



Comparison of Histopathological Characteristics of Laryngeal Squamous Cell Carcinoma in Turkish and Syrian Patient Populations

Türk ve Suriyeli Hasta Popülasyonlarında Laringeal Skuamöz Hücreli Karsinomun Histopatolojik Özelliklerinin Karşılaştırılması

Didar Gursoy¹, İlke Evrim Secinti¹, Yusuf Doran¹, Esin Dogan¹, Semsettin Okuyucu²

¹Hatay Mustafa Kemal University, Faculty of Medicine, Department of Pathology, Hatay, Turkey

²Hatay Mustafa Kemal University, Faculty of Medicine, Department of Otolaryngology, Hatay, Turkey

Abstract

Objectives: This study aimed to identify the differences between the tumors and their histopathological characteristics in the materials obtained by laryngectomy performed because of laryngeal squamous cell carcinoma (LSCC) in Turkish and Syrian patient populations.

Material and Method: Our study has a retrospective design. The present study included all the patients who were diagnosed with squamous cell carcinoma between January 2010 to January 2021 and underwent laryngectomy in our institute. Medical records, pathology and radiology reports were reviewed. Demographic and histopathological factors were statistically compared between Turkish and Syrian groups.

Results: Of 93 cases included in our study, 53 (57%) were Syrian while 40 (43%) were Turkish citizens. We have determined no statistically significant difference between two patient groups.

Conclusions: Hatay is a geography that Syrians were familiar with its culture before the war and both societies are exposed to the same environmental conditions. Therefore, we might have found no significant difference between the demographic and histopathological characteristics of laryngeal cancer in Turkish and Syrian patient populations.

Keywords: Larynx cancer, Squamous cell carcinoma, Syrian patients

Öz

Amaç: Bu çalışmada, Türk ve Suriyeli hasta popülasyonlarında laringeal skuamöz hücreli karsinom (LSCC) nedeniyle yapılan larenjektomi ile elde edilen materyallerdeki tümörler ve histopatolojik özellikleri arasındaki farklılıkların belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmamız retrospektiftir. Bu çalışmaya Ocak 2010- Ocak 2021 tarihleri arasında skuamöz hücreli karsinom tanısı alan ve kendi merkezimizde larenjektomi uygulanan tüm hastalar dahil edildi. Tıbbi kayıtlar, patoloji ve radyoloji raporları incelendi. Türk ve Suriyeli gruplar arasında demografik ve histopatolojik faktörler istatistiksel olarak karşılaştırıldı.

Bulgular: Çalışmamıza dahil edilen 93 olgunun 53'ü (%57) Suriyeli, 40'ı (%43) Türk vatandaşıydı. İki hasta grubu arasında istatistiksel olarak anlamlı bir fark saptamadık.

Sonuç: Hatay, Suriyelilerin savaştan önce de kültürüne aşina olduğu ve her iki toplumun da aynı çevre koşullarına maruz kaldığı bir coğrafyadır. Bu nedenle Türk ve Suriyeli hasta popülasyonlarında larinks kanserinin demografik ve histopatolojik özellikleri arasında anlamlı bir fark bulamamış olabiliriz.

Anahtar Kelimeler: Larinks kanseri, Skuamöz hücreli karsinom, Suriyeli hasta



INTRODUCTION

Syria crisis is the most important humanity problem of the 21st century and in its 11th year. According to the latest data; 6.7 million of Syrians had to leave their homes and 5.6 million of subjects had to settle in other countries including neighboring countries.^[1] Turkey has provided temporary protection status for more than 3.6 million of Syrians.^[2,3] Physical injury, infection, inadequate nutrition and mental health issues were the most emergent health problems for the recently coming refugees. The management of many diseases, primarily cancer, has become the most important health need after refugees accommodated to live in their new settlements.^[3,4] Cancer is one of the major economic burdens regarding both refugees and host-country citizens as well as healthcare system.^[5]

