



Survival outcomes in surgically treated patients with advanced laryngeal cancer in Serbia

Preživljavanje hirurški lečenih bolesnika sa odmaklim karcinomom larinksa u Srbiji

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Abstract

Background/Aim. Laryngeal carcinomas make 1%–3% of all head and neck malignancies. Treatment outcome and survival rates depend greatly on established stage of the disease. The purpose of this study was to examine the survival of the patients with advanced laryngeal carcinoma depending on gender, age, common risk factors (tobacco and alcohol use), primary tumor localization, histopathological tumor grade, clinical TNM (tumor, node and metastasis) stage and surgical treatment of the disease. **Methods.** Retrospective study included 252 patients treated surgically for advanced squamocellular carcinoma of the larynx in a three-year period with five-year follow-up. Patients included in the study were treated primary with surgery, with postoperative radiotherapy and chemotherapy depending on the stage of the disease, intraoperative findings and tumor resection

borders. Overall survival and disease-specific five-year survival of patients was calculated for demographical and clinical characteristics of the patients. **Results.** Overall 5-year survival of patients with operable advanced laryngeal cancer included in the study was 86.14% and disease-specific survival 86.51%. Lower overall and the disease-specific survival was associated with age, higher histological tumor grade and more extensive neck dissections. **Conclusion.** Primary total laryngectomy results in higher survival outcomes in cases of transglottic T3 and T4a laryngeal tumors. Patients should be informed of the likely increased mortality risks tied to the choice of surgical resection and treatment modality before their decision.

Key words:

laryngeal neoplasms; postoperative period; survival; risk factors; neoplasm staging.

Apstrakt

Uvod/Cilj. Karcinomi larinksa čine 1%–3% svih maligniteta glave i vrata. Terapijski rezultati i preživljavanje umnogome zavise od stadijuma bolesti. Cilj rada bio je da se ispita preživljavanje bolesnika, hirurški lečenih od odmaklih karcinoma larinksa, u zavisnosti od starosti, pola, uobičajenih faktora rizika (pušenje, konzumiranje alkohola), primarne lokalizacije tumora, patohistološkog stadijuma bolesti, tumor, nodus, metastaza (TNM) stadijuma bolesti, i primenjene hirurške terapije bolesti. **Metode.** Retrospektivnom studijom bilo je obuhvaćeno 252 bolesnika, hirurški lečenih od odmaklih karcinoma glave i vrata, sa periodom praćenja od

pet godina. Bolesnici uključeni u studiju primarno su lečeni hirurški, sa sprovođenjem postoperativne radio- i hemioterapije, u zavisnosti od lokalne i regionalne proširenosti bolesti, intraoperativnog nalaza i granica linija resekcija. Petogodišnje ukupno preživljavanje i preživljavanje bez znakova bolesti računato je u zavisnosti od demografskih i kliničkih karakteristika bolesnika. **Rezultati.** Ukupno petogodišnje preživljavanje bolesnika sa odmaklim karcinomima larinksa je iznosilo 86,14%, a petogodišnje preživljavanje bez znakova bolesti 86,51%. Smanjeno preživljavanje bilo je značajno povezano sa starošću bolesnika, višim histološkim gradusom tumora i opsežnijim disekcijama vrata. **Zaključak.** Primarna totalna laringektomija

rezultira dužim preživljavanjem u slučajevima transglotisnih T3 i T4a tumora larinksa. Pre donešenja odluke, bolesnici bi trebali biti informisani o mogućim većim rizicima od smrtnog ishoda povezanim sa izborom hirurške metode i drugih načina lečenja.

Introduction

Laryngeal carcinomas make 1%–3% of all head and neck malignancies¹. Treatment outcome and survival rates depend greatly on established stage of the disease. In the recent decades treatment concept of advanced laryngeal cancer was shifted toward organ preservation therapy, suggesting radiotherapy with concurrent chemotherapy as a preferable method for laryngeal preservation². Some studies suggested that in clinical setting, organ preservation protocols were not as efficient in providing enough survival rates as the surgical treatment combined with radiotherapy or chemoradiotherapy³. Some authors argue that traditional treatment of advanced laryngeal cancer, which most commonly includes total laryngectomy with postoperative radiotherapy, is still the best for ensuring most favorable oncological results^{4,5}.

