



The impact of preepiglottic space invasion on cervical lymph node metastases in open supraglottic laryngectomy revisited

Açık supraglottik larenjektomide preepiglottik alan invazyonunun servikal lenf nodu metastazları üzerine etkisinin gözden geçirilmesi

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ABSTRACT

Objectives: This study aims to evaluate the relationship between presence of preepiglottic space (PES) invasion and cervical nodal metastasis and their impact on disease free survival.

Patients and Methods: This retrospective cohort study included 49 patients (45 males, 4 females; mean age 65 years; range 49 to 87 years) who underwent open supraglottic laryngectomy with bilateral neck dissection. The study was conducted between January 2007 and January 2016. The background information was retrieved from patients' files. The collected data were used to assess the association between PES invasion and other possible prognostic factors.

Results: There was a statistically significant relationship between PES invasion and ipsilateral nodal metastasis ($p=0.001$). Disease free survival rate was significantly higher in patients with no PES invasion ($p=0.033$) but not in those with nodal metastasis.

Conclusion: Open supraglottic partial laryngectomy is an oncologically safe procedure that can be used in patients with early and selected advanced stage supraglottic carcinoma. Since PES invasion is a significant risk factor that causes poor prognosis, it should be rigorously evaluated via different imaging modalities before treatment.

Keywords: Cervical lymph node metastasis; preepiglottic space invasion; supraglottic laryngectomy; survival.

ÖZ

Amaç: Bu çalışmada preepiglottik alan (PEA) invazyonu varlığı ve servikal nod metastazı arasındaki ilişki ve bunların hastalısız sağkalım üzerindeki etkisi değerlendirildi.

Hastalar ve Yöntemler: Bu retrospektif kohort çalışmaya iki taraflı boyun diseksiyonu ile açık supraglottik larenjektomi geçiren 49 hasta (45 erkek, 4 kadın; ort. yaş 65 yıl; dağılım 49-87 yıl) dahil edildi. Çalışma Ocak 2007 - Ocak 2016 tarihleri arasında yapıldı. Geçmiş bilgisi hastaların dosyalarından edinildi. Toplanan veri PEA invazyonu ve diğer olası prognostik faktörler arasındaki ilişkiyi değerlendirmek için kullanıldı.

Bulgular: Preepiglottik alan invazyonu ve aynı taraf nod metastazı arasında istatistiksel olarak anlamlı bir ilişki vardı ($p=0.001$). Preepiglottik alan invazyonu olmayan hastalarda hastalısız sağkalım oranı anlamlı olarak daha yüksekti ($p=0.033$), fakat nod metastazı olanlarda anlamlı ilişki görülmedi.

Sonuç: Açık supraglottik parsiyel larenjektomi erken ve seçilmiş ileri evre supraglottik karsinomlu hastalarda kullanılabilecek, onkolojik olarak güvenilir bir işlemdir. Preepiglottik alan invazyonu kötü prognoza yol açan önemli bir risk faktörü olduğundan, tedaviden önce farklı görüntüleme yöntemleri ile titizlikle değerlendirilmelidir.

Anahtar Sözcükler: Servikal lenf nodu metastazı; preepiglottik alan invazyonu; supraglottik larenjektomi; sağkalım.

