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Original Article

Evaluation of Locoregional Recurrence Patterns Following Adjuvant (Chemo)Radiotherapy for Oral Cavity Carcinoma

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Abstract

Aims: To evaluate patterns of locoregional recurrence following adjuvant (chemo)radiotherapy for oral cavity squamous cell carcinomas.
Materials and methods: One hundred and one patients who received adjuvant radiotherapy ± chemotherapy for oral cavity squamous cell carcinoma between 2013 and 2016 were analysed. For documented locoregional recurrence, recurrence imaging was deformably co-registered to the planning computed tomography scan. The volume of recurrence was delineated (Vrec). Vrec coverage by 95% of the corresponding planning target volume prescription dose was determined and the location compared with planning target volumes. Sites of recurrence were classified using a combined volume and centroid-based method: (A) central high dose, (B) peripheral high dose, (C) central low dose, (D) central peripheral dose, (E) extraneous.
Results: The median follow-up was 36 months. Forty-three per cent and 53% of patients received radiotherapy to the ipsilateral neck only and bilateral neck, respectively. Three-year overall survival, disease-free survival, local control, regional control and distant metastases-free survival were 63.0, 65.6, 88.0, 85.1 and 85.3%, respectively. Of 10 episodes of primary site recurrences, five were type A, four type B and one was type E. Of 14 episodes of regional recurrence, five were type A, two type C, two type D and five type E. Five of 21 (24%) patients with oral tongue carcinoma with an undissected/unirradiated contralateral neck had a type E contralateral neck recurrence, including 2/11 with pN0, 1/4 with pN1 and 2/6 with pN2 disease.
Conclusions: Marginal and out-of-field recurrences remain a significant pattern of failure. We advocate generous target delineation postoperatively and, for oral tongue carcinomas, a comprehensive approach with bilateral neck irradiation.

Key words: Deformable co-registration; oral cavity carcinoma; radiotherapy; recurrence

Introduction

Postoperative (chemo)radiotherapy is commonly delivered following curative-intent surgery for oral cavity squamous cell carcinoma. By contrast with definitive radiotherapy, postoperative target volumes are not standardised [1]. There are no comprehensive internationally agreed guidelines for postoperative target volume selection and delineation [2]. In selecting target volumes, clinicians attempt to balance the risks of marginal or out-of-field recurrence and increased toxicity incumbent with increased target volumes. Target volumes can include comprehensive treatment of the primary site and bilateral neck [3–5]. However, if the indication for radiotherapy is only related to pathological features of the primary site, some clinicians would prefer not to treat nodal volumes [6]. Recent expert panel nodal contouring guidelines recommend that unilateral radiotherapy can only be considered for lateral oral tongue carcinomas (N0/1) that do not come within 1 cm of the midline [7]. Decisions on whether the contralateral neck is at sufficient risk of recurrence to justify the additional toxicity of contralateral neck irradiation can

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be a challenging decision based upon the subsite within the oral cavity and pathological risk features, with variability in practice [1,2].

Delivery of radiotherapy with intensity-modulated radiotherapy (IMRT) now represents the standard of care. IMRT provides steep dose gradients that are beneficial in sparing normal tissues adjacent to target volumes [8]. However, a risk of steep dose gradients is marginal treatment failures due to inadequate delineation of target volumes.

Analysis of recurrence patterns is essential to evaluate the quality of target volume selection and target volume contouring. However, only a limited number of series of reasonable size have described locoregional recurrence patterns following adjuvant (chemo)-IMRT for oral cavity squamous cell cancer [3,4,9]. Recurrence analysis has commonly been based upon volumetric analysis of the recurrence in relation to the 95% plan isodose [10,11]. However, this type of analysis is limited by the potential for a recurrence to develop in-field but then grow out-of-field, leading to misclassification as a marginal recurrence. In order to address this limitation, a classification of recurrence patterns using a combined spatial and volumetric dosimetric analysis using deformable image co-registration has recently been developed [3,12].

The aim of this series was to evaluate patterns of locoregional recurrence in patients receiving adjuvant (chemo)radiotherapy for oral cavity carcinoma using this novel method of recurrence classification.

Materials and Methods

Study Population

This was a retrospective single-centre study. One hundred and one patients with newly diagnosed squamous cell carcinoma of the oral cavity who underwent surgery and adjuvant radiotherapy with curative intent between January 2013 and December 2016 were identified from electronic radiotherapy records. Patients with a history of a prior head and neck cancer, macroscopic disease postoperatively or recurrence pre-radiotherapy were excluded.

Management

Surgery

Patients underwent resection with curative inten t ± unilateral or bilateral neck dissections according to the input from the multidisciplinary team meetings before surgery and assessment of the treating surgeon.

