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# Acta Otorrinolaringológica Gallega

## Artículo Original

**Salvage Total (Pharyngo)Laryngectomy after organ preservation  
treatments – experience of a tertiary Oncological Center  
(Faringo)laringectomia total de resgate após tratamentos com  
preservação de órgão – experiência de um hospital oncológico**

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## Abstract

Background: Actual management of laryngeal and hypopharyngeal tumours remains a challenge. Usual treatment options to preserve laryngeal function include transoral laser microsurgery (TLM), open partial surgery, radiotherapy (RT) or chemoradioterapy (CRT). In advanced and uncontrolled tumours, conservative treatment options are associated with poor outcomes, being salvage radical surgery the only therapeutic option for patients with locoregional persistences or recurrences.

Methods: Forty-three patients had undergone salvage total laryngectomy (TL) or pharyngolaryngectomy (PL) at a tertiary referral centre, between 2006 and 2014 because of persistent or recurrent disease after completion of other treatment modalities, namely TLM, cricohyoidopexy, RT or CRT. Clinical stage, postoperative complications, follow-up and disease-specific survival were retrospectively analyzed.

Results: Twenty-six of these patients failed after TLM, one after cricohyoidopexy, one after RT alone and fifteen after CRT. The mean follow-up period was of 17.1 months and mean interval between the first treatment and the salvage surgery was 17 and 10.1 months in patients

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submitted to TLM and CRT, respectively. Sixteen patients had postoperative complications and extended hospital stay. Seven patients underwent TL due to functional reasons. There are 16 patients alive and all currently free of disease.

Conclusions: Salvage surgery may be a treatment option for local and/or locoregional recurrences providing improvement in disease control and survival, despite possible severe complications namely after treatments with CRT and high recurrence rates.

**Key Words:** Chemoradiotherapy, Laryngeal Cancer, Total laryngectomy, Total pharyngolaryngectomy, Wound complications, Salvage surgery

### **Resumo**

Introdução: O tratamento das neoplasias laríngeas e hipofaríngeas continua a ser desafiante. As opções terapêuticas para preservação de órgão incluem a microcirurgia transoral laser (MTL), a cirurgia parcial por via externa, a radioterapia (RT) ou a quimiorradioterapia (QRT). Nas neoplasias avançadas e não controladas, os tratamentos conservadores estão associados a pior prognóstico, sendo a cirurgia radical de resgate a única opção terapêutica em doentes com persistências ou recorrências locorregionais.

Métodos: Quarenta e três doentes foram submetidos a laringectomia total (LT) ou faringolaringectomia (FL) de resgate num hospital oncológico entre 2006 e 2014. Estes doentes apresentavam persistência ou recorrência tumoral após outras modalidades terapêuticas, nomeadamente MTL, cricohioidopexia, RT ou QRT. Foram analisados retrospectivamente diversas variáveis como o estadiamento clínico, as complicações pós-operatórias, o follow-up e a sobrevida livre de doença.

Resultados: Entre doentes submetidos a cirurgia de resgate, vinte e seis tinham sido submetidos a MTL, um a cricohioidopexia, um a RT exclusivamente e quinze a QRT. O período médio de follow-up foi de 17.1 meses e o intervalo médio entre o primeiro tratamento e a cirurgia de resgate foi de 17 e 10.1 meses nos doentes submetidos previamente a MTL e QRT, respetivamente. Dezasseis doentes desenvolveram complicações pós-operatórias e tiveram internamentos prolongados. Sete doentes foram submetidos a cirurgia de resgate por motivos funcionais. Dezasseis doentes estão vivos e atualmente livres de doença.

Conclusões: A cirurgia de resgate é considerada uma opção terapêutica válida nas recorrências locais e/ou locorregionais, promovendo um melhor controle da doença e aumento da sobrevida, apesar de estar associada a complicações graves e elevadas taxas de recorrência.

**Palavras Chave:** Quimiorradioterapia, Carcinoma da laringe, Laringectomia total, Faringolaringectomia total, Complicações pós-operatórias, Cirurgia de resgate

### **Introduction**

Laryngeal and pharyngolaryngeal squamous cell carcinomas (SCC) have an average incidence of 3.7 per 100.000 persons per year, with over 3.700 related deaths around the world, being the fifth most common cancer in men<sup>1</sup>. About 60% of the tumours appear in advanced stages (stage III-IV) at the initial diagnosis.

