Chapter

The Role of Neck Dissection in Oral Cavity Carcinoma

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Abstract

Nodal status at the time of presentation for oral cavity carcinoma is the most important prognostic factor. Neck dissection is warranted for T3/T4 oral cavity carcinoma but there has been an ongoing controversy in the treatment of clinically negative neck in T1/T2. The risk of occult metastases in N0 squamous cell carcinoma of the oral cavity is 20–30%, and was found highest for tongue carcinoma. Elective neck dissection is recommended for T2N0 tongue carcinoma, and Stage I clinically N0 oral cavity carcinoma with tumor thickness >3 mm. CT scan has the highest sensitivity in detecting occult cervical lymph node metastases. Sentinel lymph node biopsy, as well as identification of biomarkers, continue to show increased utility. This chapter aims to discuss the methods of detecting nodal metastasis, the need for elective neck dissection for clinically neck node negative T1/T2 oral cavity carcinoma, the role of watchful waiting in N0 necks, the impact of tumor thickness in the risk for cervical lymph node metastasis, the role of sentinel lymph node biopsy in the detection of occult lymph node metastasis, and the role of biomarkers as predictors of occult lymph node metastasis.

Keywords: oral cavity carcinoma, neck dissection, elective neck dissection, occult cervical metastases

1. Introduction

Nodal status at the time of presentation for oral cavity carcinoma is the most important prognostic factor [1]. If the nodes are affected, the chance for cure is reduced by half [1, 2]. Historically, Shah et al., as early as 1990, demonstrated that levels I, II, and III were at greatest risk for nodal metastases from primary squamous cell carcinoma of the oral cavity [3]. Yuen et al. showed that the rate of cervical metastases is greatest for carcinoma of the oral tongue and floor of mouth, with the rate increasing with increasing T stage [4]. Curative surgery involves wide excision of the primary and neck dissection [1]. For T3/T4 oral cavity carcinoma, neck dissection is warranted even for clinically negative necks [1]. There has long been an ongoing controversy in the treatment of clinically negative neck in early stage oral cavity carcinoma (T1/T2) [1, 4, 5].

This chapter will discuss the methods of detecting nodal metastasis, the need for elective neck dissection for clinically neck node negative T1/T2 oral cavity carcinoma, the role of watchful waiting in N0 necks, the impact of tumor thickness in the risk of cervical lymph node metastasis, the role of sentinel lymph node biopsy in the detection of occult lymph node metastasis, and the role of biomarkers as predictors of occult lymph node metastasis.

2. Detection of nodal metastasis

It has been shown that the sensitivity, specificity, and accuracy of detection of neck metastases by clinical examination are 70, 65, and 68%, respectively; with an overall error of 20–30% [6].

Various imaging modalities are being utilized to detect nodal metastasis and are found to be more reliable than clinical palpation. These include computerized tomography (CT) scan, magnetic resonance imaging (MRI), ultrasound, and positron emission tomography (PET) scan. These modern imaging modalities offer similar diagnostic accuracy to diagnose clinically N0 neck [7]. Sensitivity is comparable across all modalities but CT Scan has been shown to offer the highest specificity [8, 9]. A most recent study by Bae et al. in 2019 showed a higher sensitivity for detection of occult metastasis with PET CT than that for CT/MRI for 42 patients [10].

Despite the quality of current imaging modalities, the risk of occult metastases in necks categorized as N0 in patients with oral cavity squamous cell carcinoma (SCC) has been reported to be between 20 and 30% [8].

3. Elective neck dissection for clinically neck node negative T1/T2 Oral cavity carcinoma

The rate of occult lymph node metastasis in T1 to T2 oral cavity carcinoma reaches as high as 34% [11–13]. Personal data from the experience of the authors showed an occult regional neck nodal metastasis rate of 25% (n = 4) for Stage I and 27.8% (n = 18) for Stage II oral cavity carcinoma.

The decision to observe or treat the N0 neck is left to the choice of the patient and the head and neck oncologist [6]. In oral cavity carcinoma, the only clinically N0 necks for which observation is appropriate are those associated with T1/T2 lip carcinomas, T1/T2 oral tongue carcinomas that are less than 4 mm thick, and T1/T2 floor of mouth cancers less than or equal to 1.5 mm thick [6]. A most recent systematic review by Cao et al. showed that elective neck dissection could significantly decrease neck recurrence and improve disease-free survival and overall survival compared to watchful waiting for patients with cT1-T2N0 oral cavity carcinoma [14].