Adjuvant Radiotherapy

Patients were treated supine with a five-point thermoplastic mask. Planning computed tomography (CT) scans were acquired with intravenous CT contrast and a 2 mm CT slice. Mouth bites were used at the discretion of the treating radiation oncologist. Preoperative imaging, surgical and pathological findings were used to guide target volume delineation. Treatment of the primary site, ipsilateral neck and contralateral neck were made by the treating clinician based upon patient and tumour factors, including co-morbidity, disease subsite and laterality, imaging, surgical and pathological findings. A primary tumour clinical target volume (CTV) was created to include the tumour bed and adjacent surgical changes, modified to anatomical boundaries to exclude air and/or bone without evidence of invasion. Lymph node CTVs were outlined following postoperative guidelines [13]. The planning target volume (PTV) was created by auto-expansion of the CTV isotropically by 4 mm. For patients treated from June 2015 onwards, target volume delineation was reviewed before treatment in dedicated head and neck peer review quality assurance meetings [14].

Standard doses were 60 Gy in 30 fractions over 6 weeks to the surgical bed and dissected nodal areas. For patients with high-risk features (very close margins, e.g. <1 mm or extracapsular lymph node spread or soft tissue deposits) an increased dose of 66 Gy in 33 fractions was typically delivered to the preoperative region of disease (primary site or nodal involvement). Low-risk nodal regions (undissected areas and sometimes dissected nodal regions deemed to be lower risk based upon the judgement of the treating clinician) were treated to a dose of 54 Gy in 30 fractions (or 56 Gy in 33 fractions if the treatment was delivered in 33 fractions).

Treatment was planned using the Monaco planning system and was delivered in the initial part of this era with a five to seven angle step and shoot IMRT technique, and later using volumetric modulated arc therapy.

Concurrent Chemotherapy

Patients <70 years old were considered for concurrent chemotherapy in the presence of high-risk pathological features (very close margins, e.g. <1 mm or extracapsular lymph node spread or soft tissue deposits). Standard concurrent chemotherapy was cisplatin 100 mg/m^2 on days 1 and 29. Carboplatin AUC 4 was substituted for cisplatin if creatinine clearance was <55 ml/min.

Locoregional Recurrence Analysis

A locoregional recurrence analysis was carried out for patients with radiological evidence of recurrence that was confirmed by either pathology or subsequent clinical progression. The original planning CTs were restored. The cross-sectional imaging (CT, magnetic resonance imaging or positron emission tomography-CT) acquired at the time of relapse was co-registered on to the planning CT study using Mirada RTx software (Mirada Medical, Oxford, UK). An initial manual rigid co-registration was carried out using bony landmarks for alignment followed by deformable co-registration using the planning CT as the reference image. The volume of recurrence (Vrec) was contoured on to the co-registered recurrence imaging using information documented from the clinical exami-

nation at the time of recurrence and radiological imaging acquired at the time of relapse. A 4 mm diameter centroid, presumed to be the origin of the recurrence, was generated based on a 2 mm margin around the calculated central voxel of Vrec [3,12].

Patterns of Failure Classification

Mapped Vrec were compared with the initial PTVs and dose using spatial and dosimetric criteria [3,12]. Recurrences were analysed in relation to either the primary tumour (primary recurrences) or lymph node risk levels (regional recurrences) depending upon anatomical location. The relevant PTV for analysis for each recurrence was determined by comparison of the anatomical site of the recurrence with the original PTVs. Dose volume histograms were obtained for the Vrec and coverage of Vrec by 95% of the corresponding PTV prescription dose was documented. The mean dose and location of the centroid was compared with PTVs. Recurrences were classified into five types based upon the recent methodology from the MD Anderson Cancer Centre using combined spatial and dosimetric criteria [3,12]:

(A) Central, high dose: mapped centroid of Vrec originating in the high-dose PTV and >95% of Vrec receiving >95% of the prescribed dose to the high-dose PTV;
(B) Peripheral, high dose: mapped centroid of Vrec originating in the high-dose PTV and <95% of Vrec receiving >95% of the prescribed dose to the high-dose PTV;
(C) Central, elective dose: mapped centroid of Vrec originating in the elective dose PTV and >95% of Vrec receiving >95% of the prescribed dose to the elective dose PTV;
(D) Peripheral, elective dose: mapped centroid of Vrec originating in the elective dose PTV and <95% of Vrec receiving >95% of the prescribed dose to the high-dose PTV;
(E) Extraneous dose: mapped centroid of Vrec originating outside all PTVs.

Cases with multifocal recurrence, e.g. at the primary site and lymph node or bilateral lymph nodes, were analysed with separate recurrence classifications as they could each represent independent recurrence sites.

