# The effect of surgical margin positivity on survival in laryngeal cancer surgery

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**The effect of surgical margin positivity on survival in laryngeal cancer surgery**

AIM: *The aim of this retrospective study was to investigate possible factors affecting the survival in patients who were operated due to laryngeal squamous cell carcinoma (SCC)*
MATERIAL AND METHOD: *The study included patients who underwent surgery in our clinic due to laryngeal SCC between May 2010 and June 2018. It was learned whether the patients were alive or not by hospital records, death notification system records and patient / family interviews. Surgical reports, pathology reports, tumor clinical council notes and preoperative hematological examinations were retrospectively evaluated and recorded from the hospital registry system.*
RESULTS: *The mean age of the 63 patients included in the study was 59.3 (age range; 38 to 83 years). The mean postoperative follow-up period was 56.8 months (minimum 6 months to maximum 102 months). We found that surgical margin positivity had a statistically significant negative negative effect on survival (p = 0.049, r = -0.26). Perineural invasion, perivascular invasion, the presence of neck metastasis and the effect of tumor differentiation on survival were not found to be statistically significant (p values; 0.9, 0.1, 0.9 and 0.4, respectively).*
CONCLUSION: *The absence of a tumor at the surgical margin is one of the most basic rules in oncologic surgery.*

KEY WORDS: Laryngeal carcinoma, Oncologic surgery, Survival, Surgical Margin

## Introduction

Head and neck cancer is the sixth most common cancer worldwide [1]. Laryngeal cancers are the most common cancers in this region [2]. Its incidence is 1.5-2% among all cancers [3].
Determining the factors affecting survival in laryngeal cancers will help to develop new treatment strategies in the fight against disease [4]. In the literature; many parameters have been associated with survival in this cancer. Especially, subjectivity of TNM staging systems leads to the search for new prognostic factors in this area [5].

The aim of this study is to evaluate the clinical and laboratory parameters affecting the survival of patients, operated for laryngeal squamous cell carcinoma (LSCC). In this way, while planning follow-up and treatment in our patients, we aim to create new strategies and to establish survival prediction.

## Material and Method

The cases, in which laryngeal surgery was performed in our clinic with the diagnosis of laryngeal cancer, were included in the study. The patients who received chemoradiotherapy after the diagnosis and who underwent surgical treatment due to the failure of this treatment, were also included in this study. Thus, all the patients performed laryngeal surgery in our clinic between May 2010 and June 2018 were included in this study. The patient's survival status was learned from hospital records, national death notification system records and patient / family interviews.

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Surgical reports, pathology reports, tumor clinical council notes and preoperative hematological examinations of the patients included in the study were retrospectively evaluated and recorded on the hospital registry system. All investigations were performed in accordance with the Declaration of Helsinki on biomedical studies involving human subjects.

### Statistical Analysis

The research data were evaluated by SPSS 16.0 statistical package program. Descriptive statistics are presented for categorical variables; with frequency distribution and percentage and for the variables indicated by measurement; as mean ± standard deviation. As statistical method, paired T test and Pearson correlation analysis were used. One-way analysis of variance was performed to evaluate the factors affecting survival. Statistical significance was accepted as $p< 0.05$.

## Results

The study included patients, who underwent surgery in our clinic for LSCC and later followed between May 2010 and June 2018. All the patients were smokers. The mean age of the 63 patients (61 male, 2 female) who were included in the study was 59.3 (age range; 38 to 83 years). The mean postoperative follow-up period of the patients was determined as 56.8 months (minimum 6 months to maximum 102 months). We found that 15 patients died and 48 patients were still alive.
In 13 (20.6%) of the 63 patients included in the study, the initial treatment was determined as radiotherapy (RT) or chemo-radiotherapy (CRT). However, these patients were operated because of failure of RT or CRT treatment. In the postoperative period, RT treatment was given as adjuvant therapy in 34 (68%) of 50 patients who underwent surgery as the first treatment plan. The treatment modalities and the number of patient loss according to the tratment modality were shown in Table I.
Total laryngectomy was performed in 50 (79.4%) of 63 patients. The other 13 patients were underwent partial laryngeal surgery. These partial surgeries are; Supracricoid laryngectomy was performed in 5 patients, supraglottic laryngectomy in 4 patients, vertical laryngectomy in 2 patients, frontolateral laryngectomy in 1 patient, and extended type 5a cordectomy by endolaryngeal laser in 1 patient. Laryngeal surgery types of the patients and the number of patient loss according to the laryngeal surgery type were shown in Table II.
While 51 (81%) patients underwent bilateral lateral (BLL) neck dissection, 12 (19%) patients did not undergo neck dissection. When we evaluated these patients who did not undergo neck dissection, we found that 7 patients underwent only total laryngectomy because of local recurrence / residual laryngeal carcinoma after CRT treatment while 2 patients underwent total laryngectomy as primary treatment but radiotherapy was preferred for the treatment of neck with N0 because of general condition disorder. We determined that two of the three patients, who had not undergone any other neck dissection, had vertical laryngectomy and one patient underwent frontolateral laryngectomy. These patients were clinically N0 patients and according to clinical and pathological evaluation, we determined that the patients with tumor stage T1 larynx were eligible for follow-up of the

