cases included in the SEER database suggested a trend towards worse overall survival and disease-specific survival after surgery and PORT compared to surgery alone [86]. PORT is therefore not recommended for oral VC, and re-excision is recommended in cases of incomplete excision or local recurrence.

Adjuvant treatment after surgery for oral cavity carcinoma

The following factors require consideration in the post-operative setting (see Table 2):

- Stratification into groups with low, intermediate, high risk of recurrence
- Indications for post-operative radiotherapy (PORT)
- Indications for post-operative chemo-radiotherapy (POCRT)
- Unilateral vs bilateral treatment
- Overall Treatment Package Time
- Dose of radiotherapy.

Stratification of patients into low, intermediate and high-risk groups

Several studies have attempted to stratify patients with HNSCC into risk groups, based on the presence or absence of clusters of pathological risk factors for recurrence [34,77,87,88]. Despite different nomenclatures, 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 [87]) and do not require PORT. High-risk groups, defined as patients with positive surgical margins and/or ENE, should be offered POCRT as long as there are no contraindications to this (see below). Although patients with a multiplicity of other risk factors have been deemed 'high-risk' in some studies (77, 87), there is as yet no conclusive evidence that POCRT improves outcomes compared to PORT alone in these patients. We therefore recommend that intermediate-risk groups should be offered at least PORT as a standard, with careful consideration of addition of systemic therapy on an individual basis for those patients with multiple concerning factors.

Table 2
Summary of principles underpinning decisions regarding adjuvant treatment after surgery for oral cavity carcinoma.

	Summary of principles	Treatment recommendation
Stratification into risk groups for recurrence	High-risk: Positive (<1 mm) margin/ R1 resection ENE Intermediate risk: Close margin (1–5 mm) pT3 and pT4 category pN2 and pN3 category Perineural Invasion (PNI) *[a]/ Lymphovascular Invasion (LVI)*[a] Low risk: pT1 and pT2 category with none of the primary tumour risk factors above pN1 category with single node ≤ 10 mm*[b]	High-risk: Post-operative chemo-radiotherapy (POCRT) Intermediate-risk: Post-operative radiotherapy (PORT) Low-risk: No post-operative treatment
Indications for post-operative concurrent chemo-radiotherapy	Positive (<1 mm) margin/ R1 resection Extranodal Extension (pENE)	Cisplatin-based POCRT, given: 100 mg/m[b] given 3 weekly or 40 mg/m[b] given weekly
Categorisation depending on tumour location	Lateralised OCSCCs Non-lateralised (midline) OCSCCs	Unilateral neck treatment Bilateral neck treatment
Overall Treatment Package Time (OTT)	Days from surgery to the last day of adjuvant radiotherapy Optimal: ≤ 11 weeks Less optimal: ≤ 13 weeks Problematic: >13 weeks	Start radiotherapy within 5 weeks of the date of surgery, so that 30 fractions can be completed by 11 weeks after surgery.
Post-operative radiotherapy dose	A dose > EQD_2 54 Gy is required to the tumour bed. Doses ≥ 63 Gy in 1.8 Gy fractions (EQD2 60 Gy) result in higher toxicity and may not improve LRC, particularly in the absence of pENE.	High-risk CTV: EQD_2 64–66 Gy Post-operative CTV: EQD_2 56–60 Gy Prophylactic CTV: EQD_2 50 Gy

*[1] PNI /LVI alone or in combination with other risk factors.
*[2] pN1 category with single node > 10 mm but ≤ 30 mm may be regarded as 'intermediate risk' and an indication for radiotherapy, particularly when combined with other risk factors. Adjuvant radiotherapy for a single node ≤ 10 mm is not routinely recommended but may be considered in certain circumstances, including inadequate neck dissection.

Indications for post-operative radiotherapy (PORT)

This important area has minimal randomised data, presumably because the traditional decision to offer PORT in the presence of adverse prognostic factors is reasonable in the context of the devastating implications of recurrence in these patients. Nonetheless a single small randomised controlled trial accrued 140 patients between 1990 and 1994 in India [89]. Patients had Stage III/IV squamous cell carcinoma of the buccal mucosa with the majority requiring flap reconstruction due to large defects after ablation. PORT (58–65 Gy, 1.8–2.0 Gy/fx, 5 fx per week) was administered to 80 patients compared to 60 patients who received surgery alone. Some imbalance in number between the both groups resulted from a preference of some investigators to put more

clinically node-positive cases into the PORT group. Despite this, those receiving surgery and PORT experienced a 30 % absolute improvement in disease free survival compared to surgery alone at 3 years (68 % vs 38 % $p < 0.001$). A 10 % absolute improvement in 3 year overall survival was also evident with PORT (94 % vs. 84 %) but was not statically significant, presumably due to the small sample size.

Patients with multiple (>1) positive nodes and multiple (>1) involved nodal levels should be offered PORT. The benefit of PORT/POCRT compared with surgery alone appears greater in patients with ≥ 4 positive nodes. In a retrospective review of 98 OCSCC patients who had undergone neck dissection, 5-year disease-specific survival was significantly higher in patients with 3 positive nodes vs those with 4 and ≥ 5 positive nodes ($P < 0.01$) [90]. The loco-regional control and disease-specific survival rates for the surgery alone, surgery plus PORT, and surgery plus POCRT groups were 46.2 % and 40.5 %, 66.3 % and 54.4 %, and 81.7 % and 52.4 %, respectively. For patients with ≥ 4 positive nodes, the loco-regional control rate after surgery plus POCRT was better than that observed after surgery alone (77.5 % vs. 32.6 %, $P = 0.01$). The benefit of PORT compared to surgery alone may also be greater in patients with low neck involvement. In the study of OCSCC cases in the SEER database, surgery with PORT significantly improved 5-year disease-specific survival compared with surgery alone for patients with level I to III (50.7 % vs 48.6 %, $P = 0.0109$), level IV (39.9 % vs 23.2 %, $P < 0.0001$) and level V (33.3 % vs 9.1 %, $P = 0.0005$) neck disease [57].

There are areas of uncertainty that require individualized treatment decision making. For instance, 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 usually occur 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.

Indications for concurrent post-operative chemo-radiotherapy (POCRT)

Addition of concurrent chemotherapy with cisplatin to PORT is recommended for HNSCC patients with positive resection margins around the primary tumour (R1) and/or ENE in the neck, based on the results of two landmark studies, RTOG 9501 and EORTC 22931; 26–27 % of patients in both studies had OCSCC [91,92]. Post-operative concurrent chemotherapy (cisplatin 100 mg/m^2 on weeks 1, 4 and 7) improved local control and disease-free survival rates compared with PORT alone in both studies, benefits that persisted on long-term (10 year) follow-up [93]. Overall survival was significantly improved in the European study, but not the US study, possibly due to the different eligibility criteria used. Importantly however, overall survival was significantly improved by POCRT in patients with positive margins and/or ENE on a select pooled analysis of patients having those features in both studies [94]. The benefit of POCRT was confirmed in a sub-group analysis of 5000 surgically treated patients included in the MACH-NC *meta*-analysis of chemotherapy in HNSCC [95]. Addition of concurrent chemotherapy improved overall survival (HR = 0.79 95 %CI: 0.69–0.92), a benefit that was significantly greater in women compared to men ($p = 0.001$). A lower rate of comorbidities and of mortality not related to cancer in women than men may explain the observed results, although this remains speculative. The reduced chemotherapy effect seen in patients older than 70 yrs in the updated MACH-NC *meta*-analysis [96] was not seen in the surgical sub-group, possibly because patients treated by surgery were younger (only 7.7 % were older than 70), and the smaller number of overall cases (28.6 % of the MACH-NC population) may have diluted the association. Patients > 70 yrs were excluded from EORTC 22931 and represented only 6 % (25 out of 416) of patients in RTOG 9501. Therefore there is a lack of data to generate firm conclusions regarding the use of POCRT in an older age group; in view of this and the significant toxicity associated with POCRT, its use in patients > 70 yrs of age is left to the discretion of the treating physicians.

A phase III Oral Cavity Adjuvant Therapy randomised trial (OCAT) has investigated the benefit of POCRT specifically in 900 patients with locally advanced OCSCC [97]. In addition to positive margins and ENE, high-risk features included ≥ 2 regional lymph nodes, extensive tissue infiltration, PNI, LVI. In this study, POCRT did not improve loco-regional control or survival in locally advanced OCSCCs compared to PORT alone or compared to accelerated (6 fractions per week) PORT. The authors suggest this may be related to the low margin positivity rate (<1%) and higher overall survival rates in the standard PORT arm compared with previously published POCRT studies, as well as the low dose of weekly cisplatin (30 mg/m^2) used, which appears less effective than a 3-weekly regimen at 100 mg/m^2 (see below). Post-hoc exploratory analysis suggested a benefit to intensification only in patients with multiple risk factors, (such as ENE together with advanced T [T3-4]and N [N2-3] categories) which may be explored in future studies. In the previously mentioned study from Toronto of major and minor pENE, on multivariable analysis, concurrent POCRT was associated with improved disease-free survival for major ENE (adjusted HR = 0·49; 95 % CI 0·29-0·85, p = 0·01) but not for minor ENE after adjusting for age, ECOG status, T-, N-category, margin status, and radiotherapy [44]. The NRG/RTOG 0920 phase III trial randomised 627 HNSCC patients (64 % had OCSCC) with intermediate-risk histology after surgery (patients with positive margins and/or ENE were excluded) to receive PORT or PORT with Cetuximab [98]. Addition of Cetuximab to PORT did not improve overall survival (the primary endpoint), although did improve disease-free survival, albeit at the cost of increased acute toxicity, mostly skin and mucosal effects. Based on these data, addition of systemic therapy to PORT is not routinely recommended in patients with intermediate-risk histology, although selected subgroups may benefit.

