



Identifying Occult Metastase Ratio and the related Factors in Early Stage Oralcavity Carcinoma

Erken Evre Oral Kavite Kanserlerinde Okkült Metastaz Oranı ve Oluşmasına Sebep Olabilecek Faktörlerin Belirlenmesi

Mehmet Akif Abakay¹, Selçuk Güneş², Filiz Gülüstan¹, Ercan Atasoy¹

¹ Bakırköy Dr Sadi Konuk Research And Training Hospital, Otorhinolaryngology Department, Istanbul, Turkey.

² Memorial Hizmet Hospital, Otorhinolaryngology Department, Istanbul, Turkey.

ABSTRACT

Objective: Management of clinical node-negative neck in early-stage oral cavity squamous cell carcinoma is still controversial. There are three main options to consider as watch-and-wait, elective neck dissection, and sentinel node biopsy.

Method: Patients were grouped as clinical node-negative and pathologic node-negative (group 1) and clinical node-negative and pathologic node-positive (group 2). Factors thought to affect occult metastasis such as age, tumor diameter, tumor thickness, perineural invasion, lymphovascular invasion, and differentiation were investigated using the Mann-Whitney U test, the Chi-square test, and Fisher's exact test.

Results: From 27 eligible patients, there were 12 (44.4%) females and 15 (66.6%) males. Sixteen patients were evaluated in group 1 and 11 were evaluated in group 2. The mean age of the patients was 58.20±14.05 years. The occult metastasis rates were 34% and 51% for T1 and T2 tumors, respectively. The mean tumor diameter was 24.78±12.79 mm, and the mean tumor thickness was 11.37±7.62 mm. The difference in mean values of tumor thickness between the groups was significant (p=0.024), but age (p=0.622) and tumor diameter (p=0.443) were not significantly different. The ROC analysis cut-off values for age, tumor diameter, and tumor thickness were 60 years, 23 mm, and 9.5 mm, respectively. Tumor thickness and lymphovascular invasion were significantly different between the groups, but age, differentiation, clinical T stage, and perineural invasion were not different.

Conclusion: The high rates of occult metastasis in our series imply that elective neck dissection seems a more appropriate choice for early-stage oral cavity squamous cell carcinoma rather than watch-and-wait.

Keywords: oral cavity, occult metastase, cancer

ÖZ

Giriş: Klinik olarak metastatik lenf nodu tespit edilmemiş erken evre oral kavite skuamöz hücreli karsinomlarına yaklaşım tartışmalıdır. Bekle-gör, elektif boyun diseksiyonu ve sentinel node örnekleme uygulanabilecek 3 ana yöntemdir.

Yöntem: Biz bu araştırma için retrospektif kohort çalışması planladık. Hastalar klinik nod negatif ve patolojik nod negatif (grup 1) ve klinik nod negatif ve patolojik nod pozitif (grup 2) olarak gruplandırıldı. Yaş, tümör çapı, tümör kalınlığı, perinöral invazyon, lenfovasküler invazyon ve farklılaşma gibi gizli metastazi etkilediği düşünülen faktörler, Mann-Whitney U testi, Ki-kare testi ve Fisher'in kesin testi kullanılarak araştırıldı.

Bulgular: Çalışmaya dahil edilen 27 hastadan 12 (% 44.4)'si kadın ve 15 (% 66.6)'i erkekti. Grup 1'de 16 hasta, grup 2'de 11 hasta değerlendirildi. Hastaların yaş ortalaması 58.20 ± 14.05 yılı. Gizli metastaz oranları T1 ve T2 tümörler için sırasıyla% 34 ve% 51 idi. Ortalama tümör çapı 24,78 ± 12,79 mm ve ortalama tümör kalınlığı 11.37 ± 7.62 mm idi. Gruplar arasında ortalama tümör kalınlığı değerleri arasındaki fark anlamlıydı (p = 0.024), ancak yaş (p = 0.622) ve tümör çapı (p = 0.443) anlamlı olarak farklı değildi. Yaş, tümör çapı ve tümör kalınlığı için ROC analizi kesme değerleri sırasıyla 60 yıl, 23 mm ve 9.5 mm idi. Tümör kalınlığı ve lenfovasküler invazyon gruplar arasında anlamlı olarak farklıydı, ancak yaş, farklılaşma, klinik T evresi ve perinöral invazyon farklı değildi.

