



The Role and Importance of Risk Factors in the Development of Laryngeal Cancer During the COVID-19 Pandemic

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Abstract

Background/Aim: Laryngeal cancer is one of the most common malignancies in the head and neck region, with the highest incidence among 50 years old patients. The leading risk factors are alcohol consumption and tobacco use as the most correlated behaviours. This study aimed to assess the extent of laryngeal cancer and leading risk factors for the onset of the disease during the COVID-19 pandemic.

Methods: This retrospective study included 102 patients who were treated both diagnostically and therapeutically for laryngeal cancer during a 1-year period. All patients had a previous history of being treated for COVID-19.

Results: The sample included male (88.3 %) and female (11.7 %) respondents. The age group 60-69 years was predominant (40.0 %). The youngest patient was 41 and the oldest 82. Total laryngectomy was performed in 15.7 % of patients, while partial laryngectomy was performed in 57.85 % patients. Advanced stages of the cancer (T3, T4) prevented 17.65 % patients from receiving surgery. Tobacco use was the most leading risk factor (99 %).

Conclusion: Advanced stages (T3, T4) of laryngeal cancer and radical surgical techniques with a potentially high rate of disability showed a higher incidence during the COVID-19 pandemic. The COVID-19 pandemic impacted timely diagnosis and delays between diagnosis and surgical treatment of the cancer. Old age, male gender and tobacco use proved to be the most common risk factors of laryngeal cancer.

Key words: Laryngeal cancer; Risk factors; COVID-19.

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Introduction

Laryngeal cancer comprises 20 % of head and neck malignancies, which corresponds to 1-2 % of tumour pathology and a mortality rate of around 1 %.¹⁻³ Approximately 95-99 % of all laryngeal malignancies are squamous cell carcinoma (*carcinoma planocellulare*). Invasive squamous cell carcinoma is divided into three grades: well-differentiated, moderately differentiated and poorly

differentiated. Cellular differentiation grades are important for clinical supervision of malignancy and treatment.^{1,2} Despite modern diagnostic procedures, it is still surprising that more than 50 % of cases of laryngeal cancer occur in advanced T3 and T4 stages.³ The disease mainly affects middle-aged men with peak incidence at around age 70. The gender ratio is 4.6:1 for males, while race

dependence was not found.⁴ Prevention and early diagnosis represent the most important aspects in the fight against this disease. There are four main goals when evaluating laryngeal cancer, namely to establish a pathohistological diagnosis, identify the tumour localisation and metastasis, tumour stage (assess the primary tumour, regional lymph nodes as well as potential occult or distant metastases) and identify comorbidities and their effect on the optimal choice of treatment, including potential risk factors for the occurrence of the disease.²

It should be emphasised that head and neck cancers are common in developing countries and have a significantly higher mortality rate. The World Health Organization (WHO) declared the COVID-19 pandemic on 11 March 2020. Due to this, routine surgical procedures were cancelled, except in emergency and oncological cases.^{5, 6} The new virus called for new measures and “a new way of life”, making it difficult for patients to check in for scheduled appointments at health care institutions on time. Subsequently, this caused delays in diagnosis of laryngeal and oropharyngeal cancer.^{7, 8}

This study aimed to assess the extent of laryngeal cancer and leading risk factors for the onset of the disease during the COVID-19 pandemic.

Methods

This was a retrospective cohort study, which included 102 male and female patients, both diagnostically and therapeutically treated for laryngeal cancer during the period from 1 January to 31 December 2021. Data from the Clinical Information System (CIS) and the records at the The Ear, Nose and Throat Department, University Clinical Centre of the Republic of Srpska, Banja Luka, The Republic of Srpska, Bosnia and Herzegovina (UCC RS) were used in this study. Patients with a pathohistological diagnosis and TNM (T - primary tumour; N - regional lymph nodes; M - distant metastases) staging of laryngeal cancer who had recovered from COVID-19 using the polymerase chain reaction test (PCR) for Severe Acute Respiratory Syndrome Coronavirus 2 (Sars-Cov-2) participated in the study. Clinical screening included providing historical data and a detailed otorhinolaryngological screening. Following pre-operative preparation, endoscopic and fiberoptic

laryngoscopy, including laryngomicroscopy, were performed under general endotracheal anaesthesia. The above diagnostic procedures represent standard methods used in the biopsy and clinical assessment of laryngeal cancer localisation and spread. The narrow band imaging (NBI) technique was used for larynx structures that do not vibrate and are more difficult to access through standard screening methods.