The supraglottis is distinct from other subsites of the larynx by arising from buccopharyngeal primordium without midline fusion. Meanwhile, the glottic and subglottic subsites are formed by midline fusion of paired branchial arches.^[1,2] There is an increased tendency of bilateral lymphatic drainage for cancers arising from the supraglottis owing to this developmental difference.^[2] The superior margin of the supraglottis extends from the free margins of the epiglottis and aryepiglottic folds down to the arytenoid cartilages. The inferior margin is the horizontal plane at the level of the laryngeal ventricles that extends from one side to other. The preepiglottic space (PES) is a triangular structure which contains mostly adipose tissue, loose aerolar tissue, elastic fibers and lymphatics.^[2-4] Anatomical boundaries of this space are the thyrohyoid membrane and superior part of the thyroid cartilage anteriorly; the hyoepiglottic ligament and vallecula superiorly; the lingual surface of the epiglottis posteriorly; and the thyroepiglottic ligament inferiorly.^[2,3] Carcinomas arising from the infrahyoid supraglottis can invade this space through small perforations in the elastic epiglottic cartilage.^[2,5,6] Presence of PES invasion is used as a criteria in staging the laryngeal carcinoma. According to current TNM staging (AJCC, 2010),^[7] any carcinoma that invades the PES is staged T₃. Therefore, PES invasion in supraglottic laryngeal carcinoma upgrades the patient to an advanced stage and also determines the prognosis.^[5,6] The spread of cancer to cervical lymph nodes is also another significant determinant of prognosis in laryngeal carcinoma.^[8-10] However, the clinical significance of PES invasion with regard to nodal metastasis in supraglottic laryngeal carcinoma is still under debate.^[3,4,6,8] Few articles in the literature focus on this issue, mainly in patients with supracricoid partial laryngectomy. Thus we aimed to evaluate the relationship between presence of PES invasion and cervical lymph node metastasis and their impacts on disease free survival (DFS) in patients who underwent open supraglottic laryngectomy (SGL) and bilateral neck dissection (BND).

PATIENTS AND METHODS

This retrospective cohort study was conducted among patients who underwent open supraglottic horizontal laryngectomy between January 2007 and January 2016 at the Department of

Otolaryngology, Medical Faculty of Uludağ University. This study was approved by the ethical committee of the medical school with a number of 2016-4/7 and conducted in accordance with the principles of the Declaration of Helsinki. The operations were performed under general anesthesia by senior head and neck surgeons. The decision to perform SGL was based on rigorous oncological principles. Supraglottic horizontal laryngectomy was performed on patients with T₁, T₂ and selected T₃ supraglottic carcinoma with normal vocal cord mobility. All patients underwent simultaneous bilateral neck dissection during laryngectomy. Following resections, frozen section surgical margins were evaluated by pathologists. We performed additional resections of adjacent tissue until safe margins were confirmed by the pathologist. The exclusion criteria included previous head and neck radiotherapy, existence of synchronous carcinoma in another organ, inaccessible preoperative or postoperative records, previous chemotherapy and previous neck dissection or laryngeal surgery. In total, 49 patients (45 males, 4 females; mean age 65 years; range 49 to 87 years) were enrolled in the study.

The background information of all patients including age, gender, pathological stage, presence of PES invasion, grade of carcinoma, perineural invasion, cervical lymph node positivity and corresponding neck levels, presence of extracapsular spread, follow-up time, need for adjunct treatment, locoregional recurrence and DFS time were retrieved from patient files. The patients were evaluated according to the collected clinical data. The main outcome measures were risk of cervical lymph node metastasis and survival in patients with or without PES invasion. We also assessed the relation between PES invasion and other potential risk factors. The patients were staged according to 2010 edition of AJCC.^[7]

Statistical analysis was carried out using IBM SPSS Statistics version 22.0 software (IBM Corp., Armonk, NY, USA). Defining statistics for categorical variables were given in frequency and percentage, n (%). Yates corrected chi-square test, Fisher's exact test and Fisher-Freeman-Halton test were used to compare the groups regarding categorical variables. Survival analysis was done by Kaplan-Meier survival analysis. Significance level was determined as p=0.05.

