ORIGINAL ARTICLE

Results of Total Laryngectomy as Treatment for Locally Advanced Laryngeal Cancer in the Organ-Preservation Era

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Abstract
Introduction and objectives: Total laryngectomy (TL) and postoperative radiotherapy (RT), when indicated, have proven to be effective in treating cases of locally advanced laryngeal cancer. The aim of this study was to analyse the oncological outcomes of this procedure in patients with laryngeal cancer classified T3 and T4a.

Methods: We studied 80 patients (51 T3 and 29 T4a) with primary squamous cell carcinoma of the larynx who underwent TL between 1998 and 2006. Bilateral neck dissection was performed in 54 patients, unilateral in 11, and central in 4. Twenty patients (25%) received postoperative radiotherapy.

Results: Mean age was 64 years with a male predominance (97%). As for habits, 96% were smokers and 89% consumed alcohol. Lymph node metastases occurred in 44% of patients and extracapsular invasion in 37% of them. All cases had tumour-free margins. In all, 25% of patients had loco-regional recurrence and 5% developed distant metastases. The 5-year disease-specific survival was 72% and 5-year overall survival was 55%. Variables associated with decreased disease-specific survival were T4 classification (P=.068), N2–N3 classifications (P=.005), extracapsular invasion (P=.018) and stage IV disease (P=.009). On multivariate analysis, the only variable associated with decreased disease-specific survival was the presence of N2–N3 nodal metastases (P=.008).

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Introduction

Laryngeal cancer accounts for approximately 2% of total tumours in males and 0.4% in females, and is responsible for 1% of deaths caused by cancer. The estimated incidence of laryngeal cancer in Spain in 2012 was 1.1 cases per 100,000 inhabitants for women and 12.6 cases per 100,000 inhabitants for men, and there is a trend towards a decrease in men and an increase in women which is probably related to a change in society’s toxic habits.

Laryngeal cancer is the paradigm of efforts made to try to combine the major therapeutic objectives (loco-regional control and increase in survival) with preservation of function, given the essential role of the larynx in communication. In locally advanced stages (T3, T4) total laryngectomy (TL) (with postoperative radiotherapy [RT] in cases with risk factors) has proven to be an effective treatment, and no study has obtained better oncological outcomes than this one. However, since the publication of the study by the Department of Veterans Affairs Laryngeal Cancer Study Group (VALCSG), and particularly since the publication of the Radiotherapy and Oncology Group (RTOG) 91–11 trial there has been a change in the treatment paradigm of advanced laryngeal cancer, from surgery to a combination of chemotherapy and RT, aimed at preserving laryngeal function. In accordance with this latest study, the standard treatment in stage T3 laryngeal cancer is currently concomitant chemo-radiotherapy. However, TL continues to have a role to play in those patients who are not indicated for chemo-radiotherapy due either to the tumour characteristics (bulky tumours or tumours combined with cartilage destruction), or to their general or social conditions.

Change in treatment regimes for advanced laryngeal cancer has led to a reduction in the use of TL, and also of the type of patients on whom it is performed, with few works currently showing the outcomes of TL as primary treatment for advanced laryngeal cancer. The aim of our study was to analyse the oncological outcomes obtained in patients with locally advanced laryngeal cancer on whom TL had been performed in recent years as initial treatment, prior to implementing organ preservation treatment in our hospital. Since this group of patients had been treated

Conclusions

TL is an effective treatment for the management of patients with locally advanced laryngeal cancer. Organ preservation protocols should achieve similar oncological results to those obtained with TL.

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Materials and Methods

The study included patients diagnosed with primary squamous cell carcinoma of the larynx who had not received treatment previously and who underwent TL (with complementary RT in indicated cases) between 1998 and 2006.

The indication for TL during the study period included patients in a suitable medical condition to withstand the treatment, with stage T3 and T4a laryngeal cancer, who were not candidates for partial laryngectomy. There were no cases of distant metastasis at the time of diagnosis. In all cases, diagnostic assessment included a flexible nasofibrolaryngoscopy with a biopsy and cervical and thoracic computerised tomography (CT) was performed. In those cases where it was not possible to take a biopsy in the outpatient department a direct microlaryngoscopy was performed. Therapeutic cervical dissection was performed in cases with lymph node metastases and prophylactic cervical dissection (unilateral or bilateral depending on the location of the primary tumour) in cases without clinical metastases, with several particularities: in 11 patients (stage T3NO glottis tumours) no cervical dissection was performed; in 4 patients central dissection was performed (area VI); in 11 cases ipsilateral selective lateral dissection was performed (areas II–IV); in 44 cases bilateral selective lateral dissection was performed; in 8 cases a selective lateral dissection and a radical dissection was performed; and in one case bilateral radical dissection (in 2 operations) was performed. In general, postoperative RT was administered in cases classified as pT4 or pN2–N3.

