

## PROGNOSTIC FACTORS OF LOCOREGIONAL RECURRENCES AFTER SUPRACRICOID LARYNGECTOMY

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### ABSTRACT

Supracricoid laryngectomy also named Open partial horizontal laryngectomy type II (OPH II) involves resection of the ventricular folds, vocal folds, paraglottic space, thyroid cartilage, optionally up to one arytenoid cartilage, and depending on whether it is a OPH II A or B of the epiglottis. Locoregional control of the disease is a complex phenomenon that includes the characteristics of the tumor, the patient and genetic factors. The aim of this study is to identify factors that may indicate an increased possibility of occurrence of locoregional recurrences after supracricoid laryngectomy.

Retrospective study that included 104 patients treated at the Clinic for Otorhinolaryngology and Head and Neck Surgery of the University Clinical Center of Vojvodina in the period 2002-2020. who underwent supracricoid laryngectomy. Pathohistologically verified TN stage, thyroid cartilage invasion, positive margins, vascular invasion, positive Delphi lymph node and extranodal extension of metastatic disease were estimated as predictive factors for the occurrence of locoregional recurrences.

The median time of occurrence of local recurrence was 22 months (9.5-59.5), the median time of occurrence of regional recurrence was 21 months (10-38.5). Statistical significance in the occurrence of local recurrences of the disease was recorded in the presence of pathohistologically confirmed positive margins ( $p=0.033$ ) and vascular invasion ( $p=0.029$ ). The statistical significance of vascular invasion was also observed in the occurrence of regional ( $p=0.041$ ) and locoregional recurrences ( $p=0.004$ ). The pathohistologically confirmed higher T stage showed statistical significance in the occurrence of regional metastases ( $p=0.035$ ).

Pathohistologically confirmed vascular invasion stands out as an independent factor that should be paid attention to in further postoperative therapeutic care in order to achieve high-quality locoregional control of the disease, while in local control along with vascular invasion, the importance of positive resection margins is also emphasized.

Key words: laryngeal carcinoma, organ preservative protocol, OPH II, supracricoid laryngectomy, regional recurrence, local recurrence, locoregional recurrence

## PROGNOSTIČKI FAKTORI LOKOREGIONALNIH RECIDIVA NAKON SUPRAKRIKOIDNIH LARINGEKTOMIJA

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Suprakrikoidna laringektomija, takođe imenovana i kao parcijalna horizontalna laringektomija tip II (OPH II), podrazumeva resekciju ventrikularnih nabora, glasnica, paraglotisnog prostora, tireoidne hrskavice, opciono do jedne aritenoidne hrskavice, i u zavisnosti da li se radi o podgrupi OPH II A ili B epiglotisa. Lokoregionalna kontrola bolesti predstavlja kompleksan fenomen koji podrazumeva karakteristike tumora, pacijenta i genetske faktore. Cilj ove studije jeste identifikacija faktora koji mogu ukazati na povećanu mogućnost pojave lokoregionalnih recidiva nakon suprakrikoidne laringektomije.

Retrospektivna studija u kojoj je obuhvaćeno 104 pacijenta lečena u Klinici za Otorinolaringologiju i hirurgiju glave i vrata Univerzitetskog Kliničkog Centra Vojvodine u periodu 2002.-2020. godine, kojima je načinjena suprakrikoidna laringektomija. Kao prediktivni faktori za pojavu lokoregionalnih recidiva tumora, u obzir su uzimani patohistološki verifikovan TN stadijum, invazija tireoidne hrskavice, pozitivne margine, vaskularna invazija, pozitivan Delfijski limfni čvor i ektranodalna propagacija metastatske bolesti.

Medijana vremena pojave lokalnog recidiva iznosila je 22 meseca (9.5-59.5), medijana pojave regionalnog recidiva iznosila je 21 mesec (10-38.5). Statistička značajnost u pojavi lokalnih recidiva bolesti zabeležena je kod prisustva patohistološki potvrđenih pozitivnih margina ( $p=0.033$ ) i vaskularne invazije karcinoma ( $p=0.029$ ). Statistička značajnost vaskularne invazije zapažena je i u pojavi regionalnih ( $p=0.041$ ) i lokoregionalnih recidiva ( $p=0.004$ ). Patohistološki potvrđen T stadijum pokazao je statističku značajnost u pojavi regionalnih metastaza ( $p=0.035$ ).

