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SURGICAL MEDICAL SCIENCES / CERRAHİ TIP BİLİMLERİ

The Effect of Tumor Budding on Lymph Node Metastasis in Oral Cavity Cancers

Oral Kavite Kanserlerinde Tümör Tomurcuklanmasının Lenf Nodu Metastazı Üzerine Etkisi

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Abstract

Objectives: Oral cavity cancers are the 6th most common cancer in the world and it is the 20th among cancer-related deaths and 16th among women. Tumor budding, which is a prognostic parameter that can be detected histopathologically and is associated with poor prognosis, is detected by a cheap and easy method. Tumor budding is defined as individual standing tumor cells or tumor clusters less than 5 tumor cells separated from the tumor mass at the periphery of the infiltrative area of the tumor and distributed to the surrounding stroma. In this study, we aimed to investigate the relationship between tumor budding and lymph node metastasis in oral cavity cancers.

Materials and Methods: Thirty patients who underwent neck lymph node dissection due to oral cavity cancer by ear, nose and throat and plastic surgery clinics in University of Health Sciences Türkiye, Antalya Training and Research Hospital were included in the study.

Results: The histological type of 30 oral cavity cancer cases was reported as squamous cell carcinoma. Metastasis was not observed in 18 of 19 patients who had three or fewer buds, whereas one patient had metastasis. Eleven patients who had more than three buds had more metastases in the cervical lymph nodes.

Conclusion: In early stage oral cavity cancers, tumor budding, lymphovascular invasion and poor prognostic parameters may be stimulant as a histopathological parameter. In our study, it was found that high budding was associated with more lymph node metastasis and this method did not include any cost. For this purpose, budding findings in pathology reports and follow-up of the cases in accordance with these findings may be a useful method for survival.

Key Words: Oral Cavity Cancer, Tumor Budding, Lymphadenopathy, Metastasis

Öz

Amaç: Oral kavite kanserleri dünyada en sık görülen 6. kanser olup, kanserle ilişkili ölümlerde erkekler arasında 20. sırada, kadınlar arasında ise 16. sırada yer almaktadır. Histopatolojik olarak tespit edilebilen ve kötü prognozla ilişkilendirilmiş prognostik bir parametre olan tümör tomurcuklanması ucuz ve kolay bir yöntemle saptanır. Tümör tomurcuklanması, tümörün infiltratif alanının en periferinde tümör kitlesinden ayrılarak çevre stromaya dağılan, tek tek duran tümör hücreleri ya da 5 tümör hücresinden az tümör kümesi olarak tanımlanmaktadır. Bu çalışmada, oral kavite kanserlerinde tümör tomurcuklanmasıyla lenf nodu metastaz ilişkisini araştırmayı planladık.

Gereç ve Yöntem: Sağlık Bilimleri Üniversitesi, Antalya Eğitim ve Araştırma Hastanesi'nde kulak burun boğaz ve plastik cerrahi tarafından oral kavite kanseri nedeniyle boyuna lenf nodu diseksiyonu yapılan 30 hasta çalışmaya dahil edilmiştir.

Bulgular: Otuz oral kavite kanserli olgunun histolojik tipi yassı epitel hücreli karsinom olarak rapor edilmiştir. Üç ve daha az tomurcuk yapan 19 olgunun 18'inde metastaz izlenmezken, 1 olguda metastaz görülmüştür. Üçten fazla tomurcuk yapan 11 olguda servikal lenf nodlarında fazla sayıda metastaz görülmüştür.

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Öz

Sonuç: Erken evre oral kavite kanserlerinde histopatolojik yöntemle saptanabilen bir parametre olarak tümör tomurcuklanması, lenfovasküler invazyon ve kötü prognostik parametre olarak uyarıcı olabilir. Çalışmamızda yüksek düzeyde tomurcuklanmanın daha fazla lenf nodu metastazı ile ilişkili olduğu saptanmış olup, bu yöntem herhangi bir maliyet içermemektedir. Bu amaçla patoloji raporlarına tomurcuklanma bulgularının eklenmesi ve olguların takibinin bu bulgular doğrultusunda yapılması sağkalım açısından faydalı olabilecek bir yöntem olabilir.

Anahtar Kelimeler: Oral Kavite Kanseri, Tümör Tomurcuklanması, Lenfadenopati, Metastaz

Introduction

Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity. Every year 300,000 new cases of OSCC are reported and therefore 177,000 deaths (1). OSCC is considered a very aggressive tumor and despite the maximum curative treatment, the 5-year survival rate of patients is 50%. For this reason, it is especially important to identify cases at risk for relapse (2).