Table 1. T and N stages of patients (American Joint Committee on Cancer Staging, edition 2010)

Staging	N ₀	N ₁	N ₂	N ₃	Total
T ₁	-	1	-	-	1
T ₂	15	4	8	-	27
T ₃	6	4	11	-	21
T ₄	-	-	-	-	-
Total	21	9	19	-	49

RESULTS

Pathological T stages were distributed as 15 (T₁), 14 (T₂) and 20 (T₃, due to PES invasion) respectively. Preepiglottic space invasion was present in 20 patients. There was ipsilateral lymph node metastasis in 27 patients but only 12 of these patients had contralateral metastasis (Table 1). Among metastatic lymph nodes, three showed extracapsular invasion. Eight patients received concomitant chemoradiotherapy and 20 had adjuvant radiotherapy due to extracapsular

nodal spread, multiple nodal metastases, perineural or vascular invasion. Mean duration of follow-up was 32.7 (1 to 90) months. During this time 17 patients died from locoregional recurrence (n=8), postoperative hemorrhage (n=1), early postoperative lung infection (n=2), and metachronous carcinoma of lung (n=6).

We compared the presence of ipsilateral and contralateral lymph node metastasis, perineural invasion, extracapsular invasion and grade of cancer in patients with or without PES invasion. There was a statistically significant association between PES invasion and ipsilateral (p=0.001) but not contralateral (p=0.189) nodal metastasis. Perineural invasion, cancer grade and recurrence did not reveal any significant association. In addition, the association between the presence of extracapsular spread and PES invasion was close to statistical significance (p=0.062) (Table 2). We only found significant association between ipsilateral level 2 nodal metastasis and PES invasion (p=0.004) but not with other levels (Table 3).

Table 2. Comparison of patients with or without preepiglottic space invasion according to diagnostic risk factors

Parameters	Preepiglottic space (-) (n=29)	Preepiglottic space (+) (n=20)	p
Ipsilateral nodal metastasis	10	17	0.001
Contralateral nodal metastasis	5	7	0.189
Perineural invasion	4	4	0.7
Grade of carcinoma			0.77
Well differentiated	15	11	
Moderately differentiated	12	9	
Poorly differentiated	2	-	
Extracapsular invasion	-	3	0.062
Recurrence	2	4	0.21

Table 3. Comparison of patients with or without preepiglottic space invasion according to levels of nodal metastasis

Level of nodal metastasis	Preepiglottic space (-) (n=29)	Preepiglottic space (+) (n=20)	p
Ipsilateral level 2	9	15	0.006
Ipsilateral level 3	1	4	0.144
Ipsilateral level 4	3	2	1.000
Contralateral level 2	4	7	0.096
Contralateral level 3	2	1	1.000
Contralateral level 4	-	-	-

Disease free and overall survival of patients with regard to presence of neck metastasis, carcinoma stage (early versus advanced) and PES invasion were calculated. Disease free survival was significantly higher in patients with no PES invasion ($p=0.033$). However, overall survival with PES invasion did not show statistical significance ($p=0.226$). Meanwhile, cancer stage and presence of neck metastasis revealed no difference for both disease free and overall survival (Figure 1, 2 and 3).

DISCUSSION

Open SGL is an established surgical method used for over 50 years to achieve safe oncological

margins while preserving laryngeal functions such as swallowing and voice. It is also a valid alternative to transoral laser surgery to resect tumors arising from the supraglottic larynx but not extending to the glottis, with limited tongue base and PES invasion.^[11,12] There are few well-known factors that influence survival rates in patients who underwent open SGL such as pathological stage, pathological nodal status, cartilage invasion, extralaryngeal invasion and PES invasion.^[5,6,13-16]

Among these negative prognostic factors, cervical lymph node metastasis was stated to cause worse prognosis by upgrading the disease to an advanced stage. Joo et al.^[3] showed a

