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Association between cancer surface area and histopathological parameters of laryngeal squamous cell carcinoma in total laryngectomy specimens

Veza između površine tumora i histopatoloških parametara karcinoma skvamoznih ćelija larinksa u uzorcima totalne laringektomije

Nada Tomanović*, Ana Marija Tomić*, Anton Mikić†, Jovica Milovanović†, Vladimir Djordjević†, Aleksandar Trivić†

***University of Belgrade, Faculty of Medicine, Institute for Pathology, Belgrade Serbia;**
†University Clinical Center of Serbia, Clinic for Otorhinolaryngology and Maxillofacial Surgery, Belgrade, Serbia

Abstract

Background/Aim. Numerous histopathological parameters, such as cartilage penetration, perineural and lymphovascular invasion, presence of metastatic tissue in regional lymph nodes (LNs), extranodal extension (ENE) of nodal metastases, as well as the presence of cancer tissue on resection borders, are all important factors influencing survival in patients with laryngeal squamous cell carcinoma (LSCC). The aim of the study was to determine if there is an association between cancer surface area (CSA) and these histopathological characteristics. The presence of ENE of metastatic tissue in regional LNs was also investigated. **Methods.** In a retrospective study, one hundred and forty cases of LSCC were revised and processed after total laryngectomy. The cases were found in the archives of the Histopathology Laboratory of the Clinic for Otorhinolaryngology and Maxillofacial Surgery, University Clinical Center of Serbia. **Results.** A significant difference was found in CSA depending on cancer penetration into the thyroid cartilage, perineural invasion, and positive resection margins. Cancers with larger CSA were more common in the advanced T stage. Metastases were found in 36 out of 72 (50%) neck LN samples submitted for evaluation. The difference in CSA was also found depending on the presence of metastatic tissue in regional LNs. ENE was present in 69.4% of involved LNs, and it was more frequent in LNs 3 cm in size or larger. **Conclusion.** There is a significant difference in CSA depending on the presence of cartilage penetration, perineural invasion, presence of cancer tissue on resection borders, and presence of metastases in regional LNs. Larger cancers tend to be of a higher T stage. ENE is more common in LNs 3 cm in size or larger.

Key words:
carcinoma, squamous cell; laryngectomy; laryngeal neoplasms; lymph nodes; lymphatic metastasis; neoplasm staging; prognosis; tumor burden.

Apstrakt

Uvod/Cilj. Mnogobrojni histopatološki parametri skvamocelularnog karcinoma larinksa (LSCC), kao što su proboj malignog tkiva u hrskavicu larinksa, perineuralno i limfovaskularno širenje, prisustvo metastaza u regionalnim limfnim čvorovima (LN), pojava ekstranodalne ekstenzije (ENE) metastatskog tkiva, kao i prisustvo malignog tkiva na linijama resekcije nakon hirurškog odstranjivanja tumora, su važni faktori koji utiču na preživljavanje bolesnika sa LSCC. Cilj rada je bio da se utvrdi da li postoji povezanost između površine tumora (*cancer surface area,* CSA*)* i pomenutih histopatoloških karakteristika. Ispitana je i učestalost pojave ENE u regionalnim LN vrata zahvaćenih metastazom. **Metode.** U retrospektivnoj studiji analizirano je 140 slučajeva LSCC obrađenih nakon totalne laringektomije, pronađenih u arhivi Patohistološke laboratorije Klinike za otorinolaringologiju i maksilofacijalnu hirurgiju Univerzitetskog kliničkog centra Srbije. **Rezultati.** Utvrđena je značajna razlika u CSA u zavisnosti od toga da li je postojao proboj tumora u tireoidnu hrskavicu larinksa, perineuralno širenje i prisustvo malignog tkiva na linijama resekcije. Karcinomi sa većom CSA bili su i višeg T stadijuma. Metastaze su bile prisutne u 36 od ukupno 72 (50%) dostavljena uzorka LN vrata. Postojala je razlika u CSA u zavisnosti od prisustva metastaza u regionalnim LN. Kod 69,4% zahvaćenih LN bila je prisutna ENE i to značajno češće u LN veličine 3 ili više cm. **Zaključak.** Postoji statistički značajna razlika u CSA u zavisnosti od prisustva