With the tumor, lymph node, metastasis (TNM) classification based on clinical criteria, the behavior of some OSCCs cannot be predicted. In pathological evaluation; with hematoxylin eosin (HE) staining, prognostic parameters such as tumor stage, depth of invasion (DOI), lymphovascular invasion, perineural invasion, intensity of mitotic activity and lymphocytic response to the tumor can be determined in the light microscope. Various pathological features such as DOI and extranodal spread in the metastatic lymph node play an important role in the prognosis of patients, and these pathological features have been incorporated into the new T and N stages by the American Joint Cancer Committee. However, tumor stage, mitotic activity and lymphocytic response were not found to be prominent prognostic parameters in early stage OSCC cases (3).

Histological staging is the basis for the pathological classification of squamous cell cancer (SCC) in assessing the degree of anaplasia, regardless of any clinical measurement. For this purpose, many staging systems have been proposed by Elseragy et al. (4). The World Health Organization (WHO) histological staging system is based on the Broders classification. The WHO staging system evaluates histological variations between normal epithelial tissue and tumor tissue. Although this staging system is associated with the expression of various molecular biomarkers, it has a low prognostic value in oral cavity carcinomas (5). In a meta-analysis by Almangush et al. (2), tumor budding (TB) in OSCC is shown as a potential histological marker (2). In addition, TB in OSCC is stated as a superior prognostic value compared to the histological tumor grade of WHO (4).

TB is defined as the presence of single tumor cells or small tumor clusters that "budge" from the invasive front of the main tumor. The number of cells in a tumor bud is defined as 5 or fewer tumor cells. The International Tumor Budding Consensus Conference identifies it in less than 5 cells or up to 4 cells (6,7). In this study, we based 3 and fewer tumor cell counts as criteria. Although some histopathological parameters such as perineural invasion and lymphovascular invasion are important in terms of their prognostic value, they are sometimes difficult to identify using routine HE staining and may be underreported in daily practice due to time restrictions (8,9).

Therefore, the search for a low cost, new and effective prognostic parameter that can be determined by HE staining has started. TB has been described as a promising prognostic value in OSCC in many meta-analyzes (2). In this study, we aimed to investigate the relationship between tumor budding and lymph node metastasis in oral cavity cancers.

Materials and Methods

A total of 30 cases who underwent neck dissection due to early stage oral cavity cancer were included in the study. The ethical approval was obtained from the University of Health Sciences Türkiye, Antalya Training and Research Hospital Clinical Research Ethics Committee (approval no: 2812 2017 20-2). The patients included in the study signed the scientific research consent form obtained from all patients who underwent surgery. Pathological examinations were performed by a single pathologist. The lymph node was extensively investigated with imaging techniques. All tumors were staged according to the TNM classification of the eighth edition of the American Joint Committee on Cancer, and the degree of differentiation was determined according to the class classification of the WHO (10). During the scoring of TB, the entire tumor site was scanned at low magnification (x40) to select areas with the highest TB (Figures 1, 2). In the area where the tumor shows invasion, bud structures up to 3 tumor cells were evaluated as low risk, and buds with more than 3 tumor cells were considered as high risk (Figures 3, 4).

Results

The average age of the patients included in the study was 54, 26 were male and 4 were female. 2 cases were upper lip (1M/1F), 21 cases were lower lip (18M/3F), 7 cases were tongue cancer (7M). In 7 cases with tongue carcinoma (4 T1, 3 T2), the tumor had a well-differentiated SCC, and in 21 cases with lower

lip carcinoma (14 T1-7 T2), 11 cases had a well-differentiated SCC, 7 cases moderately differentiated SCC and 3 cases was evaluated as poorly differentiated SCC. Two cases with upper lip ca (both T1) were evaluated as 1 case with good differential SCC and 1 case with moderate differential SCC.

Nineteen cases with single cell or less than 3 TB were evaluated as low-risk, and 18 of these cases had no metastasis, while 1 (T2) case had metastasis (Table 1). Eleven cases with three or more buds were evaluated as high risk. In all of these cases (2 cases T1, 9 cases T2), metastasis was observed in a large number of cervical lymph nodes.