The cancer treatment may be difficult for refugees since they cannot access to healthcare systems easily. There is only a limited data on surveillance, medical records and types of cancer as well as prognosis of the patients in many localizations of refugee settlements.^[6,7] Turkish government has initiated a program planning to afford the costs of healthcare services for the Syrian refugees to provide their access to many various healthcare services including also cancer treatment.^[3,7] Hatay has close neighborhood to Syria and the rate of Syrian refugees is very high in Hatay Province. The number of Syrian refugees living in Hatay accounts for 25.92% of whole Hatay population.^[8]

Laryngeal cancer (LC) is one of the most commonly seen cancer types in the upper aerodigestive tract and it makes up 4.5% of all malignancies. Its incidence has increased by 12% in the last 3 decades and Europe is the continent with the highest incidence and mortality rate.^[9] A major part of the cases (98%) manifest the morphology of squamous cell carcinoma (SCC).^[10-12] Many factors such as host characteristics, tumor features and implemented treatment option may affect prognosis in these patients.^[13]

In the present study, we aimed to identify the histopathological characteristics of the tumors and differences between these characteristics in the materials obtained by laryngectomy performed because of laryngeal squamous cell carcinoma (LSCC) in Turkish and Syrian patient populations.

MATERIAL AND METHOD

Our study has a retrospective design. The present study included all the patients who were diagnosed with squamous cell carcinoma between January 2010 to January 2021 and underwent laryngectomy in our institute. The demographic data of the patients (race, age and gender) were determined by screening medical records. The pathology and imaging procedure reports were reviewed to evaluate tumor size and tumor localization. The largest diameter of the tumor was recorded as the tumor size. The tumors were divided into four groups by reviewing pathology reports and imaging procedure. The tumors that involved the supraglottic

portions of larynx including epiglottis (laryngeal and lingual surfaces), aryepiglottic folds, arytenoids, false vocal cords and ventricles; the tumors that involved the glottic structures including true vocal cords, anterior and posterior commissures; the tumors that extended from 1 cm below the ventricular apex to its lower border represented by cricoid cartilage edge and the tumors that crossed the laryngeal ventricles in vertical direction and involved glottic and supraglottic larynges were grouped as supraglottic, glottic, subglottic and transglottic tumors, respectively. The histopathological characteristics of the tumors (histological grade, lymphovascular invasion, cartilage involvement, surgical margin status, thyroid parenchymal invasion) and pN stage of the patients who underwent neck dissection based on the number, size and localization of lymph nodes and extranodal extension status were determined.

The study protocol was approved by the Non-Interventional Clinical Research Ethics Board of the Hatay Mustafa Kemal University (Date: 23.12.2021, Decision No: 01).

Statistical Analysis

Study data were analyzed by IBM SPSS Statistics 21 software package. Study data were found normally distributed by Kolmogorov-Smirnov test. The (uantitative variables were expressed as mean and standard deviation while categorical variables were expressed as number (n) and percentage (%). Chi-square or Fisher's exact test were used to compare the qualitative data. The differences between Turkish and Syrian groups with respect to the (ualitative data were analyzed by T-test. A $p < 0.05$ value was accepted to be statistically significant.

RESULTS

Of 93 cases included in our study, 53 (57%) were Syrian while 40 (43%) were Turkish citizens. In Turkish citizen group; 39 (97.5%) cases were male while 1 (2.5%) case was female. Mean patient age was 63.2 ± 11.1 years in this group. Syrian patient group was composed of 51 (96.2%) males and 2 (3.8%) females. Mean patient age was 64.2 ± 11.1 years in Syrian patient group. There was no statistically significant difference between Turkish and Syrian patient groups in terms of mean age ($p = 0.654$).

Mean tumor diameter was 34.0 ± 12.9 mm in Turkish citizen group. This parameter was 38.4 ± 13.5 mm in Syrian patient group. No significant difference was present between two groups in terms of tumor diameter ($p = 0.113$).

In Turkish citizen group, tumor showed supraglottic, glottic, subglottic and transglottic localization in 9 (22.5%), 18 (45%), 2 (5%) and 11 (27.5%) cases, respectively. In Syrian patient group; tumor had supraglottic, glottic, subglottic and transglottic localization in 8 (15.1%), 17 (32.1%), 4 (7.5%) and 24 (45.3%) cases, respectively. No statistically significant difference was found between Turkish and Syrian patients in terms of tumor localization ($p = 0.063$).

