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REVIEW

A review of clinical and histological parameters associated with contralateral neck metastases in oral squamous cell carcinoma

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Oral squamous cell carcinoma (OSCC) has a high incidence of cervical micrometastases and sometimes metastasizes contralaterally because of the rich lymphatic intercommunications relative to submucosal plexus of oral cavity that freely communicate across the midline, and it can facilitate the spread of neoplastic cells to any area of the neck consequently. Clinical and histopathologic factors continue to provide predictive information to contralateral neck metastases (CLNM) in OSCC, which determine prophylactic and adjuvant treatments for an individual patient. This review describes the predictive value of clinical-histopathologic factors, which relate to primary tumor and cervical lymph nodes, and surgical dissection and adjuvant treatments. In addition, the indications for elective contralateral neck dissection and adjuvant radiotherapy (aRT) and strategies for follow-up are offered, which is strongly focused by clinicians to prevent later CLNM and poor prognosis subsequently.

***Keywords*:** oral squamous cell carcinoma; lymph node metastasis; contralateral neck metastasis; neck dissection; head and neck cancer

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Introduction

Oral squamous cell carcinoma (OSCC) is the most frequent of head and neck malignancies, which represents approximately 3% of all malignancies in the body and accounts for more than five hundred thousand newly diagnosed cancers every year worldwide. Several studies have been concerned on the cervical metastases and prognosis of OSCC. Recently, more retrospective studies have analysed some clinical-histopathologic prognosticators influencing contralateral neck metastases (CLNM) in OSCC. OSCC has a high incidence of cervical micrometastases and sometimes metastasis contralaterally because of the rich lymphatic intercommunications relative to submucosal plexus of oral cavity that freely communicate across the midline [1]. It is widely accepted that the presence of lymph node metastases is one of the most important prognosticators related to survival of OSCC, and several studies have shown this influence by the drastic decrease in survival rates in patients with positive neck nodes [2-6], with most succumbing to

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locoregional recurrence. Therefore, cervical metastases remain a topic of interest for oral surgeons [3-4]. This review details clinical-histopathologic factors for CLNM, and considers their relative merits and disadvantages, and also summarizes the indications for elective contralateral neck dissection and adjuvant treatment, timing of CLNM occurrence and strategies for follow-up.

Incidence of CLNM in OSCC

CLNM in OSCC involved complex mechanism and anatomic structures of the cervical region, while numerous biological and molecular factors may be considered. However, the exact mechanism that takes place in contralateral metastases is not yet clear. Some authors recognize that contralateral metastases of head and neck carcinomas can occur in different ways: firstly, by crossing afferent lymph vessels; and second by tumor spreading over the midline to reach efferent collateral lymphatic vessels while ipsilateral lymph nodes are extensively involved, where there is not a real midline barrier in certain anatomic areas [7]. The incidence of CLNM differs considerably among institutions from 0.9% to 36% [6, 8-21].

Diagnosis

The most important prognostic factor for tumor behavior and outcome in squamous cell carcinoma (SCC) of the oral cavity is the presence and extent of cervical lymph node metastases at initial diagnosis. The basic procedure to check cervical lymph node is physical examination, but clinical examination alone is not enough to establish the true extent of local involvement and regional metastases [22]. Therefore, auxiliary modern diagnostic modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), lymphoscintigraphy (LS), and ultrasonography (USG) and USG-guided fine needle aspiration cytology, are recommended to increase the efficacy of the neck evaluation in patients with oral carcinoma, and some having become routine screening procedures in recent years [23]. LS can supply a complete map of the lymphatic drainage preoperatively and serve to guide lymphadenectomy, making it possible to tailor selective neck dissection and reducing surgery related morbidity [24]. PET is a promising imaging tool, but its sensitivity is still insufficient for it to replace surgical lymph node staging [25].

Clinicians should especially emphasize the importance of the clinical N0 neck, which is defined as having no cervical lymph nodes palpated on physical examination and no findings on imaging studies that correlate with Mancuso's criteria [26] for benign nodes. However, there are limitations of all these imaging modalities for the detection of very small micrometastases within these nonpalpable neck nodes [23]. Metastases may unfortunately not be visible in some small positive lymph nodes by conventional imaging techniques. The researchers [27] demonstrated that approximately 25% of all clinically occult metastases are too small to be detected using any of the available imaging techniques. Lin *et al*. [28] also found that discrepancies between clinical and pathologic staging were not uncommon, with a difference of 43.4% for N stage and 29.7% for T stage. Approximately two thirds of patients were clinically over-staged for T, while two thirds were under-staged for N.