Patohistološki potvrđena vaskularna invazija izdvaja se kao nezavisan faktor na koji treba obratiti pažnju u daljem postoperativnom terapijskom zbrinjavanju radi postizanja kvalitetne lokoregionalne kontrole bolesti, dok se u lokalnoj kontroli uz vaskularnu invaziju ističe takođe i bitnost pozitivnih margina resekata.

Ključne reči: laringealni karcinomi, organ-prezervacijski protokol, OPH II, suprakrikoidna laringektomija

## INTRODUCTION

Laryngeal carcinoma is one of the most common sites of head and neck carcinomas, accounting for about 1% of all cancer cases and cancer-related deaths [1]. The incidence and mortality of laryngeal carcinoma for the year 2020 are estimated at 184,615 newly diagnosed cases and 99,840 deaths [2]. With the reduction in tobacco use, the incidence of laryngeal carcinoma has decreased by 2.4% each year over the last 10 years [3]. The 5-year survival rate of patients with laryngeal carcinomas is estimated at 80% to 90% for early stage, T1 and T2 tumors [1,3]. In contrast, survival decreases to 40% in patients diagnosed with stage IV disease [3].

Open partial horizontal laryngectomy type II (OPH II), in literature also named as supracricoid partial laryngectomy with cricohyoidopexy was first introduced as an alternative to total laryngectomy for the treatment of selected cases of glottic and supraglottic carcinoma by Mayer in 1959, while in 1974 Piquet described cricohyoidepiglottopexy as a modification of the previously mentioned procedure in the case of glottic carcinoma. This type of partial laryngectomy involves resection of the ventricular folds, vocal folds, paraglottic space, thyroid cartilage, optionally up to one arytenoid cartilage, and depending on whether it is a subgroup of OPH II A or B of the epiglottis (resection of the epiglottis present in the case of OPH II B) [4]. Preservation of at least one cricoarytenoid unit is crucial in functional recovery after surgery [5]. Retrospectively viewed results of this method showed excellent oncological and functional success in the treatment of glottic and supraglottic carcinomas [6]. The main advantage of such a surgical procedure compared to total laryngectomy is reflected in the preserved ability of speech created by bringing air from the lungs, avoiding transient or permanent swallowing disorders as well as permanent tracheostomy, with the presence of very good local control of the disease [4]. It is believed that the excellent results of the organ preservation protocol, including OPH II, will be maintained if the indications for its application are strictly followed [7]. Traditional guidelines for performing OPH type II in glottic carcinomas include T1a and T1b carcinoma with radiologically suspicious invasion of the l cartilage, T2 carcinoma, T3 carcinoma of the glottis without cancerous invasion of the cricoarytenoid joint but with possible invasion of the anterior commissure and preepiglottic space, as well as carefully selected patients with stage T4 tumors with limited cartilage involvement and extralaryngeal spread in the anterior compartment. OPH II is indicated for T2 supraglottic carcinomas in which supraglottic laryngectomy is contraindicated due to invasion of the floor of the ventricle, extension to the glottis and/or reduced mobility of the vocal cords, as well as for T3 supraglottic carcinomas involving the preepiglottic space [6,8,9]. Determining the stage of laryngeal cancer has long been considered a criterion that correlates well with locoregional control of the disease and overall survival, however prognosis is a complex phenomenon that also includes characteristics of the tumor, the patient and genetic factors. Prognosis is further complicated by the fact that negative prognostic factors have not been universally determined, although defining them would greatly facilitate the choice of therapeutic modality [10].

The aim of this study is to identify factors that may indicate an increased possibility of both local and regional recurrences of laryngeal carcinoma in patients treated with OPH II.

## MATERIAL AND METHODS

This was a retrospective study that included 104 patients treated in the Otorhinolaryngology and Head and Neck Surgery Clinic of the University Clinical Center of Vojvodina between 2002 and 2020., who underwent open partial horizontal laryngectomy type II as part of laryngeal cancer treatment. Of the 104 patients, 86 (83%) patients were male, while 18 (17%)

were female. The average age of patients at the time of operative treatment was 60 years (ranging 56 to 67 years). Patients who, in addition to laryngeal carcinoma, had one or more primary localizations of cancer in the head and neck region, as well as patients who had previously been surgically treated for laryngeal carcinoma, were excluded from the study.