Statistical analysis of the obtained data was based on descriptive statistical processing of numerical and nominal variables. The assessment of findings with all relevant parameters is presented in graphs and tables.

Results

A total of 102 patients treated for laryngeal cancer were observed. Laryngeal cancer was predominant in male patients (90, 88.3 %) (Table 1).

Of all patients, the highest incidence rate (40.2 %) was found in the age group 60-69 years, of which 40.0 % were males and 42.0 % females. The youngest hospitalised patient was 41 and the oldest was 82 years old, in both cases it was a male. There were no hospitalised patients diagnosed with laryngeal cancer under 40 or over 90 years of age.

Table 1: Age distribution in patients with laryngeal cancer

Age	Gender				Total	
	N	Male %	Female %	N	%	
≤ 40	0			0	(0.00 %)	
41-49	7	(0.00 %)	0 (0.00 %)	7	(6.86 %)	
50-59	33	(7.78 %)	0 (0.00 %)	36	(35.30 %)	
60-69	36	(36.67 %)	3 (25.00 %)	41	(40.20 %)	
70-79	10	(40.00 %)	5 (42.00 %)	14	(13.72 %)	
80-89	4	(11.11 %)	4 (33.33 %)	4	(3.92 %)	
≥ 90	0	(4.44 %)	0 (0.00 %)	0	(0.00 %)	
Total	90	(88.30 %)	12 (11.70 %)	102	(100.00 %)	

Of all 102 patients, total laryngectomy was performed in 16 patients (15.70 %), 15 males (16.67 %) and only 1 female (8.33 %). A significantly higher percentage of patients (57.85 %) underwent partial laryngectomy, 57.77 % males and 58.34 % females, respectively. Tracheotomy was performed in 9 patients (8.80 %) with acute respiratory insufficiency to secure the airway. No surgical procedures were performed in 18 patients (7.65 %), 15

Table 2: Patients with laryngeal cancer by surgical procedure

Surgical procedure	All patients		Male		Female	
	N	%	N	%	N	%
Total laryngectomy	16	15.70	15	16.67	1	8.33
Partial laryngectomy	59	57.85	52	55.77	7	58.34
Tracheotomy	9	8.80	8	8.90	1	8.33
None	18	17.65	15	16.66	3	25.00
Total	102	100.00	90	100.00	12	100.00

males (16.66 %) and 3 females (25.00 %) (Table 2). By TNM staging of laryngeal cancer, the highest instance was observed in patients with an advanced stage of the disease. In 35 patients (34.31 %), T3 stage was identified and in 28 patients T4 stage, respectively. Findings from the examined sample showed it was possible to assess the primary tumour (Tx) or identify the absence of a tumour (To) or the presence of carcinoma *in situ* (Tis) (Table 3).

Table 3: Patients with laryngeal cancer by the primary tumour metastasis

Metastasis (T)	N	%
Tis	0	0.00
Tx	0	0.00
T0	0	0.00
T1	19	18.63
T2	20	19.61
T3	35	34.31
T4	28	27.45
Total	102	100.00

Tis: the presence of carcinoma in situ, Tx: the primary tumour, To: the absence of a tumour, T1: the cancer has grown deeper but is still within the vocal cords, T2: the cancer has grown deeper but is still within the vocal cords, T3: the cancer is still in larynx, has grown into a fat filled space on either side of the paraglottic space or into the inner part of the cartilage, T4: the cancer has grown through the thyroid cartilage or has grown into prevertebral space, around the carotid artery or the mediastinum;

Table 4: Tobacco use in patients with laryngeal cancer by gender

Gender	Tobacco users	
	Yes	No
Male	89 (98.90 %)	1 (1.11 %)
Female	12 (100.00 %)	0 (0.00 %)

The analysis of social and epidemiological historical data of all patients with laryngeal cancer revealed that as many as 101 patients (99 %) admitted using or having used tobacco. Tobacco use in patients with laryngeal cancer by gender was relatively balanced (Table 4).