The purpose of this study was to examine the overall and disease-specific survival of patients surgically treated of operable advanced laryngeal carcinoma depending on gender, common risk factors (tobacco and alcohol use), histopathological tumor grade, clinical tumor (T), node (N), metastasis (M) – TNM stage, and treatment of the disease.

Methods

A retrospective study included 252 patients treated at the Clinic for Otorhinolaryngology and Maxillofacial Surgery, Clinical Center of Serbia in Belgrade. The data were obtained by processing medical charts of patients with squamocellular carcinoma of the larynx surgically treated in the period from January 1, 2010 to January 1, 2012. This study was approved by the Institutional Ethics Committee (440/IX-3/09), and all patients signed the informed consent form prior to their inclusion in the study. Patients were divided into age groups according to International Cancer Survival Standard (ICSS) using the Five Default Age Groups (15–44, 45–54, 55–64, 65–74, 75+)⁶.

The diagnosis of laryngeal carcinoma was confirmed by otorhinolaryngological clinical examination and laryngomicroscopic examination of the larynx with the biopsy and histopathologic examination of the tissue. Additional diagnostics like ultrasonography of the neck and of the abdomen, chest x-ray (radiography) and computed tomography (CT) of the neck were performed to determine the TNM stage of the disease⁷. Study included patients diagnosed with advanced stages of operable laryngeal carcinoma (T2N1-N2, T3N0-N2 and T4aN0-N2), without previous treated malignancies and distant metastases. The modality of treatment for every patient was decided on the Oncological Board (consisting of a radiotherapist, head and neck surgeons, an oncologist and a

Ključne reči:

larinks, neoplazme; postoperativni period; preživljavanje; faktori rizika; neoplazme, određivanje stadijuma.

histopathologist). Choice of primary and adjuvant treatment was decided based on the National Comprehensive Cancer Network (NCCN) and the American Society for Radiation Oncology (ASTRO) guidelines^{7,8} which are recommended and used at the Clinic for Otorhinolaryngology and Maxillofacial Surgery and the Institute for Oncology and Radiology of Serbia in Belgrade. Surgical therapy involved resection of the tumor with some form of the neck dissection in case of cervical lymphadenopathy. Radiotherapy consisted of external radiotherapy with total dose of 60 to 70 Gy in 30–35 fractions for 6–7 weeks. Patients received concomitant chemotherapy consisted of at least three courses of cisplatin (CDDP) with 5-fluorouracil (5-FU) intravenously. Follow-up period was from 63 to 82 months. Demographic characteristics (age and gender) and risk factors (cigarette and alcohol consumption) were noted. Histopathological tumor grade, the beginning of treatment with or without tracheotomy, TNM classification, type of surgical treatment, type of neck dissection, and therapy modality were also examined. Five-year overall and disease-specific survival (DSS) of patients was determined depending on all previously mentioned factors.

For statistical analysis of data, the program SPSS v20 (Statistical Package for Social Sciences, SPSS Inc, Chicago, Illinois) was used. Descriptive statistics was used for demographic characteristics, risk factors and other parameters and presented as frequencies and proportions. Overall survival (OS) and DSS rates were calculated using the Kaplan–Meier method. A Cox proportional hazards regression model along with univariate and multivariate analyses were used for estimating the impact of prognostic factors on DSS rate. Risk estimates are presented as hazard ratios (HR) with 95% confidence intervals (CI). Statistical significance was considered at $p < 0.05$.

Results

The study comprised 230 (91.3%) males and 22 (8.7%) females of an average age of 59.98 years [standard deviation (SD) \pm 8.85 years]. The youngest patient was 38, and the oldest one 84 years old. Two hundred thirty three (92.5%) of the patients were smokers, and 19 (7.5%) were non-smokers. Alcohol consumption was noted in 87 (34.5%) of the patients, while 165 (65.5%) were non-drinkers. Diagnostics of the tumor started with tracheotomy in 51 (20.2%) of the patients. Majority of carcinomas were histologically moderately differentiated tumors (74.2%) and transglottic tumors (40.9%) Out of all surgical procedures used to treat advanced laryngeal carcinoma in our study, total laryngectomy was most frequently done procedure in 216 (85.7%) of the patients. Fifty nine (23.4%) of the patients underwent neck dissection. Most of the patients were treated with surgery fol-

lowed by postoperative radiotherapy, while there were only small number of patients treated only surgically (3.6%), or with surgery with concomitant chemo-radiotherapy (5.2%) (Table 1).