Prognosis

It has been widely accepted that contralateral neck lymph nodes are strongly correlated with poor prognosis, positive contralateral metastases significantly reducing long-term survival in several studies [3-4, 6, 8, 13-14, 29-32]. Capote-Moreno *et al.* [6] found a statistical influence of contralateral lymph node metastases on survival in a study of 402 patients of oral and oropharyngeal SCC. Patients with positive contralateral metastases showed a decrease in survival rate, with a 5-year cause-specific survival rate of 41.2% versus 70% in the group with negative contralateral metastases. Similarly, Koo *et al*. [29] observed 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. In a series of 1 069 cases in whom cervical dissection was performed for the treatment of oral and oropharyngeal carcinoma, Spiro *et al*. [30] reported that the five-year survival rate in patients with ipsilateral nodal metastasis was 28%, but this rate decreased significantly to 8% in cases of bilateral metastasis. It is obviously that the prognosis of patients with CLNM in OSCC remains poor.

Clinical-histopathologic factors

In relation to primary OSCC, many clinical and histopathologic factors have been reported to be predictive for CLNM recently. Efforts have been made to elucidate tumor-related factors that could influence the appearance of CLNM in OSCC.

Tumor location

Tumor location has been speculated as a determinant

factor for CLNM in several previous reports: although, there is not a clear consensus about which location is of higher risk for contralateral metastases. Traditionally, SCC of the oral cavity located in the midline has been associated with an increase in bilateral or contralateral cervical lymph node metastasis [10, 18]. Therefore, tumors arising in the region between both canines have been excluded in several studies recently in order to determine the relationship between primary tumor features and the appearance of CLNM.

Interestingly, OSCC extending the midline have been related to the most important predictors of contralateral or bilateral metastases on multivariate logistic regression analysis [6, 8, 11, 13], due to the involvement of the contralateral lymphatic drainage. In 1951, Martin *et al*. [10] reported that primary tumor invasion crossing the midline of oral cavity was associated with a higher incidence of contralateral metastases. Sixteen percent of the tumors crossing the midline less than 1 cm developed CLNM, but this value increased to 46% in cases that invaded the midline greater than 1 cm. Koo *et al*. [29] also demonstrated 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*. [8] testified that the risks of contralateral metastases 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).

When the primary site is considered, the incidence of CLNM varies broadly in the oral cavity. Capote-Moreno *et al*. [6] 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%). Researchers [7-8, 33] have suggested that patients with primary tumor of the floor of the mouth, which is known to have a rich and bilateral lymphatic drainage pattern exhibit a higher risk of contralateral metastases than those with tongue tumors or those invading the retromolar trigone. It was also found that a higher rate of contralateral metastases in the base of the tongue, even in early tumors, than in tumors of the tonsillar fossa or the body and the tip of the tongue by Olzowy *et al*. [21] and Califano *et al*. [34]. However, diverse findings have also been reported the most-contrasting data showing a higher incidence of CLNM in cases of lower gum carcinoma (25%) in comparison with those tumors starting on the mobile tongue (15.4%) [13].

In summary, patients with tumors arising in the base of tongue and floor of the mouth have a high frequency of CLNM than those tumors associated with a significant reduction of contralateral metastases that involve the retromolar trigone area and mobile tongue.

Tumor size

According to TNM staging classification system, tumor size based on the greatest surface dimension—"tumor diameter". Several studies have widely described a correlation between large size at presentation and contralateral metastases, which are associated with an increased risk of poor survival [8, 13, 21, 29, 35-39]. Risks of CLNM for cases of tumors at stage T4 and patients seen with two involved sites are significantly higher in relation to those with tumors confined to the original site or at early stage. In a retrospective analysis of 66 patients with cancer of the oral cavity at N0–2 stage, Koo *et al*. [29] showed that the rate of contralateral occult metastasis was 8% for T2, 25% for T3, and 18% for T4, whereas no metastasis was observed in the T1 cases. It is also noteworthy that fewer bilateral metastases were seen for T1 tumors compared with more advanced primaries [21] and the patients with bilateral metastases had at least T2 disease or greater [39].