Sonuç: Çalışmamızdaki yüksek gizli metastaz oranları, elektif boyun diseksiyonunun erken evre oral kavite skuamöz hücreli karsinomu için bekle-gör yerine daha uygun bir seçim olduğunu göstermektedir.

Anahtar Kelimeler: oral kavite, okkült metastaz, kanser

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Correspondence: Mehmet Akif Abakay, Bakırköy Dr Sadi Konuk Research And Training Hospital, Otorhinolaryngology Department, Istanbul, Turkey.

E-mail: mehmetakif.abakay@saglik.gov.tr

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INTRODUCTION

Lymph node metastasis is a well-known prognostic factor for oral cavity squamous cell carcinoma. Overt lymph node metastases are treated with either neck dissection or chemo/radiotherapy or both. However, there is no consensus on the treatment strategy of patients with cN0 disease, especially at early clinical stages (cT1-2).

Neck lymph node metastasis can be detected with palpation, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET)-CT, ultrasonography (USG), USG-guided fine needle aspiration biopsy (FNAB), and sentinel lymph node biopsy (SNB). Palpation has 75% sensitivity with 28.9% false-negativity (1). In a recent meta-analysis, in patients who were clinically (physical examination) cN0, the sensitivities of CT, MRI, PET-CT, and USG were found between 47.0% and 63.3%. Ultrasound-guided FNAB had a sensitivity of 56.4%, and SNB sensitivity was found as 84.9% (2). In another meta-analysis of SNB and immunohistochemistry evaluations, the sensitivity and negative predictive values (NPV) were found as 87% and 94%, respectively (3). High rates of metastasis of 8%-49% have been reported, and even with the most recent diagnostic tools, it seems it will be challenging to detect occult metastases (OM) for a while (4). Therefore, the treatment decision becomes controversial in patients with cN0 disease, with three main options: watch-and-wait, elective neck dissection (END), and SNB.

It is recommended to perform neck dissection if the neck is included in primary tumor surgery, if the patient is unsuitable for watch-and-wait, and if clinical suspicion of metastasis is high (5). It is well known that overtreatment with END may give rise to unnecessary complications. On the other hand, even with salvage surgeries, metastatic disease may give rise to increased mortality and morbidity.

The question as to which treatment modality should be performed with which patient becomes difficult to answer. To overcome these difficulties, preoperative factors such as tumor thickness (TT), subsite, age, cT, and pathologic features such as

perineural invasion (PNI), lymphovascular invasion (LVI), and grade have been evaluated to estimate occult lymph node metastasis, especially in early-stage (cT1-2) oral cavity squamous cell carcinoma (1,4,6,7). Beside these investigations, decision analyses were performed by Weiss et al. who concluded that neck dissection should be performed if the OM risk is over 20%; subsequently, Pitman advised using a cut-off of 15% (8,9).

We perform END for early-stage oral cavity squamous cell carcinoma. Therefore, we aimed to investigate the possible parameters affecting occult lymph node metastasis and examine the necessity of END based on our results and the literature.

MATERIAL AND METHODS

Patients who were diagnosed as having oral cavity squamous cell carcinoma and surgically treated between January 2012 and January 2019 at our tertiary care center were included in this study. Ethical approval was granted by the local ethics committee (Approval number: 2020/268).

The patients' age, sex, cN, pathologic parameters (tumor location, grade, differentiation, perineural invasion, lymphovascular invasion, metastatic lymph node) and follow-up information (visit times, presence of recurrence or death) were recorded. Radiologic evaluations were performed using contrasted CT or contrasted MRI with/without PET-CT within one month preoperatively.

OM was defined as patients who were cN0 (no evidence of metastatic lymph node, neither in physical examinations nor radiologic evaluations) and pN+, and pN0 patients who had recurrence at regional nodes within one year. Then, the patients were dichotomized as cN0pN0 (group 1) and cN0pN+ (group 2).

Patients treated with previous neck dissection, previous radiation therapy, multiple primary lesions, those with stage 3-4 disease, and less than one year's follow-up were excluded from the study. A total of 27 patients were eligible for the study.

Elective neck dissection (level 1,2,3) was performed unilaterally or bilaterally according to

the tumor location and preoperative evaluation. Lymph nodes were resected in an en bloc manner as recommended by the American Head and Neck Society. Adjuvant treatment was administered according to the postoperative pathology results. Patients were classified according to the 2010 TNM classification of the American Joint Committee on Cancer (AJCC).