After the pathohistological verification of laryngeal carcinoma, all patients were presented at the Oncology Council for Malignancies of the Head and Neck Region of the University Clinical Center of Vojvodina where a decision was made regarding the patient's surgical management. As part of preoperative assessment, patients underwent contrast-enhanced computer tomography (CT scan) of the head, neck and chest as well as abdominal ultrasound. Before the procedure, each patient was counseled about the planned course of the procedure, potential complications, and the expected postoperative recovery. After the induction of general endotracheal anesthesia, a direct laryngomicroscopy was performed on each patient to gain a better insight into the current size and extent of the laryngeal involvement by the tumor. OPH II A was performed in 93 cases, which involved cricohyoidopiglottopexy as part of the neolarynx reconstruction, while OPH II B was performed in 29 patients, which meant cricohyoidopexy as part of reconstruction. Neck dissections were done as diagnostic procedure in 87 patients, and as therapeutic procedure in 17 patients, in the same acts as OPH II. After the operative treatment, and upon the arrival of the definitive postoperative pathohistological findings, the patients were diagnosed with pTNM, and then they were again presented at the Oncology Council for Malignancies of the Head and Neck Region of the University Clinical Center of Vojvodina, where a decision was made to administer adjuvant therapy, which was applied to 20 patients ( radiotherapy - 18 patients (17%), chemotherapy - 1 patient (1.0%), chemoradiotherapy - 1 patient (1.0%)). In the future, the patients were regularly controlled and monitored by the operator according to the protocol for monitoring patients after surgical treatment of malignancy in the head and neck region. Patients in whom the existence of local or regional recurrence was suspected by clinical examination underwent a CT scan of the head and neck region, on which the existence of recurrence was radiologically verified. After radiological verification of local recurrence, the patients were again presented to the Oncology Council for Malignancies of the Head and Neck Region of the University Clinical Center of Vojvodina, where a decision was made to treat the recurrence of laryngeal malignancy in the form of a conservative approach (radiotherapy, chemoradiotherapy, chemotherapy, symptomatic therapy) or surgical approach ( total laryngectomy in case of local recurrence, or modified radical, radical neck dissection or extirpation of a metastatic lymph node).

In order to determine predictive factors for the occurrence of local and regional recurrences after OPH II, the pathohistologically verified TN stage of the patient was taken into account. In addition, the parameters obtained by the pathohistological analysis after surgical treatment (invasion of the thyroid cartilage, positive resection margins, vascular invasion, positive Delphian lymph node and extranodal spread of metastatic disease) were taken into consideration. Recurrence, both local and regional, was defined as any occurrence of carcinoma at the same localization in the case of local recurrence, or regional occurrence of metastatic disease within 5 years of surgical treatment.

Statistical analyzes were performed using RStudio 2024.04.2+764 "Chocolate Cosmos" version. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables were compared between independent groups using the Wilcoxon rank sum test. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Cox proportional hazards modeling was used to examine associations between outcome and predictor variables. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were used to qualify the magnitude and direction of associations. Kaplan-Meier curves were plotted to visualize survival probabilities, stratified by relevant variables. All statistical tests

were two-tailed and an alpha level of 0.005 was set as the significance threshold. No imputation was used for missing data.

This study was approved by the Ethics Committee of the Clinical Center of Vojvodina, approval number: 00-365, approval date: 15.10.2024.

## RESULTS

A total of 104 patients participated in this retrospective study (86 men (83%) and 18 women (17%)), with previously histologically verified laryngeal carcinoma, who underwent OPH II as part of the treatment. The average age of the patients was 60 years (range 56 to 67 years). OPH II A was performed in 78 cases (75%), while OPH II B was performed in 26 patients (25%).

In 92 patients (88%), the primary site of the tumor was the glottis, while in the remaining 12 patients (12%), supraglottis carcinoma was surgically treated as the primary origin. Over half of the patients at the time of treatment had T2 stage (54 patients - 52%), while the following were slightly less represented: T3 (30 patients - 29%), T1b (17 patients - 16%), T4a (2 patients - 1.9% ) and finally T1a (1 patient - 1.0%). The largest number of patients at the time of operative treatment was in the N0 stage (87 patients - 84%), then N1 (5 patients - 4.8%), while the other groups were equally represented (N2b, N2c, N3b stages - in all four groups 3 patients each - 2.9%) (Table 1). All patients were in the M0 stage at the time of surgery (104 patients - 100%).

