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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.

Methods: 101 patients who received adjuvant radiotherapy±chemotherapy for oral cavity squamous cell carcinoma between 2013-16 were analysed. For documented locoregional recurrence, recurrence imaging was deformably coregistered to the planning CT. Volume of recurrence was delineated (Vrec). Vrec coverage by 95% of the corresponding PTV prescription dose was determined and location compared with PTVs. 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: Median follow up was 36 months. 43% and 53% of patients received radiotherapy to the ipsilateral neck only and bilateral neck respectively. 3-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. Out of 10 episodes of primary site recurrences, 5 were type A, 4 type B and 1 was type E. Out of 14 episodes of regional recurrence, 5 were type A, 2 type C, 2 type D, and 5 type E. 5/21 (24%) 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 post-operatively and for oral tongue carcinomas a comprehensive approach with bilateral neck irradiation.

Keywords: oral cavity carcinoma; radiotherapy; recurrence; deformable coregistration

Introduction

Post-operative (chemo)radiotherapy is commonly delivered following curative-intent surgery for oral cavity squamous cell carcinoma. By contrast with definitive radiotherapy, post-operative target volumes are not standardised [1]. There are no comprehensive internationally agreed guidelines for post-operative target volume selection and delineation [2]. In selecting target volumes clinicians attempt to balance 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 only can be considered for lateral oral tongue carcinomas (N0/1) which do not come within 1cm of midline [7]. Decisions on whether the contralateral neck is at sufficient risk of recurrence to justify the additional toxicity of contralateral neck irradiation can be a challenging decision based upon 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 which are beneficial in sparing normal tissues adjacent to target volumes [8]. However, a risk of steep dose gradients is of 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 of the target volumes 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 coregistration 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.

Methods

Study population

This is a retrospective single centre study. 101 patients with newly diagnosed squamous cell carcinoma of the oral cavity who underwent surgery and adjuvant radiotherapy with curative intent between January 2013-December 2016 were identified from electronic radiotherapy records. Patients with a history of a prior head and neck cancer, macroscopic disease post-operatively or recurrence pre-radiotherapy were excluded.

Management

Surgery

Patients underwent resection with curative intent ± unilateral or bilateral neck dissections according to the input from the Multidisciplinary Team meetings prior to surgery, and assessment of the treating surgeon.

Adjuvant Radiotherapy

Patients were treated supine with a 5-point thermoplastic mask. Planning CT scans were acquired with intravenous CT contrast and 2mm CT slice. Mouth bites were used at the discretion of the treating radiation oncologist. Pre-operative 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 post-operative 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 prior to treatment in dedicated head and neck peer review quality assurance meetings [14].

Standard doses were 60Gy in 30 fractions over 6 weeks to the surgical bed and dissected nodal areas. For patients with high risk features (very close margins eg. <1mm or extracapsular lymph node spread or soft tissue deposits) an increased dose of 66Gy in 33 fractions was typically delivered to the pre-operative 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 judgement of the treating clinician) were treated to a dose of 54Gy in 30 fractions (or 56Gy 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 5-7 angle step and shoot IMRT technique, and later using volumetric modulated arc therapy (VMAT).

Concurrent chemotherapy

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

Locoregional recurrence analysis

Locoregional recurrence analysis was performed for patients with radiological evidence of recurrence which was confirmed by either pathology or subsequent clinical progression. The original planning CTs were restored. The cross-sectional imaging (CT, MRI or PET-CT) acquired at the time of relapse was coregistered onto the planning CT study using Mirada RTx software (Mirada Medical, Oxford, UK). An initial manual rigid co-registration was performed 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 onto the coregistered recurrence imaging using information documented from clinical examination at the time of recurrence and radiological imaging acquired at the time of relapse. A 4mm diameter centroid, presumed as the origin of the recurrence, was generated based on a 2mm 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 (DVH) were obtained for the Vrec and coverage of Vrec by 95% of the corresponding PTV prescription dose was documented. Mean dose and location of the centroid was compared with PTVs. Recurrences were classified into 5 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 high dose PTV and >95% of Vrec receiving >95% of prescribed dose to high dose PTV