Statistical Analysis

For statistical analysis SPSS 23. version used. Categorical variables were compared using the Chi-square and Fisher’s exact test, and continuous variables were compared using the Mann-Whitney U test. Receiver operating characteristic (ROC) analysis was performed for age, depth of invasion (DOI), and tumor diameter. Logistic regression analysis was performed for univariate analysis. Statistical significance was accepted as $p < 0.05$. Follow-up data started from the date of curative surgery.

RESULTS

Between January 2012 and January 2019, a total of 32 patients with cT1-2 OCSCC were treated surgically. Three patients were cN+ and 29 were cN0. Of the 29 patients who were cN0, two underwent surgery for a recurrent tumor in the oral cavity (n=2) and were excluded from the study. Among the 27 eligible patients, there were 12 (44.4%) females and 15 (66.6%) males. The mean age of the patients was 58.20 ± 14.05 (range, 34-85) years, the mean follow-up period was 23.74 ± 15.4 (range, 12-72) months. Eighteen of the patients were pN0 and 9 was pN+. There were three recurrence cases, one was pN+, and the other two were pN0, all of them within postoperative one year, therefore they were analyzed in the occult metastatic (cN0pN+) group. Consequently, 16 patients were evaluated in cN0pN0 group and 11 were evaluated in cN0pN+ group. Seventeen patients underwent bilateral END and 10 had unilateral END. There were no deaths during the follow-up period. The patient and tumor characteristics are shown in Table 1.

The mean tumor diameter was 24.78 ± 12.79 mm, and the mean TT was 11.37 ± 7.62 mm. The Mann-Whitney test showed a significant relation between group 1 and 2 for TT ($p = 0.024$), but there was no

relation between age ($p = 0.622$) and tumor diameter ($p = 0.443$). The mean tumor values are shown in Table 2. According to the ROC analysis, the cut-off values for age, tumor diameter, and TT were 60 years, 23 mm, and 9.5 mm, respectively. Chi-square and Fisher’s exact tests were performed to investigate relations between group 1 and age, differentiation, cT, TT, PNI, LVI, and imaging modality. Only TT ($p = 0.034$), and LVI ($p = 0.027$) showed significant relations.

Logistic regression analysis performed with tumor diameter, DOI, PNI, LVI, age, pT, and differentiation, and none had a statistically significant relation.

Table 1: Patient Characteristics			
		number,%	
		Group 1	Group 2
Gender	Female	7	5
	Male	9	6
Age	<60	7	6
	60 ≤	9	5
Imaging	CT	7	3
	MRI	9	8
cT	cT1	11	5
	cT2	5	6
Subsite	Tongue	11	7
	Buccal	2	2
	Retromolar trigon	2	1
	Floor of mouth	1	1
Differentiation	Poor	3	1
	Moderate	9	8
	Well	4	2
TT	≤9.5 mm	11	3
	9.5 mm <	5	8
Diameter	<23 mm	10	4
	23 mm ≤	6	7
PNI	Absent	14	8
	Present	2	3
LVI	Absent	15	6
	Present	1	5
pT	pT1	12	3
	pT2	4	4
	PT3	2	1
	PT4		1

cT: Clinical T stage, pT: Pathological T stage, PNI: Perineural invasion, LVI: Lymphovascular invasion, TT: Tumor thickness

	Overall	Group 1	Group 2	P
Tumor thickness	11.37±7.62	9.38±6.72	14.27±8.55	0.024
Tumor diameter	24.78±12.79	23.38±13.52	26.82±11.90	0.443
Age	58.20±14.05	58.94±13.54	57.12±15.37	0.622

DISCUSSION

Occult lymph node metastasis is an important factor and should be kept in mind when evaluating patients regarding the treatment modality (10). Although metastasis rates range from 7.4-16% in the literature, definitions and diagnostic procedures may affect these ratios (1,11).

As mentioned in the introduction, none of the radiologic examination modalities has a sensitivity above 80%. Even with pathologic investigation, it only becomes around 85%. In a recent meta-analysis, MRI specificity was higher than CT, and CT sensitivity was higher than MRI in the evaluation of neck lymph node metastasis (12). We investigated 10 (37%) patients with CT and 17 (63%) with MRI. The MRI negative predictive value was 52%, and the CT negative predictive value was 70%. There were no significant relations between OM rates and radiologic examination methods.