The dose and schedule of cisplatin administered with PORT is important. A non-inferiority phase III randomised trial of low-dose weekly cisplatin at 30 mg/m^2 vs 3 weekly cisplatin at 100 mg/m^2 in 300 patients with locally advanced HNSCC, mostly in the adjuvant setting (93 %) with high-risk features (ENE, close or positive margins), showed a superior 2 year locoregional control rate with the standard 3 weekly cisplatin dose regimen compared to the weekly schedule (2 yr LRC rate 73.1 % vs 58.5 % respectively: absolute difference 14.6 % [95 % CI: 5.7 %–23.5 %] $p = 0.014$), albeit with more toxicity [99]. There was no difference between patients in both arms who received at least 200 mg/m^2, but this cumulative dose was less often achieved in the weekly low-dose arm. In comparison, a more recent multicentre, non-inferiority phase II/III randomised controlled trial conducted in Japan (JCOG1008) which included 261 patients with resected locally advanced HNSCC and high-risk features for recurrence (defined as ENE and/or positive margins), compared a weekly cisplatin 40 mg/m^2 dose regimen vs a 3 weekly cisplatin 100 mg/m^2 regimen and showed that it was non-inferior in terms of overall survival; estimated 2- and 3-year overall survival was 74.2 %/59.1 % in the 3-weekly arm and 77.7 %/71.6 % in the weekly arm [100]; at final analysis with 5-year follow-up, the non-inferiority of weekly cisplatin was confirmed [101]. Weekly cisplatin was also associated with a favourable toxicity profile in this study. Taken together, these results suggest that patients with 'high risk' features defined as a positive margin and/or ENE should receive concurrent cisplatin, at a standard 3 weekly 100 mg/m^2 dose regimen, or alternatively with a weekly 40 mg/m^2 dose regimen, but not with a lower 30 mg/m^2 dose regimen. Achieving a cumulative cisplatin dose of at least 200 mg/m2 is required for optimal outcomes [102].

Unilateral vs bilateral treatment: Lateralised and non-lateralised oral cavity cancers

In the clinically N0 neck, retrospective studies have reported a contralateral lymph node metastasis (CLNM) rate of approximately 9 % in patients with OCSCC, mostly oral tongue, who undergo contralateral neck dissection at the time of initial surgery [103,104]. Extension over the midline increases the risk of CLNM on multivariate analysis, and in most studies the risk of CLNM is higher for floor of mouth and oral

tongue cases than other OCSCCs. Ipsilateral nodal metastases and ENE appear to increase the risk of CLNM [103].

Data on the rate of contralateral neck failure (CLNF) after treatment for OCSCC are confounded by the varying definition of lateralised and non-lateralised OCSCCs used in the literature, the heterogeneity in primary and nodal risk factors included in different study cohorts, and the differences in up-front treatment to the contralateral neck (elective neck dissection, prophylactic radiotherapy, neither or both). A *meta*-analysis of 524 OCSCC patients from 8 retrospective cohort studies reported low CLNF rates (3.4 %, 95 % CI: 2.2–5.4 %) after surgery and radiotherapy to the primary site +/- ipsilateral neck only [105]. Subgroup analysis showed that the CLNF rate was higher in the N2-N3 group than N0-1 group (14.4 % vs 1.5 %, $p = 0.0008$) and in oral tongue vs non-tongue cases (6.3 % vs 2.8 %, although this was not statistically significant, $p = 0.09$). Two studies included in this *meta*-analysis have reported CLNF rates of > 30 % in patients with oral tongue or FOM primaries with N2a/b disease who did not receive contralateral neck irradiation [106,107]. In a more recent systematic review and *meta*-analysis of 1825 patients in 15 studies, the rate of CLNF among the 805 patients treated with ipsilateral nodal RT was 5.7 % [108]. The CLNF rate increased with advanced T category (56 % of CLN failures occurred in patients with T4 tumours) and advanced nodal disease (N0: 1.2 %; N1: 3.8 %; N2-N3: 17.4 %) and was significantly higher for patients with N2-N3 than N0-N1 disease ($p < 0.001$). No difference in CLNF rates was reported by site within the oral cavity; however the authors acknowledge that it was a study-level *meta*-analysis where studies were grouped into those with more 'lateralised' and those with more 'centralised' tumours. However because it was not a patient level *meta*-analysis, evaluation by each subsite within the oral cavity was not possible.

Studies that have attempted to look specifically at "lateralised" tumours include a retrospective study from the Netherlands of 123 mostly lateralised OCSCCs treated with surgery and radiotherapy to the primary +/- ipsilateral neck; in that study, the investigators defined lateralised OCSCCs as being > 1 cm from the midline [109]. They reported an overall CLNF rate of 6 %, which was higher in N2b vs N0-N2a disease ($p = 0.008$) and in cases with ENE (borderline significance, $p = 0.06$). Fifteen percent of patients in this study had oropharyngeal cancer and 27 % of OCSCC patients had oral tongue/floor of mouth cancers, making definitive conclusions about the risk of CLNF in patients with truly lateralised OCSCCs with N2b disease difficult. In a recent retrospective study of 149 patients with more strictly defined lateralised OCSCCs, including buccal/cheek, gum and retromolar subsites only, the overall CLNF rate was 3.6 %, even though ≈80 % of cases had locally advanced T3-4 disease [110]. Patients with oral tongue and floor of mouth cancers, as well as patients with level Ia involvement and ENE in the ipsilateral neck, were excluded. A proportion (20–30 %) of patients had also undergone up-front elective neck dissection or radiotherapy to the contralateral neck, which may have contributed to the low CLNF rate reported in the study. However, it does suggest that advanced T category is not in itself an indication for contralateral neck treatment in truly lateralised OCSCCs.

A retrospective study of 208 patients from India with "well-lateralised" OCSCC, defined as carcinomas of the buccal mucosa, gingiva and retromolar trigone located ≥ 1 cm from the midline, excluded cancers of the oral tongue and floor of mouth [111]. All patients underwent resection of the primary tumour and an ipsilateral neck dissection with PORT, if indicated, to the ipsilateral neck only. Isolated contralateral nodal failure (CLNF) occurred in 10 % of patients at a median follow-up of 45 months, most commonly at level IB (62 %) followed by level II. On multivariable analysis, presence of 2 or more positive ipsilateral nodes was an independent prognostic factor for CLNR ($p < 0.001$), and the authors suggest that elective treatment of the contralateral neck may be considered in these patients.

In summary, the available data show a low rate of contralateral nodal metastasis/failure rate in patients with N0-N1 disease, and in patients with lateralised OCSCCs, even in the presence of more advanced local disease. Patients with oral tongue and floor of mouth cancers, particularly patients with T3-T4 disease and N2-N3 disease, have a higher risk of CLNF and treatment of the contralateral neck is generally recommended.

Categorisation of OCSCCs into lateralised and non-lateralised (or "midline/centralised") tumours is recommended to aid decision-making regarding the optimal treatment of the contralateral, clinically N0 neck, in patients with OCSCC. As previously mentioned, definition of a lateralised tumour varies considerably in the literature, making comparison between historical studies difficult. Categorisation should be done pre-operatively, based on baseline clinical and radiological assessments, and discussed by the multi-disciplinary team so that consensus is reached about the need, or otherwise, for a contralateral neck dissection at the time of surgery to the primary and ipsilateral neck. The surgeon, radiation oncologist and other multi-disciplinary team members should agree whether treatment of the contralateral neck is required at all and, if so, whether neck dissection (+/- PORT based on histology) or radiotherapy is the preferred option. Patients who have undergone contralateral neck dissection and are pN + should be offered PORT according to the same principles as the ipsilateral neck. In patients who have not undergone contralateral neck dissection at the time of primary surgery, tumour categorisation should be discussed again post-operatively by the multi-disciplinary team, with the additional information gained from surgery and the histology report regarding the extent of the primary tumour and presence or absence of associated pathological risk factors for loco-regional recurrence.

We propose the following standardised categorisation of OCSCCs (see Fig. 1). This categorisation should be based on a comprehensive evaluation of information obtained by imaging, intraoperative assessment, and pre- and post-operative clinical examination.

Lateralised tumours

- Tumours arising in the buccal mucosa, retromolar trigone and upper & lower alveolar ridges, providing there is ≥ 10 mm clearance from midline.
- T1 and some T2 tumours (UICC 8th ed.) arising on the lateral border of the oral tongue, or laterally within the floor of mouth, providing there is ≥ 10 mm clearance from midline, and there is no involvement of the anterior third/tip of the tongue and anterior floor of mouth.