Table 1. Pathohistologically confirmed TN stage of patients at the time of operative treatment

<i>T stage</i>	<i>N (%)</i>
T1a	1 (1.0%)
T1b	17 (16%)
T2	54 (52%)
T3	30 (29%)
T4a	2 (1.9%)
<i>N stage</i>	<i>N (%)</i>
N0	87 (84%)
N1	5 (4.8%)
N2a	3 (2.9%)
N2b	3 (2.9%)
N2c	3 (2.9%)
N3b	3 (2.9%)

After obtaining a definitive pathohistological finding, it was observed that 24 patients (23%) had verified cartilage invasion. Vascular invasion was experienced by 9 patients (8.7%), while perineural invasion was experienced by 10 patients (9.6%). Positive margins were present in 5 patients (4.8%). The Delphian node was affected by metastatic disease in 6 patients (5.8%), while extranodal spread of metastatic disease (ENE at the time of operative treatment) was present in 3 patients (2.9%) (Table 2).

Table 2. Findings of pathohistological analyses

<i>Cartilage invasion</i>	<i>N (%)</i>
Yes	24 (23%)
No	80 (77%)

<b><i>Vascular invasion</i></b>		<b><i>N (%)</i></b>
Yes		9 (8.7%)
No		95 (91.3%)
<b><i>Perineural invasion</i></b>		<b><i>N (%)</i></b>
Yes		10 (9.6%)
No		94 (90.4%)
<b><i>Positive margins</i></b>		<b><i>N (%)</i></b>
Yes		5 (4.8%)
No		99 (95.2%)
<b><i>Metastasis in Delphian lymph node</i></b>		<b><i>N (%)</i></b>
Yes		6 (5.8%)
No		98 (94.2%)
<b><i>ENE</i></b>		<b><i>N (%)</i></b>
Yes		3 (2.9%)
No		101 (97.1%)

After OPH II, 84 patients (81%) did not receive adjuvant therapy, while 20 (19%) patients received adjuvant therapy, namely radiotherapy in 18 patients (17%), while polychemotherapy and chemoradiotherapy were received in 1 patient each (1.0%).

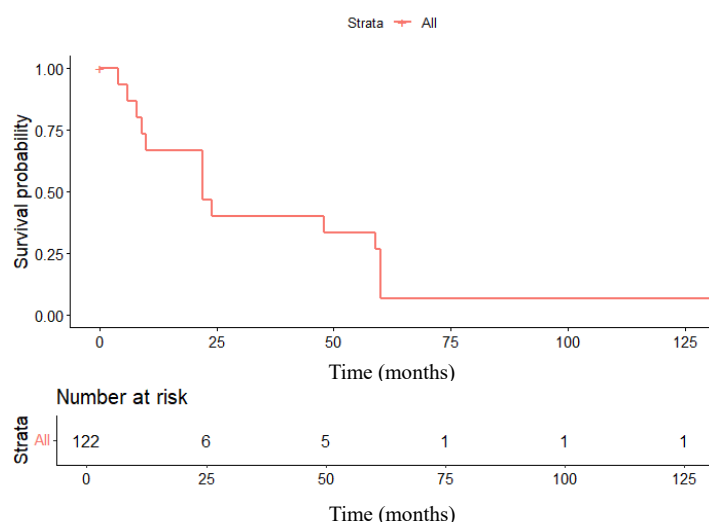
Average patient follow-up time, the period of time during which the patients regularly came for scheduled check-ups was 59 months (range from 29 to 100 months).

Overall, of 104 retrospectively observed operated patients, recurrence, neither local nor regional, did not develop in 86 patients (83%). The total number of patients with local recurrences is 9 (8.7%), while the total number of patients with regional recurrences is 15 (14.42%). Only 3 patients (2.5%) had isolated local recurrence of laryngeal cancer, isolated regional recurrence was observed in 9 patients (8.7%), while local and regional recurrence occurred together in 6 patients (5.8%) (Table 3).