Statistical Analysis

The analysis was carried out using IBM SPSS Statistics, Version 24 (Armonk, NY: IBM Corp.). The time to event end points were calculated from the final day of radiotherapy. Patients with no event were censored at the date of last follow-up visit. The outcome measures were overall survival, disease-free survival, local control, regional control and distant metastases-free survival and were calculated using the Kaplan–Meier method.

Results

Patient, Disease and Treatment Characteristics

In total, 101 patients were identified who received adjuvant IMRT for oral cavity squamous cell carcinoma between 2013 and 2016 and fulfilled the inclusion criteria. The median follow-up was 28 months (range 2–54). The median age was 63 years (range 20–82). Patient, disease and treatment characteristics are summarised in Table 1. The oral tongue was the most common oral cavity subsite (51%). The median time from surgery to the start of radiotherapy was 51 days (35–95). One hundred of the 101 patients received radiotherapy to the primary site; 43% and 53% of patients received radiotherapy to the ipsilateral neck only and to the bilateral neck, respectively. Table 2 provides details of ipsilateral and contralateral lymph node level irradiation. With regards to patients with carcinoma of the oral tongue ($n = 52$), all patients received radiotherapy to the primary site, 21 received ipsilateral neck radiotherapy and 31 received bilateral neck radiotherapy.

Outcomes

Three-year overall survival, disease-free survival, local control, regional control and distant metastases-free survival were 63.0, 65.6, 88.0, 85.1 and 85.3%, respectively. Figure 1 provides Kaplan–Meier curves for local and regional disease-free survival. In total, 10/101 (10%) patients experienced treatment failure at the primary site, 13/101 (13%) regional treatment failure; this included one patient with combined treatment failure at the primary site and regional lymph nodes. The median time from the completion of radiotherapy to recurrence was 6 months (range 0–28 months). Thirteen of 101 (13%) patients developed distant metastases; this included five patients who also had local or regional recurrence.

Of the 22 patients with local and/or regionally recurrent disease, 21 (95%) died with active disease.

Out of the 10 patients with local recurrence, eight had locally recurrent disease only, one had combined locoregional recurrence and one had synchronous distant metastases. One of these patients with an oral tongue cancer recurrence underwent salvage surgical resection and remains disease free. Of the 13 patients with regional recurrence, 10 had regionally recurrent disease only, one had combined locoregional recurrence and two had distant metastases. Five of these 10 patients underwent a salvage neck dissection and two of these patients also received post-neck dissection radiotherapy. Of the five patients undergoing a neck dissection, three recurred in the neck and the remaining two developed distant metastases. Overall, six patients received palliative chemotherapy.

Analysis of Cases of Locoregional Failure

Table 3 provides the details of the 22 cases with locoregional recurrence and an analysis of recurrence pattern by

combined spatial and dosimetric criteria. The recurrence diagnostic imaging deformably co-registered to the planning CT scan was magnetic resonance imaging for 12, CT for six and positron emission tomography-CT for four patients. For two patients, two separate recurrence classifications were made (one patient with bilateral neck recurrence after ipsilateral neck irradiation, one patient with in-field recurrence at the primary site with out-of-field contralateral neck recurrence); therefore, there were 24 recurrence classifications in total. Ten of 24 (42%) were classified as type A (central, high dose), 4/24 (17%) as type B (peripheral, high dose), 2/24 (8%) as type C (central, elective dose), 2/24 (8%) as type D (peripheral, elective dose) and 6/24 (25%) as type E (extraneous).

Local Recurrences

Of 10 patients with local primary site recurrences, five were type A (central, high dose), four type B (peripheral, high dose) and one was type E (extraneous). Figure 2 provides an example of a patient with a pT2pN2b tongue carcinoma and a type B (peripheral high dose, primary) recurrence posterior to the flap reconstruction. Figure 3 illustrates the one case of a type E (extraneous) recurrence related to the primary site in a patient with a pT4aN0 squamous cell carcinoma of the left mandible resected with a fibula reconstruction and recurrence with a 5 cm soft tissue mass surrounding and infiltrating the native right mandibular alveolus extending to the interface with the bone reconstruction.

Regional Recurrences

Regional recurrences occurred in 13 patients and 14 recurrence classifications were made to allow the description of a patient with bilateral neck recurrence following unilateral radiotherapy. Five recurrences were type A (central, high dose), two type C (central, elective dose), two type D (peripheral, elective dose) and five type E (extraneous). Type A (central, high dose) recurrences were in the high-dose PTV neck volumes after N+ neck dissections. The two type C (central, elective dose) recurrences were in-field of an undissected elective neck volume (PTV54 and PTV56 dose volumes). The two type D (peripheral, elective dose) recurrences were in PTV60 volumes of the dissected neck in patients receiving 66 Gy in 33 fractions. The five type E (extraneous) recurrences were all in the contralateral neck of patients who had received ipsilateral neck radiotherapy without treatment of the contralateral neck. Figure 4 provides an example of a type E (extraneous) neck recurrence.

