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Topic: State of the Art in the Management of Oral Squamous Cell Carcinoma

Contralateral neck dissection in oral squamous cell carcinoma: when it shoud be done?

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ABSTRACT

Oral cavity squamous cell carcinoma (OSCC) has a high incidence of cervical micrometastases and sometimes metastasizes bilaterally because of the rich lymphatics in the submucosal plexus, which freely communicate across the midline. The presence of contralateral pathologic lymph nodes has been reported previously as a critical factor influencing the survival of patients. There are a few reports in the literature with regard to the rates of contralateral neck disease and the factors that may be involved in the risk with them. An elective ipsilateral neck treatment is generally recommended for initial treatment in all OSCC. However, no consensus exists whether or not to perform an elective contralateral neck dissection or radiation. In this study, a systematic review has been performed in order to evaluate the predictive value of clinical-histopathologic factors potentially related to contralateral occult lymph node metastasis in squamous cell carcinomas of the oral cavity to form a rational basis for elective contralateral neck management.

Key words:

Contralateral neck dissection; squamous cell carcinoma; oral cavity; oral cancer

INTRODUCTION

Head and neck cancer is the fifth most common type of cancer worldwide, among all neoplasms. Approximately 40% of them occur in the oral cavity. Squamous cell carcinoma (SCC) is the most common histological type, with a frequency of approximately 90%. The presence

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of neck lymph node metastasis is the most significant prognostic and survival factor in patients with oral cavity squamous cell carcinoma (OSCC). With the exception of thin early-stage tumours in the context of clinically and radiologically node negative necks, most patients with OSCC undergo neck dissection.[1] This has the benefit of treating occult metastatic disease and providing pathological staging information to direct adjuvant therapy.[2,3] The rich lymphatic connections in the head and neck makes oral cavity malignancies susceptible to spread across the midline.[4] The SCC of the oral cavity presents a variable frequency of contralateral lymph neck metastases (CLNM) between 0.9% to 36%, reported in the literature.[5,6] The presence of such metastases decreases the survival rate of the patients, generating a poor prognosis.[7] Although elective treatment of the contralateral neck is accepted for OSCC approaching or crossing the midline, this is not routinely performed in lateralized cases. Few studies have analyzed rates of contralateralneck disease in oral cancer and thefactors that may be involved with them. In terms of treatment decision-making, the use of elective contralateral neck dissection remains controversial for patients with OSCC that does not cross the midline.

The purpose of this review was to evaluate the incidence of CLNM and analyze the factors that may predict their appearance in OSCC to form a rational basis for elective contralateral neck management.

METHODS

To address the research purpose, the authors designed and implemented a systematic review of the literature. The electronic search was perfomed in the Cochrane Library, MEDLINE via Pubmed and EMBASE using the key terms “contralateral neck dissection”, “contralateral metastases”, “oral squamous cell carcinoma” and “oral cancer”. Some of these terms were searched in combination. The references of each article obtained were checked for additional relevant studies. Only articles published in English were included in this study. One reviewer screened all titles and abstracts. A total of 103 references were retrieved, of which 34 were screened. The exclusion criteria were: (1) date of publication before 1999; (2) articles written in a language different from English; (3) required data not available; and (4) type of article: abstracts, letters, comments, editorials, expert opinions or case reports.

THE ROLE OF CLNM IN OSCC

The contralateral metastasis propagation can occur in the head and neck carcinoma in different ways: firstly, by crossing afferent lymphatic vessels, by tumor spread along the midline, when ipsilateral lymph nodes are widely involved, and secondly, in certain anatomical areas where there is not a real barrier in the midline.[7]