In these patients, the risk of contralateral neck recurrence is low and does not justify the added toxicity associated with elective treatment of the contralateral clinically N0 neck in the majority of patients.

Some patients with lateralised OCSCCs who have undergone ipsilateral neck dissection with multiple pathologically-positive nodes, particularly nodes with ENE, may benefit from prophylactic radiotherapy to the contralateral neck. In the absence of a clear evidence base to guide decisions, involvement of the multi-disciplinary team and discussion with the patient is recommended.

Non-lateralised (or midline) tumours

- All tumours arising in the floor of mouth or oral tongue, apart from some T1 and T2 tumours arising on the lateral border of the tongue and lateral floor of mouth with ≥ 10 mm clearance from midline.
- All tumours extending to within ≤ 10 mm of the midline.

In these patients, the risk of contralateral neck recurrence is comparatively high and does justify the added toxicity associated with elective treatment of the contralateral clinically N0 neck. Elective contralateral neck dissection (+/- PORT based on histology) or, if neck dissection is not performed, prophylactic radiotherapy to the

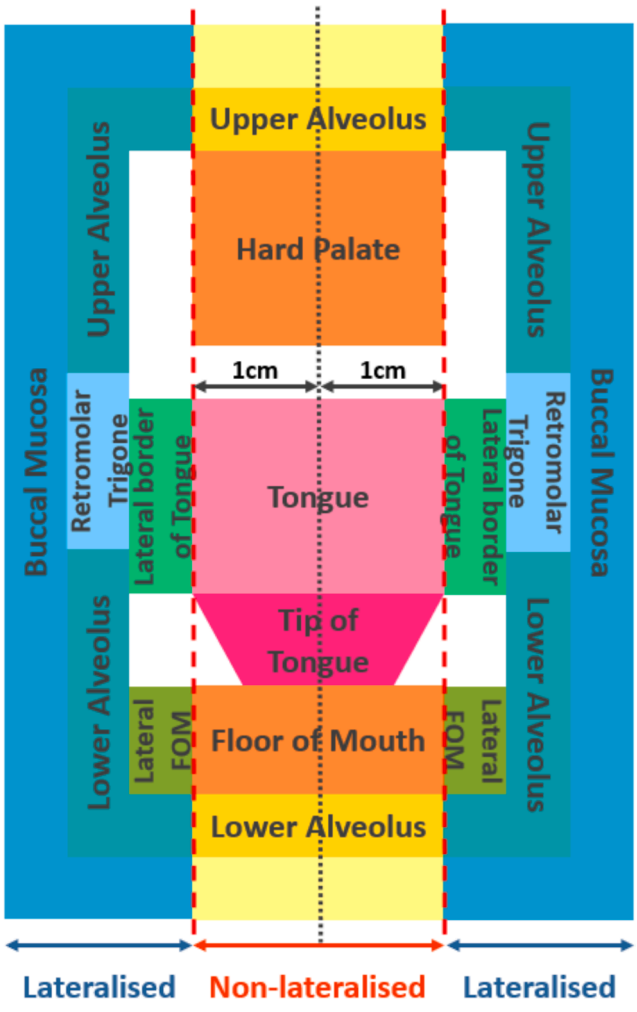

Fig. 1. Categorisation into Lateralised and Non-Lateralised Oral Cavity Squamous Cell Carcinomas (OCSCCs) Lateralised: low risk of contralateral neck recurrence which does not justify the added toxicity of treating the contralateral cN0 neck* Non-lateralised: relatively high risk of contralateral neck recurrence which does justify the added toxicity of treating the contralateral cN0 neck [*Possible exception: selected patients who have undergone ipsilateral neck dissection and have multiple pN + nodes, especially with pENE].

contralateral neck is recommended.

Overall treatment package time (TPT)

The overall treatment package time from day of surgery to the last day of radiotherapy should be as short as possible. Prolongation of the TPT > 13 weeks [87] or > 87–100 days [112,113] reduces loco-regional control and survival rates for HNSCC. Outcomes are better if combined treatment is completed in < 11 weeks, intermediate if completed between 11 and 13 weeks, and significantly poorer if completed in > 13 weeks [87]. To achieve this, PORT should commence ≤ 5 weeks and no later than 7 weeks after surgery, unless there are post-operative complications. If this interval between surgery and commencement of PORT is prolonged it is itself associated with worse outcome in patients receiving conventional fractionation [34,114] but it may be possible to compensate for a longer interval between surgery and PORT by accelerated fractionation, delivering PORT over 5 weeks rather than 7 weeks [87]. Although the available data are for PORT, and do not exist for POCRT, similar recommendations regarding the TPT are given for treatment with POCRT. Diagnostic re-staging is strongly recommended in cases where there is a significant delay between surgery and commencement of PORT to exclude an early recurrence.

Defining the optimum post-operative RT dose

Data from a number of studies that have attempted to establish the optimum dose of PORT for HNSCC have been variably interpreted, resulting in considerable differences in clinical practice. The most important study in this context was a prospective, randomised phase III study designed to assess the dose response relationship for PORT in patients with (predominantly) stage III-IV non-metastatic cancers of the oral cavity, oropharynx, larynx or hypopharynx, results of which were published in 1993 [34] and updated in 2017 [88]. Two hundred and sixty one evaluable patients were randomly assigned to receive one of three post-operative dose levels (57.6 Gy, 63 Gy or 68.3 Gy delivered at 1.8 Gy per fraction per day over 6.5, 7 and 7.5 weeks respectively) to the primary site and involved neck. A lower dose of 52.2–54 Gy was initially included but was dropped after the first interim analysis showed several early recurrences. Preliminary results, after a median follow-up of 22 months, confirmed that patients who received a dose of ≤ 54 Gy to the primary site and involved neck had a significantly higher failure rate than those receiving > 57.6 Gy ($p = 0.02$) [34]. No significant dose response was demonstrated above 57.6 Gy, except for patients with ENE, in whom recurrence rates appeared to be significantly higher at 57.6 Gy than 63 Gy delivered at 1.8 Gy per fraction. Doses above 63 Gy did not improve the therapeutic ratio and moderate to severe complications were more frequent in patients who received ≥ 63 Gy. The authors recommended a minimum dose of 57.6 Gy to the operative bed, with a dose of 63 Gy in 1.8 Gy fractions limited to sites at higher risk, particularly areas of ENE. Longer-term results from the same study [88], with more than 20 years follow-up, showed no significant dose response at doses ≥ 57.6 Gy, in either the intermediate or high-risk groups, even in patients with ENE. Overall TPT had a much more significant effect on loco-regional and survival rates than radiotherapy dose, which is consistent with the results of other studies [112]. The lack of a significant dose–response relationship was postulated to be because the beneficial effect on tumour control of doses > 57.6 Gy (in 32 fractions) was offset by tumour cell repopulation occurring during the additional time taken to deliver the higher doses at < 2 Gy per fraction [34]. Now that 2 Gy per fraction is more commonly used for PORT, equivalent doses (EQD_2) of 56–60 Gy in 30 fractions over 6 weeks are typically delivered to the primary and nodal tumour beds. It is important to clarify that this study was conducted without concurrent chemotherapy, thus the benefits (or otherwise) of dose escalation are uncertain in the context of POCRT. Randomized studies of POCRT [91,92] allowed additional boosting of high-risk areas to 66 Gy in 33 fractions, but this remains optional in ongoing trials. For these guidelines, a post-operative EQD_2 dose of 60–66 Gy is recommended in 30–33 fractions, with an elective or prophylactic EQD_2 dose of 50 Gy in 25 fractions to uninvolved and undissected nodal areas. The latter recommendation is based on historical data showing that in combination with surgery, a dose equivalent to 50 Gy in 25 fractions is sufficient to eradicate microscopic disease in HNSCC in over 90 % of cases [115].

Preparing for adjuvant radiotherapy for oral cavity carcinoma

Optimal delineation of the post-operative Clinical Target Volume (CTV) requires the collation of information from multiple sources, particularly from the radiologist, operating surgeon, and pathologist. This guideline group strongly recommends that the radiation oncologist participates in the pre-operative, multi-disciplinary discussion about the care of every patient with OCSCC so that agreed, risk-based decisions can be made prior to surgery about the need to dissect the contralateral neck, the type of reconstruction that will be carried out, and the need for pre-radiotherapy dental extractions that may be undertaken at the time of surgery. In the following sections, we focused on the information required by the oncologist post-operatively to optimise CTV delineation.