Correspondence to: Ana Marija Tomić, University of Belgrade, Faculty of Medicine, Institute of Pathology, Dr. Subotića 8, 11 000 Belgrade, Serbia. E-mail: Anamarija.tomic1@gmail.com

proboja u tireoidnu hrskavicu larinksa, perineuralnog širenja, prisustva malignog tkiva na linijama resekcije i prisustva metastaza u regionalnim LN. Veći tumori imaju višu vrednost T stadijuma. Ukoliko su zahvaćeni LN bili prečnika 3 cm ili veći, ENE je bila češća.

Ključne reči:
karcinom, planocelularni; laringektomija; larinks, neoplazme; limfne žlezde; neoplazme, limfatska metastaza; neoplazme, određivanje stadijuma; prognoza; tumorsko opterećenje.

Introduction

Laryngeal cancer (LC) is, after lung cancer, the second most common cancer of the respiratory tract, with around 40 thousand new cases in Europe each year [1]. It most frequently affects men in their sixth and seventh decade of life [2]. The most common histological type (over 95%) is squamous cell carcinoma (SCC) [3]. LC stage is determined using the tumor, node, metastasis (TNM) cancer staging system, with certain differences between clinical and pathological assessment of the N stage.

Therapy of LC depends on clinical presentation and cancer stage. Total laryngectomy followed by radiotherapy is still the leading treatment option for advanced LCs (of T3 and T4 stage), though advantages of combined chemoradiation have been shown in certain cases [3–6].

Prognostic factors linked to shorter survival after surgery and radiotherapy are the supraglottic primary site, presence of metastases in neck lymph nodes (LNs) and extranodal extension, as well as high mitotic index and aggressive histological pattern of invasion [7–10]. Cancers smaller than 2.5 cm and cancers completely surgically removed carried a significantly better prognosis [9, 11].

One of the most important independent prognostic factors for the survival rate of patients with LC is the spread of metastatic tissue beyond the limits of the affected LN (ENE). The risk of ENE is related to the higher N stage of cancer and the diameter of the largest metastatic LN [12, 13].

All of the data significant for diagnosis and prognosis is obtained only after surgical resection and histopathological evaluation of laryngeal and neck tissue. However, the size of the cancer is easily obtainable information, which may be useful in assessing the prognosis of these patients.

The aim of this study was to determine whether there is a statistically significant connection between cancer surface area (CSA) and other histopathological parameters, which are important for diagnosis, treatment, and prognosis in patients with LC. The presence of ENE in metastatic LNs was also determined.

Methods

One hundred and forty total laryngectomy samples were selected from archives of the Histopathology Laboratory of the Clinic for Otorhinolaryngology and Maxillofacial Surgery, University Clinical Center of Serbia. The samples were obtained from January 1, 2016, to November 1, 2018.

The data necessary for this study were collected from the micro- and macroscopic descriptions, which are part of standard histopathological reports. Cases were reviewed with regard to general patients' data, dimensions, cancer surface area, differentiation and type of cancer, presence of perineural and lymphovascular invasion, penetration into the thyroid cartilage, presence of cancer tissue on resection margins, and presence of metastases in regional LNs. In cases where metastatic tissue was found in the LNs, data on the diameter of the largest involved LN and ENE was collected.

CSA is a parameter of the cancer size and was calculated by multiplication of maximum length and maximum width of tumor in millimeters, estimated from the cross sections of cancer tissue samples made by a pathologist (Figures 1a and 1b).

