ORIGINAL RESEARC ORİJİNAL ARAŞTIRMA

Is Prophylactic Neck Dissection a "Must" in Early-stage Lip Cancer?

Erken Evre Dudak Kanserlerinde Profilaktik Boyun Diseksiyonu Şart mıdır?

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ABSTRACT Objective: Standard lip cancer (LC) treatment is surgical excision with therapeutic neck dissection (ND) when there is detectable metastasis to the cervical lymph nodes (LNs). Nevertheless, there is no general agreement over how to approach to N0 neck in LC. The aim of this study is retrospectively review the prognoses of T1/T2 N0 LC-cases who underwent prophylactic ND, for justification of this procedure. **Material and Methods:** The study included 50 consecutive early-stage LC-patients, who were operated on between 2013 and 2023. A retrospective review was made of the clinical findings including tumor location, T-grade, detectable regional LN involvements, surgical and adjuvant therapies, histopathological results, recurrences, and metastases. **Results:** The 50 patients comprised of 36 (72%) males and 14 (28%) females with a 70.94 years mean age. Squamous cell carcinoma was the unanimous histologic diagnosis. The tumors were T2 in 12 (24%) and T1 in 38 (76%) patients; well, moderately and poorly differentiated in 22 (44%), 27 (54%), and 1 (2%) cases, respectively. Tumor locations were as follows: 42 (84%) lower lip, 7 (14%) upper lip, 1 (2%) commissure. Resected tumor defects were repaired with primary closure or flap repairs in 38 (76%) patients and in 12 (24%) patients the operations were complemented with unilateral or bilateral (8 and 4 cases, respectively) elective supraomohyoid ND. No LN metastases were found histopathologically in the ND-specimens. Tumor recurrences occurred in 2 (4%) patients. **Conclusion:** The results of this study suggested that "wait-and-see" and close follow-up at regular intervals is a more rational approach in early-stage N0 LC than prophylactic ND.

Keywords: Lip neoplasms; lymphatic metastasis; surgery, oral; neck dissection; neoplasm staging; neoplasm recurrence, local

ÖZET Amaç: Standart dudak kanseri tedavisi, servikal lenf nodlarında saptanabilir metastaz olduğunda cerrahi eksizyon ve terapötik boyun diseksiyonu şeklindedir. Erken evre (T1 ve T2) dudak kanserlerinde lenf nodu tutulumu negatif (N0) boyuna yaklaşım tartışmalıdır. Bu çalışmanın amacı, profilaktik boyun diseksiyonu uygulanan T1/T2 N0 dudak kanseri vakalarının prognozlarını retrospektif olarak gözden geçirmektir. **Gereç ve Yöntemler:** Çalışmaya 2013 ile 2023 yılları arasında erken evre primer dudak karsinomu nedeni ile opere edilen 50 ardışık hasta dâhil edildi. Hastaların klinik özellikleri, bölgesel lenf nodu durumu, tümörün yerleşim yeri, tümör evrelemesi, patoloji sonuçları, takiplerde nüks oranları, boyun lenf nodu metastazı ve uzak metastaz oranları geriye dönük olarak incelendi. **Bulgular:** Hastaların 14'ü (%28) kadın, 36'sı (%72) erkek idi ve yaş ortalaması 70,94 yıl idi. Olguların tamamında patolojik tanı skuamöz hücreli karsinomdu. On iki (%24) hastada T2, 38 (%76) hastada T1 tümör mevcuttu. Tümörler 22 (%44) hastada iyi, 27 (%54) hastada orta, 1 (%2) hastada az derecede diferansiye idi. Kanserlerin 7'si (%14) üst dudakta, 42'si (%84) alt dudakta, 1'i (%2) ise kommissür bölgesinde izlendi. Hastaların 38'ine kitle eksizyonu ve primer ya da fleb ile onarım yapılırken, 12'sine (6 hasta pT1, 6 hasta pT2) ek olarak profilaktik boyun diseksiyonu yapıldı. Dört hastaya bilateral, 8 hastaya ise tek taraflı supraomohyoid boyun diseksiyonu yapıldı. Hastaların herhangi birinde histopatolojik lenf nodu metastazı izlenmedi. İki hastada lokal nüks izlendi. **Sonuç:** Erken evre N0 dudak kanserlerinde profilaktik boyun diseksiyonunun gerekli olmayacağı kanaati oluştu ve bu hasta grubu için "bekle ve gör" ve düzenli aralıklarla yakın takip yaklaşımının daha uygun bir seçenek gibi göründüğü sonucuna varıldı.