B. Peripheral, high dose: mapped centroid of Vrec originating in high dose PTV and <95% of Vrec receiving >95% of prescribed dose to high dose PTV

C. Central, elective dose: mapped centroid of Vrec originating in elective dose PTV and >95% of Vrec receiving >95% of prescribed dose to elective dose PTV

D. Peripheral, elective dose: mapped centroid of Vrec originating in elective dose PTV and <95% of Vrec receiving >95% of prescribed dose to high dose PTV

E. Extraneous dose: mapped centroid of Vrec originating outside of all PTVs.

Cases with multifocal recurrence, eg. at 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

Analysis was performed using IBM SPSS Statistics, Version 24(Armonk, NY: IBM Corp.). Time to event endpoints 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 (OS), disease free survival (DFS), local control, regional control and distant metastases free survival (DMFS) and were calculated by 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 2013-2016 and fulfilled the inclusion criteria. Median follow up was 28 months (range 2-54). Median age was 63 years (range 20-82). Patient, disease and treatment characteristics are summarised in Table 1. Oral tongue was the most common oral cavity subsite (51%). Median time from surgery to commencement of radiotherapy was 51 days (35-95). 100/101 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 regard 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

3 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%) of patients experienced treatment failure at the primary site, 13/101 (13%) regional treatment failure; this included 1 patient with combined treatment failure at the primary site and regional lymph nodes. Median time from completion of radiotherapy to recurrence was 6 months (range 0-28 months). 13/101 (13%) developed distant metastases; this included 5 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, 7 had locally recurrent disease only, 1 combined locoregional recurrence and 1 with synchronous distant metastases. One of these patients with an oral tongue cancer recurrence underwent salvage surgical resection and remains disease free. Out of the 13 patients with regional recurrence, 10 had regionally recurrent disease only, 1 with combined locoregional recurrence and 2 with distant metastases. 5 of these 10 patients underwent a salvage neck dissection and 2 of these patients also received post-neck dissection radiotherapy. Out of the 5 patients undergoing a neck dissection, 3 recurred in the neck and the remaining 2 developed distant metastases. Overall 6 patients received palliative chemotherapy.

Analysis of cases of loco-regional failure

Table 3 provides details of the 22 cases with locoregional recurrence and analysis of recurrence pattern by combined spatial and dosimetric criteria. Recurrence diagnostic imaging deformably coregistered to the planning CT scan was MRI for 12, CT for 6 and PET-CT for 4 patients. For two patients, two separate recurrence classifications were made (one patient with bilateral neck recurrence following 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. 10/24 (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

Out of 10 patients with local primary site recurrences, 5 were type A (central, high dose), 4 type B (peripheral, high dose) and 1 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 left mandible resected with a fibula reconstruction and recurrence with a 5cm 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 description of a patient with bilateral neck recurrence following unilateral radiotherapy. 5 recurrences were type A (central, high dose), 2 type C (central, elective dose), 2 type D (peripheral, elective dose) and 5 type E (extraneous). Type A (central, high dose) recurrences were in the high dose PTV neck volumes after N+ neck dissections. The 2 type C (central, elective dose) recurrences were in-field of an undissected elective neck volume (PTV54 and PTV56 dose volumes). The 2 type D (peripheral, elective dose) recurrences were in PTV60 volumes of the dissected neck in patients receiving 66Gy in 33 fractions. The 5 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, 5 (10%) experienced contralateral regional recurrences. These included 2/26 patients with pN0 disease, 2/9 with pN1 disease, 1/12 patients had pN2 disease and 0/1 patients had pN3 disease.