In Turkish citizen group, 13 (32.5%), 19 (47.5%) and 8 (20%) tumors were well-differentiated, moderate differentiated and poorly-differentiated, respectively (**Figure 1, 2**). In Syrian patient group, 16 (30.2%), 28 (52.8%) and 9 (17%) were well-differentiated, moderate differentiated and poorly-differentiated, respectively. Turkish and Syrian patients showed similar distribution regarding tumor differentiation ($p=0.869$).

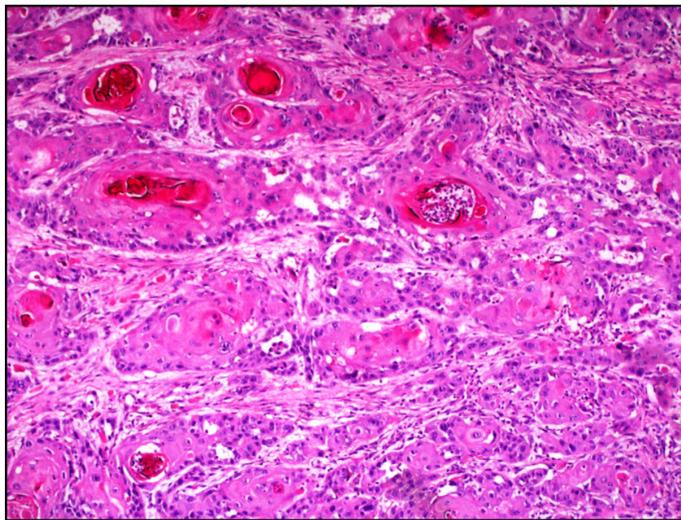


Figure 1: Well differentiated squamous cell carcinoma (H+E, x100)

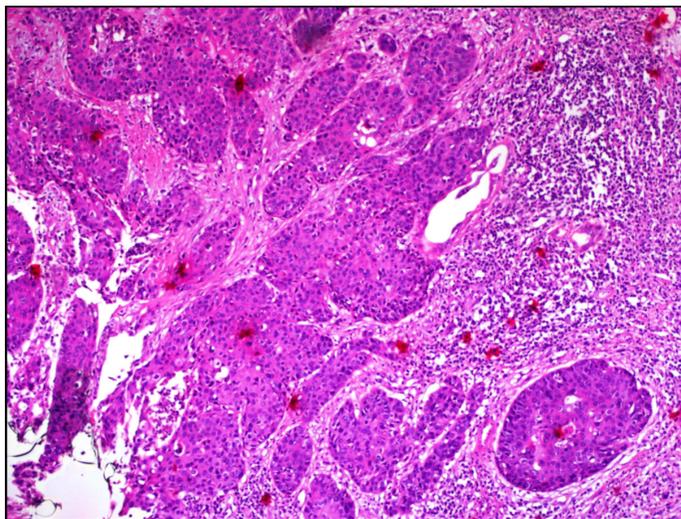


Figure 2: Poorly differentiated squamous cell carcinoma (H+E, x100)

Totally 33 (82.5%) cases were undergone neck dissection in Turkish patient group. Of the cases; 24 (72.7%), 4 (12.1%), 3 (9.1%) and 2 (6.1%) were N0, N1, N2 and N3, respectively. On the other side, totally 51 (96.2%) cases were undergone neck dissection in Syrian patient group. Among these cases, 32 (62.7%), 10 (19.6%) and 9 (17.6%) were N0, N1 and N2, respectively. Besides, totally 84 (90.3%) cases were undergone lymph node dissection without race differentiation. Lymph node metastasis was determined in totally 9 (27.3%) and 19 (37.3%) patients from Turkish

and Syrian patient groups, respectively. No statistically significant difference was identified between two groups in terms of lymph node metastasis ($p=0.343$).

Lymphovascular invasion (LVI) was found in 13 (32.5%) and 20 (37.7%) patients from Turkish and Syrian patient groups, respectively. No statistically significant difference was present between two groups regarding LVI ($p=0.601$). Cartilage invasion was detected in 13 (32.5%) and 25 (47.2%) patients from Turkish and Syrian patient groups, respectively. No statistically significant difference was present between two groups in terms of cartilage invasion ($p=0.154$).