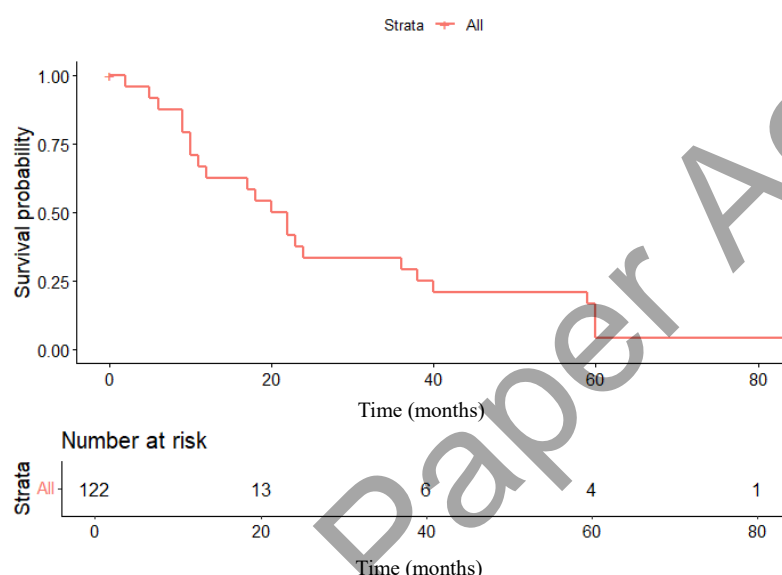
Table 3. Occurrence of local and regional recurrence after OPH II

<b><i>Cancer recurrence</i></b>		<b><i>N (%)</i></b>
No		86 (83%)
Local		3 (2.5%)
Regional		9 (8.7%)
Local + Regional		6 (5.8%)

The median time of local recurrence was 22 months (9.5-59.5) (Graph 1), while the median of regional recurrence was 21 months (10-38.5) (Graph 2).



Graph 1. Kaplan-Mayer risk curve of local recurrence



Graph 2. Kaplan-Mayer risk curve of regional recurrence

Regarding the pathohistologically confirmed T stage of laryngeal carcinoma at the time of surgical treatment, statistical significance was observed in predicting the occurrence of regional recurrences ( $p=0.035$ ), but no statistical significance was observed in the occurrence of local recurrences ( $p=0.18$ ). Although without statistical significance in terms of local recurrences, a higher frequency of recurrences was observed in laryngeal carcinomas treated with OPH II, which at the time of treatment had pathohistologically confirmed T4a disease stage (50%) (Table 4).

Table 4. Occurrence of local and regional recurrences in relation to pathohistologically confirmed T stage of laryngeal carcinoma at the time of operative treatment

	<i>T1a</i> N=1	<i>T1b</i> N=18	<i>T2</i> N=60	<i>T3</i> N=39	<i>T4a</i> N=4	<i>p</i>
Local recurrence N (%)						0.18
No	1 (100%)	17 (100%)	48 (89%)	28 (93.3%)	1 (50%)	
Yes	0 (0%)	0 (0%)	6 (11%)	2 (6.7%)	1 (50%)	
Regional recurrence N (%)						0.035
No	1 (100%)	17 (100%)	42 (78%)	28 (93.3%)	1 (50%)	
Yes	0 (0%)	0 (0%)	12 (22%)	2 (6.7%)	1 (50%)	

When it comes to pathohistologically confirmed N stages of metastatic disease of laryngeal carcinoma at the time of surgical treatment, no statistical significance was observed, both in local recurrences ( $p=0.71$ ) and in regional recurrences ( $p=0.36$ ). Although without statistical significance, we can still observe a higher percentage of regional recurrences in patients who at the time of OPH II had pathohistologically confirmed N3b stage (67%) (Table 5).

Table 5. Occurrence of local and regional recurrences in relation to pathohistologically confirmed N stage of metastatic disease of laryngeal carcinoma at the time of operative treatment