Table 1
Demographic and clinical characteristics of the patients

Patients' characteristics	Patients n (%)
Age (years)	
< 45	9 (3.6)
45–54	64 (25.4)
55–64	101 (40.1)
65–74	65 (25.8)
> 75	13 (5.1)
Gender	
male	230 (91.3)
female	22 (8.7)
Smoking	
smokers	233 (92.5)
non-smokers	19 (7.5)
Alcohol	
consumers	87 (34.5)
non-consumers	165 (65.5)
Histological grade	
G1	44 (17.5)
G2	187 (74.2)
G3	21 (8.3)
Tumor localization	
supraglottis	53(21)
glottis	94(37.3)
subglottis	2(8)
transglottic	103(40.9)
Diagnostics started with tracheotomy	
yes	51 (20.2)
no	201 (79.8)
Tumor stage	
T2	9 (3.6)
T3	213 (84.5)
T4a	30 (11.9)
Nodus stage	
N0	203 (80.6)
N1	43 (17.1)
N2	6 (2.4)
Type of surgery	
total laryngectomy	216 (85.7)
subtotal laryngectomy	16 (6.3)
haemilaryngectomy	11 (4.4)
supraglottic laryngectomy	9 (3.6)
Neck dissection	
none	193 (76.6)
selective or modified radical dissection	27 (10.7)
radical dissection	13 (5.2)
expanded radical dissection	19 (7.5)
Treatment	
OP	9 (3.6)
OP+ RT	230 (91.3)
OP+RT+CT	13 (5.2)

OP – surgery; RT – radiotherapy; CT – chemotherapy.

Overall 5-year survival of patients with operable advanced laryngeal cancer included in the study was 86.14% and the DSS 86.51%. OS did not differ much from the DSS in relation to different age groups, except in the group of patients older the 75 years, mostly because of other comorbidities (Tables 2 and 3). Females had lower 3-year and 5-year survival rates comparing to male patients (3-year OS and DSS were 81.8 and 87.4, respectively; 5-year OS was 72.7 for females and 80.9 for males, and DSS was 72.7 for females and 81.2 for males). Non-smokers had better DSS compared to smokers included in the study, but the difference was not statistically significant. Patients who did not consumed alcohol had higher OS and DSS comparing to those who consumed alcohol. Patients with poorly differentiated tumors had lower survival rates comparing to patients with good and moderately differentiated tumors. Tumor localization significantly influenced on OS (Log rank, $p = 0.017$) and DSS (Log rank, $p = 0.025$). Tumors with primary supraglottic localization had significantly lower survival rates comparing to other localization. Totally, 20.1% of patients started their diagnostic process with tracheotomy, which significantly influenced their DSS (Log rank, $p = 0.041$). Patients with T2 advanced laryngeal tumors had lower OS and DSS comparing to those with T3 and T4a tumors (3-year DSS was 77.8, 88.2 and 83.3, respectively; 5-year DSS was 66.7, 81.1 and 80, respectively), but the regional spreading of the disease present in these patients should be taken into account in explaining the results. OS (Log rank $p = 0.046$) and DSS (Log rank $p = 0.037$) were significantly lower in patients with the N2 nodal disease comparing to those with the N0 and N1 stages of the disease (3-year OS and DSS were 88.1, 86 and 66.7, respectively; 5-year OS and DSS were 82.7, 74.4 and 50, respectively). 5-year OS and DSS were lower in patients who underwent partial supraglottic laryngectomy comparing to other operative procedures conducted. 5-year OS (Log rank $p = 0.032$) and DSS (Log rank $p = 0.024$) in patients who underwent radical and expanded radical neck dissection were significantly lower comparing to other patients, which was directly associated with the advancement of the nodal disease. Patients who were treated only surgically, without postoperative radiotherapy or chemotherapy had higher OS and DSS one year, three years and five years after the treatment.