Discussion

Due to their manifestation and mortality rate, malignancies represent one of the biggest public health challenges today. Numerous risk factors contribute to the onset and development of malignancies: genetic predisposition, lifestyle (eg tobacco use, alcohol consumption, improper diet, obesity, lack of physical activity), exposure to radiation, occupational exposure, exposure to carcinogens in the environment, infections, some immunodeficiencies and medications. According to WHO data, 30-50 % of malignant tumours can be prevented.⁹⁻¹¹

In this study, the majority of laryngeal cancer patients were older males (the age group 50-70 years). Previous research has shown that patients suffering from head and neck cancer come mainly from lower socioeconomic group of the population. Tobacco use and alcohol consumption are considered socially acceptable behaviours and patients usually check in for the first screening after several months of developing and manifesting first symptoms.¹⁰⁻¹²

Today, the number of patients among the female population is on the rise precisely because of the increase in the number of female smokers, although previous studies have shown that men are more often affected than women. Chen et al showed a significant link between comorbidity and patient age. Patients who were older than 70 years had higher comorbidity compared to younger patients. Paleri et al found a significantly higher comorbidity in people over 65 years of age. The aforementioned indicates that preventive measures be taken for timely prevention of the disease.¹³⁻¹⁶

According to the data from the International Agency for Research on Cancer (IARC), the number of newly discovered different types of cancer in 2018 at the world level was 16,099,208 of

which 177,422 (1.10 %) were laryngeal cancer. Age index shows that laryngeal cancer commonly occurs in people between 60 and 70 years of age and only 1 % in people under 30 years of age. According to the National Comprehensive Cancer Network (NCCN) guidelines from 2020, follow-up of all patients with laryngeal cancer is recommended for a minimum of five years after treatment completion.¹⁷⁻²⁰

The world was unprecedentedly affected by the new coronavirus in December 2019. As a result, many governments introduced quarantine measures. Health care services were only provided in emergencies and for treating malignancies. However, many patients who needed these services did not check in for fear of contracting COVID-19. A large number of studies have confirmed that lockdown measures have had a significant impact on the number of patients visiting clinics and being surgically treated for laryngeal cancer. During the COVID-19 pandemic, routine health services were limited, scheduled surgeries were not performed, except in emergencies.⁵⁻⁷

This study found that the exceptional circumstances of the COVID-19 pandemic greatly impacted the time interval from first symptom to diagnosis, patient delays for screening and a higher incidence of patients with advanced cancer (T3, T4). Likewise, there were delays between diagnosis and surgical treatment of laryngeal cancer, leading to more radical treatments. Galletti et al also found the statistically significant difference in tumour staging at the time of diagnosis between the “before COVID-19” and “during COVID-19” groups, with a higher mean value in the latter. The authors reported that the COVID-19 pandemic has led to a delay in early diagnosis, negatively influencing the staging at the time of the first otolaryngologists visit and the subsequent therapeutic approach to be offered to the patient.²¹

Findings from different countries point to a rise in advanced cancer in patients hospitalised post COVID-19 pandemic. Prevalence of hospitalised younger patients to their older counterparts may be the result of older patients avoid visiting health care institutions for fear of contracting COVID-19.⁵⁻⁷

The limitations of this study refer to its retrospective nature, thus potentially increasing the risk of biasness. The limitations also include the lack of comparative analysis with results from the period before the COVID-19 pandemic. Educating the public about preventive measures, exposure and risk factors is of great importance. All this is necessary to protect and improve general health status, especially in exceptional circumstances such as the COVID-19 pandemic.¹⁸⁻²⁰

Conclusion

Advanced stages (T3, T4) of laryngeal cancer and radical surgical techniques with a potentially high rate of disability showed a higher incidence during the COVID-19 pandemic. The COVID-19 pandemic impacted timely diagnosis and delays between diagnosis and surgical treatment of the cancer. Old age, male gender and tobacco use proved to be the most common risk factors of laryngeal cancer.

Ethics

The study protocol was approved by the Ethics Committee of the Ethics Committee of the University Clinical Centre of the Republic of Srpska, decision No: 01-19-138-2/24, dated 20 April 2024. All the data obtained from this study were stored according to the Law on Protection of Personal Data, adhering to the principle of the Declaration of Helsinki.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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References