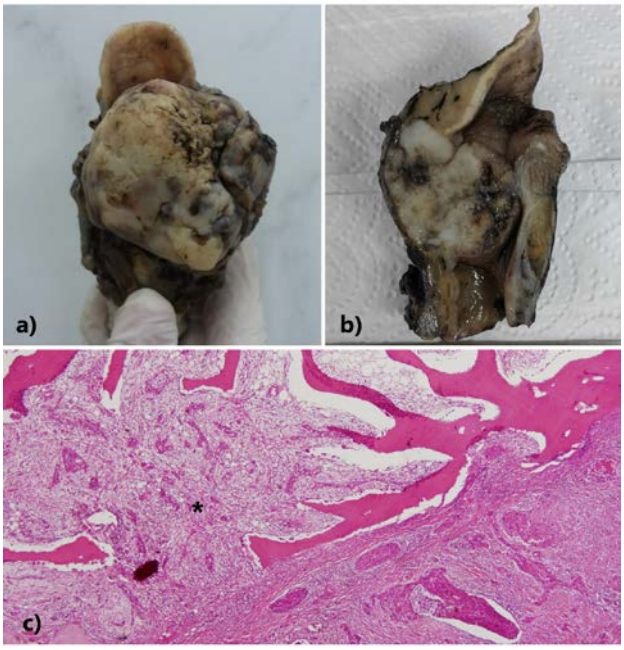


Fig. 1 − a) and b) Gross image of transglottic bilateral laryngeal squamous cell carcinoma; c) Ossified thyroid cartilage infiltrated by squamous cell carcinoma (*hematoxylin and eosin staining, original magnification ×400).

Data were processed by descriptive and analytical statistic methods in the IBM SPSS Statistics program (V21.0.0). Data with normal distribution were described by the arithmetic mean and standard deviation, while data with non-normal distribution were described using median, minimum, and maximum values. Categorical variables were described using frequencies. Based on the type of data, the following tests were used: Spearman rank order correlation, Mann-Whitney *U* test, Kruskal-Wallis test, χ^2 test, and Student's *t*-test.

Results

Out of the 140 patients with laryngeal squamous cell carcinoma (LSSC), 120 were male (85.7%) and only 20 were female (14.3%). Patients' ages ranged from 38 to 83 years, with a mean age of 65.41 ± 7.16 years. The average CSA was 860 mm^2 (225−4,680 mm^2).

In 81 cases, cancer was staged as T4 (57.9%), in 57 cases, it was T3 (40.7%), and only two cases were of T2 stage (1.4%). The average CSA of T4 stage cancers was 1,222 mm^2, of T3 stage cancers 912 mm^2, and of T2 stage cancers 291 mm^2. The smallest cancer to penetrate laryngeal cartilage had a CSA of 300 mm^2. There was a significant difference in CSA based on cancer T stage; namely, cancers of higher T stage were larger (Figure 2, $p = 0.005$).

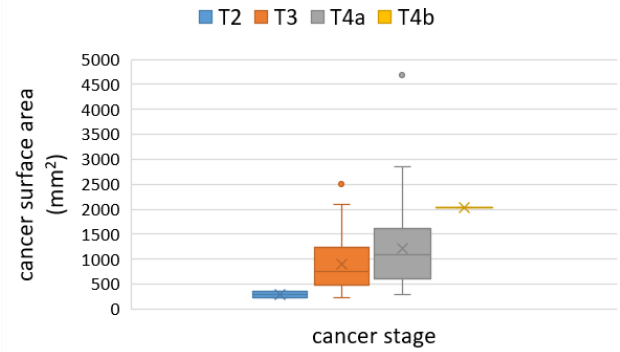


Fig. 2 – Cancers of higher tumor (T) stage had larger cancer surface area (as per Kruskal-Wallis test, $p = 0.005$).