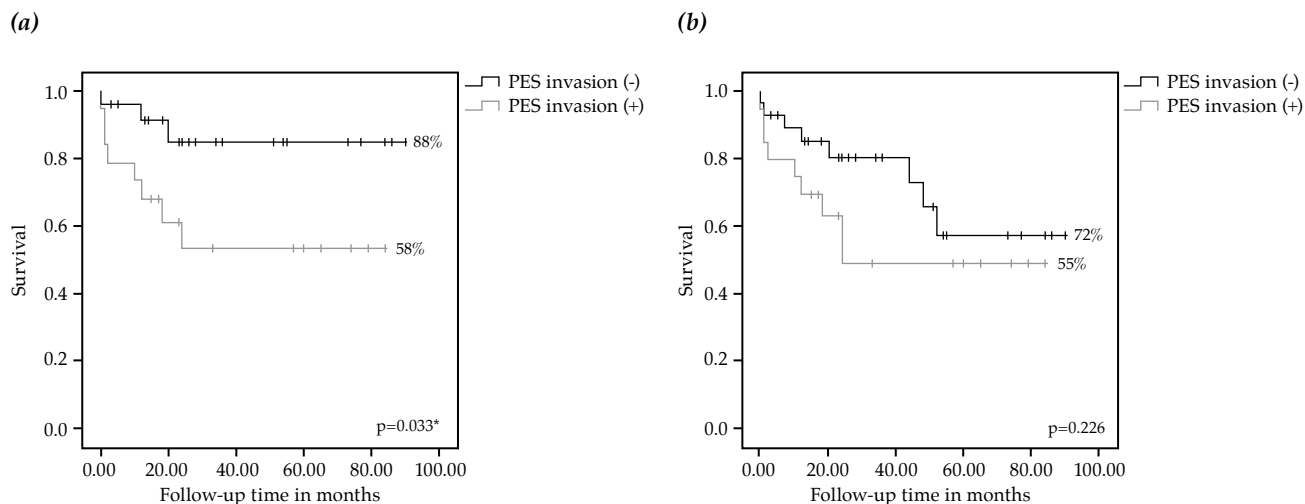


Figure 1. (a) Kaplan-Meier disease free survival and (b) overall survival rates calculated according to presence of preepiglottic space invasion.

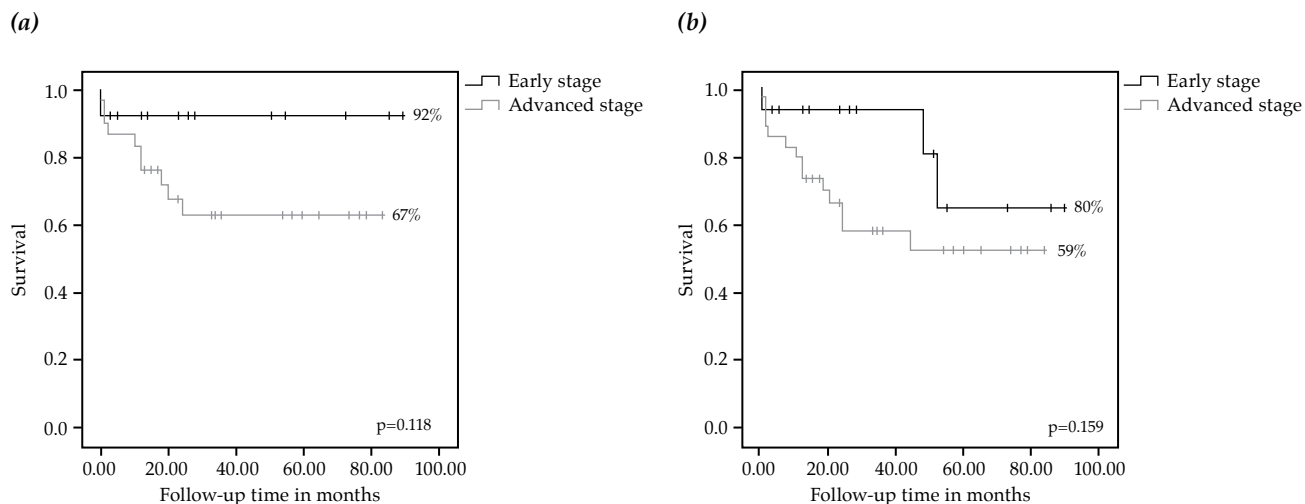


Figure 2. (a) Kaplan-Meier disease free survival and (b) overall survival rates calculated according to stage of carcinoma.

