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# Factors Associated with Outcomes Following Salvage Surgery for Recurrent Laryngeal Cancer: A Retrospective Study of 50 Cases from a Single Center in Poland

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**Background:** This retrospective study from a single center in Poland aimed to identify factors associated with outcomes following salvage surgery in 50 patients with recurrent laryngeal cancer.

**Material/Methods:** The study group consisted of 50 patients with recurrent laryngeal cancer after primary organ preservation treatment (12 patients after partial surgery, 30 patients after radiation therapy, and 8 patients after prior treatment using both methods). None of the patients received chemotherapy before salvage surgery. All patients with recurrence of laryngeal cancer underwent total laryngectomy with elective bilateral nodal surgery. Local and/or nodal recurrence was considered the failure of primary organ preservation treatment. Efficacy of treatment was assessed in relation to overall survival (OS), disease-free survival (DFS), local control (LC), and locoregional control (LRC).


**Results:** Treatment results showed a poor prognosis in patients with local and/or nodal recurrence of laryngeal cancer. In the study group, the updated 5-year rates were as follows: OS rate of 26%; DFS rate of 25%; LC rate of 44%; and LRC rate of 39%. Univariate analysis showed that the stage before primary treatment was a predictive factor of OS ( $P=0.012$ ).

**Conclusions:** The findings from this retrospective study of 50 patients with recurrent laryngeal carcinoma showed that salvage surgery following organ preservation treatment resulted in a 5-year OS rate of 26%.

**Keywords:** **Laryngeal Neoplasms • Head and Neck Neoplasms • Laryngectomy • Treatment Refusal**

**Abbreviations:** **OS** – overall survival; **DFS** – disease-free survival; **LC** – local control; **LRC** – locoregional control; **DSS** – disease-specific survival; **cT** – extent of primary tumor; **cN** – clinical regional lymph node involvement

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## Background

Treatment of patients with recurrent laryngeal cancer after the failure of conservative treatment is a serious diagnostic and therapeutic problem [1]. It is possible that a growing number of supporters of conservative treatment contribute to this phenomenon. Conservative treatment helps preserve the function of the larynx [2]; however, the consequences of decisions made at the onset of treatment should be considered since they significantly affect patients' condition and survival [3]. Even many years of experience in patient enrollment for appropriate therapy of laryngeal cancer does not guarantee success of treatment, and therapeutic decisions are associated with a high risk to the health and survival of patients. Patients with laryngeal cancer constitute a group of patients in whom the prognosis has not improved despite the introduction of many modern treatment methods over the last 30 years [4]. The 5-year survival rate in patients undergoing salvage surgery after failed conservative treatment of laryngeal cancer ranges from 16% to 60% [5-8]. For example, Sullivan et al reported that 5-year overall survival (OS) rates were not significantly different between primary total laryngectomy and salvage total laryngectomy [9]. Other authors indicated worse treatment outcomes in patients with recurrent laryngeal cancer, compared with those primarily treated with organ preservation. Esteller et al reported a 5-year survival rate of 34% in a group of 32 patients [10]. Weiss et al observed a 5-year OS rate of 39.4%, disease-specific survival (DSS) rate of 44.6%, and locoregional control (LRC) rate of 68.8% in a group of 54 patients with advanced tumors treated by salvage total laryngectomy [6]. Similar results were reported by Li et al in a group of 28 patients in the advanced-stage group after salvage surgery: LRC rate of 70% and 5-year DSS rate of 55.2%. They also noticed that total laryngectomy was an effective treatment method of recurrent laryngeal cancer in carefully selected patients [7]. Scharph et al obtained a 2-year OS rate of 65% in patients after salvage laryngectomy and noticed that sarcomatoid pathology, lymphovascular space invasion, and an advanced initial stage before salvage treatment were associated with inferior disease-free survival (DFS) [11].

Several important factors influence such a large discrepancy in results, including that few studies have described the results of treatment failure and single-center analyses are conducted on small groups of patients. Therefore, in this retrospective study from a single center in Poland, we aimed to identify factors associated with outcomes following salvage surgery in 50 patients with recurrent laryngeal cancer.