Tumor thickness

Tumor thickness is determined by the vertical measurement starting from the line of the mucosa up to the maximum point of the invasion using a millimetric lens (0/20 mm) [40-42]. Both for exophytic and invasive tumors, the upper point of the measurement is the line of the mucosa [43]. Thickness is a direct micrometer measurement by the pathologist of the vertical bulk of tumor regardless of the histologic structure of the ulcerative or exophytic form of tumor growth [44]. Consequently, studies on measurement standard of tumor thickness or depth are very controversial in the literature [45-47], it is possible that the cut of the paraffin block is not exactly vertical depth.

Otherwise, tumor thickness is now recognized as a more accurate histological prognosticator of cervical nodal metastasis, local recurrence, and survival than diameter [8, 20, 42, 48-53]. Bier-Laning *et al*. [20] found an approximately 5% increased risk of CLNM for every 1-mm increased in tumor thickness, and there were no cases of contralateral nodal metastases when the primary tumor had a thickness <3.75 mm. Others [8, 53] have also demonstrated that risks of contralateral metastases were higher in cases of tumors with over 6 mm in relation to cases of up to 3 mm thickness and tumor thickness>4 mm were independent factors predicting for late cervical metastases in early-stage oral tongue cancer. Nevertheless, González-García *et al*. [18] failed to show

tumoral thickness greater than 2 mm as predictive for CLNM, which could be attributable to the insufficient sample size where 7.1% of the patients with tumor thickness greater than 2 mm developed CLNM in comparison with 0% of the patients with tumor thickness less than 2 mm.

Clinical stage

Kowalski *et al*. [8] reported that the clinical stage was the most important predictors of contralateral metastasis. Meanwhile, several independent studies have also shown that patients with advanced tumors are at a higher risk for contralateral lymph node metastasis in SCC of oral cavity [8, 13, 18, 29]. For example, Kowalski *et al*. [8] found that the risk of contralateral metastases in the 297 cases eligible for analysis, the groups of clinical stage (CS) II, III, and IV had risks from 1.8 to 9.6 times higher than the cases of CS I.

Surgical margin status

The surgical margins include both the surface mucosa at the edge of the tumor and the submucosal and deeper connective tissues all around the defect [54]. The involvement of tumor cells at surgical margins has been regarded as one of the most important prognosticator in patients with SCC of oral cavity. Many studies have suggested that complete tumor excision with an adequate margin is an important clinical procedure [55-58]. Even the relative risk of death associated with a close margin is similar to that associated with nodal metastasis [59]. In a nearly recent report, Nason *et al*. [60] found that the survival improved with each additional millimeter of clear surgical margin, each 1-mm increase in clear surgical margin decreased the risk of death at 5 years by 8%. On univariate correlation analysis for contralateral metastases, authors have demonstrated that surgical margins had a statistical association with a high risk of contralateral lymph node metastases developing [6, 18].

Therefore, the precise definition of the clear or adequate surgical margin is an important prognostic consideration and even determines adjunctive treatments for certain patients with OSCC. Histological margin is considered involved when the presence of invasive carcinoma and/or carcinoma "in situ" on the margins of the mucosa is identified and/or the distance of tumor to the normal mucosa margin is less than 5 mm [6, 43]. According to UK guidelines, the status of both the mucosal and deep margins and designate margins of 5 mm or more are considered as clear, 1–5 mm as close, and less than 1 mm as involved. Woolgar [54] suggests that even 5 mm may not be ''clear'' when the pattern of invasion is highly unfavorable with widely separated tumor satellites. However, in a retrospective study based on a historical cohort of 277 surgically treated patients with oral cancer, Nason *et al*. [60] recently suggested that an inadequate or close margin was defined as tumor within 3 mm of the inked resection margin and that the widely accepted definition of a close margin as within 5 mm needs to be reassessed. Considering the shrinkage effect of surgical specimens, on the order of 40% to 50%, when fixed in formalin [61], it is generally accepted that the surgical resection margin presenting 1 cm or more of non-affected tissue around the tumor is considered adequate. Illustratively, authors reported that only 4% of patients in groups of specimens with more than 1 cm of non-affected tissue around the tumor developed CLNM in contrast to 11.6% of patients with surgical resection margin presenting less than 1 cm [18].