Tumor was present on the inferior surgical margin in 1 (1.9%) case from Syrian patient group. We detected surgical margin positivity in none of the Turkish patients. In Turkish patient group, thyroidectomy was implemented in 19 (51.4%) patients and no patient had thyroid parenchymal invasion. Whereas, thyroidectomy was implemented in 33 (62.3%) patients in Syrian patient group and 1 (1.9%) of the cases had thyroid parenchymal invasion. The histopathological characteristics of the tumors in the Turkish and Syrian patients were presented in **Table 1**.

Table 1: Histopathological characteristics of the tumors in the Turkish and Syrian patients

	Syrian n (%)	Turkish n (%)	Total n (%)	P value
Sex				
Male	51 (96.2)	39 (97.5)	90 (96.8)	
Female	2 (3.8)	1 (2.5)	3 (3.2)	
Localization				0.063
Supraglottic	8 (15.1)	9 (22.5)	17 (18.3)	
Glottic	17 (32.1)	18 (45)	35 (37.6)	
Subglottic	4 (7.5)	2 (5)	6 (6.5)	
Transglottic	24 (45.3)	11 (27.5)	35 (37.6)	
Histologic grade				0.869
G1	16 (30.2)	13 (32.5)	29 (31.2)	
G2	28 (52.8)	119 (47.5)	47 (50.5)	
G3	9 (17)	8 (20)	17 (18.3)	
Lymphovascular invasion				0.601
Negative	33 (62.3)	27 (67.5)	60 (64.5)	
Positive	20 (37.7)	13 (32.5)	33 (35.5)	
Inferior surgical margin				
Negative	52 (98.1)	40 (100)	92 (98.9)	
Positive	1 (1.9)	0 (0)	1 (1.1)	
Cartilage				0.154
Negative	28 (52.8)	27 (67.5)	55 (59.1)	
Positive	25 (47.2)	13 (32.5)	38 (40.9)	
Lymph mode				0.343
Negative	32 (62.7)	24 (72.7)	56 (66.7)	
Positive	19 (37.3)	9 (27.3)	28 (33.3)	
Thyroid parankime				
None	20 (37.7)	18 (48.6)	38 (42.2)	
Negative	32 (60.4)	19 (51.4)	51 (56.7)	
Positive	1 (1.9)	0 (0)	1 (1.1)	

DISCUSSION

Turkey has a long border line with Syria (911km) and is the country who hosted the largest number of Syrian refugees with 3.6 million of people.^[2,3] Many noncontagious diseases including cancer have become an important health problem as well as physical injury, malnutrition, infections and mental health issues by development of adaptation to humanitarian crisis in the course of time.^[3,4,6,14] Cancer is an important public health problem and its incidence has increased in both developed and non-developed countries.^[3,7,15] Cancer has become the most important death cause following cardiac diseases and injuries among Syrian refugees along war.^[16] Refugee health has created an important concern for Turkish state authorities and has not been considered differently from domestic public health in the perspective of human rights.^[7,17] It has been reported in a study conducted by the Ministry of Health of the Republic of Turkey between 2012-2015 based on the data from a public hospital that breast, colon and lung cancer were the most commonly seen cancer types among the Syrian adults aged over 19 years.^[7] Kutluk et al. have reported the similar results and a prevalence of 2.2% for laryngeal cancer in their study.^[3]

LC is the cancer of respiratory tracts and 184,404 new cases with related 99,840 deaths have been reported in the year of 2020 worldwide. LC has made up 1% of all newly diagnosed cancer cases and cancer-related deaths.^[12,18] Many factors such as host characteristics, tumor features and the implemented treatment option may affect prognosis in these patients.^[13] Host factors involve age, gender, nutritional status, physical and psychological performance states, comorbidities and immunological response while tumor factors comprise tumor localization, tumor grade and stage and presence of a secondary primary cancer (synchronous or metachronous), treatment factors are constituted by available therapeutic approaches and various combinations of these approaches.^[13] The 5-year survival rate for the patients with early-stage LSCC is 70-90% whereas advanced stage patients have a 5-year survival rate of 30%.

