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Review

Current thinking in management of the neck (including contralateral neck) in ipsilateral recurrent or second primary oral squamous cell carcinoma

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Abstract

Metastasis to the neck in patients with oral squamous cell carcinoma (SCC) has a huge impact on long-term survival and prognosis, and its incidence varies. Due consideration therefore should be given to management of the neck in each individual case. The pathways in patients with primary oral SCC are well-established, but there is a paucity of published papers on management of the neck in those with ipsilateral recurrent or second primary oral SCC whose necks have previously been operated on with or without radiotherapy or chemoradiotherapy, or treated with radiotherapy or chemoradiotherapy alone. These patients may be under treated because of failure to stage the most likely drainage site, and are likely to have a worse outcome if there is macroscopic recurrence in the neck after independent treatment of the recurrent or second primary tumour. Based on the current review, we think there is a need for a multicentre, collaborative, retrospective review of the outcomes of patients with ipsilateral second primaries or recurrent oral SCC in the previously treated neck. Our recommendations include consideration of positron emission tomography-computed tomography in all patients with recurrent or second primary oral SCC (if "hot" – neck dissection, if "cold" - sentinel node biopsy); consideration of sentinel node biopsy in all patients with recurrent or second primary oral SCC who have previously had treatment to the neck; and finally, consideration of definitive management of the sentinel biopsy zone or region if the node is invaded.
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Introduction

Metastasis to the neck nodes is the single most important prognostic factor in the survival of patients with oral squamous cell carcinoma (SCC);[1–4] the cure rates drop to nearly half when the regional lymph nodes are involved.[3–6] In primary oral SCC, if the clinical staging of the neck is N0 and the primary site has been treated by operation, it is routine practice to offer either sentinel node biopsy or elective selective neck dissection depending on the T stage of the primary tumour.[7]

There is a paucity of published studies on the drainage pattern in the neck after operation, operation and radiotherapy or chemoradiotherapy, or radiotherapy or chemoradiotherapy alone. In the event of an ipsilateral recurrent or second primary tumour, nodal basins could include the contralateral neck, retropharyngeal lymph nodes (RPLN), central non-irradiated laryngeal strip, parotid nodes, or undissected ipsilateral basins such as Robbins level IIB, IV, or V. In the

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case of a recurrent or second primary tumour, therefore, standard treatment of the levels at risk in the neck (as applied in the primary operation) may not be possible or appropriate after previous operation or radiotherapy, or both, to the neck.[8]

The focus of our review was to look at the management of the neck, including the contralateral neck, in patients with ipsilateral recurrent, or second primary, oral SCC.

Recurrent and second primary tumours

In oral SCC, clinicians may use "recurrence" and "second primary tumour" interchangeably, so it is important to define the difference. A second primary malignancy presents either simultaneously or after diagnosis of the index tumour.[9–11] A synchronous second primary is detected simultaneously or within six months of diagnosis of the index tumour, and a metachronous second primary is diagnosed more than six months after diagnosis of the index tumour.[9–11] The classic criteria proposed by Warren and Gates[12,13] for the diagnosis of a second primary malignancy include:

- histological confirmation of malignancy in both the index and secondary tumours
- at least 2 cm of normal mucosa between the tumours, and those in the same location separated in time by at least five years
- exclusion of the probability that one is result of metastasis from the other.

The criteria for a second primary were modified by Hong et al.[14] According to them, "a second primary tumour of the same histological type as the first had to be separated from it by more than two centimetres of normal epithelium or had to occur at least three years after the diagnosis of the first primary tumour. Any tumour of different histological type qualified as a second primary tumour, without the requirement of a separation of more than two centimetre".[14]

If a new oral SCC (after treatment of the primary index tumour on the ipsilateral side) does not satisfy the above criteria, it is considered to be a recurrence.