- Janošević Lj, Đukić V. [Otorhinolaryngology with maxillofacial surgery]. Beograd: Zavod za udžbenike; 2014. Serbian.
- Đukić V, Milovanović J, Folić M, Pavlović B, Jotić A, Trivić A, et al. [Carcinoma of the larynx]. Beograd: Partenon; 2017. Serbian.
- Spremo S, Špirić S, Špirić P, Gnjatić M. [Otorhinolaryngology]. Banja Luka: Faculty of Medicine; 2014. Serbian.
- Špirić P. [Modifications of total laryngectomy and immediate postoperative treatment in patients with malignant laryngeal tumour]. Doctoral thesis. Banja Luka, University of Banja Luka, 2011. Serbian.
- Rawaf S, Yamamoto HQ, Rawaf D. Unlocking towns and cities: COVID-19 exit strategy. *East Mediterr Health J.* 2020;26(5):499–502. doi: 10.26719/emhj.20.028.
- Nassisi M, Audo I, Zeitz C, Varin J, Wohlschlegel J, Smirnov V, et al. Impact of the COVID-19 lockdown on basic science research in ophthalmology: the 160 Cranio-maxillofacial Trauma & Reconstruction 14(2) experience of a highly specialized research facility in France. *Eye (Lond).* 2020;34(7):1187–8. doi: 10.1038/s41433-020-0944-7.
- Dore B. Covid-19: collateral damage of lockdown in India. *BMJ.* 2020;369:m1711. doi: 10.1136/bmj.m1711.
- Gupta B, Johnson NW, Kumar N. Global Epidemiology of head and neck cancers: a continuing challenge. *Oncology.* 2016;91(1):13-23. doi: 10.1159/000446117.
- Vrdoljak E, Krajina Z, Šamija M, Kusić Z, Petković M, Gugić D. [Clinical oncology]. Zagreb: Medicinska naklada; 2013. Croatian.
- Parkin DM. Tobacco-attributable cancer burden in the UK in 2010. *Br J Cancer.* 2011;105(S2):S6-S13. doi: 10.1038/bjc.2011.475.
- Altieri A, Garavello W, Bosetti C, Gallus S, La Vecchia C. Alcohol consumption and risk of laryngeal cancer. *Oral Oncol.* 2005;41:956-65. doi: 10.1016/j.oraloncology.2005.02.004.
- Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. Light alcohol drinking and cancer: a meta-analysis. *Ann Oncol.* 2013;24(2):301-8. doi:10.1093/annonc/mds337.
- Dyba T, Randi G, Bray F, Martos C, Giusti F, Nicholson N, et al. The European cancer burden in 2020: Incidence and mortality estimates for 40 countries and 25 major cancers. *Eur J Cancer.* 2021;157:308-47. doi: 10.1016/j.ejca.2021.07.039.
- Chen AY, Matson LK, Roberts D, Goepfert H. The significance of comorbidity in advanced laryngeal cancer. *Head Neck.* 2001;23(7):566-72. doi: 10.1002/hed.1079.
- Paleri V, Wight RG, Davies GR. Impact of comorbidity on the outcome of laryngeal squamous cancer. *Head Neck.* 2003;25(12):1019-26. doi: 10.1002/hed.10333.
- World Health Organisation. Larynx cancer [Internet]. 2018. Available at <https://platform.who.int/mortality/themes/theme-details/topics/indicatorgroups/indicator-group-details/MDB/larynx-cancer>. [Cited: 6-Dec-2022].
- International agency for research on cancer. EUCAN [Internet]. Country factsheets: Croatia. Available at: <http://eco.iarc.fr/eucan/Country.aspx?ISOCountryCd=191>. [Cited: 22-Sep-2022].
- International agency for research on cancer. Cancer epidemiology [Internet]. Available at: <http://www.iarc.fr/en/publications/pdfs-online/epi/cancerepi/CnacerEpi-0.pdf>. [Cited: 20-Sep-2022].
- International agency for research on cancer. EUREG [Internet]. Available at: <http://eco.iarc.fr/eureg/ViewCancer.aspx>. [Cited: 19-Sep-2022].
- Croatian Institute of Public Health, Cancer Registry. Cancer incidence in 2011 [Internet]. Available at: http://www.hzjz.hr/publikacije/rak_36.pdf. [Cited: 20-Sep-2022]. Croatian.
- Galletti C, De Marco L, Ciodaro F, Freni F, Saraniti C, Galletti F, et al. Impact of the Sars-COVID-19 pandemic on the "early diagnosis" of laryngeal tumors: data from monocentric tertiary care hospital of south Italy. *J Voice.* 2024;S0892-1997(23)00404-6. doi: 10.1016/j.jvoice.2023.12.013.