Particularly for early stage (Stage I and Stage II) oral cavity carcinoma, previous studies have shown a lower risk of regional recurrence rate with elective neck dissection compared to watchful waiting [11, 15–18]. Five-year survival rate is higher for elective neck dissection versus watchful waiting; and specific death rate from regional recurrence is less for elective neck dissection than watchful waiting [11, 17, 18]. Regional recurrence rate for 154 Stage I and II N0 patients was found to be higher for patients who did not receive elective neck dissection [11].

4. Neck dissection general recommendations for Oral cavity carcinoma

The standard treatment for N0 neck (and even N1) is neck dissection of levels I, IIA, and III [19]. However, when level IIA is involved, there is a 22% risk of level IIB involvement, therefore, level IIB has to be included in the dissection [19]. Controversy about level IV involvement has come into play which may justify its dissection because of a reported 15% risk of involvement [20, 21]. Level V is rarely involved in oral cavity that is why it is hardly resected.

For N2/N3, neck dissection of levels I to V are indicated with or without resection of IJV, SCM, or SAN [1].

5. The impact of tumor thickness in the risk of cervical lymph node metastasis and the role of sentinel lymph node biopsy

The National Comprehensive Cancer Network Guidelines (2019) recommends that elective neck dissection be based on the risk of occult metastasis in the appropriated nodal basin [1]. Selective neck dissection of at least levels I–III is recommended for N0 oral cavity carcinoma.

Particularly, for oral cavity squamous cell carcinoma, sentinel lymph node biopsy or the primary tumor depth of invasion should guide decision making and these are currently the best predictors of occult metastatic disease [1, 22]. Earlier versions of NCCN state that for Stage I clinically N0 oral cavity cancer, elective neck dissection is recommended for tumor thickness >4 mm but recent evidence supports the effectiveness of elective neck dissection in patients with oral cavity cancers >3 mm depth of invasion [1, 22].

It is worthy of mention that the recently proposed 8th edition of the American Joint Committee on Cancer (AJCC) staging system for oral cavity squamous cell carcinoma is the addition of depth of invasion (DOI) as a modifier for the T category in the TNM staging [23]. It remains a controversy whether it is reasonable to substitute tumor thickness for DOI, since tumors with a larger DOI or thickness are associated with an increased risk of nodal metastasis and worse survival outcomes [24]. It has been concluded in a 2017 study by Dervin et al. that the T category and TNM stage prognostic performance of the eighth edition AJCC staging of oral cancer is similar regardless of whether DOI or thickness is used as the T-category modifier; hence, in centers or institutions without complete DOI data, it is reasonable to use tumor thickness [24].

Accuracy of sentinel lymph node biopsy for nodal staging of early oral cavity carcinoma has been tested extensively against the reference standard of immediately performed neck dissection or subsequent extended follow-up, with a pooled estimate of sensitivity of 0.93 and negative predictive values ranging from 0.88 to 1, with comparable survival outcomes [1, 22, 25–29]. A more recent systematic review revealed that sentinel lymph node biopsy is advantageous because it improves the accuracy of tumor staging, is a minimally-invasive procedure, avoids unnecessary nodal dissection, and results in limited morbidity and mortality with negative predictive value of 90–95% [6]. The disadvantages include posing difficulty for peri-tumoral injection for bulky invasive primary tumors that invade adjacent anatomic subsites, difficulty in floor of mouth tumors and those with proximity to the draining lymphatic basin, clinically positive nodes that are difficult to be identified by sentinel node mapping because of poor uptake of tracer, and the need for additional second stage surgery in case of positive neck node [6].

In addition, sentinel lymph node biopsy is a technically demanding procedure, with its success rates for sentinel node and occult lymphatic metastasis identification much dependent on technical expertise and experience [1]. Thus, sufficient caution must be exercised when offering it as an alternative to elective neck dissection [1].

6. Biomarkers as predictors of occult lymph node metastasis

Table 1 shows the various biomarkers which have been studied to detect occult lymph node metastasis.

Harada et al. showed that in normal squamous epithelium, cyclin B1 was localized in the nucleus and was expressed only in several cells of the basal and parabasal layers. In tumor tissues, however, cyclin B1 was expressed mainly in the cytoplasm. Cyclin B1 overexpression was positively correlated with occult cervical lymph node metastases and the number of mitotic cells [30].

Predictor	Non-predictor
Cyclin B-1	Vascular endothelial growth factor-C (VEGF-C)
Secreted protein acidic and rich in cysteine (SPARC)	High mobility group box 1 (HMGB1)
E-cadherin (ECAD)	
Podoplanin	
Matrix metalloproteinase-7 (MMP-7)	
Activin A	
partial epithelial-to-mesenchymal transition	

Table 1.
Predictors and non-predictors of occult lymph node metastases in oral cavity carcinoma.