A clear margin has been believed to assure adequate treatment by surgery. However, this concept has recently been challenged by several studies in which pathologically document that adequate margins cannot necessarily guarantee tumor cells are removed completely [62-66] and patients with clear margins do not always have good clinical outcomes, as local recurrence rates with clear margins in tongue cancer ranged from 4% to 18% [56, 58, 62]. As a result, there is not a single definition for an adequate resection margin. Several variables, including tumor thickness, the pattern of tumor invasion, tumor satellites, tumor satellite distance, and other clinical factors should be considered.

Parameters of the cervical (regional) lymph nodes

The prognostic importance of the presence and extent of cervical lymph node metastasis in SCC of oral cavity has been recognized for many decades. Numerous independent authorities have reported an association between occurrence of CLNM and homolateral lymph node metastasis: although, there is no general agreement on which features are the best prognosticators [6-8, 10-11, 13-14, 18-19, 32, 67]. In relation to several features of cervical lymph node affectation [54], the number and the level of ipsilateral lymph node metastasis has been widely investigated while extracapsular spread (ECS) has been commonly confirmed.

Patients with metastatic homolateral cervical lymph nodes have a high risk of contralateral metastases (4.8 times higher) in comparison with the cases with no metastases on the same side of the neck, as reported by Kowalski *et al*. [8]. Other authors [13, 21] have further demonstrated that patients with multiple ipsilateral positive nodes (two or more) presented with a higher risk for contralateral metastases or bilateral metastases than those with a single positive node or negative nodes.

For example, Kurita *et al*. [13] reported that the incidence of CLNM was higher in patients with multi-node involvement (50%) than in those with single node involvement (26.1%). The level of homolateral node metastasis was also correlated with CLNM. Level IV/V lymph node metastasis was an independent risk factors for the five-year rates of CLNM [19]. Interestingly, a few authors have reported that CLNM never occurred in patients without homolateral lymph node metastasis, but only simultaneously with and after homolateral neck node metastasis [13, 68], which suggests CLNM is unlikely if homolateral node metastasis has not occurred. A possible explanation is that the performance of elective neck dissection together with primary tumor resection may predispose patients to aberrant migration of in-transit carcinomatous cells to the opposite side of the neck [68]. Therefore, the management of contralateral N0 neck in early SCC of oral cavity also may need to considered in order to prevent later cervical metastasis, according to these findings [15].

The extent of ECS is recorded as ‘‘macroscopic’’ and ‘‘microscopic’’, when it is obvious on laboratory inspection and only evident on histological assessment, respectively [54]. The prognostic importance of ECS has also been emphasized by several studies and it is commonly recognized as a simple, sensitive and highly discriminating indicator [3, 19, 39, 54, 69-72]. In a series of 913 patients, Liao *et al*. [19] have shown that the five-year CLNM rate was significantly higher in patients with ECS (39%) than in those without (12%). Furthermore, the five-year OS was 48% in patients without ECS, whereas it dropped to 16% in those with ECS.

Histological grading

The histological grading OSCC is adopted by Broders’/WHO grading system which recommends three categories: grade 1 (well differentiated), grade 2 (moderately differentiated), and grade 3 (poorly differentiated). It mainly takes into account a subjective assessment of the degree of keratinisation, cellular and nuclear pleomorphism, and mitotic activity [73].

More and more authorities now recognize that Broders’/WHO grade alone shows poor correlation with prognosis and response to treatment in an individual patient [51-52, 73]. It is probably attributed to the lack of discrimination inherent in Broders’/WHO grading system: over 90% of oral and oropharyngeal tumors are grade 2 [54].

However, results of a few previous studies have suggested that histological grading is a significant and independent predictor for cervical lymph node metastasis in head and neck SCC [13, 17, 74-76]. It was also reported that a higher degree of histopathological grading created at a higher risk for CLNM in SCC of oral cavity [13, 18-19]. In a series of 315 consecutive patients with primary OSCC, Gonz ález-Garc á *et al*. [18] found that 13.5% of the patients with poor-difference SCC developed CLNM, in comparison with 5.2% of patients with well-differentiated tumors.

However, one must consider that the influence of histological subtypes of OSCC to CLNM has not been reported in the literature, and more studies are needed.