Patients Receiving Ipsilateral and Not Bilateral Neck Radiotherapy

Of the 48 patients who did not receive contralateral neck radiotherapy, five (10%) experienced contralateral regional recurrences. These included 2/26 patients with pN0 disease, 2/9 with pN1 disease, 1/12 patients with pN2 disease and 0/1 patients had pN3 disease.

With regards to patients with an oral tongue primary, 21 received adjuvant radiotherapy to the ipsilateral neck without irradiation of the contralateral neck. All cases were

Table 1
Patient and disease characteristics and treatment details ($n = 101$)

	n (%)
Gender	
Male	58 (57.4)
Female	43 (42.6)
Tobacco use at diagnosis	
Ex-smoker	45 (44.6)
Current smoker	36 (35.6)
No smoker	17 (16.8)
Not recorded	3 (3.0)
Anatomic subsite	
Floor of mouth	17 (16.8)
Tongue	52 (51.5)
Retromolar trigone	10 (9.9)
Mandibular alveolus	15 (14.9)
Buccal mucosa	7 (6.9)
Hard palate	0 (0)
pT stage	
T1	11 (10.9)
T2	40 (39.6)
T3	9 (8.9)
T4a	41 (40.6)
T4b	0 (0)
pN stage	
N0	37 (36.6)
N1	16 (15.8)
N2a	1 (1.0)
N2b	36 (35.6)
N2c	10 (9.9)
N3	1 (1.0)
Stage group	
I	6 (5.9)
II	13 (12.9)
III	13 (12.9)
IVa	69 (68.3)
Histopathological differentiation	
Well differentiated	4 (4.0)
Moderately differentiated	53 (52.5)
Poorly differentiated	43 (42.6)
Unclassified	1 (1.0)
Margin status	
Positive ($\leq$1 mm)	20 (19.8)
Close ($>1 < 5$ mm)	44 (43.6)
Clear ($\geq$5 mm)	35 (34.7)
Not reported	2 (2.0)
Perineural invasion	
Yes	59 (58.4)
No	41 (40.6)
Not reported	1 (1.0)
Lymphovascular invasion	
Yes	50 (49.5)
No	48 (47.5)
Not reported	2 (2.0)
Nodal involvement	
Yes	73 (72.3)
No	28 (27.7)
Nodal ECE (nodal involvement $n = 73$)	
Yes	30 (41.1)
No	43 (58.9)
Surgery	
Primary + unilateral neck dissection	70 (69.3)

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Table 1 (*continued*)

	n (%)
Primary + bilateral neck dissection	27 (26.7)
Primary only	4 (4.0)
Concurrent chemotherapy	
Yes	25 (24.8)
No	76 (75.2)
Concurrent chemotherapy ($n = 25$)	
Cisplatin based	21 (84.0)
Carboplatin based	3 (12.0)
Cisplatin and carboplatin based	1 (4.0)
Number of concurrent chemotherapy courses	
0	77 (76.2)
1	2 (2.0)
2	22 (21.8)
Radiotherapy dose	
66 Gy in 33 fractions	53 (52.5)
60 Gy in 30 fractions	46 (45.5)
50 Gy in 25 fractions	1 (1.0)

ECE, extracapsular extension.

Table 2
Lymph node levels irradiated with intensity-modulated radiotherapy

Nodal level ($n = 101$)	Ipsilateral neck radiotherapy ($n = 97$)	Contralateral neck radiotherapy ($n = 53$)
IA	52	30
IB	97	46
II	93	52
III	89	49
IV	90	47
V	55	21
VIIa	37	4
VIIb	28	1

considered preoperatively to have lateralised oral tongue carcinomas based upon clinical examination and imaging and had undergone an ipsilateral-only neck dissection. Five of 21 (24%) patients experienced contralateral neck recurrences. Within this group of 21 patients, recurrences were in 2/11 with pN0 disease, 1/4 with pN1 disease and 2/6 with pN2 disease.

Discussion

Recurrence analysis is a key step in evaluating the quality of radiotherapy. An in-field recurrence implies radioresistance. A recurrence marginal to target volumes suggests the possibility that inadequate target delineation may have been contributory to recurrence. An out-of-field recurrence implies an issue with target volume selection. The methodology of recurrence analysis is challenging and relies upon accurate reconstruction of the site of recurrence upon the original planning CT scan prior to dosimetric evaluation. Rigid image registration (RIR) has been used for recurrence reconstruction in several previous reports [15–17]. However, RIR is limited by inevitable anatomical and positional changes that often occur between planning