Table I - *The treatment modalities that was performed for the patients with laryngeal squamose cell carcinoma and number of patient loss according to the treatment modality*

| Treatment modalities | Number of patients | Number of patient lost during the follow up period |
|---|---|---|
| Primary surgery | 16 | 3 |
| Primary surgery and postoperative radiotheraphy or chemoradiotheraphy | 34 | 8 |
| Failure of primary radiotherapy or chemoradiotheraphy, and salvage total laryngectomy with or without neck dissection | 13 | 4 |

Table II - *Laryngeal surgery types of the patients and the number of patient loss according to the laryngeal surgery type*

| Laryngeal surgery type | Number of patients | Number of patient lost during the follow up period |
|---|---|---|
| Total laryngectomy(primary treatment) | 37 | 8 |
| Salvage total laryngectomy (due to failure after chemoradiotheraphy) | 13 | 4 |
| Supracricoid laryngectomy | 5 | 2 |
| Supraglottic laryngectomy | 4 | - |
| Vertical laryngectomy | 2 | 1 |
| Frontolateral laryngectomy | 1 | - |
| Extended type 5a cordectomy | 1 | - |

Table III - *Differences between the groups in terms of hematological parameters*

| Parameter viewed | Surviving group (n = 48) | Exitus group (n = 15) | P value |
|---|---|---|---|
| Haemoglobin | 13.7 ± 2.3 | 14.1 ± 2.4 | 0.57 |
| Hematocrit | 41.7 ± 6.5 | 41.8 ± 6.5 | 0.9 |
| White Blood Cell | 10.1 ± 2.8 | 9.5 ± 2.5 | 0.56 |
| Neutrophile | 7.1 ± 2.8 | 6.9 ± 2.5 | 0.74 |
| Lymphocytes | 1.9 ± 0.7 | 2.1 ± 0.9 | 0.45 |
| Neutrophile-to-lymphocyte ratio | 4.4 ± 2.9 | 3.5 ± 1.3 | 0.08 |
| Platelet | 278000 ± 92000 | 261000 ± 83000 | 0.5 |
| Red Cell Distribution Width | 14.5 ± 2.2 | 13.6 ± 0.9 | 0.026 |

neck (2 patients) while the patients with tumor stage T2 recieved postoperative RT to the neck region.

When the tumor differentiations of the patients were evaluated, we found that 16 (25.5%) patients had low, 29 patients (46%) had moderate and 12 patients (19%) had good differentiation and furthermore, 6 (9.5%) patients were evaluated as basaloid squamous cell carcinoma.

The patients, who were still alive and died, were evaluated as two separate groups and retrospective patient files (tumor surgery council notes, chemotherapy and radiotherapy notes, operation notes, postoperative pathology reports and baseline laboratory findings) were screened and the presence of factors affecting the survival were investigated through available data. Reviewed hematological parameters and the differences between the groups are shown in Table III.

When the postoperative pathology reports were evaluated, 14 (27.5%) of 51 patients who underwent BLL neck dissection had neck metastasis and found that the mean number of metastatic lymph nodes was 1.25 ± 2.6 (minimum 0 and maximum 12). We also found that the mean number of lymph nodes removed from BBL neck dissection was 53.6 ± 21.4 (minimum 15 and maximum 115 lymph nodes).

When the effects of the data obtained from the pathology results were evaluated with correlation analysis, we found that surgical margin positivity had a statistically significant negative effect on survival (p = 0.049, r = -0.26). When the patients were evaluated, 2 (4.2%) of the 48 surviving patients had surgical margin positivity, while 3 (20%) of the 15 patients who died had surgical margin positivity.

The effects of perineural invasion, perivascular invasion, the presence of neck metastasis and tumor differentiation on survival were not found to be statistically significant (p values; 0.9, 0.1, 0.9 and 0.4, respectively).

4 of the 13 patients (30.8%), who had undergone surgery due to the failure of CRT treatment after the diagnosis of laryngeal cancer, were lost during the follow-up period, while 11 of the 50 patients (22%), who were treated surgically in the beginning, were lost during the follow-up period.

## Discussion

Laryngeal cancers constitute approximately 45% of head and neck cancers. Even this ratio may be the sole reason for the search for new strategies and foresight in the fight against this disease.