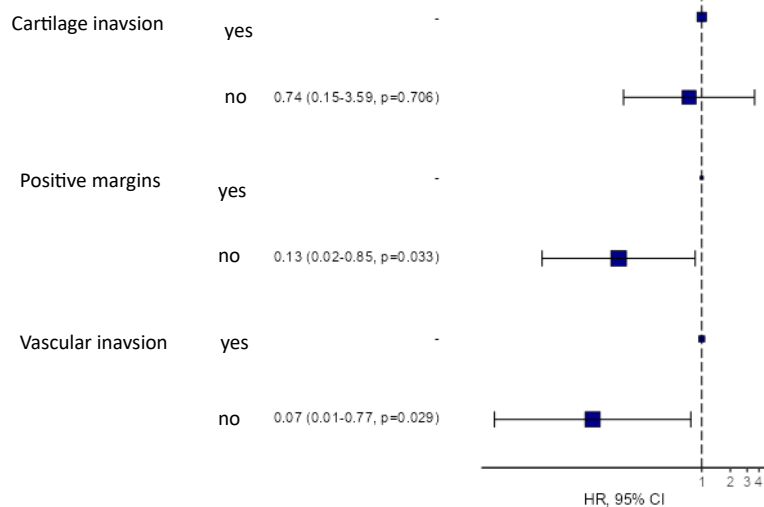
	<i>N0</i> N=102	<i>N1</i> N=5	<i>N2a</i> N=3	<i>N2b</i> N=4	<i>N2c</i> N=4	<i>N3b</i> N=4	<i>p</i>
Local recurrence N (%)							0.71
No	79 (90.8%)	5 (100%)	3 (100%)	3 (100%)	2 (67%)	3 (100%)	
Yes	8 (9.2%)	0 (0%)	0 (0%)	0 (0%)	1 (33%)	0 (0%)	
Regional recurrence N (%)							0.36
No	75 (86%)	5 (100%)	2 (67%)	3 (100%)	2 (67%)	2 (67%)	
Yes	12 (14%)	0 (0%)	1 (33%)	0 (0%)	1 (33%)	1 (33%)	

Statistical significance in the occurrence of local recurrences of the disease was recorded in the presence of pathohistologically confirmed positive resection margins ( $p=0.033$ ), as well as vascular invasion ( $p=0.029$ ) (Graph 3.).



### Hazards Regression Plot

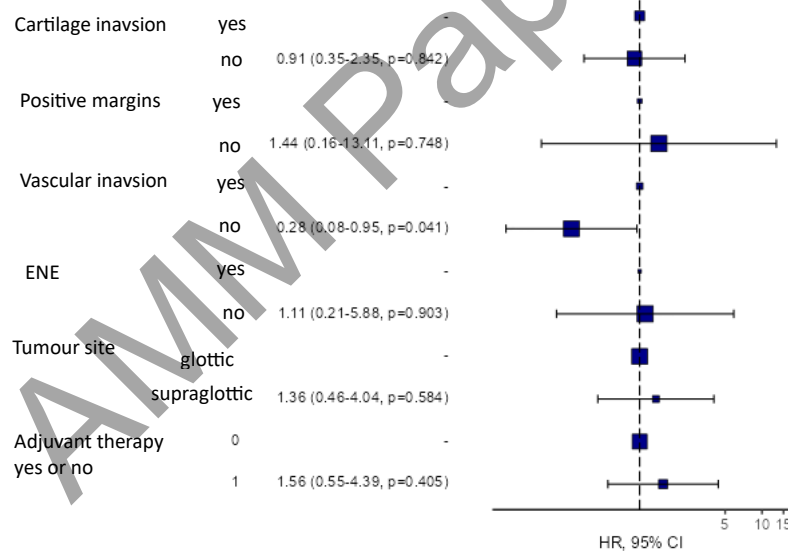
Survival: HR (95% CI, p-value)



Graph 3. Forest plot of multivariate COX analysis of risk of local recurrence

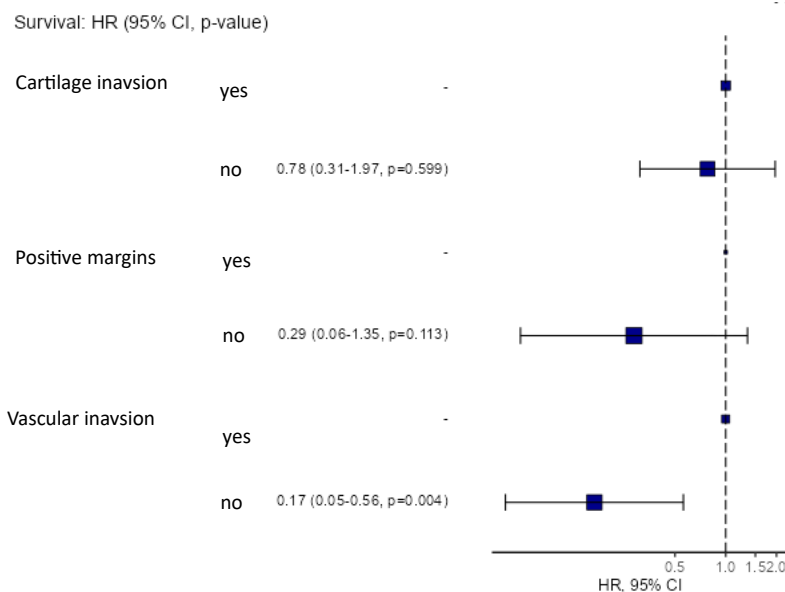
Statistical significance in the occurrence of regional recurrences was observed in vascular invasion ( $p=0.041$ ). Although without proven statistical significance in the Forest plot for the COX proportional hazard model with a confidence interval of 95%, we can see that the presence of ENE can indicate an overall greater possibility of regional recurrences of laryngeal cancer (Graph 4).