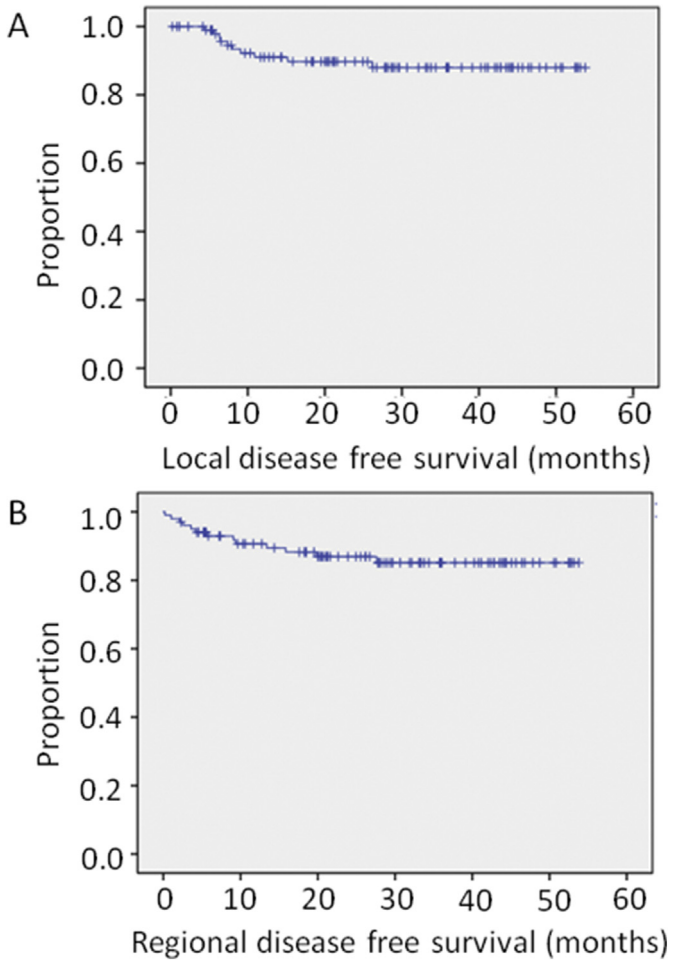

Fig 1. Local and regional disease-free survival outcomes for a cohort of 101 patients receiving adjuvant intensity-modulated radiotherapy. Kaplan–Meier curves for (A) local disease-free survival, (B) regional disease-free survival.

CT and imaging at the time of recurrence detection. We have previously carried out this step by using deformable image registration (DIR) in parallel with manual side-by-side contouring [11,18]. Due *et al.* [19,20] have previously used DIR to transfer focal points of recurrence to planning CT scans and found superior reproducibility with DIR. Validated DIR has recently been strongly recommended for recurrence analysis compared with RIR based upon qualitative superiority [3,12].

Analyses in the postoperative setting by ourselves [11] and others [4,9] have primarily been based upon the volumetric classification described in 2000 by Dawson *et al.* [10]; this is based on the percentage of Vrec encompassed by 95% of the prescription isodose [10,18]. However, this volumetric method is inherently limited in that a tumour can recur in-field and subsequently grow out-of-field, leading to misclassification as a marginal or out-of-field recurrence. An alternative approach is to make an assumption that the recurrence subsequently grew symmetrically from the point-of-origin defined as a geometrically central point in Vrec [11,19]. This centre-of-origin method is limited by the assumption of symmetrical growth

Table 3
Details of analysis of patients with locoregional recurrences ($n = 22$)