Information required from the radiologist

Acquisition of pre-operative, CT and/or MRI cross-sectional imaging

of the head and neck is crucial to enable MDT decision-making about surgery and to aid delineation of the post-operative CTVs. The key information required from the radiologist is summarised in Table 3, and a few issues are worth highlighting:

- Pre-operative evaluation of DOI on imaging for OCSCC is a controversial issue. A *meta*-analysis of DOI in oral tongue SCC including 36 studies and > 3000 DOI measurements reported pooled correlation coefficients between radiologic DOI (rDOI) and pathologic DOI (pDOI) of 0.86 (95 % CI: 0.82–0.88) for MRI, 0.80 (95 % CI: 0.70–0.87) for CT and 0.89 (95 % CI: 0.82–0.94) for USS [116].
- While tumours arising in the oral tongue may be relatively distant from bone structures, even small lesions arising from other subsites are close (buccal mucosa) or directly adjacent (alveolar ridge, floor of mouth, retromolar trigone) to bone structures (alveolar process, mandible, maxillary bone). Pre-operative imaging should aim to report DOI from mucosa into soft tissues, and into the cortical rim and medullary (or spongiform) bone. For mandibular invasion, it is critical to differentiate the level of bone infiltration as it will affect the surgical approach [117].
- Local disease extent into neighbouring structures should be clearly described. Locally advanced disease classified as T4b (AJCC/UICC TNM8) indicates a poor prognosis and suggests that the primary is unresectable, although this is not always the case. The extent of masticator space/infratemporal fossa invasion is important and T4b tumours may be sub-divided into those that extend below the mandibular notch (infra-notch), which carry a better prognosis vs those that extend above it (supra-notch) that are associated with a worse prognosis.

Information required from the surgeon:

Detailed, first-hand information is required on: the clinical extent of the tumour; the surgical procedure undertaken to resect the primary tumour; management of the neck including whether sentinel node biopsy was initially undertaken, and the type of neck dissection performed according to the American Head and Neck Society (AHNS) Committee for Neck Dissection [118]; the reconstruction performed (e.g. pediculated or free flap). This information is essential for optimal selection and delineation of the post-operative target volumes. The key information required from the surgeon/operative note is set out in Table 3.

Information required from the pathologist:

The post-operative histopathology report provides crucial information about the presence or absence of risk factors for recurrence, both at the primary site and in the neck. This information allows the multidisciplinary team to stratify patients into low-, intermediate- or high-risk groups for recurrence, thus enabling recommendations to be made about adjuvant treatment. The key information required from the pathologist/histopathology report is set out in Table 3.

Decalcification of bony samples may take many weeks, thereby delaying the final pathology report and presenting a challenge for post-operative treatment planning. In these cases, an interim histopathology report that includes details of soft tissue component can be helpful to allow timely planning of radiotherapy. The final histopathology report incorporating details of the bone resection specimen can then be issued later.

Early recurrence after surgery:

A 15 % risk of early recurrence, defined as recurrence after surgical resection before initiating planned PORT, has been reported in patients with OSCC and portends a worse prognosis [119]. On multivariate analysis oral tongue subsite, microscopic positive resection margin and advanced stage (T3-4 N2-N3) were significantly associated with early recurrence. Salvage radiotherapy in patients with early loco-regional recurrence, but no distant metastases, results in a 3 year recurrence-free rate of 36 % (95 % CI: 23–47 %). This required customised

Table 3
Information required from the radiologist, surgeon, and pathologist to enable post-operative CTV delineation for post-operative (chemo)-radiotherapy (PORT) in oral cavity SCC.

	Specific information required	Source of information
Information required pre-operatively from the **radiologist**	Description of primary tumour to include: Description of nodal disease to include: Presence/absence of metastatic disease. Additionally, for selected patients (with suspected disease and/or prolonged interval between surgery and adjuvant treatment): • T category/tumour extent: maximum dimension, depth of invasion (mm), invasion of adjacent structures including bone (informs surgery and staging classification) and infratemporal fossa (informs operability/prognosis). • Likely resectability (T4b disease involving masticator space, pterygoid plates, skull base, and/or encasing internal carotid artery generally inoperable) • Evidence of Perineural Tumour Spread (PNTS) along the branches of the trigeminal nerve • Distance of the primary tumour from midline (to inform laterality) • N category: size and configuration (number and level) of malignant nodes • Presence or absence of ENE and/or matted nodes on imaging • Presence or absence of contralateral nodes on imaging • Assessment of post-operative imaging (planning CT and/or additional scans) for presence of residual disease, or early recurrence.	Primary OCSCCs of the oral tongue and floor of mouth are best visualised on MRI DOI is optimally assessed on intra-oral USS Gingivo-buccal cancers require CT to detect bone and soft tissue invasion Perineural Tumour Spread (PNTS) is best assessed on MRI PET and/or FNA may be needed to clarify status of equivocal nodes CT Chest or PET-CT scan to assess for distant metastases.
Information required post-operatively from the **surgeon**	Description of surgical procedure undertaken to include: • Realistic assessment of surgical intent (radical or palliative) • Intra-operative findings including tumour extent and areas where margins may be close due to extent of tumour and/or anatomical considerations • Clips inserted to mark the tumour bed and/or close margins; any additional sections/biopsies taken e.g. in areas of close margins • Type of reconstruction and how it applies to the orientation/position of the tumour bed • Type of neck dissection(s) carried out, including levels resected and if ipsilateral	

(*continued on next page*)

Table 3 (*continued*)

	Specific information required	Source of information
	and/or contralateral neck dissection undertaken. • Whether sentinel node biopsy (SNB) +/- completion neck dissection was initially undertaken.	
Information required post-operatively from the **pathologist** [35,36]	Description of primary to include: Description of nodal dissection to include: • Histologic type of squamous cell carcinoma • Tumour maximum dimension (mm) • Grade (well, moderately, poorly differentiated) • Depth of invasion (mm) below the top of the adjacent mucosa (not synonymous with tumour thickness) • Presence/absence of bone invasion and its extent: erosive or infiltrative, cortical or medullary bone involvement • Presence/absence of perineural invasion (PNI) and if ahead of the advancing front or not • Presence/absence of lymphovascular invasion (LVI) • Pattern of invasion/Worst Pattern of Invasion (WPOI): cohesive corresponding to WPOI 1–3, non-cohesive/ WPOI 4, or widely dispersed/WPOI 5 • Margin status of all mucosal and deep margins: clear (>5 mm), close (1–5 mm), positive or involved (<1 mm). • Presence/absence of dysplasia at the margins. • Lymph node yield • Number, size and levels of lymph node metastases • Presence/absence of ENE and extent of tumour extension beyond the capsule (in mm).	

treatment planning with close review of the post-operative planning CT scan to exclude early recurrence amenable to modified dose and volume considerations to address detected gross disease compared to conventional adjuvant radiotherapy. Additional diagnostic imaging with or without selected biopsy should be requested if early recurrence is suspected and/or in cases where the interval between surgery and start of adjuvant treatment is prolonged.

Conclusion

Oral cavity squamous cell carcinoma (OCSCC) is typically managed by surgery followed by post-operative radiotherapy, and thus being able to delineate primary and nodal Clinical Target Volumes (CTVs) for radiotherapy in this setting is an important element of head and neck radiation/clinical oncologists' practice. This manuscript sets the background evidence and context required to underpin the development of consensus guidelines. This statement highlights the importance of engagement with the multi-disciplinary team, and the key information required from radiology, surgical, and pathology colleagues to guide decision-making in the adjuvant setting. The companion manuscript will build on this information and set out new international consensus guidelines for CTV delineation in the post-operative setting.

CRediT authorship contribution statement

Mererid Evans: Writing – original draft, Data curation, Conceptualization. **Pierluigi Bonomo:** Writing – review & editing, Data curation. **Po Chung Chan:** Data curation. **Melvin L.K. Chua:** Writing – review & editing, Data curation. **Jesper Grau Eriksen:** Writing – review & editing, Data curation. **Keith Hunter:** Writing – review & editing. **T.M. Jones:** Writing – review & editing. **Sarbani Ghosh Laskar:** Writing – review & editing, Data curation. **Roberto Maroldi:** Writing – review & editing, Data curation. **Brian O'Sullivan:** Writing – review & editing, Supervision, Data curation. **Claire Paterson:** Writing – review & editing, Data curation. **Luca Tagliaferri:** Writing – review & editing. **Silke Tribius:** Writing – review & editing, Data curation. **Sue S. Yom:** Writing – review & editing, Data curation. **Vincent Gregoire:** Writing – review & editing, Supervision, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Hong TS, Tome WA, Harari PA. Heterogeneity in head and neck IMRT target design and clinical practice. Radiotherapy and Oncology 2012;103:92–8.
[2] van der Veen J, Gulyban A, Nuyts S. Interobserver variability in delineation of target volumes in head and neck cancer. Radiotherapy and Oncology 2019;137: 9–15. https://doi.org/10.1016/j.radonc.2019.04.006.
[3] Chen AM, Farwell DG, Luu Q, Chen LM, Vijayakumar S, Purdy JA. Marginal Misses After Postoperative Intensity-Modulated Radiotherapy for Head and Neck Cancer. International Journal of Radiation Oncology Biology Physics 2011; 80 (5): 1423-1429, ISSN 0360-3016. doi: 10.1016/j.ijrobp.2010.04.011.
[4] Gupta T, Jain S, Agarwal JP, Ghosh-Laskar S, Phurailatpam R, Pai-Shetty R, et al. Prospective Assessment of Patterns of Failure After High-Precision Definitive (Chemo)Radiation in Head-and-Neck Squamous Cell Carcinoma. International Journal of Radiation Oncology Biology Physics 2011;80 (2): 522-531, ISSN 0360-3016, doi: 10.1016/j.ijrobp.2010.01.054.
[5] Kristensen MH, Holm AIS, Hansen CR, Zukauskaite R, Samsøe E, Maare C, et al. High-dose loco-regional pattern of failure after primary radiotherapy in p16 positive and negative head and neck squamous cell carcinoma - A DAHANCA 19 study. Clin Transl Radiat Oncol 2024 Mar;30:100772. https://doi.org/10.1016/j.ctro.2024.100772.
[6] Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, et al. for the PARSPORT trial management group. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. The Lancet Oncology 2011;12:127–36. https://doi.org/10.1016/S1470-2045(10)70290-4.
[7] Nutting CM, Finneran L, Roe J, Sydenham MA, Beasley M, Bhide S, et al. Dysphagia-optimised intensity-modulated radiotherapy versus standard intensity-modulated radiotherapy in patients with head and neck cancer (DARS): a phase 3, multicentre, randomised, controlled trial. The Lancet Oncology 2023; 24:868–80.
[8] Grégoire V, Evans M, Le QT, Bourhis J, Budach V, Chen A, et al. Delineation of the primary tumour Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO. TROG consensus guidelines Radiother Oncol 2018 Jan;126:3–24. https://doi.org/10.1016/j.radonc.2017.10.016.
[9] Budrukkar A, Guinot JL, Tagliaferri L, Bussu F, García-Consuegra A, Kovacs G. Function Preservation in Head and Neck Cancers. Clinical Oncology 2023; 35(8): 497-506, ISSN 0936-6555, doi: 10.1016/j.clon.2023.01.022.
[10] Priya SR, D'Cruz AK, Pai PS. Cut margins and disease control in oral cancers. *J Can Res Ther* 2012;8:74–9.
[11] Sunkara PR, Graff JT, Cramer JD. Association of Surgical Margin Distance With Survival in Patients With Resected Head and Neck Squamous Cell Carcinoma: A Secondary Analysis of a Randomized Clinical Trial. Journal of the American Medical Association Otolaryngol Head Neck Surg 2023 Apr 1;149:317–26. https://doi.org/10.1001/jamaoto.2022.5186.