The OSCC has a high incidence of micrometastases and often bilaterally metastases due to the rich submucosal lymphatic plexus, that communicates freely crossing the middle line.[8] It presents a variable incidence of CLNM between 0.9% to 36%, reported in the literature. Diverse factors can be held responsible for such differences, among them the diversity of the anatomic regions considered for study, problems in clinical staging, and exclusion of cases not considered eligible for treatment. Kowalski *et al*.[6] found a rate of 36% of contralateral positive nodes after bilateral neck dissection. Kurita *et al*.[5] observed an incidence of CLNM in early oral tongue SCC of 12.2%. In the paper reported by Koo *et al*.[8] the overall rate of occult contralateral metastasis in OSCC was 11%, and the rate was 21% in cases of ipsilateral pathologic metastasis. In the study of Bier Laning *et al*.[9] the incidence was 10%. This corresponds to the findings of Mukherji *et al*.[10] who found that oral tongue and floor-of-mouth cancers had an expected drainage to contralateral lymph nodes in up to 9% of cases. On the other hand, Lim *et al*.[11] in their study detected only a 4% rate of contralateral occult metastases in a series of early tongue carcinomas and did not recommend elective contralateral neck treatment. González-García *et al*.[12] in a large series of 315 patients with oral squamous cell carcinoma of the oral cavity, reported an incidence rate of 5.7% for CLNM, which is similar to the 5-year CLNM rate of 4.1% reported by Feng *et al*.[13] while another large cohort study by Huang *et al*.[14] showed a 7.1% 5-year CLNM rate.

In relation to prognosis, it has been widely accepted that CLNM dramatically reduce the long-term survival and prognosis in these patients is described as extremely poor.[6,8,15,16] Capote-Moreno *et al*.[7] reported a decrease in the 5-year survival rate in patients with OSCC, from 70% in patients with negative contralateral lymph nodes to 41.2% in those with CLNM. These rates were similar to those found by other authors; for example, Koo *et al*.[8] found a 5-year cause-specific survival rate of 43% in patients with contralateral disease compared with 73% in metastasis-free patients in a series of 173 cases with oral and oropharyngeal SCC, which emphasizes the prognostic importance of CLNM.

With respect to the time of appearance, most studies corroborate that CLNM mainly happens within two years postoperatively.[17-20] For instance, González-García *et al*.[20] in a series of 203 patients with oral squamous cell carcinoma of the tongue, with especial consideration in excluding those cases involving the midline or at a distance less than 1 cm, reported CLNM occurring within the first 2 years after surgery in 89.9% of the affected patients. Therefore, special effort should be paid early detecting nodal relapse in the cervical región,while a careful follow-up is mandatory during this period of time.

PREDICTIVE FACTORS

Several clinical and pathological factors have been proposed

to be correlated with the risk of contralateral lymph node metastasis as well as with patient survival. We consider it important to analyze these factors. It is currently unclear whether CLNM are underestimated in OSCC patients at initial presentation. Therefore, correct identification of risk factors associated with CLNM is paramount to improve the clinical outcome of this patient group, especially because ultrasound diagnostic imaging and computed tomography scannings are not sensitive enough to sufficiently detect occult disease. Prediction of tumors at high risk for contralateral involvement may determine a better therapeutic management of the contralateral neck and may improve OSCC prognosis [Table 1].

Tumor location

One of the factors that has been speculated as a determinant prognosticator for contralateral metastases is tumor location, although there is not a clear consensus about which location is of higher risk for cross-metastases.

The importance of tumor midline involvement had been already exposed by Martin *et al*.[21] Risk increased to 16% in cases with tumors crossing the midline by less than 1 cm and reached 46% in those where the crossing was of more than 1 cm. In the same way, Koo *et al*.[8] also demonstrated that the rate of contralateral occult neck metastasis was significantly higher in cases in which the primary lesion showed extension across the midline, compared with early-stage or unilateral lesions. In a series including 513 consecutive cases, Kowalski *et al*.[6] testified that the risks of CLNM were significantly higher in cases of tumors extending to 1 cm or less of the midline or crossing such medial margin (relative risk from 2.8 to 12.7). In the study of Kurita *et al*.,[5] patients with tumors showing radiological evidence of extension crossing the midline were at a higher risk for CLNM (53.8%) than patients without an extension crossing the midline (10.3%).