Tumor thickness and DOI are the most important factors in decision-making with early-stage cN0 neck tumors. Measurement of DOI is well described in the 8th AJCC classification (13). It is well known that TT and DOI are different parameters (14). Although recommended in the 8th classification, the sensitivity of DOI identification through clinical methods is questionable. However, the examined measurements appear to be TT rather than DOI. As our patients underwent surgery before this classification system, we thought it might be more appropriate to use the term TT. In the literature, different cut-off values were evaluated for TT and DOI. For DOI cutoff values of 4-4.5 mm and 4-8 mm for TT were evaluated in different studies, and it was concluded that higher DOI or TT was related

to increased OM rates (1,15-17). As expected, TT was significantly higher in the pN+ group in our study (mean value for pN0: 9.38±7.72, pN+: 14.27±8.55) (p=0.024). According to the ROC analysis results, we used a cut-off value of 9.5 mm, and similar to the literature, there was a significantly higher OM in the TT >9.5 mm group. There were only three patients (none was pN+) with a TT of 4 mm or less in our study, so we were unable to compare this with the literature.

Tumor differentiation is important, it can give information before surgery about assessing OM in oral cavity squamous cell carcinoma. It has proven with various studies that differentiation is related to OM (11,18-22). Van Lanschot et al. observed a statistically significant relation between differentiation and DOI (18). In our study, we observed no significant relation between differentiation and OM. Despite similar results existing in tongue squamous cell carcinoma in the literature, our contrary results to many other investigations may be due to the relatively low number of patients (22).

Tumor size, also used in the TNM system, is investigated in oral cavity squamous cell carcinoma. We performed ROC analysis (cut-off = 23 mm) and investigated an additive length. Whether grouped according to T (20 mm) or 23 mm, we found no significant relation between size and OM. In a meta-analysis, the rate of OM was between 0-26.5% (average was 11.5%) for T1 tumors, and between 11.6-45% (average: 24.5%) for T2 tumors (4). They advised watch-and-wait for T1 tumors. In our study, the rate of the OM was 31% for T1 tumors and 54% for T2 tumors, relatively higher than in the literature.

In our study, there was no significant relation between OM and age, similar to the literature (23).

Perineural and lymphovascular invasion are well-known prognostic factors in head and neck squamous carcinoma. Also, it has been proven that perineural and lymphovascular invasion is related to OM (4). In this study, none of the factors was significantly correlated with OM in logistic

regression analysis. However, lymphovascular invasion was significantly correlated with OM in Fisher's exact test.

D'cruz et al. performed a prospective randomized controlled trial with 500 patients with early-stage oral cavity squamous cell carcinoma, and their results proved that END had better 3-year overall survival (OS), and disease-free survival (DFS) (24). In a recent meta-analysis, END had 32-52% better DFS and 18% OS compared with watch-and-wait. Moreover, for patients with cNOpN+ disease, END had better survival than watch-and-wait (25). We had no mortality during our follow-up period; therefore, we were unable to perform survival analysis. However, based on literature data and our results, performing END should be better than the watch-and-wait strategy (26-27).

Our study has several limitations. Although oral cavity carcinoma is not the most common cancer of the head and neck region, our sample size was small relative to other studies. We were unable to use the 8th AJCC classification system because we did not want to use DOI and TT interchangeably. However, when compared with the literature, because most studies were performed before 2018, the evaluation of T values may become confusing. Martinez-Gimeno scoring system was described to estimate occult metastase for oral cavity carcinoma. Clinicopathological variables such as microvascular invasion, T stage, grade, TT, perineural invasion, shape of invasion, and inflammatory invasion are scored, and classified in 4 groups. Since we did not have inflammatory invasion and shape of invasion data, we were unable to compare our results in this system (28).

Conclusion

The most appropriate neck treatment option for early-stage oral cavity squamous cell carcinoma is still controversial. Based on literature data, SNB seems to be an appropriate choice. However, for centers in which SNB is not possible, watch-and-wait and END are the remaining choices. We observed OM at a rate of 31% for cT1 tumors and 54% for cT2 tumors and overall 40.7% for clinically early-stage oral cavity squamous cell carcinoma.

We prefer to perform END, at least until a novel diagnostic method with higher sensitivity and specificity is developed to detect OM. With this approach, we can cure OM without evidence of manifested disease, and more accurate staging can be performed, which giving rise to appropriate add-on treatment.

Conflict of Interest

There is no conflict of interest.

Financial Support

No financial support was received.

Ethics Committee Approval

Ethical approval was obtained the Local Ethics Committee (Protocol No: 2020-2896) and the Ministry of Health for this study.

Informed Consent

This a retrospective study.

Authors contributions: All authors contributed to the study conception. All authors approved the final manuscript.

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