Anahtar Kelimeler: Dudak neoplazileri; lenfatik metastaz; cerrahi, oral; boyun diseksiyonu; tümör evrelemesi; tümör rekürrensi, lokal

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Lip cancer (LC) is one of the most frequent malignancies of the head and neck region and constitutes around 25% of oral cavity cancers.[1] The incidence has been reported as 12.7/100,000 in North America, 12/100,000 in Europe, and 13.5/100,000 in Oceania.[2] Sunlight exposure (ultraviolet radiation effect), alcohol intake, smoking, male gender, fair skin, advanced age, and viral infections are accepted as risk factors.[3-5] It typically manifests with ulcerated or exophytic crusting lesions, and discoloration, thinness, and leukoplakia in the adjacent lip in some cases. It grows relatively slowly and in advanced stages, becomes ulcerated and/or infiltrating lesions develop.[2-5] Although basal cell carcinoma, melanoma, minor salivary gland tumors, and various metastatic tumors may also involve the lip, over 90% of lip malignancies are squamous cell carcinoma (SCC).[3,4]

In early-stage LCs, the success rates of radiotherapy (RT) and surgery are reported to be similar both functionally and cosmetically. However, due to the known disadvantages of RT, such as longer treatment periods, limitations of reconstructive option of the radiated area in the course of the disease, mandibular osteoradionecrosis, serious mucositis, dry mouth, and long-term pain, surgery is considered as the first option.[3-5] However, there is no consensus in the literature about the approach to the neck in T1/T2 N0 LC. The aim of this study was to retrospectively evaluate the mid and long-term results of early-stage LC cases who were treated with tumor resection and prophylactic neck dissection (ND).

MATERIAL AND METHODS

This study was approved by the local ethics committee (Non-interventional Clinical Research Ethics Committee, decision date and number: February 8, 2023/02-06) and the study was conducted in line with the Helsinki Declaration. Informed consent was obtained from all individual participants included in the study. Within the scope of the study, 50 consecutive patients who had been operated on for early LC (T1 and T2) were included. Patients were excluded from the study if they had advanced stage LC, had received primary RT, or were clinically and/or radiologically N (+). The patients' demographic data, detailed anamnesis, head and neck physical examinations, and imaging (ultrasonography, cervical magnetic resonance imaging, and computed tomography) results were retrieved from the hospital records. Clinical characteristics of the tumors, including location, size, and extension (T-staging), enduration, ulceration, exophytic growth, and the presence of palpable regional lymph nodes (LN) mainly in the cervical and parotid regions, operation reports, and the histopathology examination results of both tissue biopsies, and surgical specimens were also extracted and recorded. It was aimed for all primary surgical resections to be performed observing minimum 0.5 cm surgical margins, and frozen-section examinations were used in 12 cases to confirm clear surgical margins. Patients with no detectable enlarged cervical LNs either on the physical examination or imaging were accepted as "N0" cases and included in the study. Regular follow-up examinations were scheduled for every 3 months in the first year, and at 6 month intervals thereafter when there were no detectable recurrences.

STATISTICAL ANALYSIS

Data obtained in the study were analyzed statistically using IBM SPSS vn. 21.0 software. (IBM Corp. Armonk, NY: USA). Data were presented with descriptive statistical methods (frequency, percentage, mean±standard deviation values). In the comparison of categorical variables, the Pearson's chi-square test and the Fisher's exact test were used. The results were evaluated at the 95% confidence interval and a value of $p<0.05$ was accepted as the level of statistical significance.

RESULTS

CLINICAL AND HISTOLOGICAL FINDINGS

The histopathologic diagnosis of all the patients was SCC. The patients comprised 36 (72%) males and 14 (28%) females with a mean age of 70.94±10.7 years. Oncological grading was made in accordance with the American Joint Committee