[12] Bulbul MG, Tarabichi O, Sethi RK, Parikh AS, Varvares MA. Does Clearance of Positive Margins Improve Local Control in Oral Cavity Cancer? A Meta-analysis *Otolaryngol Head Neck Surg* 2019;161:235–44.

[13] Calabrese L, Tagliabue M, Grammatica A, Berardinis RD, Corso F, Gazzini L, et al. Compartmental tongue surgery for intermediate-advanced squamous cell carcinoma: A multicentric study. Head & Neck 2023;45:2862–73. https://doi.org/10.1002/hed.27517.

[14] Alterio D, Augugliaro M, Tagliabue M, Bruschini R, Gandini S, Calabrese L, et al. The T-N tract involvement as a new prognostic factor for PORT in locally advanced oral cavity tumors. Oral Diseases 2023;29:128–37. https://doi.org/10.1111/odi.13885.

[15] D'Cruz AK, Vaish R, Kapre N, Dandekar M, Gupta S, Hawaldar R, et al. for the Head and Neck Disease Management Group. Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer. N Engl J Med 2015;373:521–9. https://doi.org/10.1056/NEJMoa1506007.

[16] Hutchison IL, Ridout F, Cheung SMY, Shah N, Hardee P, Surwald C, et al. Nationwide randomised trial evaluating elective neck dissection for early stage oral cancer (SEND study) with meta-analysis and concurrent real-world cohort. British Journal of Cancer 2019;121:827–36. https://doi.org/10.1038/s41416-019-0587-2.

[17] van Lanschot CGF, Klazen YP, de Ridder MAJ, Mast H, Ten Hove I, Hardillo JA, et al. Depth of invasion in early stage oral cavity squamous cell carcinoma: The optimal cut-off value for elective neck dissection. Oral Oncol 2020;111:104940. https://doi.org/10.1016/j.oraloncology.2020.104940.

[18] Ebrahimi A, Clark JR, Amit M, Yen TC, Liao CT, Kowalski LP, et al. Minimum Nodal Yield in Oral Squamous Cell Carcinoma: Defining the Standard of Care in a Multicenter International Pooled Validation Study. *Ann Surg Oncol* 2014;21:3049–55.

[19] Farrokhian N, Holcomb AJ, Dimon E, Karadaghy O, Ward C, Whiteford E, et al. Assessing Prognostic Value of Quantitative Neck Dissection Quality Measures in Patients With Clinically Node-Negative Oral Cavity Squamous Cell Carcinoma. JAMA Otolaryngology. Head & Neck Surgery 2022;148:947–55. https://doi.org/10.1001/jamaoto.2022.2312.

[20] Zenga J, Divi V, Stadler M, Massey B, Campbell B, Shukla M, et al. Lymph node yield, depth of invasion, and survival in node-negative oral cavity cancer. Oral Oncology 2019;98:125–31. https://doi.org/10.1016/j.oraloncology.2019.09.028.

[21] Divi V, Harris J, Harari PM, Cooper JS, McHugh J, Bell D, et al. Establishing quality indicators for neck dissection: Correlating the number of lymph nodes with oncologic outcomes (NRG Oncology RTOG 9501 and RTOG 0234). Cancer 2016;122:3464–71. https://doi.org/10.1002/cncr.30204.

[22] Koyfman SA, Ismaila N, Crook D, D'Cruz A, Rodriguez CP, Sher DJ, et al. Management of the Neck in Squamous Cell Carcinoma of the Oral Cavity and Oropharynx: ASCO Clinical Practice Guideline. Journal of Clinical Oncology 2019;37:1753–74. https://doi.org/10.1200/JCO.18.01921.

[23] Khalil C, Khoury M, Higgins K, Enepekides D, Karam I, Husain ZA, et al. Lymph node yield: Impact on oncologic outcomes in oral cavity cancer. Head & Neck 2024;46:1965–74.

[24] Iocca O, Farcomeni A, De Virgilio A, Di Maio P, Golusinski P, Malvezzi L, et al. Prognostic significance of lymph node yield and lymph node ratio in patients affected by squamous cell carcinoma of the oral cavity and oropharynx: Study protocol for a prospective, multicenter, observational study. Contemporary Clinical Trials Communications 2019;14:100324. https://doi.org/10.1016/j.conctc.2019.100324.

[25] Schilling C, Stoeckli SJ, Haerle SK, Broglie MA, Huber GF, Sorensen JA, et al. Sentinel European Node Trial (SENT): 3-year results of sentinel node biopsy in oral cancer. European Journal of Cancer 2015;51:2777–84. https://doi.org/10.1016/j.ejca.2015.08.023.

[26] Garrel R, Poissonnet G, Moyà Plana A, Fakhry N, Dolivet G, Lallemant B, et al. Equivalence Randomized Trial to Compare Treatment on the Basis of Sentinel Node Biopsy Versus Neck Node Dissection in Operable T1-T2N0 Oral and Oropharyngeal Cancer. Journal of Clinical Oncology 2020;38:4010–8. https://doi.org/10.1200/JCO.20.01661.

[27] Hasegawa Y, Tsukahara K, Yoshimoto S, Miura K, Yokoyama J, Hirano S, et al. HNCMM Research Group. Neck Dissections Based on Sentinel Lymph Node Navigation Versus Elective Neck Dissections in Early Oral Cancers: A Randomized, Multicenter, and Noninferiority Trial. J Clin Oncol 2021;39:2025–36. https://doi.org/10.1200/JCO.20.03637.

[28] Gupta T, Maheshwari G, Kannan S, Nair S, Chaturvedi P, Agarwal JP. Systematic review and meta-analysis of randomized controlled trials comparing elective neck dissection versus sentinel lymph node biopsy in early-stage clinically node-negative oral and/or oropharyngeal squamous cell carcinoma: Evidence-base for practice and implications for research. Oral Oncology 2022;124:105642.

[29] Carsuzaa F, Lapeyre M, Gregoire V, Maingon P, Beddok A, Marcy PY, et al. Recommendations for postoperative radiotherapy in head & neck squamous cell carcinoma in the presence of flaps: A GORTEC internationally-reviewed HNCIG-endorsed consensus. Radiotherapy and Oncology 2021;160:140–7. https://doi.org/10.1016/j.radonc.2021.04.026.

[30] Bittermann G, Wiedenmann N, Voss P, Zimmerer R, Duttenhoefer F, Metzger MC. Marking of tumor resection borders for improved radiation planning facilitates reduction of radiation dose to free flap reconstruction in head and neck cancer surgery. J Craniomaxillofac Surg 2015;43:567–73. https://doi.org/10.1016/j.jcms.2015.02.021.

[31] Feldman M, Fletcher GH. Analysis of the parameters relating to failures above the clavicles in patients treated by postoperative irradiation for squamous cell carcinomas of the oral cavity or oropharynx. International Journal Radiat Oncol Biol Phys 1982;8:27–30.

[32] Huang D, Johnson CR, Schmidt-Ulrich R, Grimes M. Postoperative radiotherapy in head and neck carcinoma with extracapsular spread and/or positive resection margins: a comparative study. IJROBP 1992;23:737–42.

[33] Lydiatt WM, Patel SG, O'Sullivan B, Brandwein MS, Ridge JA, Migliacci JC, et al. Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67(2):122–37.