No correlation was found between CSA and the age of the patients ($p = 0.863$). No statistically significant difference in CSA was found depending on cancer differentiation ($p = 0.153$) and histological type ($p = 0.963$). On the contrary, a significant difference in CSA was found depending on the presence of penetration of tumor tissue into the laryngeal cartilage (Figure 1c), i.e., cancers that penetrated the cartilage more often had a larger CSA value (Figure 3, $p = 0.001$). Cancers with larger CSA were also linked to a more frequent perineural invasion (Figure 4, $p = 0.005$). In all the total laryngectomy samples, a lymphovascular invasion was present. A significant difference in CSA was also found depending on the presence of cancer tissue on the resection margins, or less than 0.5 mm distance from them (Figure 5, $p = 0.031$).

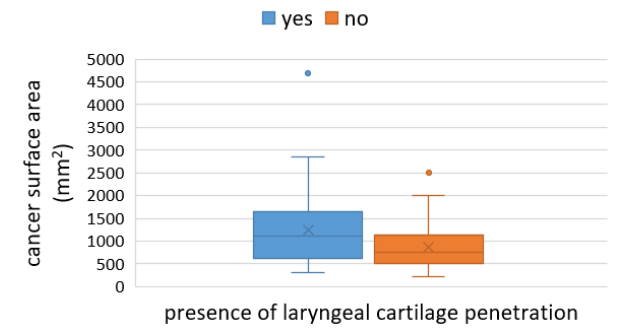


Fig. 3 – Laryngeal cartilage penetration was more often in cancers of larger surface area (as per Mann-Whitney *U* test, $p = 0.001$).

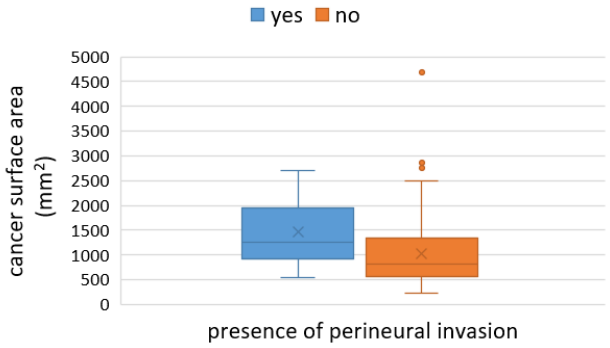


Fig. 4 – The presence of perineural invasion was more often in cancers of larger surface area (as per Mann-Whitney *U* test, $p = 0.005$).

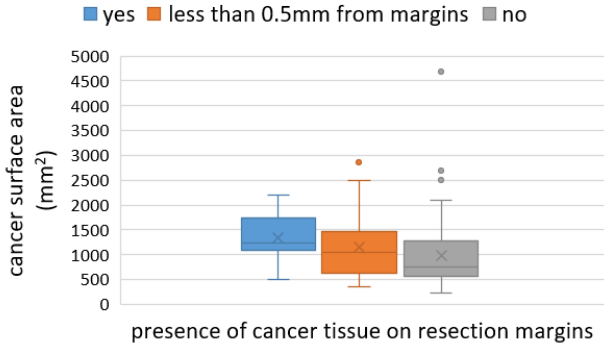


Fig. 5 – Incidence of the presence of cancer tissue on resection margins grew with cancer surface area (as per Kruskal-Wallis test, $p = 0.031$).

Out of 140 cases, LNs were submitted to analysis with 72 total laryngectomy samples (51.4%). LC metastases were found in 36 out of 72 LNs (50%). A significant difference in CSA was found depending on the presence of metastases in LNs (Figure 6, $p = 0.001$).