of Cancer guidelines, according to which the tumors were classified as T2 in 12 (24%) [8 lower lip (19.05%), 3 upper lip (42.86%), 1 commissure (100%)] patients and T1 in 38 (76%) cases [34 lower lip (80.95%), 4 upper lip (57.14%)].[6,7] Histopathological gradings were evaluated as well differentiated in 22 (44%) [2 upper lip (28.57%), 20 lower lip (47.61%)] cases, moderately differentiated in 27 (54%) [4 upper lip (57.14%), 22 lower lip (52.38%), 1 commissure (100%)], and poorly differentiated in 1 (2%) [1 upper lip (14.28%)]. Most of the primary tumors were located in the lower lip (42 cases, 84%), followed by upper lip in 7 (14%), and commissure in 1 (2%) (Table 1). Four of the upper lip (57.14%) tumors were T1 and 3 were (42.86%) T2 tumors. Two of upper lip tumors were evaluated well differentiated (28.57%), 4 were moderately differentiated (57.14%), and 1 was poorly differentiated (14.28%). Bilaterally prophylactic ND was performed on one T2 tumor of the upper lip (14.28%). Surgical margins were positive in only one of the 7 upper lip tumors (14.28%) operated on, and the patient underwent extended resection.

The surgical defects were repaired primarily in 23 cases (21 T1 and 2 T2 tumors) or with flap in 27

(10 T2, and 17 T1 tumors). In 38 (76%) cases, excision of the tumor with a healthy-looking margin appeared to be sufficient treatment. In the remaining 12 (24%) patients [6 T1 6 lower lip (14.28%) and 6 T2 4 lower lip (9.52%), 1 upper lip (14.28%)], 1 commissure cases (100%), the surgeries were complemented with prophylactic supraomohyoid ND; 8 performed unilaterally [8 lower lip (19.04%)] and 4 [1 upper lip (14.28%), 1 commissure (100%), 2 lower lip (4.76%)] bilaterally because of the midline location of the tumor. The surgeries were performed by different surgeons working in our clinic. In these early stage N0 LC cases, some surgeons have preferred to follow up with wait and see, while some surgeons have preferred to perform ND according to their own approaches. Nine (18%) patients were referred for adjuvant RT due to perineural invasion, upper lip location of the primary tumor, recurrence or positive surgical margin, as one of them declined RT. No metastatic LNs were determined in any of the 12 patients who underwent ND. No late regional neck or distant organ metastasis was detected in any patient at the follow-up examinations. Surgical margins were positive in 2 (4%) [1 lower lip (2.38%), 1 upper lip (14.28%)] patients, and local recurrence occurred in another 2 (4%) [2 lower lip (4.76%)] patients (one T1 and one T2). All 4 patients underwent re-operation for local eradication of the disease. In 4 (8%) patients, simultaneous secondary malignancy was determined; 3 (6%) in the head and neck, determined as larynx SCC, facial skin SCC, and external ear SCC, and one prostate SCC.

FOLLOW-UP AND PROGNOSIS

The mean follow-up period was 10.3 months (range, 1-64 months). In 12 (24%) patients (cases operated on between 2013 and 2018), the follow-up period was ≥5 years and no mortality due to LC was determined, showing a 5-year survival rate of 100% (9 died of un-related causes before the termination of this period). The 3-year survival rate of the 9 (18%) patients operated on between 2019 and 2020 was also 100%. The effect of elective ND on recurrence was examined, and recurrence was determined in one case (8.3%) from the neck-dissected group and one case (2.6%) from the non-neck-dis-

TABLE 1: Demographic and pathological characteristics of the patients.		
	n	%
Age (X̄±SD)	70,94±10,7	
Gender		
Male	36	72
Woman	14	28
Localization		
Lower lip	42	84
Upper lip	7	14
Commissure	1	2
T stage		
T1	38	76
T2	12	24
Differentiation		
Well	22	44
Moderately	27	54
Poorly	1	2

SD: Standard deviation.

sected group. The difference was not statistically significant (p=0.426).

DISCUSSION

There has been reported to be clear male predominance in the gender distribution for LC occurrence as was the case in the current series (72% vs. 28%), with a peak in the 6th and 7th decades of life, and that primary tumors mostly involve the lower lip (90%), less frequently the upper lip (7%) and are rarely encountered in the commissure (3%).[2-5] Sunlight exposure is an important risk factor for LC. Therefore, persons working outdoors such as farmers, and fishermen who are naturally exposed to sunlight are more prone to the disease, whereas women are relatively protected by mostly remaining indoors and wearing face creams and lipstick.[2-8] Despite the better chance of treatment than other head and neck cancers, the rates of recurrence and 5-year survival have been reported to be 15% and 89%, respectively.[1] The rate of secondary tumor occurrences together with LC has been reported as 5.5%.[9] When the demographic and clinical findings of the current study cases were compared with the literature data, the age (mean 70.94 years), location (lower lip involvement in 84% of the cases), male predominance (72%) and the rate of secondary head and neck malignities (6%), the figures appeared to be compatible.