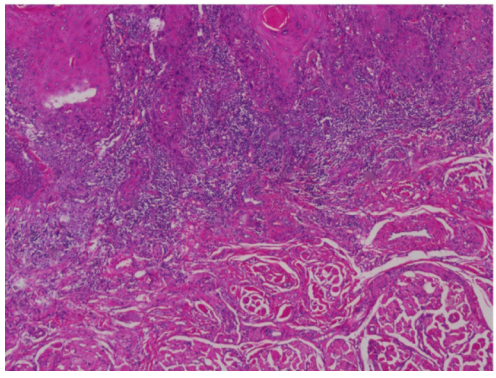

Figure 1: Pathological examination with X40 magnification under a light microscope

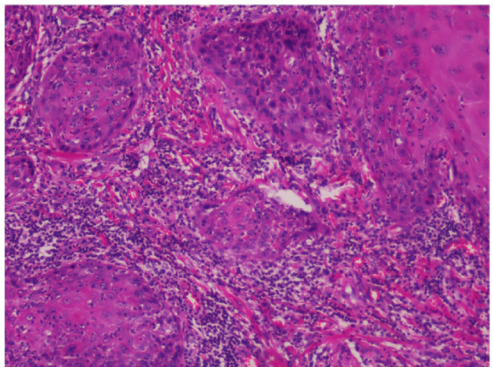

Figure 2: Detailed pathological examination with X100 magnification under light microscope

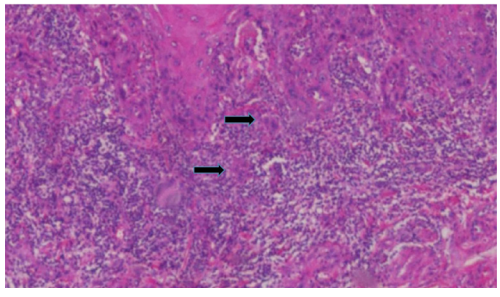

Figure 3: High power view of the tumor buds i.e clusters having less than 5 tumor cells (black arrows) into the underlying connective tissue at the invasive front of oral squamous cell carcinoma

Discussion

TB has recently emerged as an important negative prognostic factor in different types of cancer such as colorectal cancer, head and neck SCC, breast cancer, esophageal cancer, stomach

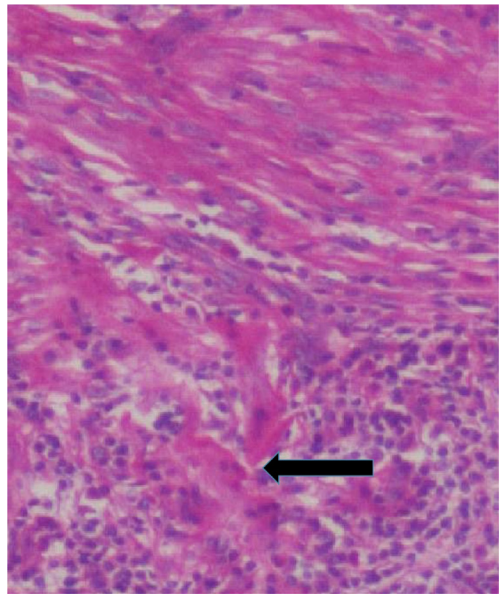

Figure 4: High-power appearance of tumor buds, i.e. clusters with less than 3 tumor cells (black arrows)

Table 1: Clinicopathological features

Variables	n
Age	
Average	54
Gender	
Male	26
Female	4
Differentiation	
Good	19
Mild	8
Bad	3
Tumor stage	
Tongue T1	4
T2	3
Lower lip T1	12
T2	7
Upper lip T1	2
Tumor Budding Score	
Low (<3)	19
High (≥3)	11
Hidden neck metasasis	
Low risk	1
High risk	11

cancer, cervical cancer. TB is believed to represent a type of epithelial-mesenchymal transition because tumor cells gain migration ability, with cell-cell adhesions and loss of polarity, the first biological steps in the metastasis pathway. In many recent studies on colorectal cancer, TB has been associated with higher tumor stage, lymph node metastasis, high recurrence and reduced disease-free survival, and has been included as a reportable feature in the Colorectal Cancer Protocol (7,11). In the latest classification of head and neck tumors in 2017, TB has been proposed as a strong prognostic value in the histopathological staging of OSCC (4,12). In 2 reviews that were meta-analyzed in oral cancers, the importance of TB in OSCC has been confirmed and high bud activity has been shown to be associated with a poor prognostic factor, often lymph node metastasis (2,13).