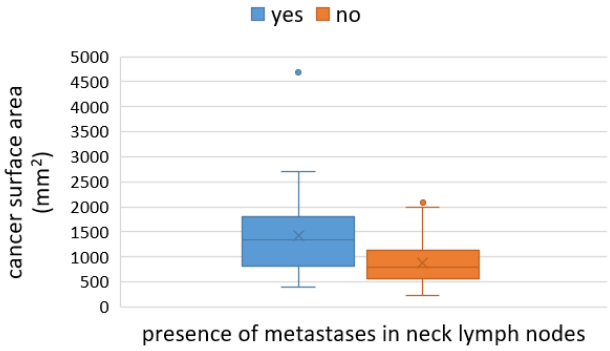


Fig. 6 – Metastases in neck lymph nodes were more often found in cancers of larger surface area (as per Mann-Whitney *U* test, $p = 0.001$).

Out of 36 cases with LN involvement, ENE was found in 25 cases (69.4%). No significant association was found between CSA and the presence of ENE. However, it was determined that ENE was more likely to occur if the largest diameter of the affected LN is 3 cm or more than if it is less than 3 cm (Table 1, $p = 0.002$).

Table 1

Extranodal extension (ENE) was more frequent in lymph nodes (LNs) 3 cm in size or larger (as per χ^2 test, $p = 0.002$)

ENE	LN diameter < 3 cm	LN diameter ≥ 3 cm
+	4	20
-	9	3

+ – ENE present; - – ENE absent.

Discussion

This study shows that CSA is significantly related to several prognostic factors: cancer stage, cartilage penetration, presence of perineural invasion, presence of cancer tissue on resection margins, and presence of metastases in LNs.

Association between CSA and cancer stage is of great importance since the cancer T stage is directly linked to patients' survival rates. In a study published in Canada in 2012, the two-year survival rate for T3 stage cancer was 89% and 60% for T4 stage [14]. Another study published in Germany in 2011 showed similar results (80% for the T3 stage and 64% for the T4 stage) [15].

Penetration of cancer tissue into the thyroid cartilage indicates a worse prognosis and is linked to more frequent cancer recurrence [16, 17]. The significance of cartilage penetration is also seen in the fact that its presence is one of the criteria for the classification of cancer in stage T4 [7].

Presence of perineural invasion is another prognostic factor associated with shorter survival and increased incidence of local recurrence [18, 19].

Cancer tissue was present on the resection margins in 10 cases (7.1%), and in 37 (26.4%), it was very close to resection margins, i.e., less than 0.5 mm from them. The presence of cancer tissue on resection margins is associated with a more frequent recurrence of cancer, as well as shorter survival [20, 21].

As already noted, metastases in neck LNs are more often if cancer has a higher CSA value, as was shown in other studies. It is also suggested that T3 and T4 stage cancers give regional metastases in more than 50% of the cases [22], which agrees with our results. Metastases were present in exactly 50% of the cases in which LNs were delivered for examination.

CSA is linked to shorter survival as an independent prognostic factor as well. A study conducted in Spain showed that cancers with the largest diameter of 2.5 cm or less carry a significantly better prognosis [9].

ENE was present in 25 of 36 cases with affected neck LNs (69.4%). Different studies have linked the presence of ENE with the size of the metastatic LN; more precisely, ENE occurs more frequently if the diameter of the LN is 3 cm or larger. Results obtained in our study agree with this hypothesis. ENE is a significant prognostic factor associated with the presence of distant metastases and recurrence of cancer; both have an impact on shorter survival rates [12, 13].

Given that the size of LC has been associated with these histopathological parameters significant for the prognosis, clinical estimation of cancer size could itself have a certain prognostic value. The size of the cancer is, clinically, most accurately determined by different visualization methods, such as computerized tomography and nuclear magnetic resonance [23, 24].

The main limitation of this study was the lack of data on patients' survival that could be related to CSA. This way, we determined the significance of CSA on the prognosis only indirectly by studying the association between CSA and already known prognostic factors.

Conclusion

There is a significant difference in CSA depending on the presence of cartilage penetration, perineural invasion, the presence of cancer tissue on resection borders, and the presence of metastases in regional LNs. Larger cancers tend to be of a higher T stage. ENE is more common in LNs 3 cm in size or larger.

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