With regard to patients with an oral tongue primary, 21 received adjuvant radiotherapy to the ipsilateral neck without irradiation of the contralateral neck. All cases were considered pre-operatively to have lateralised oral tongue carcinomas based upon clinical examination and imaging and had undergone an ipsilateral-only neck dissection. 5/21 (24%) of these 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 prior reports [15-17]. However, RIR is limited by inevitable anatomical and positional changes which often occur between planning CT and imaging at the time of recurrence detection. We have previously performed this step by using 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 post-operative 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 with [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 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 have 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]. Out of 106 patients, we reported 4 ‘marginal’ and 9 ‘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, 4 out of 10 primary site recurrences were type B (peripheral, high dose) and 1 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 regard 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 5 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 prior 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 lateralized 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 summarized these in tabular form. Chan et al. [4] identified locoregional recurrences in 38/180 patients, and 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 3 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 likely to be 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 neck [17]. Recent expert panel guidelines have suggested the that the contralateral neck can be omitted for lateral oral tongue cancers which are >1cm from midline and N0/1 [7]. Some reports (including our prior 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 of >4mm 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.

Limitations of this series include the retrospective nature. Our prior 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 post-operative setting and for oral tongue carcinomas a comprehensive approach with bilateral neck irradiation.

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Figure legends

Figure 1: Local and regional disease free survival outcomes for cohort of 101 patients receiving adjuvant IMRT. Kaplan-Meier curves for A) local disease free survival, B) regional disease free survival.

Figure 2: Example of type B recurrence at primary site (peripheral high dose). Patient with pT2pN2bM0 squamous cell carcinoma of right lateral tongue. Treatment was with partial glossectomy, free flap reconstruction and right selective neck dissection followed by adjuvant chemoradiotherapy to primary site and bilateral neck 66Gy in 33 fractions. 4 months post-radiotherapy had local recurrence posterior to flap (biopsy proven). A) Pre-operative MRI (T1 fat saturation with gadolinium enhancement) showing tumour right lateral tongue. B) Recurrence posterior to flap contoured on recurrence MRI deformed to planning CT (yellow). C) Recurrence on planning CT (contoured on MRI deformably coregistered to planning CT) showing CTV (pink) and PTV (blue). D) Coronal view of planning CT showing CTV (pink), PTV (blue), recurrence (yellow), centroid of recurrence (green) along with colourwash of dosimetry, showing centroid of recurrence within high dose volume. E) Axial slice planning CT near inferior part of recurrence showing part of recurrence (yellow) extending out of high dose volume.

Figure 3: Example of type E recurrence at primary site (extraneous, primary). Patient with pT4apN0MO squamous cell carcinoma of left mandible. Treatment was with hemimandibulectomy, fibula reconstruction and ipsilateral neck dissection followed by adjuvant radiotherapy 66Gy in 33 fractions. A) Pre-operative MRI (fat saturated T1 with gadolinium) showing tumour left hemimandible. B) MRI (T1W) showing recurrence around native right hemimandible (extended to junction with graft) 8 months post-radiotherapy. C) Planning CT with site of recurrence shown (yellow) following contouring on deformably coregistered recurrence MRI with centroid (green) of recurrence volume, with colourwash of plan dosimetry. Centroid and majority of recurrence volume lie beyond high dose volume.

Figure 4: Example of type E recurrence in nodal region (extraneous neck). Patient with a pT2pN1M0 squamous cell carcinoma of right lateral tongue. Treatment was with partial glossectomy, free flap reconstruction and right selective neck dissection followed by adjuvant radiotherapy to primary site and ipsilateral neck. Recurrence in left neck occurred 8 months following completion of treatment. A) Diagnostic MRI (T1 fat saturation with gadolinium enhancement; demonstrates well lateralized lesion right tongue (white arrow). B) MRI (T1W) at recurrence deformably coregistered to planning CT and left neck recurrence contoured (yellow). C) Recurrence on planning CT (contoured on MRI deformably coregistered to planning CT). D) Planning CT with plan dosimetry; CTV in red, PTV in blue, left neck recurrence delineated by deformable coregistration of MRI in yellow.