The local recurrence rate in head and neck SCC is 10% - 30%, and the annual risk for a second primary tumour is 3% - 4%.[8,15–18]

Review of management of the neck in recurrent or second primary oral SCC

Machado et al[19] reported two patients with oral SCC and a N0 neck who were treated by primary resection and ipsilateral neck dissection. One also had postoperative radiotherapy to the local tumour bed. One had presented with an ipsilateral metachronous SCC with no neck recurrence and had been treated by local resection and contralateral level I-III neck dissection that showed two of 29 positive lymph nodes with no extracapsular extension.[19] After postoperative radiotherapy to the contralateral neck (levels I-III) and ipsilateral neck (levels I-II) the patient presented 17 months later with an ipsilateral level IV mass (fine needle aspiration cytology showed SCC). This was resected and the patient treated with radiotherapy. The other patient (also with ipsilateral metachronous SCC) had the second primary resected and a contralateral level I-III neck dissection. The contralateral harvested nodes did not show any metastatic disease so no radiotherapy was warranted, but positron emission tomography-computed tomography (PET-CT) showed a left (ipsilateral) level IV hypermetabolic mass (confirmed as SCC), which was resected.[19] The authors concluded that in cases of oral SCC, previous operation or radiotherapy, or both, can alter the lymphatic drainage pathway, and this (particularly regarding the ipsilateral level IV nodal basin) should be taken into account when planning the treatment of recurrent intraoral carcinomas.[19]

In terms of metastases to the retropharyngeal lymph nodes (RPLN), Tseng et al[20] retrospectively analysed 2678 patients with oral SCC who had previously been treated surgically, and found 26 cases in whom the tumours in the RPLN relapsed when recurrent disease was restaged using fluorodeoxyglucose (FDG) PET-CT. They reported that the incidence of metastases to the RPLN in oral SCC was less than 1%, and two-thirds of these cases were identified in patients with recurrent disease.[20] A total of 11 patients with recurrent disease and metastasis to the RPLN had salvage treatment (concurrent chemoradiation with curative intent in 10, and operation and concurrent chemoradiation in one).[20] The risk factors for invasion of the RPLN included an advanced tumour in cases of primary and recurrent disease, involvement of the lymph nodes in the neck in the primary and relapse group, involvement of levels I-III in the primary and relapse group, and extracapsular spread in primary and recurrent disease (which showed that involvement of the RPLN was more common in highly-aggressive tumours).[20] This retrospective analysis was conducted in an area where the chewing of betel nut was endemic. The authors concluded that in patients with recurrent oral SCC and invaded RPLN, salvage treatment should be targeted to patients with ipsilateral RPLN disease (identified by PET-CT) in the absence of disease in the contralateral RPLN or contralateral neck nodes, because of the high morbidity and low survival.[20]

In their retrospective study, Liu et al[21] analysed 72 patients with T1-3N0 oral SCC who had been treated by operation alone. A quarter (18 patients) had recurrences: nine in the ipsilateral neck, seven at the primary site, and two had simultaneous recurrences in the primary tumour and the neck. Surgical salvage was attempted in all those with recurrence and was successful in 6/7 who had local, and 5/9 who had regional, recurrences.[21]

González-Garcia et al[22] retrospectively reviewed 522 patients with SCC of the oral cavity who were primarily treated by operation. Of these, 28 (5.6%) developed a second primary within the oral cavity or oropharynx, or both, 95 (19%) developed a local recurrence, and 71 (14.2%) a

cervical recurrence. The authors recommended aggressive surgical treatment after the appearance of a second primary tumour or local recurrence.[22] This included operation alone (n = 43, 34.95%), radiotherapy alone (n = 8), chemotherapy alone (n = 16), operation and radiotherapy (n =14), operation and chemotherapy (n = 2), operation, chemotherapy, and radiotherapy (n = 2); and radiotherapy and chemotherapy (n = 6). Disease-specific survival in patients with second primary tumours or local recurrence was 67.2% at five years postoperatively. It is not clear from the study if patients with second primaries or local recurrence had neck dissections and if so, whether they were ipsilateral or contralateral.[22]

Risk factors for metastasis to the contralateral neck

Feind and Cole[23] proposed three routes for contralateral spread of metastases in the head and neck. First, by the crossing of lymphatic afferent vessels; secondly, by actual spread over the midline through efferent lymphatic vessels after regional nodes had become extensively involved and collateral lymphatic flow taken place; and, finally, if certain anatomical areas in the head and neck where there is no definite midline had become involved. The authors showed that contralateral metastases were common from lesions of the lip, base of the tongue, and those in the middle of the floor of the mouth.[23]

It is relevant to this review that the risk of metastasis to the contralateral neck in oral SCC may increase in patients with a second primary ipsilateral cancer who have had the primary lesion treated by operation or postoperative radiotherapy. It is therefore important to investigate the remaining or newly-established lymphatic channels, such as the contralateral neck. The authors recognised the possibility that the original index tumour may have seeded the contralateral neck, but the incidence of this is up to 13% if the first primary is positioned laterally.[24]