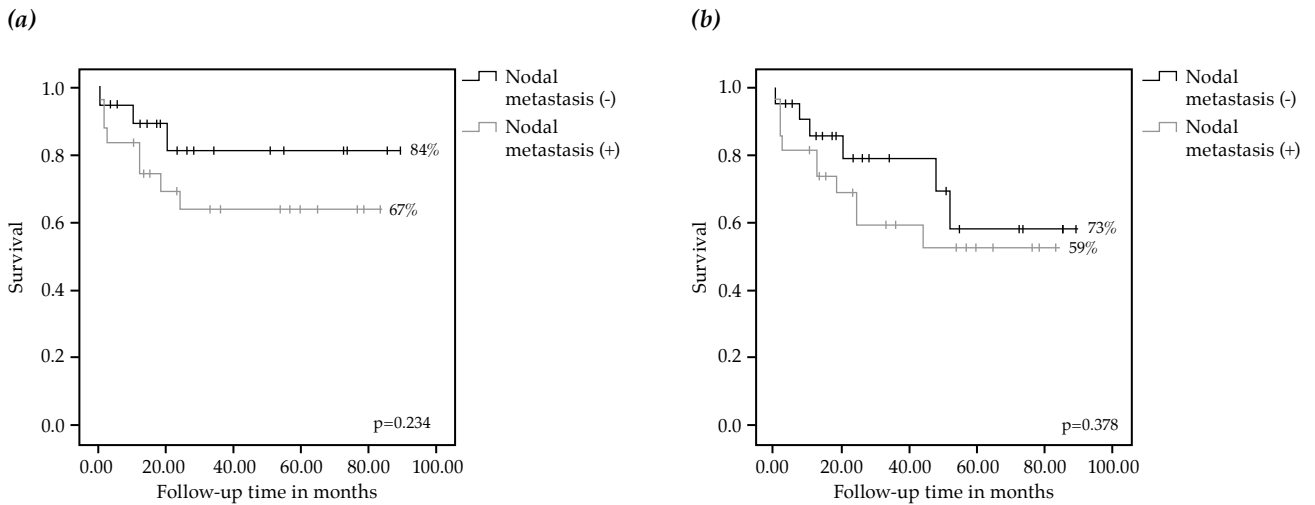


Figure 3. (a) Kaplan-Meier disease free survival and (b) overall survival rates calculated according to presence of cervical nodal metastasis.

significant correlation between cervical nodal metastasis and DFS in patients who underwent supracricoid laryngectomy. Similarly, Suoglu et al.^[8] pointed out that presence of cervical lymph node invasion significantly correlated with worse prognosis. Pathological cervical lymph node involvement by cancer was indicated as a significant negative prognostic factor for both locoregional control and DFS in the study of Succo et al.^[13] They conducted that study on patients who underwent open partial horizontal laryngectomy due to advanced stage laryngeal carcinoma. In other studies including ours, although the presence of nodal metastasis did reveal worse prognosis and low DFS, it did not reach significant levels.^[14] Suoglu et al.^[8] and Joo et al.,^[3] both mentioned that in patients with PES invasion there were higher incidences of cervical nodal metastasis compared to patients with no invasion. We know that laryngeal cancers arising from the supraglottic larynx metastasize to lymphatics via the PES draining through the thyrohyoid membrane. However, whether the nodal metastasis itself or the PES invasion by promoting cancer cells to spread to cervical lymph nodes results with poor prognosis is still uncertain.

The PES is a triangular area composed of mainly adipose tissue and lymphatics. Involvement of this loose areolar tissue with malignant cells influences spread of cancer to cervical lymph nodes. The lymphatic flow of the supraglottic

larynx is through the thyrohyoid membrane which is the anterior boundary of the PES.^[17] Some studies have previously addressed the topic of PES invasion and its relation with prognosis in patients who underwent supracricoid partial laryngectomy. They reported that PES invasion was significantly related to presence of cervical nodal metastases and it is also a significant prognostic factor that decreases the DFS in these patients. Despite the T stage, early supraglottic cancers with PES invasion have higher incidences of cervical metastasis.^[18] Some authors even suggest to stage supraglottic laryngeal cancers which have PES invasion as T₄, like tumors with extralaryngeal spread.^[5] On the contrary, Suoglu et al.^[8] did not find any significant association between gross or minimal PES invasion and five year overall survival in patients who underwent supracricoid partial laryngectomy.