Multivariate analysis revealed that age, histological grade of the tumor and undertaken selective or modified radical neck dissection were significant prognostic factors for DSS in patients with advanced laryngeal cancer (Table 4). Age of the patients (HR 1.042, $p = 0.013$), histological G2 (moderately differentiated) (HR 3.453, $p = 0.027$) and G3 (poorly differentiated) (HR 4.069, $p = 0.036$) tumor grade had a negative impact on DSS. Undertaken selective or modified radical neck dissection had a positive impact on DSS (HR 0.132, $p = 0.02$). DSS was significantly better for patients with supraglottic (HR 0.405, $p = 0.009$) and glottic localization of the tumor (HR 0.478, $p = 0.023$), but only by univariate analysis.

Table 2

Overall survival for patients included in the study

Patients' characteristics	1-year survival (%)	3-year survival (%)	5-year survival (%)	Log rank
Age (years)				
< 45	100	100	100	
45–54	100	88.5	85.2	<i>p</i> = 0.127
55–64	99	88.3	81.6	
65–74	97	84.8	74.2	
≥ 75	92.3	69.2	61.5	
Gender				
male	98.3	87.4	80.9	<i>p</i> = 0.453
female	100	81.8	72.7	
Smoking				
smokers	98.7	87	80	<i>p</i> = 0.996
non-smokers	94.7	84.2	78.9	
Alcohol				
consumers	96.5	83.7	75.6	<i>p</i> = 0.327
non-consumers	99.6	88.5	82.4	
Histological grade				
G1	100	95.5	90.9	<i>p</i> = 0.083
G2	98.4	86.6	78.6	
G3	95.2	71.4	71.4	
Tumor localization				
supraglottis	98.1	79.2	66	<i>p</i> = 0.017*
glottis	96.8	90.4	85.1	
subglottis	100	100	100	
transglottic	100	87.4	82.5	
Diagnostics started with tracheotomy				
yes	96.1	86.3	70.6	<i>p</i> = 0.05
no	99	87.1	82.6	
Tumor stage				
T2	100	77.8	66.7	<i>p</i> = 0.265
T3	98.6	87.8	80.8	
T4a	100	83.3	80	
Nodus stage				
N0	98.5	87.7	82.8	<i>p</i> = 0.046*
N1	97.7	86	74.4	
N2	100	66.7	50	
Type of surgery				
total laryngectomy	98.1	86.6	80.1	<i>p</i> = 0.724
subtotal laryngectomy	100	87.5	81.3	
haemilaryngectomy	100	100	90.9	
supraglottic laryngectomy	100	77.8	66.7	
Neck dissection				
none	98.4	87.6	83.4	<i>p</i> = 0.032*
selective or modified radical dissection	96.3	85.2	74.1	
radical dissection	100	93.3	61.5	
expanded radical dissection	100	78.9	68.4	
Treatment				
OP	100	100	100	<i>p</i> = 0.105
OP+RT	98.7	86.5	80	
OP+RT+CT	92.3	84.6	69.2	

OP – surgery; RT – radiotherapy; CT – chemotherapy.

**p* < 0.05.

Table 3

Disease-specific survival for patients included in the study

Patients' characteristics	1-year survival (%)	3-year survival (%)	5-year survival (%)	Log rank
Age (years)				
< 45	100	100	100	
45–54	100	88.5	85.2	<i>p</i> = 0.241
55–64	99	88.3	81.6	
65–74	97	84.8	74.2	
≥ 75	100	75	66.7	
Gender				
male	98.7	87.8	81.2	<i>p</i> = 0.422
female	100	81.8	72.7	
Smoking				
smokers	98.7	87	80	<i>p</i> = 0.629
non-smokers	100	94.4	83.3	
Alcohol				
consumers	97.7	84.7	76.5	<i>p</i> = 0.427
non-consumers	99.4	88.5	82.4	
Histological grade				
G1	100	95.5	90.9	<i>p</i> = 0.086
G2	98.9	87.1	79	
G3	95.2	71.4	71.4	
Tumor localization				
supraglottis	98.1	79.2	66	<i>p</i> = 0.025*
glottis	97.9	91.4	86	
subglottis	100	100	100	
transglottic	100	87.4	82.5	
Diagnostics started with tracheotomy				
yes	96.1	86.3	70.6	<i>p</i> = 0.041*
no	99.5	87.5	83	
T stage				
T2	100	77.8	66.7	<i>p</i> = 0.246
T3	98.6	88.2	81.1	
T4a	100	83.3	80	
N stage				
N0	99	88.1	82.7	<i>p</i> = 0.037*
N1	97.7	86	74.4	
N2	100	66.7	50	
Type of surgery				
total laryngectomy	98.6	87	80.5	<i>p</i> = 0.703
subtotal laryngectomy	100	87.5	81.3	
haemiaryngectomy	100	100	90.9	
supraglottic laryngectomy	100	88.9	66.7	
Neck dissection				
none	99	88	83.9	<i>p</i> = 0.024*
selective or modified radical dissection	96.3	85.2	74.1	
radical dissection	100	92.3	61.5	
expanded radical dissection	100	78.9	68.4	
Treatment				
OP	100	100	100	<i>p</i> = 0.099
OP+RT	99.1	86.9	80.4	
OP+RT+CT	92.3	84.6	69.2	