Pattern of tumor invasion

To overcome some of the problems associated with the Broders’/WHO grading system, Jakobbson *et al*. [77] firstly introduced a multifactorial histological malignancy grading system, considering multiple features of both the tumor cells and the interface between the tumor cells and the host tissues. Subsequently, several modifications followed in order to search for a better histologic prognosticator of the outcome of patients with OSCC [49, 74, 78-82], Anneroth *et al*. [80] and Bryne *et al*. [81]. advocated a new grading system based on the pattern of tumor invasion (POI) from the deep tumor margin to surrounding connective tissues. This system includes four categories: grade 1 tumors have pushing borders with well-defined delineations; grade 2 tumors have advancing fronts with solid cords, bands, and strands; grade 3 groups or cords of infiltrating tumor islands, consisting of greater than 15 cells per island, are identified in the invasive border; grade 4 tumors have obvious tumor cell dissociation in small groups, less than 15 cells per island, at the inter-face of the main tumor and the surrounding tissue.

Several independent workers have found POI showing a better prognostic value than the conventional Broders’/WHO grading system in predicting nodal metastasis, local recurrence, and survival [53, 81-84]. For example, Brandwein-Gensler *et al*. [63] also demonstrated that POI was more significant than positive surgical margin in predicting local recurrence and overall survival in patients with OSCC. Based on a retrospective study of 129 patients with SCC in the oral cavity, Kurita *et al*. [13] also found that POI was correlated with CLNM; although, it was not a significant independent predictor for CLNM.

Tumor satellites and Tumor satellite distance

Tumor satellites are defined as separate islands of tumor cells of any size, with intervening normal tissue at the tumor and nontumor interface [63]. By the same rule, tumor satellite distance (TSD), which reflects the sprea-

ding ability of tumor satellites and is regarded as a prognosticator in hepatocellular carcinoma initially, is defined as the distance from the main tumor to the most distant tumor satellite [85]. It has been demonstrated that TSD can also serve as a significant prognosticator of SCC in the oral cavity.

It has been reported that microsatellite tumor spread could reach as far as 1.8 cm [86], where microscopic tumor cells located at the deep margin were often invisible and impalpable during surgery [87]. Therefore, tumors may leave distant tumor satellites beyond the surgical scope and lead to consequently local recurrence, cervical nodes metastasis, and poor outcomes when surgical margins are considered clear intraoperatively. Yang *et al*. [64] reported that tumor satellites occurred in 92% of tumors and were significantly associated with betel nut exposure. Patients with TSD more or less than 0.5 mm had statistical significance for prognosis while patients with TSD >0.5 mm had a higher incidence of local recurrence, shorter intervals to neck recurrence, and a higher propensity to contralateral or bilateral cervical nodal metastasis.

Lymphovascular invasion

Lymphovascular invasion, as part of the multifactorial grading system proposed by Jakobbson *et al*. [77]. is classified according to the presence or absence of tumor cells, located both in the wall and in the light of the blood or lymphatic vessels [43] and implies an increasing the likelihood of successful metastatic growth. It is difficult to define and recognize with certainty while considering the presence and extent of lymphovascular involvement.

It has been shown that lymphovascular invasion has a significant association with tumour site, size, and thickness, perineural invasion, histological grading, pattern of invasion, cervical nodal metastasis, status of surgical margins, local recurrence, and survival [8, 37, 59, 83]. Kowalski *et al*. [8] suggested the presence of lymphovascular involvement, as well as of perineural infiltration were significantly associated to higher rates of risks of contralateral metastases in OSCC.

Perineural invasion

The definition of perineural invasion is similarly to lymphovascular invasion which is considered presence of the tissue adjacent to the peri and/or intra-tumoral nerves involved by neoplasic cells. Several previous researchers [6, 8, 19, 37, 59, 83, 88] have recognized it is a valuable prognosticator for neck metastases.

Its correlation with contralateral metastases of oral carcinoma has been analyzed in a few studies [6, 8, 18]. For example, Gonz ález-Garc á *et al*. [18] reported perineural infiltration of the primary tumor of OSCC was highly predictive for CLNM, as was illustrated by the appearance of pathologic contralateral lymph neck nodes in 17.02% of patients with perineural infiltration, in comparison with only 4.1% of those patients without perineural involvement.

Muscular infiltration

Muscular infiltration is a factor that can be measured in an objective manner. It describes whether or not there is tumoral cells observed adjacent to either the surface or deep muscular tissue. It has been have reported to be a reliable and sufficient predictive factor of lymph node metastasis [43, 89-90] although, a few reports described it as not being an important prognostic factor [67, 91-92]. Byers *et al*. [90] reported that the probability of occult metastasis increased if muscular invasion exceeded 4 mm. It was also found that muscular infiltration showed a higher probability of occult metastasis and lower disease-free survival when tumors located to tongue and floor of the mouth in the initial stages by Pimenta Amaral *et al*. [43]. However, there has been no correlation found between CLNM in oral carcinoma and muscular infiltration thus far.