LSCC is more frequently seen in male gender and male/female ratio ranges between 1/5-1/30 in different races.^[19] That rate is 1/7 in Europe.^[19-21] It has been found in the study of Adeel et al. that 93.5% of the cases were male.^[22] On the other side, Gupta et al. have determined that 80% of the cases were male in their study.^[23] In our study, 96.8% of the patients were male without nationality differentiation and male/female gender ratio was compliant with literature. LC is more frequently seen in male gender since alcohol and cigarette use is more common among males. However, increased cigarette and tobacco products use among females may elevate the incidence of LC in this gender.^[23] In our study, mean age of Turkish patients was 63.2±11 years whereas that rate was 64.2±11.1 years among Syrian patients and these results were similar with the literature. However, there was no statistically significant difference between the patient groups in terms of gender and mean age.

In the light of literature, LC is most frequently seen in the glottic region whereas subglottic tumors are rarely seen.^[19,24] However, localization of LC differs among the countries. In the present study, tumors showed supraglottic, glottic, subglottic and transglottic localization in 18.3%; 37.6%, 6.5% and 37.6% of the cases without nationality differentiation, respectively. Glottic tumors were most commonly (45%) seen in the Turkish patient group whereas Syrian refugee group were found to have transglottic tumors as the most frequently seen type (45.3%). However, no statistically significant difference between the patient groups in terms of tumor localization.

Thyroid gland has close neighborhood with larynx. Therefore, thyroid parenchymal invasion may be seen through direct invasion or LVI in advanced stage LSCC.^[25] The prevalence of thyroid gland involvement in the presence of advanced stage LSCC ranges between 1-30% in the literature.^[25,26] Without nationality differentiation, 56% of the patients included in our study were undergone thyroidectomy and 1 (2%) of those patients had thyroid parenchymal invasion. This patient was a 54-year old Syrian male refugee.

In the present study, we have compared the histopathological characteristics (differentiation, LVI, cartilage involvement, surgical margin positivity) and lymph node involvement, however, we have determined no statistically significant difference between two patient groups in terms of these parameters.