Oral cavity subsite	pTNM (7th edition)	Neck dissection	Adjuvant treatment	Failure site (related PTV)	Local versus regional recurrence	Time to recur (months post-RT)	%Vrec in 95% isodose	Mean dose to centroid/Gy	Recurrence classification
Tongue	T1N1	Unilateral	RT 60 Gy bilateral neck	Contralateral neck level III OF	R	1	0	5.7	E (extraneous, neck)
Mandible	T4aN0	Bilateral	RT 60 Gy bilateral neck	Buccal mucosa PTV60	L	3	36	59.1	B (peripheral, high dose)
Tongue	T2N1	Unilateral	RT 60 Gy unilateral neck	FOM/ventral tongue PTV60	L	6	99	62	A (central, high dose)
Tongue	T2N0	Unilateral	RT 60 Gy unilateral neck	Oral tongue PTV60	L	2	99	60.7	A (central, high dose)
Tongue	T2N2c	Bilateral	RT 60 Gy bilateral neck	FOM PTV60	L	5	98	60.2	A (central, high dose)
Tongue	T2N2b	Unilateral	RT 60 Gy bilateral neck	Ipsilateral level II LN PTV54	R	6	100	55	C (central, elective dose)
Tongue	T2N1	Unilateral	RT 60 Gy unilateral neck	Contralateral neck level III OF	R	4	0	9.2	E (extraneous, neck)
Tongue	T1N0	None	RT 60 Gy unilateral neck	Ipsilateral neck levels II-IVa and contralateral neck level II PTV60 (ipsilateral) and OF (contralateral)	R	28	Ipsilateral neck 97 Contralateral neck 0	60.6 5.4	A (central, high dose, ipsilateral neck) E (extraneous, contralateral neck)
Tongue	T4aN2c	Bilateral	RT 60 Gy bilateral neck	Bilateral levels Ib PTV60	R	2	Ipsilateral neck 100 Contralateral neck 100	61.5 60.2	A (central, high dose, bilateral neck)
Tongue	T2N2b	Unilateral	RT 60 Gy unilateral neck	Tongue Contralateral levels I–IVa OF	LR	9	Primary 100 Contralateral neck 0	60.6 Multifocal, centroid of each >60 Gy	A (central, high dose, primary) E (extraneous, contralateral neck)
Tongue	T2N0	Unilateral	RT 50 Gy unilateral neck	OF	R	0	0	Multifocal, centroid of each <50 Gy	E (extraneous, neck)
Tongue	T2N2b	Unilateral	RT 66 Gy bilateral neck	Ipsilateral level IVa PTV56	R	9	99	58.7	C (central, elective dose, neck)
Mandible	T4aN0	Unilateral	RT 66 Gy unilateral neck	Contralateral mandible OF	L	8	2.6	26.9	E (extraneous, primary)
Tongue	T4aN0	Unilateral	RT 66 Gy bilateral neck	Ipsilateral neck, levels II–III PTV66	R	4	100	67.8	A (central, high dose, neck)
Buccal	T4aN2c	Bilateral	RT 66 Gy bilateral neck	Adjacent tongue PTV66	L	5	71.8	65.3	B (peripheral high dose)

(*continued on next page*)

Table 3 (*continued*)

Oral cavity subsite	pTNM (7th edition)	Neck dissection	Adjuvant treatment	Failure site (related PTV)	Local versus regional recurrence	Time to recur (months post-RT)	%Vrec in 95% isodose	Mean dose to centroid/Gy	Recurrence classification
Tongue	T4aN2b	Unilateral	RT 66 Gy unilateral neck	Ipsilateral levels Ib–II, contralateral III PTV66	R	15	96	67.2	A (central, high dose, neck)
RMT	T1N1	Unilateral	RT 66 Gy unilateral neck	Ipsilateral level II PTV66	R	8	100	66.5	A (central, high dose, neck)
Tongue	T4aN1	Unilateral	RT 66 Gy bilateral neck	Oral tongue PTV66	L	9	98.1	67.2	A (central, high dose, primary)
Mandible	T4aN0	Unilateral	RT 66 Gy bilateral neck	Posterior tongue, masticator space PTV66	L	6	85.5	67.1	B (peripheral high dose, primary)
Tongue	T2N0	Unilateral	RT 66 Gy bilateral neck	Oral tongue adjacent to flap PTV66	L	4	84.6	67.0	B (peripheral high dose, primary)
Tongue	T2N2c	Unilateral	RT 66 Gy unilateral neck	Ipsilateral levels II/III PTV60	R	4	20.6	58.6	D (peripheral, elective dose, neck)
Buccal	T4aN1	Unilateral	RT 66 Gy bilateral neck	Ipsilateral levels I–III PTV60	R	1	60.1	60.5	D (peripheral, elective dose, neck)

ECE, extracapsular extension; FOM, floor of mouth; L, local; LN, lymph node; OF, out-of-field; PTV, planning target volume; R, regional; RMT, retromolar trigone; RT, radiotherapy; Vrec, recurrence volume.

from the origin. Reported series have shown differences in the classification of recurrences when comparing volume-based and central point-of-origin methodology [11,19,20]. Recently, the MD Anderson Cancer Centre reported on a novel method of combining spatial and dosimetric data to classify locoregional recurrences [3,12] and we have adopted this methodology in this current analysis.

We have previously reported on recurrence patterns following adjuvant (chemo)radiotherapy for oral cavity carcinoma treated predominantly in the pre-IMRT era [11]. Of 106 patients, we reported four 'marginal' and nine 'out-of-field' recurrences. This included 7/21 (33%) contralateral regional recurrences in patients with pN2a/b disease who did not receive contralateral neck irradiation.