The management of these tumours remains a challenge. In the last years, larynx-sparing surgeries and chemoradiation (CRT) are growing interest. Actually, early-stage lesions are treated with radiotherapy (RT), endoscopic laser surgery or partial (pharyngo)laryngectomy.

Salvage surgery for laryngeal or hypopharyngeal tumours following treatments with RT or CRT has shown equivalent overall survival rates, when compared to primary total laryngectomy (TL) or pharyngolaryngectomy (PL)<sup>2-4</sup>. Therefore, chemo(radiotherapy) is a well-accepted option for organ preservation in laryngeal and hypopharyngeal tumours<sup>5</sup>. Currently the effectiveness of organ preservation protocols has been increasingly discussed, concentrating particularly in cost-effective parameters.

Transoral laser microsurgery (TLM) was first introduced by Strong and Jako for early laryngeal tumours in 1972<sup>6</sup>. Since then, this technique is widely used for more advanced laryngeal or pharyngolaryngeal tumours<sup>7,8</sup>. In selected cases TLM is associated with complete tumour removal, being possible in some patients avoid radiotherapy side effects, swallow and voice significant disturbs, short hospital stay and low treatment costs<sup>9</sup>.

Management of the clinically negative neck, remains subject of debate. The rate of occult metastasis at salvage surgery for patients with a clinically negative neck is about 10-14% for glottis and 20-30% for supraglottic and hypopharyngeal tumours<sup>9-11</sup>.

Salvage total pharyngo(laryngectomy) remain the gold standard for management of failures of such treatment options, and is more frequently associated with postoperative complications such as pharyngocutaneous fistulas, wound infection, chyle leak, swallowing and airway problems. These complications are associated to prolonged hospital stay, increased morbidity and mortality, and higher health care costs. Pharyngocutaneous fistula usually occurs related to dehiscence of the pharyngeal sutures, leading to leakage of saliva from the pharynx to the skin and/or into the trachea. It may conduce to complications like pneumonia, major vessel exposure and rupture with consequent death. The incidence of this complication ranges from 12% to 18% in salvage surgeries<sup>12,13</sup>.

Head and neck cancer patients have a serious risk of undernourishment due to frequent alcohol and or nicotine abuse, disadvantaged socio-occupational situation and, more important, pain and dysphagia. The nutritional status also deteriorates during CRT or RT, and these aspects can be related with increased postoperative complications and negative effects in morbidity, mortality and survival<sup>14</sup>.

This study aims to evaluate the experience of a tertiary centre about salvage total laryngectomy or total (Pharyngo)Laryngectomy after organ preservation treatments.

## **Methods**

This is a retrospective analysis of our practice based in all patients undergoing salvage pharyngo (laryngectomy) between January 2006 and December 2014 in a tertiary referral centre. All patients had laryngeal or hypopharyngeal tumours, all underwent a complete staging supported by clinical examination, computed tomography (CT) or magnetic resonance (MRI) imaging of the neck and thorax and all received prophylactic antibiotics (cefazolin and clindamycin) prior to surgery.

Details regarding patient and tumour characteristics, previous treatments, surgical outcomes, mean follow-up time, and recurrence were recorded.

Postoperative complications such as pharyngocutaneous fistulas, bleeding, infections, and other complications as skin necrosis were analyzed in each group.

Patients with disease detected after 3 years were excluded, because they were considered second primary tumours.

In this study, we defined salvage surgery when a total laryngectomy or total pharyngolaryngectomy was performed in patients who either had biopsy-proven evidence of persistent or recurrent disease after TLM, partial surgery, RT or CRT or in patients with a non-functional larynx due to chondronecrosis or chronic aspiration. Patients without response to induction chemotherapy in organ preservation protocols, who underwent sequential radical surgery, were excluded from this analysis.

Disease-specific survival (DSS) was measured from the date of diagnosis to the last date that patients were reported as alive.

CRT was defined as the use of combined RT and chemotherapy, concurrently or sequentially, as primary treatment option of laryngeal or hypofaryngeal tumours.

Statistical analysis was performed using SPSS Version 10.0.8 software (IBM). T-test or  $\chi^2$  test were used to calculate the significance of any correlations between variables. Differences with p value less than 0.05 were considered statistically significant.

## **Results**

Between January 2006 and December 2014 we performed 501 total (pharyngo)laryngectomies. Fifty of them fulfilled our criteria for salvage surgery. We will focus on these patients.