CONCLUSION

With respect to social geography, the border between Turkey and Syria is a political and artificial border. Although, the people in Turkey and Syria live in different geographies and countries, marriages commonly occur between the two societies. Hatay is a geography that Syrians were familiar with its culture before the war and both societies are exposed to the same environmental conditions. At the same time, Syrian refugees can easily access to the healthcare service systems in our country. Therefore, we might have found no significant difference between the demographic and histopathological characteristics of laryngeal cancer in Turkish and Syrian patient populations.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the Non-Interventional Clinical Research Ethics Board of the Hatay Mustafa Kemal University (Date: 23.12.2021, Decision No: 01).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. UNHCR: Syria Emergency. <https://www.unhcr.org/syria-emergency.htm>. Accessed 11 May 2021.
2. UNHCR: TurkeyStats. <https://www.unhcr.org/tr/n/unhcr-turkey-stats>. Accessed 16 June 2021.
3. Kutluk T, Koç M, Öner İ, et al. Cancer among syrian refugees living in Konya Province, Turkey. *Confl Health* 2022;16.
4. El Saghir NS, Pérez De Celis E, Fares JE, Sullivan R. Cancer care for refugees and displaced population: middle east conflicts and global natural disasters. *Am Soc Clin Oncol Educ B* 2018;38:433–40.
5. Abdul-Khalek RA, Guo P, Sharp F, et al. The economic burden of cancer care for Syrian refugees: a population based modelling study. *Lancet Oncol* 2020;21(5):637–44.
6. Spiegel P, Khalifa A, Mateen FJ. Cancer in refugees in Jordan and Syria between 2009 and 2012: challenges and the way forward in humanitarian emergencies. *Lancet Oncology* 2014;15: 290–7.
7. Göktaş B, Yılmaz S, Gönenc İM, Akbulut Y, Sözüer A. Cancer incidence among Syrian refugees in Turkey, 2012–2015. *J Int Migrat Integrat* 2018;19(2):253-8.
8. Temporary Protection. Republic of Turkey, Ministry of Interior (MoI), Directorate General of Migration Management. <https://en.goc.gov.tr/temporary-protection>. Accessed 24 Aug 2021.
9. Allegra E, Bianco MR, Ralli M, Greco A, Angeletti D, de Vincentiis M. Role of clinical-demographic data in survival rates of advanced laryngeal cancer. *Medicina* 2021;57(3):267.
10. Lin Z, Lin H, Chen Y, et al. Long-term survival trend after primary total laryngectomy for patients with locally advanced laryngeal carcinoma. *J Cancer* 2021;12(4):1220.
11. Gong H, Zhou L, Hsueh CY, et al. Prognostic value of pathological tumor size in patients with supraglottic carcinoma. *Am J Otolaryngol* 2021;42(1):102757.
12. He Y, Cheng Y, Huang Z, et al. A deep convolutional neural network-based method for laryngeal squamous cell carcinoma diagnosis. *Ann Transl Med* 2021;9(24).
13. Bradford CR, Ferlito A, Devaney KO, Mäkitie AA, Rinaldo A. Prognostic factors in laryngeal squamous cell carcinoma. *Laryngoscope Invest Otolaryngol* 2020; 5(1):74-81.
14. Jawad M, Millett C, Sullivan R, Alturki F, Roberts B, Vamos EP. The impact of armed conflict on cancer among civilian populations in low and middle income countries: a systematic review. *E Cancer Med Sci* 2020;14:1039.
15. Salman O, Mona M, Robert AF, et al. Literature Review and Profile of Cancer Diseases Among Afghan Refugees in Iran: Referrals in Six Years of Displacement. *Med Sci Monit* 2015;21:3622-8.
16. Marzouk M, Kelley M, Fadhil I, et al. "If I have a cancer, it is not my fault I am a refugee": a qualitative study with expert stakeholders on cancer care management for Syrian refugees in Jordan. *PLoS ONE* 2019;14(9):1–19.
17. Akbulut Y, Göktaş B, Kutlu G. An Evaluation of Syrian Refugees' Utilization of Health services in Turkey. 2nd International Congress on Applied Sciences: Migration, Poverty and Employment-UUBK'2016;250–4.
18. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209-49.
19. Alhomsy K, Alamine I, Raiy A, Hadid H, Alkhuja I, Faizeh AQ. Study of squamous cell carcinomas of the larynx and the regional lymph nodes involvement 2019.
20. Castillo-López IY, Govea-Camacho LH, Sánchez-Robles EE, Palacios-López JC. Caracterización clínico-patológica del cáncer de laringe en la población mexicana. *Revista Médica del Instituto Mexicano del Seguro Social* 2021;59(1):27-33.
21. Kadriyan H, Sulaksana MA, Aryani IGAT, et al. Risk factors and characteristics of laryngeal carcinoma in the developing region of Indonesia. *IOP Conference Series: Earth and Environmental Science*. Vol. 712. No. 1. IOP Publishing, 2021.
22. Adeel M, Faisal M, Rashid A, et al. An overview of laryngeal cancer treatment at a tertiary care oncological center in a developing country. *Cureus* 2018;10(6).
23. Gupta A, Gupta P, Jamwal PS. Clinicopathological Study of Cancer Larynx. *Int J Sci Study* 2019;7(3):34-8.
24. Canova C, Richiardi L, Merletti F, et al. Alcohol, tobacco and genetic susceptibility in relation to cancers of the upper aerodigestive tract in northern Italy. *Tumori* 2010;96:1–10.
25. Al-Hakami HA, Garni MAA, AlSubayea H, et al. The incidence of thyroid gland invasion in advanced laryngeal squamous cell carcinoma. *Brazil J Otorhinolaryngol* 2021;87:533-7.
26. Elliott MS, Odell EW, Tysome JR, et al. Role of thyroidectomy in advanced laryngeal and pharyngolaryngeal carcinoma. *Otolaryngol Head Neck Surg* 2010;142:851-5.