In the current analysis, four of 10 primary site recurrences were type B (peripheral, high dose) and one was type E (extraneous). With the caveat of the potential for disease to recur in-field and grow out-of-field, these data suggest the need for generous target delineation at the primary site. With regards to the 14 cases of regional recurrence, 7/14 were in-field recurrences [type A (central, high dose) and type C (central, elective dose)] and only 2/14 were type D (peripheral, elective dose), suggesting in most cases adequate target delineation but radioresistance. However, 5/14 regional recurrences were type E (extraneous), all in a non-irradiated contralateral neck. All of these five type E recurrences occurred in patients with oral tongue carcinoma; overall 5/21 patients with oral tongue carcinoma recurred out-of-field in the contralateral neck following ipsilateral neck dissection and radiotherapy to the primary site and ipsilateral neck only. By contrast with our previous analysis [11], the risk of contralateral neck recurrence for oral tongue carcinoma also appeared to be in patients with pN0/1 disease (contralateral out-of-field neck recurrences in 2/11 with pN0 disease, 1/4 with pN1 disease). There were 0/27 type E contralateral recurrences in patients with non-tongue primary subsites, suggesting the safety of this approach for lateralised non-tongue primaries.

A limited number of other series have analysed recurrence patterns following adjuvant IMRT for oral cavity cancer, finding significant risks of marginal and out-of-field recurrences [3,4,9,17]. Mohamed *et al.* [3] have recently summarised these in tabular form. Chan *et al.* [4] identified locoregional recurrences in 38/180 patients; 12/38 recurrences were marginal or out-of-field. Geretschlager *et al.* [9] found that of 12 locoregional recurrences in 53 patients treated, 10/12 were marginal or out-of-high dose volumes. In the series from the MD Anderson Cancer Centre [3], 54/289 recurrences were analysed and almost half of these patients with recurrences had non-central high dose recurrences and three patients had nodal type E (extraneous) recurrences in the contralateral undissected/unirradiated neck. The lower rate of contralateral out-of-field neck recurrence in this series [3] compared with our current data is probably related to their preferred approach of 'comprehensive bilateral irradiation for patients with tumours in central oral cavity sites, such as the oral tongue and floor of mouth'. Others similarly recommended a comprehensive irradiation approach with inclusion of the contralateral

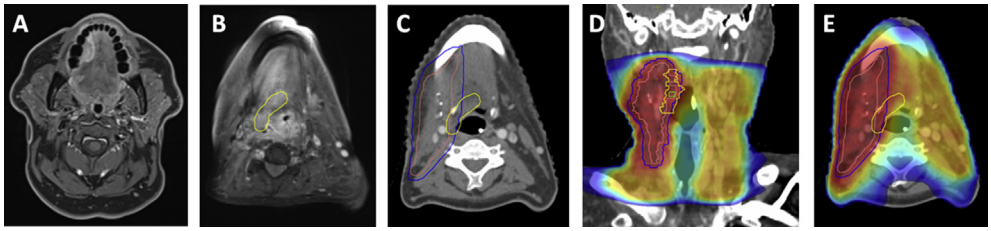

Fig 2. Example of type B recurrence at the primary site (peripheral, high dose). Patient with pT2pN2bM0 squamous cell carcinoma of the right lateral tongue. Treatment was with partial glossectomy, free flap reconstruction and right selective neck dissection followed by adjuvant chemoradiotherapy to the primary site and bilateral neck 66 Gy in 33 fractions. Four months after radiotherapy there was local recurrence posterior to the flap (biopsy proven). (A) Preoperative magnetic resonance imaging (MRI; T1 fat saturation with gadolinium enhancement) showing tumour on the right lateral tongue. (B) Recurrence posterior to the flap contoured on recurrence MRI deformed to the planning computed tomography (CT) (yellow). (C) Recurrence on planning CT (contoured on MRI deformably co-registered to planning CT) showing the clinical target volume (CTV; pink) and planning target volume (PTV; blue). (D) Coronal view of planning CT showing CTV (pink), PTV (blue), recurrence (yellow), centroid of recurrence (green), together with a colourwash of dosimetry, showing the centroid of recurrence within the high-dose volume. (E) Axial slice planning CT near the inferior part of the recurrence showing part of the recurrence (yellow) extending out of the high-dose volume.