Forty-three patients underwent salvage surgery due to recurrent or persistent tumour and 7 patients because of functional motifs. All patients were men and mean age was 61 years (range, 37-77 years). Almost all patients had history of tobacco or heavy alcohol consume. The majority of patients had primary tumours in the larynx (n=38) rather than in the hypopharynx (n=12). Table 1 represents the sample characteristics.

In our study, persistent tumour was detected in 12 patients (6 submitted to TLM and 6 to CRT), locoregional recurrent tumour in 31 patients (20 submitted to TLM, 9 to CRT, 1 to RT alone and 1 to CHP), cartilage necrosis in 2 and chronic aspiration in all patients. Seven patients underwent salvage surgery due to functional reasons: 3 after TLM, 2 after CRT and 2 after RT alone (table 2).

Now we will focus on patients with persistent or recurrent disease (n=43). 78% of these patients had complaints related with disease and were symptomatic. Persistent or recurrent disease occurred in 33 patients with laryngeal tumours and in 10 patients with hypofaryngeal tumours. The location of the tumours before primary treatment and the location of the persistence or recurrence were the same in the entire sample. There were performed 28 total laryngectomies and 15 total pharyngolaryngectomies.

Overall, 8 patients presented stage I, 15 stage II, 17 stage III and 3 stage IV, before initial treatment according to American Joint Committee on Cancer (AJCC) classification, 7<sup>th</sup> edition. About initial clinical T, there were included 8 T1, 15 T2, 20 T3. With regard to lymph node metastasis, 36 were preoperatively

Table 1: Patient, treatment and salvage laryngectomy characteristics.

	<b>No. of patients</b>	<b>%</b>
<b>Gender</b>		
Male	50	100 %
Female	0	0 %
<b>Age (years)</b>		
< 50	7	14 %
≥ 50	43	86 %
<b>Smoking</b>		
No	4	8 %
Yes	46	92 %
<b>Alcohol</b>		
No	14	28 %
Yes	36	72 %
<b>Tumour location</b>		
Larynx	38	76 %
Hypopharynx	12	24 %
<b>Initial treatment</b>		
RT alone	3	6 %
CRT	17	34 %
TLM	29	58 %
CHP	1	2 %
<b>Salvage Surgery</b>		
Total Laryngectomy	33	66 %
Pharyngolaryngectomy	17	34 %

RT: Radiotherapy; CRT: Chemoradiotherapy; CHP: Cricohyoidopexy; TLM: Transoral laser microsurgery.

Table 2 – Patients requiring functional surgery

	<b>TLM</b>	<b>CRT</b>	<b>RT</b>	<b>Total</b>
<b>Cartilage necrosis</b>		<b>1</b>	<b>1</b>	<b>2</b>
Larynx			1	
Hypopharynx		1		
<b>Chronic aspiration</b>	<b>3</b>	<b>2</b>	<b>2</b>	<b>7</b>
Larynx	3		2	
Hypopharynx		2		
<b>Total of patients</b>	<b>3</b>	<b>2</b>	<b>2</b>	<b>7</b>

RT: Radiotherapy; CRT: Chemoradiotherapy; TLM: Transoral laser microsurgery.

staged as N0, 1 patient as N1, 3 patients as N2 and 3 patients as N3. No patients presented distant metastasis.

Initial therapy consisted in TLM in 26, cricohyoidopexy (CHP) in 1, RT in 1 and CRT in 15 patients. All TLM surgeries were done with therapeutic perspective and none of these patients underwent additional treatments, such as RT or CRT. Detailed TNM and stage descriptions are presented in table 3.

Mean interval time from TLM to the detection of disease was 14.8 months compared with 9.2 months in patients submitted to CRT, but this aspect wasn't statistically significant (p-value = 0.101).

Mean time from TLM to salvage surgery was 17 months compared with 10.1 months from CRT to salvage surgery. Disease-specific survival was significantly higher in patients submitted to TLM compared with CRT (38.7 and 19.9, respectively. P-value = 0.01).

Of the 43 patients, bilateral neck dissection was performed in 29 and unilateral neck dissection in 4: 12 were modified radical neck dissections and 21 selective neck dissections (level II-IV).

About postoperative complications, pharyngocutaneous fistula occurred in 9, wound infection in 4, hemorrhage in 1 and flap necrosis in 2 patients (Table 4). 8 patients were submitted to LT and 8 to FLT. Univariate analysis showed no significant difference in the frequency of complications for patients submitted to CRT comparing with TLM (P-value = 0.264). Reconstruction of surgical defects was required in 4 patients and a pectoralis major myocutaneous flap was chosen in all cases.

Salvage functional surgeries were not associated to major complications.