In relation to the location of the primary tumor, a higher risk for CLNM in patients with tumors of the floor of the mouth and the anterior third of the tongue in detriment of the retromolar region or the lateral gum has been reported.[6] Cross-drainage in the oral tongue and floor of mouth cancer is common, thereby placing both sides of the neck at risk for nodal metastases, as reported in the study by Mukherji *et al*.[10] Califano *et al*.[22] found a higher rate of contralateral involvement in the base of the tongue even in early tumors than in the body and the tip of the tongue and recommended prophylactic bilateral neck dissection in all tongue base carcinomas. The data of Olzowy *et al*.[23] also showed that tumors of the base of tongue had a higher risk of contralateral metastases than that of tumors of the tonsillar fossa. Moreover, although not statistically significant, tumors of the soft palate and the pharyngeal walls also seemed to have a higher risk of CLNM. Capote-Moreno *et al*.[7] observed a higher tendency for contralateral metastases in tumors located in the tongue base (31.4%) and the floor of the mouth (11%), with a lower frequency in the mobile tongue (7.2%) and the oropharynx (6.3%). However, in the study of Kurita *et al*.,[5] the incidence of CLNM was higher in cases of lower gum carcinoma (25%) than in those with mobile tongue carcinoma (15.4%). They suggested that the direction of tumor invasion is a more important factor for CLNM than the original tumor location in patients with

Table 1: Chart review of the main articles that analyze risk factors for CLNM

Study	Year	Number	Mean age (years)	Male:female	Follow-up (months)	CLNM (number of patients)	Predictive factors
Kowalski *et al*.[6]	1999	513	56.4	437:76	-	38	TNM stage and ipsilateral metastases
Kurita *et al*.[5]	2004	126	66	74:55	21	19	T-stage, ipsilateral metastases, and histo-pathologic grading
Koo *et al*.[8]	2006	66	53	52:14	44	7	T-stage and ipsilateral metastases
González-García *et al*.[20]	2007	203	59	72:28	71	9	Histo-pathologic grading and peritumoural inflammation
González-García *et al*.[12]	2008	315	60	222:93	> 5 years	18	TNM stage, histopathologic grading, surgical margins, ipsilateral neck dissection and perineural invasion
Liao *et al*.[31]	2009	913	49	852:61	> 24	55	ECS, tumor location, ipsilateral metastases and histo-pathological grading
Capote-Moreno *et al*.[7]	2010	402	59	293:109	> 12	20	ECS, tumor location, ipsilateral metastases and histo-pathological grading
Olzowy *et al*.[23]	2011	352	56.8	274:78	-	75	Tumor location, T-stage and ipsilateral metastases
Lin *et al*.[38]	2012	683	> 50	624:59	-	36/676	Tumor location and histo-pathologic grading
Feng *et al*.[13]	2014	1,482	60	822:66	> 5 years	35/844	ECS
Habib *et al*.[33]	2016	481	64	288:193	160	14	Ipsilateral metastases and histo-pathologic grading

CLNM: contralateral lymph neck metastases; TNM: tumor node metastasis; ECS: extracapsular spread

who underwent observation of the contralateral neck and those who underwent contralateral END, even when those in the observation group who received radiation therapy were excluded.

Although the reason for these findings is unclear, it has been suggested that END, in conjunction with primary tumor resection, may predispose patients to aberrant migration of intransit carcinomatous cells to the opposite side of the neck.[12] Chow *et al*.[28] failed to show bilateral neck dissections reduced the contralateral neck relapse by statistical testing. Remarkably, only 1 of the 12 patients undergoing bilateral neck dissection as part of their definitive treatment developed contralateral nodal recurrence. In contrast, 8 of the 46 patients undergoing only ipsilateral neck dissection developed contralateral or bilateral nodal recurrence. In the same way, for González-García *et al*.[12] unilateral cervical dissection was predictive for CLNM. In fact, only 1.8% of the patients that primarily underwent bilateral neck dissection developed CLNM, in comparison with 7.4% of those patients undergoing unilateral neck dissection. Remarkably, only 2 of 64 patients undergoing bilateral neck dissectionas definitive treatment developed CLNM. In contrast, 14 of 149 patients undergoing ipsilateral neck dissection developed CLNM. However, despite these results, they stated that the low reported incidence of CLNM and the added morbidity supported recommendation for bilateral neck dissection in selected patients with tumors primarily arising in the midline.

Lanzer *et al*.[4] did neither show a statistical benefit of elective CND in patients with contralateral clinically negative neck. Neither locoregional recurrence-free survival nor overall survival rates differed.

In another study, performed by Liao *et al*.,[31] the independent risk factors for the 5-year CLNM rate were poor differentiation, perineural invasion, and level IV/V lymph node metastases. A prognostic scoring system was thus formulated by summing up the three significant factors identified by multivariate analysis. In order to reduce the incidence of CLNM, CND and adjuvant therapy were recommended in high-risk patients with tongue cancer [score 2-3, 5-year nonrenal clearance rate (CLNR) 40%]. In the intermediate-risk group (score 1, 5-year CLNR 15%), neck ultrasound examinations were recommended every 3 months until 24 months postoperatively. Observation should be considered sufficient for low-risk patients (score 0, 5-year CLNR 3%).