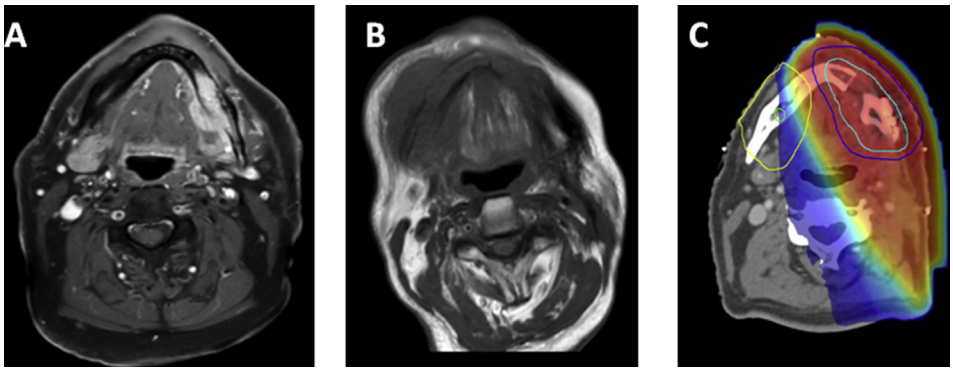

Fig 3. Example of type E recurrence at the primary site (extraneous, primary). Patient with pT4apN0MO squamous cell carcinoma of the left mandible. Treatment was with hemimandibulectomy, fibula reconstruction and ipsilateral neck dissection followed by adjuvant radiotherapy 66 Gy in 33 fractions. (A) Preoperative magnetic resonance imaging (MRI; fat saturated T1 with gadolinium) showing tumour on the left hemimandible. (B) MRI (T1W) showing recurrence around the native right hemimandible (extended to the junction with the graft) 8 months after radiotherapy. (C) Planning computed tomography scan with the site of recurrence shown (yellow) following contouring on deformably co-registered recurrence MRI with centroid (green) of recurrence volume, with a colourwash of the plan dosimetry. The centroid and most of the recurrence volume lie beyond the high-dose volume.

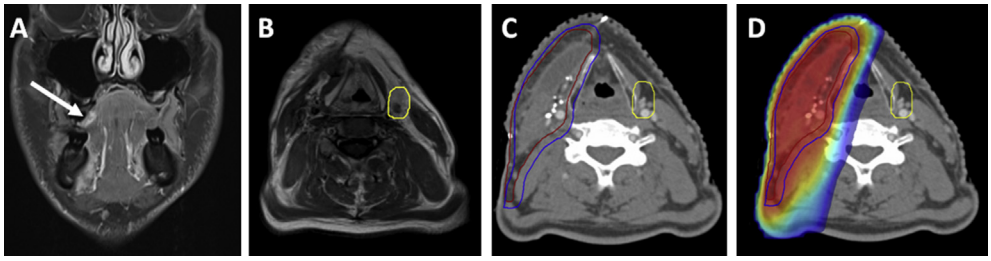

Fig 4. Example of type E recurrence in the nodal region (extraneous neck). Patient with a pT2pN1M0 squamous cell carcinoma of the right lateral tongue. Treatment was with partial glossectomy, free flap reconstruction and right selective neck dissection followed by adjuvant radiotherapy to the primary site and ipsilateral neck. Recurrence in the left neck occurred 8 months after the completion of treatment. (A) Diagnostic magnetic resonance imaging (MRI; T1 fat saturation with gadolinium enhancement) shows a well-lateralised lesion on the right tongue (white arrow). (B) MRI (T1W) at recurrence deformably co-registered to the planning computed tomography (CT) scan and left neck recurrence contoured (yellow). (C) Recurrence on planning CT (contoured on MRI deformably co-registered to planning CT). (D) Planning CT with plan dosimetry; clinical target volume in red, planning target volume in blue, left neck recurrence delineated by deformable co-registration of MRI in yellow.

neck [17]. Recent expert panel guidelines have suggested that the contralateral neck can be omitted for lateral oral tongue cancers that are >1 cm from the midline and N0/1 [7]. Some reports (including our previous analysis) [11,21,22] have suggested that contralateral neck recurrences do not occur in the absence of ipsilateral lymph

node involvement. However, a series of 164 patients with low-risk oral tongue carcinoma, pT1/2pN0, managed with ipsilateral neck dissection and no adjuvant radiotherapy, revealed that tumour depth >4 mm was a significant predictor of risk of regional failure and that nearly 40% of regional failures were in the contralateral neck [23]. This is consistent with our data in which contralateral neck recurrences did occur in patients with oral tongue cancer with ipsilateral pN0 disease and who did not receive radiotherapy to the contralateral neck.

The limitations of this series include the retrospective nature. Our previous analysis [11] had already identified the risks of contralateral neck failure, particularly in patients with oral tongue carcinoma. This has informed our current practice, with a low threshold for treating comprehensive target volumes for adjuvant radiotherapy for oral tongue carcinoma, including the primary site and bilateral neck. However, many of the patients in this current IMRT-based series were treated before this prior analysis and reflect our historical approach to treatment. Peer review quality assurance meetings were only introduced in our institution towards the end of the study period; for oral cavity tumours we have found a 12% rate of contour change from this process [14].

In summary, marginal and out-of-field recurrences remain a significant pattern of failure in the era of adjuvant IMRT for oral cavity carcinoma. Oral tongue carcinomas are particularly prone to contralateral neck recurrences in an undissected/unirradiated contralateral neck. We advocate generous target volume delineation in the postoperative setting and for oral tongue carcinomas a comprehensive approach with bilateral neck irradiation.

Conflict of Interest

The authors declare no conflicts of interest.

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