Zhang et al. showed that the secreted protein acidic and rich in cysteine (SPARC) has a positive rate in 49.1% of tongue cancer tissues and 0% in normal tissues. The expression of SPARC was positively correlated with occult lymph node metastasis and recurrence [31].

Huber et al. showed that the differentiation grade and down-regulation of E-cadherin expression significantly correlate with positive lymph node status in univariate and multivariate analyses. Thus, E-cadherin immunohistochemistry may be used as a predictor for lymph node metastasis in squamous cell carcinoma of the oral cavity and oropharynx [32].

Huber et al. showed that podoplanin expression correlated significantly with sentinel lymph node metastasis and remained a significant predictor for lymph node status even after controlling for tumor stage [33]. In relation to this, a more recent study revealed the association of podoplanin and SOX2 in the progression of oral squamous cell carcinoma [34]. OX2 is a transcription factor related to the maintenance of stem cells in a pluripotent state. Podoplanin is a type of transmembrane sialoglycoprotein, which plays an important role in tumor progression and metastasis [34]. There was a significant inverse correlation between the expression of SOX2 and podoplanin with the tumor grade, survival analysis showed that a high expression of SOX2 correlated positively with the disease-free survival, and a significant positive association between the pattern of SOX2 and podoplanin expression [34].

Mäkinen et al. showed that matrix metalloproteinase-7 (MMP-7) expression was associated with presence of occult metastases (OR 3.67; $p = 0.013$); increased invasion depth (OR 4.60; $p = 0.005$); high tumor grade (OR 3.30; $p = 0.007$). MMP-7 was predictive of poor outcome ($p = 0.021$) [35].

In a study by Kelner et al. in 2015, it was found that high immunohistochemical expression of activin A was significantly associated with presence of occult lymph node metastasis in oral tongue squamous cell carcinoma [36].

Non-predictors of occult lymph node metastases as shown in **Table 1** include vascular endothelial growth factor-C (VEGF-C) and High mobility group box 1 (HMGB1). No statistically significant difference was found between OSCC with and without occult lymph node metastasis in regard to VEGF-C immunoexpression by malignant cells [37]. Isolated VEGF-C expression by malignant cells is not of predictive value for occult lymph node metastasis in early stages of oral squamous cell carcinoma [37]. Likewise, Prediction of occurrence of late neck metastasis in early tongue squamous cell carcinoma by evaluating HMGB1 (high mobility group box 1) expression in the primary lesion showed that immunohistochemistry study of HMGB1 in early tongue squamous cell carcinoma did not appear to be very useful for predicting occult neck metastasis [38].

Most recently, immunohistochemistry quantification of partial epithelial-to-mesenchymal transition (p-EMT) in oral cavity squamous cell carcinoma primary tumors

has been reliably shown to be associated with nodal metastases, perineural invasion, and high grade [39]. EMT is thought to be a potential driver of invasiveness and metastasis in a variety of epithelial cancers [39]. It has been said that with prospective validation, p-EMT biomarkers may aid in decision making over whether to perform a neck dissection in the N0 neck and/or for adjuvant therapy planning [39].

7. Post-operative follow-up

Based on the algorithm proposed by Paler et al., follow-up CT scan may be done for N1 disease and PET CT for N2/N3 disease 12 weeks after treatment [40]. CT scan may also be done for N0 neck [1].

The NCCN guidelines follow-up recommendations for oral cavity carcinoma include a complete head and neck examination every 1–3 months for the first post-operative year, every 2–6 months for the second post-operative year, every 4–8 months for years 3–5, and every 12 months beyond 5 years post-operatively. Speech/hearing and swallowing evaluation, nutritional evaluation and rehabilitation, smoking cessation and alcohol counseling, and surveillance for depression are included in the post-operative supportive care recommendations [1].

8. Conclusions

Despite advances in imaging studies in detecting occult metastasis, the risk of occult metastases in necks categorized as N0 in patients with oral cavity squamous cell carcinoma (SCC) remains and the need for neck dissection should carefully be examined. Elective neck dissection, specifically, selective neck dissection, is recommended for Stage II oral cavity carcinoma given the high risk of occult metastasis. For Stage I clinically N0 oral cavity carcinoma, elective neck dissection has been historically recommended for tumor thickness >4 mm but recent evidence supports the effectiveness of elective neck dissection in patients with oral cavity carcinoma >3 mm depth of invasion. The role of sentinel lymph node biopsy in detection of occult cervical lymph node metastasis is promising but requires technical expertise and experience. Identification of biomarkers in predicting the presence of cervical lymph node metastasis may prove to have increasing utility.

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