## Material and Methods

The study was approved by the bioethics committee of the Medical University of Silesia (resolution no. 9/2011). Informed consent for participation in the study was obtained from all patients. Information about deceased patients was obtained from cancer registries. In all patients who were primarily treated with conservative treatment, the histological assessment of laryngeal lesions confirmed squamous cell carcinoma. The tumor, node, metastasis (TNM) classification stage was defined according to the 7<sup>th</sup> edition of the American Joint Committee on Cancer [12]. A group of 50 patients underwent total laryngectomy for histologically confirmed local and/or nodal recurrence of laryngeal cancer. Thirty of the patients had undergone primary radical radiotherapy. In 12 patients, recurrence occurred after partial surgery, and in 8 patients recurrence occurred after partial surgery with subsequent adjuvant radiotherapy. We used the European Laryngological Society classification to indicate the types of cordectomy [13]. No chemotherapy regimens were used before salvage surgery.

A retrospective analysis of subjects was conducted based on medical history records, outpatient visits, and follow-up examinations. The median follow-up was 5 years. Local and/or nodal recurrence (confirmed by histological examination) was considered the primary treatment failure. The efficacy of treatment was assessed in relation to OS, DFS, local control (LC), and LRC. The analysis of updated rates was used to assess the above parameters. OS was calculated from the date of salvage surgery to the date of death from any cause (uncensored) or last information on patient status. DFS was calculated from the date of salvage surgery to local, regional, or distant disease progression or to death from any cause (uncensored). All other observations were censored at the date of the last follow-up of patients. LC was calculated from the date of salvage surgery to local recurrence. LRC was calculated from the date of salvage surgery to local and/or nodal recurrence.

## Statistical Analysis

The Kaplan-Meier method was used to calculate survival curves, taking into account patients lost to follow-up [14]. The analysis allowed for the determination of the percentage of patients in whom a particular event occurred, including patients lost to follow-up and the time to event. The level of statistical significance was  $P \leq 0.05$ . The variables which did not reach statistical significance but revealed some statistical trend were considered in the multivariate analysis, and hence the  $P$  value of  $\leq 0.1$  was used instead of  $P \leq 0.05$ . To identify patient and tumor factors predictive of survival outcome, the following variables were analyzed in univariate analysis using the Cox proportional hazard test: age, initial T and N stage, grading, and

staging. Multivariate analysis was not attempted because of the small number of patients involved.

## Results

Men constituted the majority (94%) of 50 patients, and the mean age of the study group was 60 years. In the group of 20 patients after primary partial surgery, all 12 patients with recurrence underwent laser type V cordectomy (Table 1). The other 8 patients underwent partial surgery with subsequent adjuvant radiotherapy (postoperative adjuvant radiotherapy was used in the dose of 45 to 50 Gy, and all patients who qualified for postoperative irradiation had risk factors  $\geq T3$ , N+, or R1 resection). In the group of 30 patients who were previously primarily treated with radiotherapy, conformal radical radiation therapy of 66 to 72 Gy was administered. None of the patients underwent chemotherapy before salvage surgery because radiotherapy alone was the standard of treatment that was an alternative to surgery during the years of the study.

In all patients, salvage total laryngectomy with bilateral neck dissection was performed. The procedure was elective in patients without clinical signs of metastases to the neck lymph nodes (74%) and selective in the remaining patients (26%) (Table 2). In all patients, squamous cell carcinoma was detected in postoperative laryngeal specimens. In 7 patients, postoperative surgical margins in the postoperative specimens were positive (14%). Postoperative pharyngocutaneous fistula occurred in 24 patients (48%). All pharyngocutaneous fistulas were treated conservatively.

The characteristics of clinical factors in the study group that were related to the condition before primary oncological treatment showed that the largest group (68%) included patients with locally advanced cancer (cT3) without nodal metastases at the time of cancer diagnosis (cN0: 74% of patients). Cancer was primarily located in the epiglottis in 38% of patients, whereas, in 36% of patients, it was located in the epiglottis and glottis. Patients with clinical stage III cancer comprised more than 50% of the study group before primary treatment (Table 2).