OP – surgery; RT – radiotherapy; CT – chemotherapy.

**p* < 0.05.

Table 4
Cox proportional hazard for disease-specific survival in patients with advanced laryngeal cancer

Patients parameters	Univariate			Multivariate		
	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
Age (per year)	1.044	1.009–1.074	0.005*	1.042	1.009–1.077	0.013*
Gender						
female	1	0.310-1.694	0.457	1	0.306-1.975	0.597
male	0.724			0,778		
Smoking						
non-smokers	1	0.360–2.274	0.996	1	0.354–3.776	0.810
smokers	0.998			1.156		
Alcohol consumption						
non-consumers	1	0.758–2.278	0.331	1	0.720–2.604	0.338
consumers	1.314			1.369		
Histological grade						
G1	1	0.972–7.543	0.057	1	4.153–10.339	0.027*
G2	2.708	1.058–13.29	0.041*	3.453	1.093–15.146	0.036*
G3	3.749			4.069		
Tumor localization						
transglottic	1			1		
supraglottis	0.405	0.206–0.797	0.009*	0.498	0.232–1.072	0.075
glottis	0.478	0.253–0.904	0.023*	0.499	0.243–1.028	0.059
subglottis	0.000	0.00– -	0.975	0.000	0.00– -	0.984
Diagnostics started with tracheotomy						
yes	1			1		
no	0.563	0.313–1.012	0.055	1.736	0.886–3.402	0.108
Tumor stage						
T2	1	0.626–7.862	0.217	1	0.086–12.243	0.985
T3	2.218	0.415–2.289	0.952	1.024	0.426–2.567	0.923
T4a	0.974			1.045		
Nodus stage						
N0	1	0.097–1.022	0.054	1	0.245–1.245	0.496
N1	0.315	0.154–1.898	0.317	2.115	0.199–1.425	0.989
N2	0.541			0.989		
Type of surgery						
total laryngectomy	1			1		
subtotal laryngectomy	0.448	0.1561–1.246	0.124	1.098	0.109–11.035	0.936
haemilaryngectomy	0.404	0.090–1.804	0.235	0.863	0.066–11.239	0.936
supraglottic laryngectomy	0.366	0.067–2.001	1.247	0.872	0.085–8.085	0.908
Neck dissection						
none	1			1		
selective or modified radical dissection	0.378	0.174–0.818	0.014*	0.132	0.024–0.723	0.02*
radical dissection	0.608	0.220–1.676	0.336	0.288	0.069–1.199	0.087
expanded radical dissection	0.867	0.283–2.650	0.802	0.496	0.145–1.700	0.264
Treatment						
OP	1	0.000- -	0.964	1	0.0- -	0.969
OP+RT	0.000	0.202–1.273	0.148	0.00	0.195–1.559	0.262
OP+RT+CT	0.507			0.552		

HR – hazard ratio; CI – confidence interval; OP – surgery; RT – radiotherapy; CT – chemotherapy.