Survival: HR (95% CI, p-value)



Graph 4. Forest plot of multivariate COX analysis of risk of regional recurrence

When locoregional recurrences occur, a statistically significantly higher frequency of pathohistologically confirmed presence of vascular invasion was observed ( $p=0.004$ ). (Graph 5).



Graph 5. Forest plot of the multivariate COX analysis of the risk of simultaneous local and regional recurrence

Surgical management of local recurrences included total laryngectomy (6 patients, 67%) and pharyngolaryngectomy (1 patient, 16.5%) (Table 6).

Table 6. Surgical management of local recurrences of laryngeal carcinomas

<i><b>Surgical management</b></i>	<i><b>N(%)</b></i>
Without surgery	1 (16.5%)
Total laryngectomy	6 (67%)
Pharyngolaryngectomy	1 (16.5%)

In most cases of regional recurrences (40%), conservative therapy (chemotherapy, radiotherapy, chemoradiotherapy or symptomatic therapy) was applied. Surgical management of regional recurrences in the same number of cases included radical dissection (3 patients, 20%) and selective dissection (3 patients, 20%), then modified radical dissection (2 patients, 13.3%) and finally node extirpation (1 patient, 6.7 %) (Table 7).

Table 7. Surgical treatment of regional recurrences of laryngeal carcinomas

<i><b>Surgical management</b></i>	<i><b>N(%)</b></i>
Without surgery	6 (40%)
Extirpation of metastatic lymph node	1 (6.7%)
Selective neck dissection	3 (20%)
Radical neck dissection	3 (20%)
Modified radical neck dissection	2 (13.3%)

## DISCUSSION

Laryngeal carcinomas in 70% of cases originate in the glottis, then the supraglottis and finally the subglottis, and squamous cell carcinoma is the main histological type of laryngeal malignancies. The National Comprehensive Cancer Network (NCCN) has developed clinical

practice guidelines for the screening, prevention, diagnosis, treatment, and follow-up of patients with various types and locations of cancer, including cancers of the head and neck region [2]. Historically, the main therapeutic modality for patients with advanced laryngeal carcinoma has been total laryngectomy, which is associated with functional deficits and was often followed by poor survival if not followed by adjuvant therapy. The treatment strategy for T1/T2 cancer of the larynx involves an organ preservation protocol, either surgical or conservative, emphasizing the importance of adequate patient selection. The spread of the disease, adequate visualization and comorbidities must be taken into account when choosing the treatment modality [11]. As a possible source of confusion, the large heterogeneity within the T3 and T4a groups of tumors can be mentioned (T3- minimal vs massive involvement of the paraglottic space, with or without cartilage invasion, with or without involvement of the preepiglottic space, different levels of reduced mobility of the vocal cords; T4a anterior extralaryngeal expansion vs postero-inferior extension through the lateral part of the cricothyroid membrane and the cricothyroid space). The level of diagnostic confusion has been reduced by endoscopic and radiological visualization of laryngeal carcinoma, but none of these methods have yet established a definitive way to determine the cause of vocal cord fixation [7]. Currently, multiple surgical and nonsurgical organ-preserving options are available for the treatment of T3 and T4a cancers that are competitive in terms of locoregional control, overall survival, and survival without the need for total laryngectomy. Multiple studies with a large number of patients as one of the options of an organ preservation protocol with a high rate of locoregional control, overall survival and better functional results compared to total laryngectomy have highlighted OPH [7]. In a multicentric study conducted in Italy, it was observed that the overall five-year survival after OPH II was 87.92% and the five-year survival without signs of the disease was 81.87%, which in itself indicates its success [5]. OPH II has been highlighted as a type of laryngectomy with relatively low morbidity, good overall survival, better oncological control than OPH III and long survival without the need for total laryngectomy [7,13]. A systematic review of several studies conducted in the USA indicated that the percentage of local recurrences after a supracricoid laryngectomy in a five-year period was 1.85% [9]. Low percentages of local recurrences in the same period of 2.5% were also observed in our study. In our study, we can point out that locoregional control was achieved in 83% of patients, and that 5.77% of all treated patients required total laryngectomy, only 1 patient (0.96%) pharyngolaryngectomy as part of the surgical management of local recurrences of laryngeal carcinomas by which we can only confirm previously the claims made. If we take into consideration only patients with present local disease, we note that of which 67% were candidates for total laryngectomy, 16.5% for pharyngolaryngectomy, which means that 83.5% were operable at the time of local recurrence of the disease. The same frequency in the surgical management of regional recurrences was equally distributed between radical and selective neck dissection (20% each). However, the majority of patients with regional recurrences (40%) were not candidates for operative treatment.