Open supraglottic partial laryngectomy is still a commonly performed surgery when indicated. However there are only very few articles that evaluated the impact of PES invasion on prognosis after such surgery.^[6,19] Despite the small number, the articles contain controversies with regard the impact of PES invasion on survival. Fiorella et al.^[19] reported that there was higher percentage of recurrence in patients with subclinical PES invasion and it must be considered to effect prognosis. On the contrary, Dursun et al.^[6] demonstrated that in the majority of supraglottic cancers, there was PES invasion

regardless of cervical nodal metastasis. Therefore they concluded that PES invasion should not be considered as a prognostic factor. In our study, PES invasion was found to effect DSF significantly but not cervical nodal metastasis. Our surgical motto is to perform elective bilateral neck dissection rather than close observation in clinically node negative patients. We argue that performing elective bilateral neck dissection on all supraglottic cancer patients can explain the reason why pathological nodal status did not affect survival analysis in our study. Early detection of subclinical PES invasion is crucial in the management of patients with glottosupraglottic laryngeal carcinoma. This is easy in cases when extralaryngeal spread is clinically obvious but if the tumor is at T₁ or T₂ stage and confined to the endolaryngeal surface of the epiglottis or false vocal cord it is rather difficult. There is a risk of understaging for this group of patients by endoscopic examination only. Thus to overcome the understaging problem in patients with suspected PES invasion, different imaging modalities are used.^[4,16,20,21]

Hermans et al.^[16] investigated the value of computed tomography (CT) by assessing several tumor parameters and their clinical importance on locoregional outcomes after primary radiotherapy for laryngeal carcinoma. They found that the degree of PES involvement on CT was a significant independent predictor of local recurrence. In another study by Rapoport et al.,^[4] the authors indicated that there was a statistical inter-observer and intra-observer agreement in the involvement of PES and CT images that was confirmed by biopsy. Therefore, they suggest CT as a reliable method in the diagnosis of PES invasion. Pre-treatment magnetic resonance imaging (MRI) is a good and reliable alternative to CT in the determination of prognostic risk factors for locoregional control. Ljumanović et al.^[20] pointed out that PES invasion diagnosed by MRI in patients who underwent definitive radiotherapy for supraglottic carcinoma was a significant predictor of local control rates. Becker et al.^[21] reviewed the efficacy of three commonly used modalities-- CT, MRI and positron emission tomography (PET)/CT in the diagnostic work-up of laryngeal structures including PES that are relevant to tumor spread. They mentioned that both CT and MRI are highly sensitive and well suited to demonstrate replacement of normal

fatty tissue by tumor within PES at axial and sagittal planes. In addition, the authors valued PET/CT in the detection of recurrent tumors and also advocated its use in the differentiation of recurrences from post-radiation changes. Since early detection of PES invasion before surgery has vital importance in both staging and deciding appropriate surgical procedure, one should evaluate this compartment via aforementioned imaging modalities. Thus we routinely order a contrast enhanced CT of the larynx in the management of supraglottic laryngeal carcinoma despite any T stage in daily practice. In cases of gross PES invasion, tumor spread to vallecula, base of tongue or pyriform sinus and impaired vocal cord mobility, an additional MRI can be useful.

In conclusion, supraglottic partial laryngectomy is an oncologically safe procedure that can be used in patients with early and selected advanced stage supraglottic carcinoma. PES invasion was found to be significantly associated with the presence of cervical nodal metastasis. In addition, involvement of the PES in these patients is an important risk factor that is associated with poor prognosis.

Declaration of conflicting interests

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