[34] Peters LJ, Goepfert H, Ang KK, Byers RM, Maor MH, Guillamondegui O, et al. Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. International Journal of Radiation Oncology, Biology, Physics 1993;26:3–11. https://doi.org/10.1016/0360-3016(93)90167-t.

[35] Hunter K., Da Forno P., Hall G., Jones A., Thomas G. Dataset for the histopathological reporting of cancers of the oral cavity -October 2023. https://www.rcpath.org/static/c4a9faf7-393a-4ba8-9532f719d8cdff3b/349be235-567f-407d-a63c21c8da2dadc8/Dataset-for-histopathology-reporting-of-carcinomas-of-the-oral-cavity.pdf.

[36] Protocols for the. examination of specimens from patients with carcinomas of the lip and oral cavity. College of American Pathologists. http://www.cap.org/web/home/protocols-and-guidelines.

[37] Bullock MJ. Current challenges in the staging of oral cancer. Head and Neck Pathology 2019;13:440–8. https://doi.org/10.1007/s12105-019-01014-4.

[38] de Juan J, García J, López M, Orus C, Esteller E, Quer M, et al. Inclusion of Extracapsular Spread in the pTNM Classification System. A Proposal for Patients With Head and Neck Carcinoma. JAMA. Otolaryngology and Head and Neck Surgery 2013;139:483–8. https://doi.org/10.1001/jamaoto.2013.2666.

[39] Mernod M, Tolstonog G, Simon C, Monnier Y. Extracapsular spread in head and neck squamous cell carcinoma: A systematic review and meta-analysis. Oral Oncology 2016;62.

[40] Ridge JA, Lydiatt WM, Patel SG, et al. Lip and oral cavity. In: Amin MB, editor. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.

[41] Best DL, Jazayeri HE, McHugh JB, Udager AM, Troost JP, Powell C, et al. Extent of Extranodal Extension in Oral Cavity Squamous Cell Carcinoma is Not Independently Associated With Overall or Disease-Free Survival at a 2.0-mm Threshold. J Oral Maxillofac Surg 2022;80:1978–88. https://doi.org/10.1016/j.joms.2022.08.019.

[42] Prabhu RS, Hanasoge S, Magliocca KR, Moeller BJ, Milas ZL, Hall WA, et al. Extent of pathologic extracapsular extension and outcomes in patients with nonoropharyngeal head and neck cancer treated with initial surgical resection. Cancer 2014;120:1499–506. https://doi.org/10.1002/cncr.28596.

[43] Wreesmann VB, Katabi N, Palmer FL, Montero PH, Migliacci JC, Gönen M, et al. Influence of extracapsular nodal spread extent on prognosis of oral squamous cell carcinoma. Head & Neck 2016;38 Suppl 1(Suppl 1):E1192–9. https://doi.org/10.1002/hed.24190.

[44] de Almeida JR, Truong T, Khan NM, Su JS, Irish J, Gilbert R, et al. Treatment implications of postoperative chemoradiotherapy for squamous cell carcinoma of the oral cavity with minor and major extranodal extension. Oral Oncol 2020;110:104845. https://doi.org/10.1016/j.oraloncology.2020.104845.

[45] Byers RM, Wolf PF, Ballantyne AJ. Rationale for elective modified neck dissection. *Head & Neck Surg* 1988;10:160–7. https://doi.org/10.1002/hed.2890100304.

[46] Spiro JD, Spiro RH, Shah JP, Sessions RB, Strong EW. Critical assessment of supraomohyoid neck dissection. *American Journal of Surgery* 1988;156:286–9. https://doi.org/10.1016/s0002-9610(88)80293-9.

[47] Contreras JA, Spencer C, DeWees T, Haughey B, Henke LE, Chin R-I, et al. Eliminating postoperative radiation to the pathologically node-negative neck: long-term results of a prospective phase II study. Journal of Clinical Oncology 2019;37:2548–55.

[48] Lang P, Contreras J, Kalman N, Paterson C, Bahig H, Billfalk-Kelly A, et al. Preservation of swallowing in resected oral cavity squamous cell carcinoma: examining radiation volume effects (PRESERVE): study protocol for a randomized phase II trial. Radiation Oncology 2020;15:196. https://doi.org/10.1186/s13014-020-01636-x.

[49] Arun I, Maity N, Hameed S, Jain PV, Manikantan K, Sharan R, et al. Lymph node characteristics and their prognostic significance in oral squamous cell carcinoma. Head & Neck 2021;43:520–33. https://doi.org/10.1002/hed.26499.

[50] Ghadjar P, Schreiber-Facklam H, Gräter R, Evers C, Simcock M, Geretschläger A, et al. Quantitative analysis of extracapsular extension of metastatic lymph nodes and its significance in radiotherapy planning in head and neck squamous cell carcinoma. International Journal Radiat Oncol Biol Phys 2010;76:1127–32. https://doi.org/10.1016/j.ijrobp.2009.03.065.

[51] Arun P, Arun I, Jain P, Manikantan K, Sharan R. Determinants of prognosis in patients with oral squamous cell carcinoma metastasizing to a single cervical lymph node. Oral Oncol 2021;123:105586. https://doi.org/10.1016/j.oraloncology.2021.105586.

[52] Suresh K, Cramer JD. Postoperative radiation therapy vs observation for pN1 oral cavity squamous cell carcinoma. Head & Neck 2019;41:4136–42. https://doi.org/10.1002/hed.25958.

[53] Cooper JS, Pajak TF, Forastiere A, Jacobs J, Fu KK, Ang KK, et al. Precisely defining high-risk operable head and neck tumors based on RTOG #85-03 and #88-24: targets for postoperative radiochemotherapy? Head & Neck 1998;20:588–94. https://doi.org/10.1002/(sici)1097-0347(199810)20:7<588::aid-hed2>3.0.co;2-f.

[54] Ho AS, Kim S, Tighiouart M, Gudino C, Mita A, Scher KS, et al. Metastatic Lymph Node Burden and Survival in Oral Cavity Cancer. J Clin Oncol 2017;35:3601–9. https://doi.org/10.1200/JCO.2016.71.1176.

[55] Zumsteg ZS, Luu M, Kim S, Tighiouart M, Mita A, Scher KS, et al. Quantitative lymph node burden as a 'very-high-risk' factor identifying head and neck cancer patients benefiting from postoperative chemoradiation. Annals of Oncology 2019 Jan 1;30:76–84. https://doi.org/10.1093/annonc/mdy490.

[56] Patel SG, Amit M, Yen TC, Liao CT, Chaturvedi P, Agarwal JP, et al. International Consortium for Outcome Research (ICOR) in Head and Neck Cancer. Lymph node density in oral cavity cancer: results of the International Consortium for Outcomes Research. British Journal of Cancer 2013;109:2087–95. https://doi.org/10.1038/bjc.2013.570.

[57] Marchiano E, Patel TD, Eloy JA, Baredes S, Park RC. Impact of Nodal Level Distribution on Survival in Oral Cavity Squamous Cell Carcinoma: A Population-Based Study. Otolaryngology and Head and Neck Surgery 2016;155:99–105. https://doi.org/10.1177/0194599816636356.

[58] Giresh A, Parida PK, Chappity P, Adhya AK, Nayak A, Pradhan P, et al. Prevalence of Skip Metastases to Cervical Lymph-Nodes in Oral cavity Cancer in Eastern India-an observational study. Indian J Otolaryngol Head Neck Surg 2022;74: 6374–83. https://doi.org/10.1007/s12070-021-03048-z.

[59] Shah JP, Candela FC, Poddar AK. The patterns of cervical lymph node metastases from squamous carcinoma of the oral cavity. Cancer 1990;66:109–13. https://doi.org/10.1002/1097-0142(19900701)66:1<109::aid-cncr2820660120>3.0.co;2-a.

[60] Lea J, Bachar G, Sawka AM, Lakra DC, Gilbert RW, Irish JC, et al. Metastases to level IIb in squamous cell carcinoma of the oral cavity: a systematic review and meta-analysis. Head & Neck 2010;32:184–90. https://doi.org/10.1002/hed.21163.

[61] Byers RM, Weber RS, Andrews T, McGill D, Kare R, Wolf P. Frequency and therapeutic implications of 'skip metastases' in the neck from squamous carcinoma of the oral tongue. *Head & Neck* 1997;19:14–9. https://doi.org/10.1002/(sici)1097-0347(199701)19:1<14::aid-hed3>3.0.co;2-.

[62] Warshavsky A, Rosen R, Nard-Carmel N, Abu-Ghanem S, Oestreicher-Kedem Y, Abergel A, et al. Assessment of the Rate of Skip Metastasis to Neck Level IV in Patients With Clinically Node-Negative Neck Oral Cavity Squamous Cell Carcinoma: A Systematic Review and Meta-analysis. Journal of the American Medical Association Otolaryngol Head Neck Surg 2019;145:542–8. https://doi.org/10.1001/jamaoto.2019.

[63] Kuroshima T, Onozato Y, Oikawa Y, Ohsako T, Kugimoto T, Hirai H, et al. Prognostic impact of lingual lymph node metastasis in patients with squamous cell carcinoma of the tongue: a retrospective study. *Sci Rep* 2021;11:20535. https://doi.org/10.1038/s41598-021-99925-2.