Desmoplastic reaction and peritumoral inflammation

To the best of our knowledge, no report has considered the possible correlation between CLNM and desmoplastic reaction, but a few have reported that desmoplastic reaction and peritumoral inflammation are significant predictive factors of cervical metastasis [17, 43, 93]. Gonz ález-Garc á *et al*. [17] reported that peritumoral inflammation was statistically significant in relation to CLNM in a retrospective analytic study of 203 patients with SCC of the tongue. They offer a possible explanation for this association that a low host immunological response around the primary tumor could allow easier dissemination of cancer cells through lymphatic drainage.

The impact of clinical treatment

Neck dissection

To prevent CLNM in oral carcinoma, neck dissection has been given much attention by surgeons. Although the importance of treatment of the neck in patients with palpable or radiologic positive lymph nodes is beyond doubt, elective treatment of the clinically negative neck continues to generate controversy. To the best of our knowledge, no consensus has been achieved on the use of contralateral neck treatment in OSCC patients at early

stage. The central point is whether prophylactic neck dissection for contralateral clinical N0 should be performed.

Numerous retrospective studies have supported the role of elective neck dissection in contralateral N0 oral cavity SCC when patients present a high risk for later CLNM. Elective neck dissection of the contralateral neck in OSCC can safely be performed as neck dissection of regions I, II, III, and IV [94-96]. As a limited procedure, the neck dissection has few complications or long-lasting side effects, and offers the advantage of an accurate classification [97-98] and the status of contralateral lymph nodes, which is closely linked to adjuvant treatments. Therefore, neck dissection is not only a therapeutic procedure, but also a diagnostic one [21], and an elective contralateral neck treatment is generally recommended for initial treatment in certain patients with oral cavity SCC. It has been reported that isolated unilateral cervical dissection is predictive for CLNM, accounting for 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 [18].

Several independent authorities suggest one should carefully consider performing elective contralateral neck dissection (cN0) for oral squamous cell carcinoma patients in some certain situations, as follows:

I: tumors arising in the base of tongue and the floor of the mouth [6-8, 21, 34];

II: tumors crossing the midline [6, 17-18, 29, 99];

III: advanced staging (cT3–4) [8, 11, 13, 15, 17-18, 29];

IV: primary tumor more than 3.75 mm thick [20];

V: multiple ipsilateral nodes involvement [8, 13, 21, 29].

In contrast, elective neck dissection for the contralateral N0 neck in early oral carcinoma is not supported by others. On the one hand, some authors in their studies detected a very low incidence of contralateral occult metastases in early oral carcinoma, and there has not been an accurate marker that can predict the occurrence of bilateral or contralateral lymph node metastasis currently. Therefore, some surgeons advocate an observation-only policy for the contralateral neck [15]. On the other hand, bilateral neck dissection was not significantly associated with a decrease in contralateral metastasis [14, 17] and has not been shown to have an advantage in previous reports. For example, Lim et al found that the difference between the disease-free survival rates of 82% for the "observation" group and 68% for the elective neck dissection group was not statistically significant [15]. Lin *et al*. [28] also demonstrated that patients with buccal carcinoma after radical resection, ipsilateral neck radiation was adequate, since bilateral prophylactic neck treatment did not confer an added benefit.

In summary, 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.

Adjuvant radiotherapy

It suggested that the adjuvant radiotherapy (aRT) of the neck was individualized, and prophylactic radiotherapy has been performed in a few cases with other high-risk factors [6]. A few institutions have reported that adjuvant radiotherapy associated with an increase of contralateral regional control for patients with SCC in oral cavity. For example, Koo *et al*. [29] detected that the contralateral regional control rate was 100% in patients who received adjuvant radiotherapy, comparing to 97% of those who did not receive adjuvant radiotherapy. However, it is considered that it inappropriate to compare the contralateral regional control rate between those patients who did receive adjuvant radiotherapy and those who did not. One possible reason may be the fact that the patients who received adjuvant radiotherapy were those who had an advanced staging disease or worse prognosis, which would correlate to a high incidence of the contralateral metastasis. We have summarized the indications for contralateral and local-regional adjuvant radiotherapy (Table 1).