The most frequently used parameters in terms of follow-up, treatment planning and survival prediction in laryngeal cancers are made according to tumor prevalence and whether there is lymph node in neck. However, it should be noted that there may be other factors related to the course of the disease.

Laryngeal cancers are more frequently observed in populations over 50 years of age, especially in males [6-8]. The mean age of the patients in our study was determined as 59.3 ± 9.6 and almost all of our patients were male. The relationship between smoking and laryngeal cancers is indisputable [6]. In our study, it was determined that all of the patients were cigarette users. Less survival rate in patients with a higher package x year ratio and the non-termination of smoking after treatment plays an important role in survival. Also, Human Papilloma Virus (HPV) types are known as important oncogenic stimulators both for oropharyngeal cancers and laryngeal cancers. However, when we checked the data collected from the patients' files, we did not find any documentation about HPV presence in our patients. In the last few years, especially in cases of oropharyngeal cancer HPV began to be investigated at our hospital.

Recent studies have concluded that systemic inflammatory response is important for tumor prognosis and postoperative survival, especially in some cancers [9-12].

Particularly, inflammatory mediators released by tumor-induced inflammation can lead to changes in platelet and lymphocyte counts and functions [13,14]. These changes can also lead to cell transformation, proliferation, angiogenesis, and invasion and migration [15].

Although PLR was emphasized to have the possibility to be a guide in clinical therapy [16], and a good prognostic factor in some gastrointestinal cancers, breast cancer and colorectal cancer as well as LSCC [17-20], relationship between NLR, PLR and survival was not significantly

evaluated in our study. The number of patients being limited may play a role in these results.
Although there was a significant relationship between histological differentiation and survival in the Fararourei et al. study [21], the tumor stage was found to be more important than the degree of differentiation in many studies [22-24]. In our study, no significant relationship was found between the degree of differentiation and survival in parallel with the studies in the literature. The survival rate was found to be lower in patients with higher stages.
The absence of a tumor at the surgical margin is one of the most basic rules in oncologic surgery. Alicandri-Ciufelli et al. found a significant relationship between negativity of the surgical margin and survival, in their study [25]. Spector et al. also concluded that patients with negative surgical margins are advantageous in terms of survival, recurrence, and post-operative complications [26]. In our study, a significant relationship was found between surgical margin negativity and survival in a similar way to these studies ($P < 0.05$). Although, all the surgical margins of the laryngeal anatomical structures, and neighboring pharyngeal structures were checked with frozen-section pathological examination, unfortunately permanent pathological result was reported as positive surgical margin.
When many factors are evaluated together, we understand that surgical margin positivity has a negative effect on the expected life span from the studies present in the literature and from the findings of our study. In addition, we could not find a correlation between the presence of metastatic lymph nodes, which is considered to be a particularly bad prognostic factor, perineural invasion and survival, but this may be the result of the low number of cases and combined evaluation of the patients at different stages.
It is impossible for all the parameters discussed to be present in patients alone. There is a mixed interaction between tumor characteristics and the patient's clinical parameters. These discussed factors can change the result by affecting each other.

## Conclusion

In laryngeal squamous cell carcinomas, tumor negativity at the surgical margin is an important parameter affecting survival. There is a need for prospective studies in which a larger patient population is included.

## Riassunto

Lo scopo di questo studio retrospettivo è stato quello di studiare i possibili fattori che influenzano la sopravvivenza in pazienti operati per carcinoma a cellule squamose laringee (SCC)
Nello studio sono stati compresi i pazienti sottoposti ad intervento chirurgico nella nostra clinica per SCC laringea tra maggio 2010 e giugno 2018, controllando la sopravvivenza dai registri ospedalieri, dal registro delle notifiche dei decessi, e da interviste al paziente e alle famiglie. Referti chirurgici, referti anatomo-patologici, appunti dal consiglio clinico del tumore ed esami ematologici preoperatori sono stati valutati e considerati retrospettivamente dal sistema di registro ospedaliero.
L'età media dei 63 pazienti inclusi nello studio era 59.3 (fascia d'età, da 38 a 83 anni). Il periodo di follow-up postoperatorio medio è stato di 56,8 mesi (da un minimo di 6 mesi ad un massimo di 102 mesi). Abbiamo trovato che la positività al margine chirurgico aveva un effetto negativo statisticamente significativo sulla sopravvivenza ($p = 0{,}049$, $r = -0{,}26$). L'invasione perineurale, l'invasione perivascolare, la presenza di metastasi al collo e il grado di differenziazione del tumore sulla sopravvivenza non sono risultate statisticamente significative (valori p: 0,9, 0,1, 0,9 e 0,4, rispettivamente).
In conclusione l'assenza di residui neoplastici sul margine chirurgico è una delle regole più basilari da osservare nella chirurgia oncologica del cancro del laringe a cellule squamose.

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