Because this is a retrospective study, we were unable to assess the impact of nutritional status in the development of postoperative complications. Concerning voice rehabilitation, in our sample, there are 12 patients using tracheoesophageal voice with satisfactory speech.

From patients submitted to salvage surgery due to persistent or recurrent tumour, 27 patients died, 2 due to natural causes and 25 due to tumour progression (12 previously submitted to CRT and 13 to TLM). There are 16 patients alive and all currently free of disease.

The mean follow-up period was 17.1 months (range, 1-77 months).

Table 3: Initial treatment, TNM and stage classification in patients submitted to salvage surgery due to recurrent or persistent disease (No. of patients)

	<b>TLM</b>	<b>CRT</b>	<b>RT</b>	<b>CHP</b>	<b>Total</b>
<b>T classification</b>					
1	8	0	0	0	8
2	14	0	1	0	15
3	4	15	0	1	20
<b>N classification</b>					
0	26	8	0	1	36
1	0	1	0	0	1
2	0	3	0	0	3
3	0	3	0	0	3
<b>M classification</b>					
0	26	15	1	1	43
<b>Stage</b>					
I	8	0	0	0	8
II	14	0	1	0	15
III	4	12	0	1	17
IV	0	3	0	0	3

RT: Radiotherapy; CRT: Chemoradiotherapy; CHP: Cricohyoidopexy; TLM: Transoral laser microsurgery.

Table 4: Initial treatment and postoperative complications after salvage surgery in patients with tumour persistence or recurrence.

	TLM	CRT	RT	CHP	Total
<b>Pharyngocutaneous fistula</b>	3	6	0		9 (21%)
<b>Wound infection</b>	4				4 (9%)
<b>Flap necrosis</b>		2			2 (5%)
<b>Haemorrhage</b>	1				1 (2%)
<b>None</b>	18	7	1	1	27 (63%)

RT: Radiotherapy; CRT: Chemoradiotherapy; CHP: Cricohyoidopexy; TLM: Transoral laser microsurgery.

### Discussion

Laryngeal and hypopharyngeal tumours are not uncommon and so we can consider these pathologies as a major health problem.

TLM, partial (pharyngo) laryngectomy, RT and CRT produce comparable survival outcomes, when compared with primary laryngectomy and postoperative RT or CRT with the proposal of preserving the voice and swallowing in a significant number of patients<sup>15-17</sup>. However, there are many patients that have disease recurrence after treatment apparent success. This analysis transmits the experience of a Portuguese tertiary centre. In our patient population, the median time to recurrence from initial diagnosis was 9 to 15 months, which emphasizes the importance of frequent follow-up for at least 2 years after the initial treatment with long-term follow-up to allow an early intervention in case of persistent or recurrent disease. Salvage surgery for these patients usually requires FLT or LT and is an important issue for head and neck surgeons.

Previous studies have reported increased postoperative complications for salvage surgery when compared with primary FLT or LT. This incidence is also increased after RT or CRT treatments comparing with primary surgery<sup>18</sup>. Both radiotherapy and chemotherapy produce adverse effects on wound healing with a synergistic interaction when used together<sup>19</sup>. Identification of risk factors that may predispose patients to fistula formation and taking measures to minimize these complications is a really important issue. In recent years, it appears that fistula rate has decreased, probably due to advances in surgical techniques, liberal use of regional or free flaps for reconstruction, antibiotics and better postoperative care. However, this may be also attributed to advances in RT (better delivery and tissue sparing, smaller RT portals and more accurate dosing)<sup>20</sup>. To reduce the rate of wound complications following CRT, the use of vascularized reconstruction flaps has been recommended in addition to general precautions such as the gentle handling of tissue and the avoidance of trifurcated neck incisions. In our sample, 4 patients were reconstructed with a pectoralis major myocutaneous flap and in two patients the flaps died, associated to important local infection.

It was also reported that preoperative anaemia, hypoalbuminemia and a history of weight loss 6 months before surgery were independent predictors of wound complications after laryngectomy<sup>21</sup>. That's why a prophylactic gastrostomy in patients proposed for CRT may reduce morbidity in advanced head and neck tumours<sup>22</sup>. In our centre all the patients are followed in Nutrition consultations and have periodical Internal Medicine observations before surgery.