[64] Kikuchi M, Harada H, Asato R, Hamaguchi K, Tamaki H, Mizuta M, et al. Lingual lymph node metastases as a prognostic factor in oral squamous cell carcinoma-a retrospective multicenter study. *Medicina (Kaunas)* 2021;57:374. https://doi.org/10.3390/medicina57040374.

[65] Gvetadze SR, Mudunov AM, Roshchina EA, Solodkiy VA, Nudnov NV, Chkhikvadze VD, et al. Surgical anatomy of the lingual lymph nodes: systematic literature analysis and proposition for topographic classification. Surgical and Radiologic Anatomy 2023;45:227–39. https://doi.org/10.1007/s00276-023-03078-y.

[66] Wittekind C., Compton C.C., Greene F. L., Sobin L. H. TNM residual tumour classification revisited. Cancer 2002; 94 (9): 2511-2516. TNM residual tumor classification revisited - Wittekind - 2002 - Cancer - Wiley Online Library).

[67] Chen TY, Emrich LJ, Driscoll DL. The clinical significance of pathological findings in surgically resected margins of the primary tumor in head and neck carcinoma. International Journal Radiat Oncol Biol Phys 1987;13:833–7.

[68] Harley RJ, Iheagwara UK, Faraji F, Sridharan S, Kubik MW. Postoperative Radiotherapy and Survival in Oral Cavity Squamous Cell Carcinoma With Mandibulectomy. Journal of the American Medical Association Otolaryngol Head Neck Surg 2024;150:233–9. https://doi.org/10.1001/jamaoto.2023.4444.

[69] Shrime MG, Gullane PJ, Dawson L, Kim J, Gilbert RW, Irish JC, et al. The impact of adjuvant radiotherapy on survival in T1-2N1 squamous cell carcinoma of the oral cavity. Arch Otolaryngol Head Neck Surg 2010;136:225–8. https://doi.org/10.1001/archoto.2010.22.

[70] Torrecillas V, Shepherd HM, Francis S, Buchmann LO, Monroe MM, Lloyd S, et al. Adjuvant radiation for T1-2N1 oral cavity cancer survival outcomes and utilization treatment trends: Analysis of the SEER database. Oral Oncol 2018;85: 1–7. https://doi.org/10.1016/j.oraloncology.2018.07.019.

[71] Kämmerer PW, Tribius S, Cohrs L, Engler G, Ettl T, Freier K, et al. Adjuvant Radiotherapy in Patients with Squamous Cell Carcinoma of the Oral Cavity or Oropharynx and Solitary Ipsilateral Lymph Node Metastasis (pN1)-A Prospective Multicentric Cohort Study. Cancers 2023;15:1833. https://doi.org/10.3390/cancers15061833.

[72] Matos LL, Dedivitis RA, Kulcsar MAV, de Mello ES, Alves VAF, Cernea CR. External validation of the AJCC Cancer Staging Manual 8th edition in an independent cohort of oral cancer patients. Oral Oncol 2017;71:47–53.

[73] Sultania M, Chaudhary I, Jain P, Ghalige H, Rajan D, Sudkhar G, et al. Margin to Depth of Invasion Ratio: A Significant Predictor of Survival in Patients With Oral Cancer. JCO Glob Oncol 2023;9:e2300144. https://doi.org/10.1200/GO.23.00144.

[74] Ebrahimi A, Gil Z, Amit M, Yen TC, Liao CT, Chaturvedi P, et al. International Consortium for Outcome Research (ICOR) in Head and Neck Cancer. Depth of invasion alone as an indication for postoperative radiotherapy in small oral squamous cell carcinomas: An International Collaborative Study. Head & Neck 2019;41:1935–42. https://doi.org/10.1002/hed.25633.

[75] Carter RL, Tanner NSB, Clifford P, Shaw HJ. Perineural spread in squamous cell carcinomas of the head and neck a clinicopathological study. Clinical Otolaryngology 1979;4:271–81.

[76] Nair D, Mair M, Singhvi H, Mishra A, Nair S, Agrawal J, et al. Perineural invasion: Independent prognostic factor in oral cancer that warrants adjuvant treatment. Head & Neck 2018;40:1780–7. https://doi.org/10.1002/hed.25170.

[77] Langendijk JA, Slotman BJ, van der Waal I, Doornaert P, Berkof J, Leemans CR. Risk-group definition by recursive partitioning analysis of patients with squamous cell head and neck carcinoma treated with surgery and postoperative radiotherapy. Cancer 2005;104:1408–17.

[78] Huang S, Zhu Y, Cai H, Zhang Y, Hou J. Impact of lymphovascular invasion in oral squamous cell carcinoma: A meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:319–328.e1. https://doi.org/10.1016/j.oooo.2020.10.026.

[79] Köhler HF, Vartanian JG, Pinto CAL, da Silva Rodrigues IFP, Kowalski LP. The impact of worst pattern of invasion on the extension of surgical margins in oral squamous cell carcinoma. Head & Neck 2022;44:691–7. https://doi.org/10.1002/hed.26956.

[80] Singh M, Thankappan K, Balasubramanian D, Pillai V, Shetty V, Rangappa V, et al. Head and Neck Cooperative Oncology Group. Incorporation of adverse features in advanced oral cancer improves precision in staging and patient prognostication. Head & Neck 2022;44:964–74. https://doi.org/10.1002/hed.26990.

[81] Tian Q, Jiang L, Dai D, Liu L, Shi X, Guo Y, et al. Impact of Postoperative Radiotherapy on the Prognosis of Early-Stage (pT1-2N0M0) Oral Tongue Squamous Cell Carcinoma. Journal Clinical Oncology 2024;42:1754–65.

[82] Merlotti A, Alterio D, Orlandi E, Racadot S, Bonomo P, Franco P, et al. AIRO GORTEC consensus on postoperative radiotherapy (PORT) in low-intermediate risk early stages oral squamous cell cancers (OSCC). Radiotherapy and Oncology 2022;177:95–104. https://doi.org/10.1016/j.radonc.2022.10.035.

[83] Ward MJ, Thirdborough SM, Mellows T, Riley C, Harris S, Suchak K, et al. Tumour-infiltrating lymphocytes predict for outcome in HPV-positive oropharyngeal cancer. British Journal of Cancer 2014 21;110(2):489–500.. https://doi.org/10.1038/bjc.2013.639.

[84] Chung CH, Zhang Q, Kong CS, Harris J, Fertig EJ, Harari PM, et al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. Journal of Clinical Oncology 2014;32:3930–8. https://doi.org/10.1200/JCO.2013.54.5228.

[85] Zafereo ME, Xua L, Dahlstrom KR. Squamous cell carcinoma of the oral cavity often overexpresses p16 but is rarely driven by human papillomavirus. Oral Oncology 2016;56:47–53.

[86] Mohan S, Pai SI, Bhattacharyya N. Adjuvant radiotherapy is not supported in patients with verrucous carcinoma of the oral cavity. The Laryngoscope 2017; 127:1334–8. https://doi.org/10.1002/lary.26443.

[87] Ang KK, Trotti A, Brown BW, Garden AS, Foote RL, Morrison WH, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. International Journal of Radiation Oncology, Biology, Physics 2001;51:571–8. https://doi.org/10.1016/s0360-3016(01)01690-x.

[88] Rosenthal DI, Mohamed ASR, Garden AS, Morrison WH, El-Naggar AK, Kamal M, et al. Final Report of a Prospective Randomized Trial to Evaluate the Dose-Response Relationship for Postoperative Radiation Therapy and Pathologic Risk Groups in Patients With Head and Neck Cancer. International Journal Radiat Oncol Biol Phys 2017;98:1002–11. https://doi.org/10.1016/j.ijrobp.2017.02.218.

[89] Mishra RC, Singh DN, Mishra TK. Post-operative radiotherapy in carcinoma of buccal mucosa, a prospective randomized trial. European Journal of Surgical Oncology 1996;22:502–4.

[90] Takahashi H, Yanamoto S, Yamada S, Umeda M, Shigeta T, Minamikawa T, et al. Effects of postoperative chemotherapy and radiotherapy on patients with squamous cell carcinoma of the oral cavity and multiple regional lymph node metastases. International Journal of Oral and Maxillofacial Surgery 2014; 43(6): 680-685, ISSN 0901-5027, doi: 10.1016/j.ijom.2013.11.013.

[91] Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Radiation Therapy Oncology Group 9501/Intergroup. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937–44. https://doi.org/10.1056/NEJMoa032646.

[92] Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH, et al. European Organization for Research and Treatment of Cancer Trial 22931. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945–52. https://doi.org/10.1056/NEJMoa032641.

[93] Cooper JS, Zhang Q, Pajak TF, Forastiere AA, Jacobs J, Saxman SB, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. International Journal Radiat Oncol Biol Phys 2012;84:1198–205. https://doi.org/10.1016/j.ijrobp.2012.05.008.

[94] Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bouhris J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: A comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). Head & Neck 2005;27:843–50. https://doi.org/10.1002/hed.20279.