In the study group, the updated 5-year OS rate was 26% (Figure 1), updated 5-year DFS rate was 25% (Figure 2), and updated 5-year LC rate was 44% (Figure 3), whereas the updated 5-year LRC rate was 39% (Figure 4).

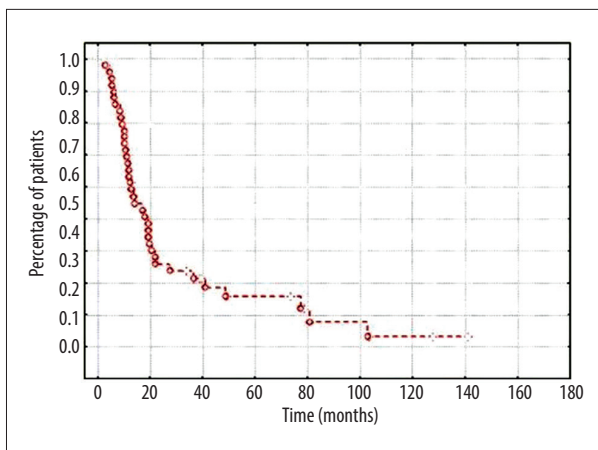
Univariate analysis showed that only stage before primary treatment was a predictive factor of OS ( $P=0.012$ ). Other factors of OS, such as age, extent of primary tumor (cT) stage, cN stage, and grading were not statistically significant (Table 3).

**Table 1.** Type of partial surgery in the group of 50 patients with primary laryngeal cancer (n=20).

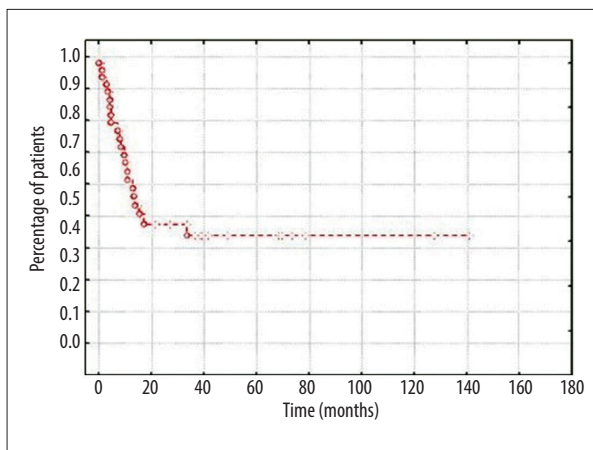
Type of partial surgery	Number of patients
Cordectomy	12
Hemilaryngectomy	4
Leroux-Robert partial laryngectomy	3
Laser partial laryngectomy	1

**Table 2.** Clinical factors in the group of 50 patients with recurrence of laryngeal cancer before conservative treatment (n=50).

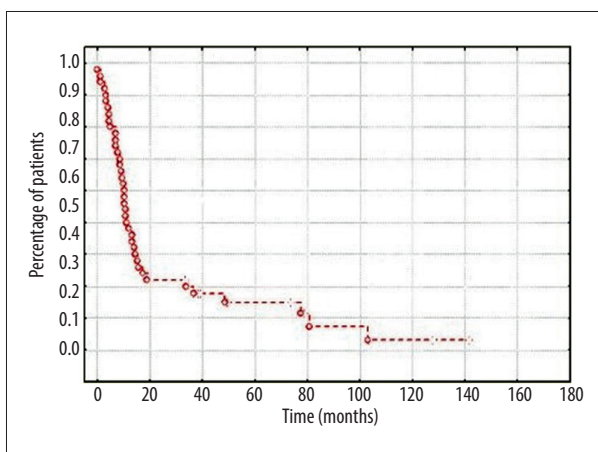
	Salvage surgery N=50 (100%)
Age mean (range)	60 (36-76 years)
Sex	
Male	47 (94%)
Female	3 (6%)
cT stage	
T2	2 (4%)
T3	34 (68%)
T4	14 (28%)
cN stage	
N0	37 (74%)
N+	13 (26%)
Staging	
II	1 (2%)
III	27 (54%)
IVa	22 (44%)
IVb	0 (0%)
Grading (G)	
Gx	33 (66%)
G1	5 (10%)
G2	11 (22%)
G3	1 (2%)
Cancer location	
Glottis	13 (26%)
Epiglottis	19 (38%)
Epiglottis+glottis	18 (36%)