Other relevant factors

Time of initial diagnosis

It is interesting that a few authorities have remarked that the time of initial diagnosis is correlated to CLNM. In a series of 315 consecutive patients, 23.8% of the patients who were diagnosed 12 or more months after the appearance of the primary tumor developed CLNM, in comparison to 2.45% of those patients who were diagnosed within the first year, and the relative risk represented 9.71 [18]. As a matter of fact, the time of initial diagnosis is strongly related to tumor progress and affects the later metastasis and survival.

Local-regional recurrence

Only a few institutions have demonstrated the significant relationship between local-regional recurrence and CLNM. Liao et al. detected that local recurrence was an independent risk factor for CLNM of patients with oral cavity SCC. They observed that CLNM occurred

Table 1 Indications for local-regional and contralateral aRT

Location of aRT	Indications
Local-regional aRT	Advanced T classifications (pT3 or more) [17-19, 29, 100]
	A positive resection margin in the specimen or surgical-free margins less than 1 cm [17-19, 29, 100]
	Multiple pathologic lymph neck nodes (with 3 or more) [6, 17-19, 29, 71, 100]
	TSD>0.5 mm, lymph or blood vessel invasion and ECS [6, 17-19, 71, 100]
	Tongue carcinoma with thickness more than 9.5 mm [24]
Contralateral aRT	Tumors crossing the midline [28-29]
	pT3 tumors or more [29]
	Positive contralateral neck affectation [6, 17-18, 28]
	Multiple positive nodes on the homolateral side [29]

pT3: pathologic T3.

more frequently in patients with local recurrence, revealing 18% in patients with local recurrence and 5% in those without [19].

Time of CLNM occurring and follow-up

Most studies corroborate that CLNM mainly happens within two years postoperatively [8-9, 13, 17-19, 101-105]. For example, González-García *et al*. [17] reported CLNM occurred within the first two years after surgery in 89.9% of the affected patients. A few institutions have reported the details of the time that CLNM usually occurring (Table 2).

Table 2 Time of CLNM occurring in follow-up month

Author	Mean	Median	Range
Kowalski *et al.* [8]	7.5	5.6	2–26
Kurita *et al.* [13]	–	6	2–22
González-García *et al.* [17]	11.4	–	3–27
González-García *et al.* [18]	12.52	–	3–49
Liao *et al.* [19]	8.6	6	1–41

Due to the increased risk of CLNM within the first two years after surgery, special efforts should be made to detect early metastasis for SCC of the oral cavity, and close follow-up is mandatory during this period of time, lest the recurrence be beyond salvage [2, 5, 9, 13, 17-19, 102, 106-107]. Regular ultrasound and some other modern diagnostic modalities such as CT, MRI, PET, LS and USG-guided fine needle aspiration cytology, are worthy of consideration since they are more sensitive than clinical examination to detect occult nodal metastasis. Authors have given the regular frequencies of follow-up after surgery, as follows:

first year: every month [14, 108];
second year: every 2 months [14];
third year: every 3 months [13-14];
thereafter: biannually for life [13-14].

Conclusion

CLNM are not unusual in patients with OSCC, but it is an inarguable truth that patients presenting with CLNM in OSCC have a poor prognosis. At the same time, it is not practical or advisable to perform prophylactic neck dissection for contralateral clinical N0 in all patients with OSCC. Therefore, they should be carefully screened and clinical-histopathologic prognosticcators must be globally considered for each individual case. It is important for clinicians to pay careful attention to prognostic variables of CLNM and adopt more aggressive prophylactic strategies, such as surgery and adjuvant treatment. However, we have obviously found that the UICC TNM classification is not suitable for predicting later metastasis, especially CLNM. A more comprehensive classification system is therefore necessary to guide clinically therapeutic strategies, particularly in the prediction of later cervical lymph node metastases. Some of well-established histological predictive factors should be included as part of this routine system, such as tumor thickness, histological grading, and ECS. We also found that the incidence and some related prognosticators of CLNM differ considerably among reports, diverse factors can be held responsible for such differences: inherent selection bias, problems in tumor staging, the lack of standard for clinical strategies, and pathological protocols. Therefore, exchange and cooperation among different centers should provide useful and reliable information in the future.

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