**p* < 0.05.

Discussion

In our study OS and DSS were significantly lowered with age. Age of the patients proven to be an important risk factor which other studies confirmed as well^{9, 10}. In female patients in our study, 3-year and 5-year survivals were lower comparing to those in male patients, which differs from other studies where females had significantly higher survival

rates^{11, 12}. Smoking and alcohol consumption were also associated with lower survival in our patients. In this study, gender, smoking and alcohol consumption were not significant prognostic factors for DSS. Less differentiated advanced carcinoma had higher risk for mortality. These data do not differentiate significantly from other research data available^{9, 10}. This study involved patients with advanced laryngeal carcinoma which included the T2 stage with nodal disease, and

the T3 and T4 stages with and without nodal disease. Patients with higher T stage of the disease had, as expected, lower OS and DDS survival. Presence of the nodal disease also lowered survival in the patients included in our study.

The evolution of treatment for advanced laryngeal carcinoma in Serbia was interesting during the last half of the century. In the 1960s' radiotherapy was considered to be primary treatment for laryngeal cancer. In the 1970s' functional and radical laryngeal surgery started to emerge as the primary curative treatment, with postoperative radiotherapy and chemotherapy¹³. It was considered that extended surgery was needed for successful oncological treatment of advanced laryngeal cancer. With the advances of chemotherapeutic drugs and radiotherapy, new treatment protocol for organ preservation were presented in the last three decades^{2, 14, 15}. Nonsurgical therapy was suggested to be as efficient as surgical therapy in treating advanced laryngeal cancer. Since then, numerous studies showed that in the clinical settings, surgical therapy still resulted in better OS and DSS in patients treated for advanced laryngeal cancer comparing to chemoradiotherapy and radiotherapy alone^{3, 16, 17}.

Patients with T4a tumors in our study had high 3-year and 5-year OS and DSS (83.3% and 80%, respectively) and were all treated with total laryngectomy with postoperative chemoradiotherapy. In the recent systematic review which included 24 studies, Francis et al.¹⁸ reported that OS for the T4a laryngeal carcinoma, treated with total laryngectomy, varied from 30% to 100% at 2-years and from 10% to 80.9% at 5-years. In 2010, Olsen¹⁹ stated that tumors that extend through the laryngeal cartilage should be treated with total laryngectomy, followed by postoperative RT or chemoradiotherapy depending on primary tumor pathologic findings and presence of neck metastases.

In Serbian leading medical centers, surgery is considered the preferable primary method of treatment for advanced laryngeal carcinomas. Adherence to new recommended protocols for treating advanced laryngeal carcinoma is significantly influenced by health care organization. Small number of radiology and oncology centers and prolonged waiting period for radiotherapy, is surely influencing the de-

cision on treatment choice, leaving surgery as the best and reliable method. There are limited number of papers written on the matter, without significant stratification of data. In older studies done in Serbia, 3-year OS in patients with advanced laryngeal carcinoma treated with total laryngectomy from 1971 to 1981 was 68.49%¹³. In the period from 1990 to 1997, 5-year OS in patients with advanced laryngeal carcinomas who underwent total laryngectomy reported to be 63%²⁰. Stankovic et al.²¹ reported DSS of 61.3% in 387 patients with advanced laryngeal cancer who underwent total laryngectomy from 1995 to 2007. In this study, patients treated with total laryngectomy had 3-year OS of 86.6% and DSS of 87%, and 5-year OS of 80.1% and DSS of 80.5%.

Most of the patients included in the study had clinically negative enlarged lymph nodes of the neck (203 patients, 80.6%), and neck dissection was not done in 193 (76.6%) of the patients. Current recommendations support selective neck dissection in advanced laryngeal carcinoma without clinically positive neck^{22, 23} which should be implemented in our clinical practice. In our study, 31 (12.7%) of the patients underwent radical of extended radical neck dissection. 5-year OS was significantly lower in these patients, which is surely connected with the advanced regional spread of the disease. Selective or modified radical neck dissection positively influenced DSS. There are few studies that suggest that with the careful selection of patients without massive lymphadenopathy, nodal fixation, gross extracapsular spread and history of previous neck surgery or radiotherapy, selective neck dissection could resolve the N1 to N3 nodal disease²⁴.

Conclusion

This study indicates that lower OS and DSS were significantly associated with patients' age, higher histological grade of the disease and more extensive neck dissections. Primary total laryngectomy results in higher survival outcomes in cases of transglottic T3 and T4a laryngeal tumors. Patients should be informed of the likely increased mortality risks tied to the choice of surgical resection and treatment modality before their decision.

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