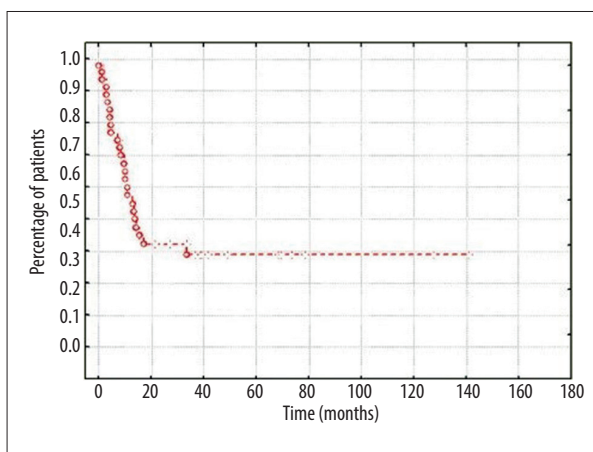
**Figure 1.** The updated 5-year overall survival rate in the group of 50 patients with recurrent laryngeal cancer.



**Figure 3.** The updated 5-year local control rate in the group of 50 patients with recurrent laryngeal cancer.



**Figure 2.** The updated 5-year disease-free survival rate in the group of 50 patients with recurrent laryngeal cancer.



**Figure 4.** The updated 5-year locoregional control rate in the group of 50 patients with recurrent laryngeal cancer.

**Table 3.** Predictive factors of overall survival.

	No. of patients N=50 (100%)	p value
Sex		0.27*
Male	94%	
Female	6%	
cT stage		0.19*
T2	4%	
T3	68%	
T4	28%	
cN stage		0.12*
N0	74%	
N+	26%	

	No. of patients N=50 (100%)	p value
Staging		0.012*
II	2%	
III	54%	
IVa	44%	
IVb	0%	
Grading (G)		0.93*
Gx	66%	
G1	10%	
G2	22%	
G3	2%	

\* Univariate analysis Cox proportional hazard test.

## Discussion

The results of our study showed that the prognosis of patients undergoing salvage surgery after failed conservative treatment of laryngeal cancer was highly unsatisfactory. Salvage surgery following conservative treatment resulted in a 5-year OS rate of 26% and a 5-year LRC rate of 39%.

An important issue that can affect the discrepancy of treatment results is the fact that the study groups are usually heterogeneous and comprise patients after failure of radiation therapy and surgical conservative treatment of laryngeal cancer, and patients having undergone both treatment methods. Our study is no exception in this respect. Similarly, Józefowicz-Korczyńska et al reported a 5-year OS rate of 39% in a group of 58 patients with failed radiation therapy and surgical conservative treatment of laryngeal cancer combined with postoperative radiation therapy [15]. Djordjevic et al divided patients into 2 groups – patients with recurrence after radiotherapy and those with recurrence after previous surgical conservative treatment of laryngeal cancer – and reported 5-year OS rates of 27% and 33%, respectively [16]. Our treatment results of patients who underwent radical radiotherapy as the primary treatment method are in line with some studies in the literature. Holsinger et al reported a total mortality of 73% in a group of 73 patients who underwent total laryngectomy after failed radiation therapy [17]. A similar analysis was conducted by Parsons et al who observed a 5-year OS of 29% following radiation failure in squamous cell carcinoma of the supraglottic larynx [18].

Compared with our study, Maj et al and Żyłka et al reported poorer results. They analyzed a heterogeneous groups of patients, including patients undergoing salvage therapy as a result of past failed treatment related to laryngeal cancer, and observed 5-year survival rates of 11% and 13%, respectively [19,20]. Young et al described the results in a group of patients with local recurrence after surgical conservative treatment of laryngeal cancer and reported a mortality rate of 85% [21].