In a multicentric study conducted in several centers in Italy, it was noted that in case of relapse, the highest percentage goes to local relapses, then regional and finally locoregional (40% vs 25% vs 5.7% of patients with relapses) [7]. A somewhat different trend was observed in our study, where the highest percentage was represented by regional recurrences (8.7%), then locoregional (5.8%), and finally local (2.5%). Such a discrepancy between the results can be interpreted as a discrepancy between the pTN patients who participated in the study. While in the previously mentioned study only patients with pT3 and pT4a laryngeal carcinomas participated, in our study only 30.9% of all operated patients were in these two stages. This can actually lead to a conclusion about the importance of the pT stage in the development of local recurrences.

In a multicentric study conducted in two centers in Italy, the results indicate that only pathohistologically confirmed vascular invasion ( $p=0.001$ ) affects overall survival, while disease-free period was influenced by pT ( $p=0.0001$ ), pN stage ( $p=0.083$ ) and vascular invasion ( $p=0.006$ ). Based on this, perivascular invasion was defined as an independent prognostic factor associated with lower overall survival and disease-free period [5]. In our study, vascular invasion proved to be a statistically significant factor in the occurrence of local recurrences ( $p=0.029$ ), regional recurrences ( $p=0.041$ ), as well as the occurrence of locoregional recurrences ( $p=0.004$ ). Pathohistologically confirmed vascular invasion, as the only factor that appeared in all three groups of recurrence, is a very strong predictive factor for the occurrence of recurrence. By correlating these results with the results of the previously mentioned study, we underline the importance of this factor in the predictive model of recurrence and in taking it into account when deciding on the application of adjuvant therapy. In addition to vascular invasion, in terms of the occurrence of local recurrences, the statistically significant factor in our study was positive resection margins ( $p=0.033$ ). Positive margins stood out as an important factor for predicting locoregional recurrences in a study conducted at the University Hospital of Santa Lucia, where it was observed that disease recurrence was present in 22.5% of patients with positive margins, while recurrence was present in 6.1% of patients who did not have positive margins [14]. In our study, statistical significance was observed in terms of pT stage and occurrence of regional recurrences ( $p=0.035$ ). Statistical significance in terms of local recurrences was not recorded, however, it can be noted that in pT4a stage recurrences were present in 50% of cases, which highlights the importance of this factor in the case of local disease control. The absence of statistical significance regarding the pN stage in the prediction of both regional and locoregional recurrences can be explained by the great heterogeneity between the groups, which are the origin of the indications when performing this operation. It is noted that the majority of patients with OPH II were treated in the pN0 stage (84%), while only 2.9% of patients were treated in the pN3b stage. Similar results regarding the importance of vascular invasion and positive margins ( $p<0.001$ ) were published by a study that sublimated the results from two centers in Italy - Rome and Milan. Also like the previously mentioned study, this one highlights the importance of pN status in predicting recurrence [15].

In a multicentric study conducted in two centers in Italy, loco-regional recurrences occurred  $23.5 \pm 14.8$  SD months after OPH II [5]. In our study, the median time of occurrence of local recurrence was 22 months (9.5-59.5), while the median time of occurrence of regional recurrence was 21 months (10-38.5). These results particularly emphasize the importance of regular monitoring of the patient, especially in the first two to three postoperative years, considering the greatest possibility of recurrence during that period of time.

## CONCLUSION

With proper consideration of factors related to the patient and tumor, adequate locoregional control of patients treated with an organ preservation protocol is achieved. Pathohistologically confirmed vascular invasion emerges as an independent factor that warrants close attention in postoperative management to achieve optimal locoregional disease control, while in local control along with vascular invasion, the importance of positive resection margins is also emphasized.

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