In a recent study by Fan *et al*.,[37] all indications for contralateral END in oropharyngeal SCC were summarised as leading to: (1) tumours crossing the midline; (2) advanced staging (cT34); (3) primary tumour more than 3.75 mm thick; (4) multiple ipsilateral node involvement; and (5) tumours arising in the base of the tongue and floor of the mouth.

The location of the primary tumor plays an important role in other studies. The carcinoma of the base of tongue seems to have a high propensity to produce bilateral neck metastases. For Olzowy *et al*.,[23] in the case of involvement of the base of tongue, the neck should be operated on bilaterally, independent of T classification of the primary. In carcinomas of the soft palate greater than T1, bilateral neck dissection should also be recommended because of a high frequency of bilateral metastases. For Lin *et al*.,[38] prophylactic CND is suggested for primary oral tumors with mouth floor invasion or midline crossing, or at advanced tumor stage (> T3). This recommendation is not supported by most authors.

In summary, despite facing a high number of occult lymph node metastasis in the ipsilateral and contralateral neck in oral cancer, the locoregional recurrence rate seems to be low. Surgeons should take into account the detailed and individual study of risks and potential benefits of elective neck treatment for contralateral N0 neck while considering the small percentage of patients with oral carcinoma that finally develop CLNM.

Adjuvant radiotherapy

The alternative to the bilateral neck dissection is radiotherapy (RT) of the contralateral neck in the case of a relevant risk of bilateral metastases, particularly in patients receiving planned adjuvant RT postoperatively. In this way, Capote-Moreno *et al*.[7] recommended bilateral treatment of the neck with surgery or RT in patients with several risk factors. On the other hand, Koo *et al*.[8] showed that the patients who received adjuvant RT had a lower locoregional control and survival rate compared with those who did not receive adjuvant RT. However, this was attributed to the fact that the patients who received adjuvant RT were those who had an advanced-stage disease or worse prognosis, which would have affected the locoregional control and survival rate. Finally, they suggested elective contralateral neck management with surgery or RT in the treatment of OSCC patients with ipsilateral node metastasis and/or those with tumors either greater than stage T3 or crossing the midline.

The results of the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer trials have provided evidence that in patients with head and neck cancer surgery plus concomitant chemoradiation (CCRT) had a better impact on clinical outcome compared with surgery plus RT.[39,40] The benefits of CCRT were especially evident in head and neck cancer patients with positive margins and ECS.[40] In the study performed by Feng *et al*.,[13] postoperative CCRT compared with surgery alone improved the 5-year disease-specific survival in these high-risk patients but did not decrease the 5-year CLNM rate. However, it is important to take in mind that the use of CCRT in the adjuvant setting, which is highly toxic, may cause immunosuppression.[41] For these authors, whether high-risk patients benefit from

contralateral neck dissection plus adjuvant CCRT can only be answered in a prospective trial.

To come to conclusions, when RT is employed as the elective treatment modality, the threshold for treating the contralateral neck is low, taking in mind the difficulty of future treatment in cases of recurrence, and the relative low additional morbidity associated with the therapy. Thus, in patients at a moderate-high risk of developing CLNM, contralateral neck should be included in the radiation field.

CONCLUSION

The OSCC presents a variable incidence of CLNM, reported between 0.9% to 36% and it has been widely accepted that CLNM dramatically reduce long-term survival and prognosis. Several predictive factors have been proposed to be correlated with the risk of contralateral lymph node metastasis, such as tumor location, size or thickness, ipsilateral lymph node metástasis, ECS, TNM stage, surgical margins, grade of hystological differentiation, tumor satellite distance, perineural and lymphovascular invasion, peritumoral inflammation and local recurrence.

It is important for clinicians to pay careful attention to these prognostic variables that must be globally considered for each individual case. Surgeons should take into account the detailed and individual study of risks and potential benefits of elective neck treatment for contralateral N0 neck while considering a small percentage of patients with oral carcinoma that finally develop CLNM.

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Conflicts of interest
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