[95] Dauzier E, Lacas B, Blanchard P, Le QT, Simon C, Wolf G, et al. MACH-NC Collaborative Group. Role of chemotherapy in 5000 patients with head and neck cancer treated by curative surgery: A subgroup analysis of the meta-analysis of

chemotherapy in head and neck cancer. Oral Oncol 2019;95:106–14. https://doi.org/10.1016/j.oraloncology.2019.06.001.
[96] Lacas B, Carmel A, Landais C, Wong SJ, Licitra L, Tobias JS, et al. MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC Group. Radiotherapy and Oncology 2021;156:281–93. https://doi.org/10.1016/j.radonc.2021.01.013.
[97] Laskar SG, Chaukar D, Deshpande M, Chatterjee A, Sinha S, Chakraborty S, et al. Oral cavity adjuvant therapy (OCAT) -a phase III, randomized controlled trial of surgery followed by conventional RT (5 fr/wk) versus concurrent CT-RT versus accelerated RT (6fr/wk) in locally advanced, resectable, squamous cell carcinoma of oral cavity. European Journal of Cancer 2023;181:179–87. https://doi.org/10.1016/j.ejca.2022.12.016.
[98] Machtay M, Torres-Saavedra P, Thorstad WL, Nguyen-Tan PF, Siu LL, Holsinger FC, et al. Randomized Phase III Trial of Postoperative Radiotherapy with or without Cetuximab for Intermediate-Risk Squamous Cell Carcinoma of the Head and Neck (SCCHN): NRG/RTOG 0920. International Journal of Radiation Oncology Biology Physics 2023; 117(4):e1, ISSN 0360-3016, doi: 10.1016/j.ijrobp.2023.08.025.
[99] Noronha V, Joshi A, Patil VM, Agarwal J, Ghosh-Laskar S, Budrukkar A, et al. Once-a-Week Versus Once-Every-3-Weeks Cisplatin Chemoradiation for Locally Advanced Head and Neck Cancer: A Phase III Randomized Noninferiority Trial. J Clin Oncol 2018 Apr 10;36:1064–72. https://doi.org/10.1200/JCO.2017.74.9457.
[100] Kiyota N, Tahara M, Mizusawa J, Kodaira T, Fujii H, Yamazaki T, et al. Head and Neck Cancer Study Group of the Japan Clinical Oncology Group (JCOG-HNCSG). Weekly Cisplatin Plus Radiation for Postoperative Head and Neck Cancer (JCOG1008): A Multicenter, Noninferiority, Phase II/III Randomized Controlled Trial. J Clin Oncol 2022;40:1980–90. https://doi.org/10.1200/JCO.21.01293.
[101] Tahara M, Kiyota N, Fujii H, Asada Y, Mitani H, Hirayama Y, et al. 851MO ESMO 2024 - Final analysis of a phase II/III trial of post-operative chemoradiotherapy comparing 3-weekly cisplatin with weekly cisplatin in high-risk patients with squamous cell carcinoma of the head and neck (JCOG1008). Annals of Oncology 2024;35:S613–55. https://doi.org/10.1016/annonc/annonc1594.
[102] Szturz P, Wouters K, Kiyota N, Tahara M, Prabhash K, Noronha V, et al. Low-Dose vs. High-Dose Cisplatin: Lessons Learned From 59 Chemoradiotherapy Trials in Head and Neck Cancer. Front. Oncol 2019;9:86. https://doi.org/10.3389/fonc.2019.00086.
[103] Capote-Moreno A, Naval L, Muñoz-Guerra MF, Sastre J, Rodríguez-Campo FJ. Prognostic factors influencing contralateral neck lymph node metastases in oral and oropharyngeal carcinoma. J Oral Maxillofac Surg 2010;68:268–75. https://doi.org/10.1016/j.joms.2009.09.071.
[104] Vidya K, Riju J, Rajinikanth J, Tirkey AJ, Kothandan P. Contralateral Nodal Metastasis from Tongue Malignancy. Indian J Otolaryngol Head Neck Surg 2022;74:1949–54. https://doi.org/10.1007/s12070-020-01921-x.
[105] Kao YS, Hsu Y. Adjuvant contralateral neck irradiation for oral cavity cancer - A systematic review and meta-analysis. Am J Otolaryngol 2021;42:102885. https://doi.org/10.1016/j.amjoto.2020.102885.
[106] Metcalfe E, Aspin L, Speight R, Ermiş E, Ramasamy S, Cardale K, et al. Postoperative (Chemo)Radiotherapy for Oral Cavity Squamous Cell Carcinomas: Outcomes and Patterns of Failure. Clinical Oncology (Royal College of Radiologists) 2017;29:51–9. https://doi.org/10.1016/j.clon.2016.09.008.
[107] Waldram R, Taylor AE, Whittam S, Iyizoba-Ebozue Z, Murray L, Frood R, et al. Evaluation of Locoregional Recurrence Patterns Following Adjuvant (Chemo) Radiotherapy for Oral Cavity Carcinoma. Clin Oncol R Coll Radiol 2020;32:228–37. https://doi.org/10.1016/j.clon.2019.10.002.
[108] Razavian NB, Shenker RF, D'Agostino Jr RB, Hughes RT. Association of ipsilateral radiation therapy with contralateral lymph node failure in patients with squamous cell carcinoma of the oral cavity: A systematic review and meta-analysis. Head & Neck 2023;45:1967–74. https://doi.org/10.1002/hed.27421.
[109] Vergeer MR, Doornaert PA, Jonkman A, Kaanders JH, van den Ende PL, de Jong MA, et al. Ipsilateral irradiation for oral and oropharyngeal carcinoma treated with primary surgery and postoperative radiotherapy. International Journal Radiat Oncol Biol Phys 2010;78:682–8. https://doi.org/10.1016/j.ijrobp.2009.08.042.
[110] Cheng YJ, Lin HY, Tsai MH, Pao TH, Hsu CH, Wu YH. Contralateral Neck Irradiation Can Be Omitted for Selected Lateralized Oral Cancer in Locally Advanced Stage. Current Oncology 2022;29:6956–67. https://doi.org/10.3390/curroncol29100547.
[111] Swain M, Budrukkar A, Murthy V, Pai P, Kanoja A, Ghosh-Laskar S, et al. Contralateral Nodal Relapse in Well-lateralised Oral Cavity Cancers Treated Uniformly with Ipsilateral Surgery and Adjuvant Radiotherapy With or Without Concurrent Chemotherapy: a Retrospective Study. Clin Oncol (R Coll Radiol) 2024;36:278–86. https://doi.org/10.1016/j.clon.2024.02.003.
[112] Rosenthal DI, Liu L, Lee JH, Vapiwala N, Chalian AA, Weinstein GS, et al. Importance of the treatment package time in surgery and postoperative radiation therapy for squamous carcinoma of the head and neck. Head & Neck 2002 Feb;24:115–26. https://doi.org/10.1002/hed.10038.
[113] Tribius S, Donner J, Pazdyka H, Münscher A, Gröbe A, Petersen C, et al. Survival and overall treatment time after postoperative radio(chemo)therapy in patients with head and neck cancer. Head & Neck 2016;38:1058–65. https://doi.org/10.1002/hed.24407.
[114] Harris JP, Chen MM, Orosco RK, Sirjani D, Divi V, Hara W. Association of Survival With Shorter Time to Radiation Therapy After Surgery for US Patients With Head and Neck Cancer. Journal of the American Medical Association Otolaryngol Head Neck Surg 2018;144:349–59. https://doi.org/10.1001/jamaoto.2017.3406.
[115] Fletcher GH. Elective irradiation of subclinical disease in cancers of the head and neck. Cancer 1972;29:1450–4. https://doi.org/10.1002/1097-0142(197206)29:6.
[116] Voizard B, Khoury M, Saydy N, Nelson K, Cardin GB, Létourneau-Guillon L, et al. Preoperative evaluation of depth of invasion in oral tongue squamous cell carcinoma: A systematic review and meta-analysis. Oral Oncol 2023;136:106273. https://doi.org/10.1016/j.oraloncology.2022.106273.
[117] Mahajan A, Dhone N, Vaish R, Singhania A, Malik A, Prabhash K, et al. Prognostic Impact of Pattern of Mandibular Involvement in Gingivo-Buccal Complex Squamous Cell Carcinomas: Marrow and Mandibular Canal Staging System. Front Oncol 2022;11:752018. https://doi.org/10.3389/fonc.2021.752018.
[118] Robbins KT, Clayman G, Levine PA, Medina J, Sessions R, Shaha A, et al. American Head and Neck Society; American Academy of Otolaryngology-Head and Neck Surgery. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. Arch Otolaryngol Head Neck Surg 2002;128:751–8. https://doi.org/10.1001/archotol.128.7.751.
[119] Hosni A, Huang SH, Chiu K, Xu W, Su J, Bayley A, et al. Predictors of Early Recurrence Prior to Planned Postoperative Radiation Therapy for Oral Cavity Squamous Cell Carcinoma and Outcomes Following Salvage Intensified Radiation Therapy. International Journal Radiat Oncol Biol Phys 2019;103:363–73. https://doi.org/10.1016/j.ijrobp.2018.09.013.