In our study, lymphatic metastasis wasn't observed in 18 patients with 3 or fewer tumor buds, and was observed in 1 patient (Stage T2). Lymphatic metastasis was observed in 11 cases with more than 3 TB, and these were evaluated as high-risk groups. Of these 11 cases, 2 were detected in the T1 and 9 in the T2. In the 8th edition of the TNM classification, AJJC added DOI and worst pattern of invasion as an additional factor to the T criteria. But didn't add TB. The clinical significance of these factors, especially in early stage oral cancers, is not fully explained in the AJJC 8th edition. Therefore, a comparison between TB and other known histopathological features is required to develop a treatment strategy in early stage oral cancers. Early stage OSCC, which is assumed to have no clinically and radiologically significant nodal metastases patients have hidden metastases of 20-40% at the time of diagnosis (14). Elective neck dissection has been shown to significantly improve the survival rate of T1-2 N0 OSCC patients (15). However, considering that the majority of patients experience unnecessary surgical complications, it is difficult to decide whether elective lymph node dissection should be performed in patients with N0 OSCC only according to TNM classification.

Specific molecular markers associated with tumor invasion and metastasis are can provide new insights to be identified (16). TB, isolated small neoplastic cell located on the invasive front of neoplastic cells or tumor corresponds to the presence of clusters. This phenomenon is two major aggressive of malignant tumors feature: cell adhesion loss and local invasion (17). In OSCC in terms of metastatic potential of cancer cells located between tumor and intact border It is thought to be more aggressive (16). Clinical staging for the detection of hidden metastases as well as early stage OSCC due to lack of correct routine biomarkers patients undergo elective neck dissection. Especially in tongue OSCC patients, although it is involved in low risk group in TNM classification hidden neck metastasis can be seen in 14-45% and fatal results are emerging. Sakata et al. (18) T2 N0 tongue OSCC patients with tumor islands (≤15 cells) close to the main tumor (<1 mm) or in the presence of scattered tumor satellites at a distance of ≥1 mm, tumor depth ≥3.3 mm, TB score ≥4 and latent metastases showing patients are evaluated to have poor prognosis (15).

To date, various indicators of hidden neck metastasis such as tumor depth, vascular invasion and lymphatic invasion have been suggested. In particular, the National Comprehensive Cancer Network Clinical Practice Guidelines when tumor depth is ≥4 mm, recommends elective neck dissection for N0 OSCC (19). However, a recent randomized clinical trial, with a tumor depth of 4 mm reported that only 16.9% of patients had lymph node metastases; hence, such criteria remain unreliable in these patients (15).

Study Limitations

It is controversial whether to treat patients who are not clinically diagnosed with nodal metastasis by elective neck dissection to improve prognosis, or to apply follow-up and waiting strategies. TB is a morphological marker of tumor invasion for OSCC. In our study, we investigated TB which is a new histopathological indicator. But the main limitation of this study is that only the specimens resected during surgery were examined. Investigating TB in preoperative biopsy samples may help predict occult neck metastases and therefore decide treatment in T1-T2 early-stage SCCs. More comprehensive studies are needed in this perspective.

Conclusion

Identifying patients at high risk for occult neck metastases by evaluating histopathological indicators such as TB can guide the prognosis of patients with early-stage OSCC and provide new practical information for planning treatment strategies.

Ethics

Ethics Committee Approval: The ethical approval was obtained from the University of Health Sciences Türkiye, Antalya Training and Research Hospital Clinical Research Ethics Committee (approval no: 2812 2017 20-2).

Informed Consent: The patients included in the study signed the scientific research consent form obtained from all patients who underwent surgery.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept: K.B., Ö.E.G., N.E., M.Ş., G.İ., R.T.S., D.Ş.D., D.S., Design: K.B., Ö.E.G., N.E., M.Ş., G.İ., R.T.S., D.Ş.D., D.S., Data Collection and Processing: K.B., Ö.E.G., N.E., M.Ş., G.İ., R.T.S., D.Ş.D., D.S., Analysis or Interpretation: K.B., Ö.E.G., N.E., M.Ş., G.İ., R.T.S., D.Ş.D., D.S., Literature Search: K.B., Ö.E.G., N.E., M.Ş., G.İ., R.T.S., D.Ş.D., D.S., Writing: K.B., Ö.E.G., N.E., M.Ş., G.İ., R.T.S., D.Ş.D., D.S.

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