For T1/T2 N0 LC cases, resection of the tumor with a margin is usually considered a sufficient treatment. A 5 mm surgical margin was observed in the current series and in only two cases, surgery was extended for tumor continuity in the margin of the surgical specimen. Primary RT in the treatment of LC is selected only for patients with surgical contraindication because of comorbidities.[3] Regional (cervical) LN metastasis has been reported to be found in 5-20% of cases and is cited as the most important prognostic factor which decreases the survival rate by up to 50%.[1,10,11] Regional LN metastasis is related to the size of the primary tumor, the degree of differentiation, local recurrence, and location (other than lower lip involvement).[1,11-13] The review of the current cases neither confirmed nor contradicted these prognostic indicators, as there was one case of local recurrence in each of the neck-dissected and non-neck dissected patient groups, and the difference was not statistically significant. Cervical pathologic LN or distant metastasis was not present in any of the current patients. Therapeutic LN dissection is highly recommended for N (+) necks.[14] However, for early stage N0 LC, there is no consensus of how to approach the neck. One of the options is sentinel LN biopsy beforehand to avoid over-surgery such as unnecessary ND, but as the sensitivity and specificity of the procedure is not very high, its indication is also debatable.[15-17] Nevertheless, some authors advocate routine prophylactic ND due to a high probability of occult neck metastasis.[18-20]

Lymphatic drainage of the lower lip is to the submental and submandibular LNs, whereas the upper lip drains into the preauricular and intraparotid LNs.[3] Therefore, for lower LC, elective supraomohyoid LN dissection includes I-III cervical LN zones, bilaterally for tumors invading the middle third of the lips and unilaterally for those located in the lateral thirds.[14] Nevertheless, it has been argued by some in the literature that any elective ND for LCs should be reserved for high-grade tumors or recurrences.[14-21] The National Comprehensive Cancer Network guidelines, version 1.2023, also suggest considering ND for N0-N3 oral cancers (including mucosal lip) and it has been stated that ND is not generally indicated in T1-3 N0 mucosal LCs.[22] Califano et al. performed ND only in cases of lip SCC with palpable cervical LNs and found LN metastasis in 4 of 25 (16%) patients, whereas metastases were determined in 3 of the 80 (3.75%) patients with non-palpable LNs.[13] Similarly, in a study by Olgun et al., no LN metastasis was determined in any T1-T2 N0 LC cases.[23] In one of the largest series, Varthanian et al. performed elective ND in 107 of 617 LC patients and found LN metastasis at the rate of 4.3% in T1-T2 N0 tumors, although this percentage increased in tumors that involved the oral commissure (15.4%) and in T3-T4 tumors (23.3%).[17] The United Kingdom Oral Cavity and Lip Cancer National Multidisciplinary Guidelines also recommend no ND if there is no clinically detectable LN involvement.[5] Adjuvant RT has been

recommended for perineural invasion, local recurrence and for cases where extensive surgery is not possible. In the current study, 9 (18%) patients were referred with the same indications. When the clinical findings and results of the surgical approach in the current study were compared with the aforementioned literature data, both local recurrence rate and positive surgical margins were 4% in the current study, which was seen to be comparable with the data of previously reported series.[9-20]

CONCLUSION

This retrospective review of T1-T2 N0 LC cases showed similar demographic, clinical, and prognostic findings with those of the literature. However, these results also demonstrated that elective ND for N0 neck in patients with T1-T2 lip SCC is not justified, as no occult LN metastases were found in any of the dissection specimens histopathologically. Close follow-up of patients at regular intervals would be an appropriate approach.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Buğra Subaşı, Nadir Yıldırım; Design: Buğra Subaşı; Control/Supervision: Buğra Subaşı, Nadir Yıldırım; Data Collection and/or Processing: Mehmet Varol, Nurullah Türe, Sercan Şimşek; Analysis and/or Interpretation: Nadir Yıldırım; Literature Review: Buğra Subaşı, Nurullah Türe; Writing the Article: Buğra Subaşı, Nadir Yıldırım; Critical Review: Nadir Yıldırım; References and Fundings: Nadir Yıldırım, Buğra Subaşı, Nurullah Türe; Materials: Sercan Şimşek.

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