Management of cervical lymph nodes in patients proposed to laryngeal salvage surgery for recurrent or residual disease is still controversial. Some authors recommend bilateral neck dissection for all patients with recurrent T3-4 or supraglottic tumours<sup>11</sup>. Thirty-three of our patients were submitted to neck dissection (12 modified radical neck dissection and 21 selective neck dissection) and in nine of them positive nodes were observed. To avoid under or over treating the neck, diagnostic imaging techniques that detect lymph nodes metastasis are warranted. CT for neck metastasis presents a negative predictive value of 94-97% and good sensitivity (75-97%) but with specificity ranging from 24% to 93%<sup>23-25</sup>. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) presents better sensitivity, specificity and negative predictive value, concluding that neck dissection can safely be withheld in PET-negative patients<sup>26-28</sup>. Recent studies suggest that sentinel node biopsy has a sensitivity of 89%, being promising in the future<sup>29-30</sup>.

Fortunately, salvage surgery is infrequent, representing a small number of acts when compared with primary laryngectomies. However, we expected to see a decreasing rate over the time, but anyway we have 50 surgeries in the last 8 years. Since surgery is the only option for cure, physicians and patients will be tempted to perform salvage surgery even if there is uncertainty about getting free surgical margins<sup>31</sup>.

Problematic complications following salvage pharyngolaryngectomy include fistula formation. This occurred in 24% of our patients, which is comparable with other reports in the literature, ranging from 10.9 to 39%<sup>32,33</sup>. Patients with pharyngocutaneous fistulas tend to need longer periods of hospitalization until the initiation of oral intake. Complication rates vary depending on patients' factors, type of complications evaluated and CRT protocols used.

Post-operative infection occurs in about 40-61% of salvage laryngectomies. This complication occurred in 8% of our patients. The most frequent organisms isolated in these patients are typical hospital-acquired pathogens: methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Serratia marcescens*, *Proteus mirabilis* and *Enterococcus faecalis*. Therefore, an extended course of antibiotics should be performed after standard prophylaxis, avoiding nosocomial infections. To reduce infection rate is important to improve metabolic state of all patients and health professionals should also be aware of cross-infection, using preventing measures<sup>34</sup>.

Larynx-sparing surgeries and chemoradiation have been increasingly used in the last years, nevertheless salvage surgery remains the gold standard when these therapies fail. Salvage surgery for pharyngolaryngeal tumours following treatments with CRT has shown equivalent overall survival rates, when compared to primary surgery. Otherwise, the implementation of TLM, even in advanced pharyngolaryngeal tumours, actually under discussion, will be associated to less radiotherapy dose and side effects, with concurrent best results in functions like swallowing and voice, aspects observed in our population. Also, in our sample, postoperative complications were more frequent and disease-specific survival lower in patients submitted

to CRT than TLM. Instead values were not statistically significant, we can explain these best results due to the lesser extension of tumours.

As the trend in pharyngolaryngeal cancer treatment is towards organ-preservation protocols or partial surgeries, patients more often maintain communication and swallowing capacities. Therefore, the majority of patients who undergo RT, CRT, TLM and other partial laryngectomies communicate by laryngeal voice. Patients submitted to salvage TL or PL usually communicate with alaryngeal speech methods, including electrolarynx, esophageal or tracheoesophageal voice. Patients using tracheoesophageal voice reported significantly better voice scores than patients using other communication methods and present better good quality of life<sup>35</sup>.

Adequate swallowing and speech functions can improve a patient's emotional health and quality of life. Therefore, to attain these objectives voice and swallowing therapy is a necessary component of the rehabilitation process following treatment for head and neck cancers. Fortunately, almost all patients return to functional communication and oral feeding<sup>36,37</sup>.

Salvage surgery result in permanent disabilities with decreased functional capacity and psychological distress. Close monitoring of these patients and investing in speech rehabilitation are essential to preserve their quality of life.

The use of organ preservation therapies is constantly developing. It is necessary to have more studies about these regimens.

The small number of patients included in each group and the fact of being a retrospective study are the most important limitations of our study. We recommend prospective studies in the future to validate the available data.

### **Conclusions**

Salvage surgery continues to remain the preferred treatment option when larynx-sparing therapies fail. In our series, postoperative complications were more frequently associated with CRT than TLM, although the difference was not statistically significant. Disease-specific survival was higher in patients submitted to TLM rather than CRT and these results are supported by different TNM stages. Salvage surgery is a real treatment option for pharyngolaryngeal and regional recurrences providing improvement in disease control and survival, despite severe complications and high recurrence rates. These treatments often have an impact on physical, social, and psychological functions. Further studies are required to define standard protocols to provide the best treatment option.

### **Conflict of interest**

None declared.

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