Role of PET-CT

Current staging techniques for the assessment of the neck include CT, and magnetic resonance imaging (MRI), which is used to stage lymph nodes by size and detect the presence of both central necrosis and indistinct nodal margins. Published papers report that CT and MRI detect lymph node metastases with a sensitivity of 36% - 94% and specificity of 50% - 98%.[25]

Other imaging techniques such as fluorine 18 fluorodeoxyglucose (^{18}F-FDG) PET and PET-CT are being used to evaluate cervical lymph node metastases. Most authors report that ^{18}F-FDG PET-CT can reliably exclude distant metastases and detect second primaries in high-risk patients.[26,27]

The negative predictive value of PET-CT is high for recurrences in the neck, with values between 94% and 100%.[28,29] Tseng et al found 26 cases of relapse of RPLN when recurrent disease was restaged with PET-CT,[20] and suggested that this may be of value in all cases of recurrent or second primary oral SCC. If the scan shows the neck to be clear, then sentinel node biopsy should be considered.

Role of sentinel node biopsy in recurrent or second primary oral SCC

Sentinel node biopsy is generally advocated in patients with early T1-T2 oropharyngeal and oral SCC who have not had treatment to the neck.[8,24,30–34]

Flach et al[8] studied 22 patients with recurrent or second primary oropharyngeal and oral SCC and clinically N0 necks after previous treatment to the neck (neck dissection, chemotherapy, radiotherapy, or a combination). Eighteen had previously had treatment of the ipsilateral or bilateral neck, and four had had treatment of the contralateral neck only. All 22 had had sentinel nodes biopsied, and the negative predictive value was 100%, as none of the patients whose biopsy was clear developed regional metastases. Median follow up, however, was only 22 months. The authors also found that 67% of patients who had previously had ipsilateral or bilateral neck treatment and 25% of those who had had contralateral treatment, had unexpected drainage patterns that included mainly levels IV and V, and the opposite side for those who had previously had one side treated. This study supports the theory that distorted lymphatic drainage pathways in the neck after previous treatment can lead to unexpected patterns of metastases.[8]

In another study, Hart et al reported the success of sentinel node biopsy in all 11 previously treated patients.[35] It is also of note that the Eighth International Symposium on Sentinel Node Biopsy in Head and Neck Cancer (2018) recommended that it should be offered to patients who have had previous treatment to the neck.[24]

Transoral robotic surgery for metastases to the RPLN

If a PET-CT indicates invasion of RPLN in cases of recurrent or second primary disease in a previously treated neck, then nodes can be dissected using transoral robotic surgery (TORS), and Byeon et al reported five cases.[36] Park et al recently published data on 71 patients who had dissection of these nodes using TORS with minimal morbidity, and showed that they can be accessed easily.[37] As these studies suggest, robotic surgery can be used to treat cases of aberrant lymphatic drainage after previous treatment of RPLN. It follows that an invaded node found on biopsy could be harvested using robotics, together with the usual single photon emission CT (SPECT) with technetium guidance (gamma finders) after injection of blue dye or fluorescence at the second primary tumour or site of recurrence. If this sentinel node is clear, salvage or complex dissections can be avoided. If it is invaded, the patient could be offered further minimal-access nodal clearance, chemoradiotherapy or radiotherapy if feasi-

ble, or more invasive approaches such as transmandibulotomy through a transcervical approach.

Recommendations

Our recommendations include:

- A multicentre, collaborative, retrospective review of outcomes of patients with ipsilateral second primary or recurrent oral SCC in previously treated necks. Outcomes should include those who did or did not have neck dissections, the level or site at which they failed or relapsed, and survival.
- PET-CT should be considered in all cases of recurrent or second primary disease (if "hot" – neck dissection, if "cold" – sentinel node biopsy)
- Sentinel node biopsy should be considered in all patients with recurrent or second primary disease who have previously had treatment to the neck
- Definitive management should be considered of the sentinel biopsy zone or region subsequent to a positive node:

◯ Laryngeal positive sentinel node - levels VI and VII neck dissection
◯ Ipsilateral undissected zone with an invaded sentinel node - completion neck dissection
◯ Contralateral undissected zone with an invaded sentinel node - contralateral neck dissection
◯ Retropharyngeal invaded sentinel node - surgical (minimal-access robotic or open) or non-surgical treatment.

Ethics statement/confirmation of patients' permission

Not needed

Conflict of interest

We have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bjoms.2019.07.015.

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