There are several multi-center studies with larger groups of patients with better results than ours. For instance, Francis et al analyzed a large heterogeneous group of 913 patients after failed consecutive treatment of laryngeal cancer. The 5-year post-recurrence survival rate for laryngeal cancer patients was 41%, which is a good result considering such a cohort of patients. They showed that patients with glottic cancer had the best post-recurrence life expectancy. These results were probably influenced by the fact that such patients accounted for nearly 65% of the whole study group [22]. Better results were demonstrated by Dequanter et al who reported a 5-year OS rate of 40% in a group of 75 patients treated after radical radiotherapy [23].

Lyhne et al analyzed a large group comprised of 1511 patients with recurrent laryngeal cancer after radiation therapy in Denmark between 1971 and 2011. The comparison of the study results between the 1970s and the first decade of the 21<sup>st</sup> century showed a 5-year survival rate of 68% between 2000 and 2011 [24]. Other authors also obtained better results than those of our present study [25-29].

Of note, statistical analyses often include patients with locally advanced cancer (cT1 and cT2) at the time of initial diagnosis. In those patients, the prognosis after salvage surgery is better, which corresponds to a higher 5-year survival rate in the whole study group. For instance, Mimica et al reported a 5-year DSS rate of 57% in the group of patients undergoing salvage surgery for recurrent laryngeal cancer. However, early stage (I/II) disease was identified in 72% of patients at initial diagnosis, which improved the prognosis [27]. Similarly, Ganly et al reported an OS rate of 50% in the group of patients with early-stage squamous cell carcinoma of the glottic larynx who underwent total laryngectomy after radiation therapy [30]. Importantly, Cheraghlou et al showed that clinical outcomes were similar to those of patients undergoing salvage total laryngectomy in patients who experienced recurrence after radiation for T1/T2 laryngeal cancer and underwent conservation salvage laryngeal surgery [31]. In the present study, only 2 patients presented with locally advanced laryngeal cancer (cT2), and the largest group (68%) was comprised of patients staged cT3. In our study, poor survival and cure rates were mainly due to the fact that the study group was comprised mostly of patients staged III/IVa (only 1 patient was stage II at diagnosis). The selection of the study group had a significant impact on the outcomes and prognosis of patients. None of our patients underwent partial salvage surgery, which was due to the stage of the disease at the time of recurrence.

The statistical analyses of studies are frequently based on a short follow-up (2-3 years), which automatically improves treatment outcomes. For example, Scharph et al observed a 2-year OS rate of 65% and LRC rate of 21% in patients after salvage laryngectomy [11]. De Virgilio et al reported a 3-year OS rate of 38% in patients who had undergone supracricoid laryngectomy and of 52% in patients after cordectomy [32]. Moreover, Korolkowa et al observed a 3-year OS rate of 56% in patients after failed treatment of laryngeal cancer [33]. De Ridder et al reported a 2-year OS rate of 31% in patients with recurrent laryngeal cancer after chemoradiotherapy [34]. The results of Aydil et al showed a 3-year OS rate of 19% in patients with recurrent laryngeal cancer after chemoradiotherapy [35]. Of note, in our study, we based our treatment outcomes on 5-year survival and control rates.

It should be added that local and nodal staging at the time of cancer diagnosis is one of the factors affecting the results of

salvage surgery in patients with recurrence after oncological treatment [5,8,16,20,25,27,36,37]. For example, Davidson et al reported a 3-year OS rate of only 22% in 108 patients with advanced laryngopharyngeal carcinoma who underwent salvage treatment after failed radiation therapy [36]. Also, Elbers et al observed that salvage total laryngectomy in patients with recurrence following radiotherapy or chemoradiation resulted in a 5-year OS rate of 37% [38]. Putten et al reported a 5-year OS rate of 27% in 60 patients with advanced laryngeal and hypopharyngeal carcinoma [39].

The comparison of the results with those reported in the literature is difficult and does not always allow for drawing reliable conclusions. Also, it is important to note that treatment of local recurrence of laryngeal cancer poses a real challenge to the surgeon. Total laryngectomy is often the only chance for survival for this group of patients. It should be emphasized that a small sample size, use of a single center, and dependence on the information available from medical records were significant limitations of this study that may have affected our results.

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## Conclusions

The findings from this retrospective study of 50 patients with recurrent laryngeal carcinoma showed that salvage surgery following conservative treatment resulted in a 5-year OS of 26%.

## Conflicts of Interest

None.

## Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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