The clinical–pathological and demographic data were obtained from hospital medical records. Informed consent was obtained from all patients and the study was approved by the hospital’s clinical research ethics committee. The variables analysed were age, gender, toxic habits, comorbidities (diabetes, chronic obstructive pulmonary disease, cardiopathy, hepatopathy), location of tumour, TNM classification (according to TNM staging by the International Union against Cancer [7th edition]), histological grading, treatment complications and patient evolution.

The statistical programme IBM-SPSS version 19.0 was used for the analysis. Comparison between the qualitative variables was made using the Chi-square test or the Fisher exact test. Survival was calculated using the Kaplan–Meier method and the differences between survivors were analysed using the logarithmic range method. Minimum follow-up of patients included was 36 months or up to death. Cox regression was used for multivariable analysis. All testing was bivariate and the significance level was established at $P < .05$.

Results

During the period of study, 80 patients were identified with carcinoma of the larynx who had initially been treated by TL. Patient characteristics are shown in Table 1. The mean age was 64 (range: 36–86 years of age), with a clear predominance of males (97%). Almost all the patients had a history of smoking (96%), and the majority also of alcohol consumption (89%). Thirty-nine (49%) percent of patients presented some of the comorbidities studied (Table 1). Distribution was similar regarding tumour location and there was a predominance of stage T3 patients (64%). Following an anatomopathological study, approximately half of the patients (44%) presented with lymph node metastases. In 13 of 35 patients (37%) with lymph node metastases, extra-capsular invasion was present. Regarding the histological grading, well and moderately differentiated cases predominated (85% of cases). In all cases the surgical resection margins were tumour-free. Twenty patients (25%), all stage IV, received postoperative RT.
The most frequent complication in the postoperative period was surgical wound infection, which presented in 25 patients (31%); in 22 cases (27%) this presented as a pharyngeal cutaneous fistula and in 3 (4%) as purulent drainage. Four patients (5%) presented with postoperative haemorrhage which required surgical review of the wound. Surgical intervention did not lead to death in any cases. Mean postoperative stay was 28 days (median of 17 days), with a range of between 9 and 195 days. The duration of the mean stay is related to the appearance of a pharyngeal cutaneous fistula: mean stay in cases without a fistula was 18 days, compared with 49 days in the cases which presented fistulae ($P$<.001). All the patients managed adequate oral nutrition by the end of treatment.

During follow-up 20 patients (25%) presented with a local and/or regional relapse and 4 (5%) developed distant metastases (all in the lung and which in one case had spread to the liver and bones). In 12 patients (15%) a second primary tumour appeared; the most frequent site was the lung (6 patients), followed by the ENT area (4 patients) and the oesophagus (2 patients). Twenty patients (25%) died as a result of the tumour and 15 (19%) due to non-related causes. Specific survival for the disease for the total patient series was 77% at 3 years and 72% at 5 years, and overall survival was 71% at 3 years and 55% at 5 years. Specific survival per disease stage at 5 years was 78% for stage III patients and 48% for stage IV patients and overall survival at 5 years was 57% for stage III patients and 30% for stage IV patients.

The variables associated with lower survival specific to the disease were the presence of lymph metastases classified as N2–N3 ($P$=.005; Fig. 1A), the presence of extracapsular invasion ($P$=.018; Fig. 1B) and stage IV tumour ($P$=.009; Fig. 1C). T4 classification presented a quasi-significant association ($P$=.068; Fig. 1D). The presence of comorbidities was not related to specific survival ($P$=.081), tumour location ($P$=.037), or histological grade ($P$=.084). In multivariate analysis the only variable which had a significant relationship to specific survival for the disease was the presence of lymph node metastases N2–N3 ($P$=.008; relative risk: 3.36; confidence interval of 95%: 1.38–8.19).

Lower overall survival was associated with the presence of N2–N3 lymph node metastasis ($P$=.002; Fig. 2A), the presence of extra-capsular invasion ($P$=.001; Fig. 2B) and stage IV tumour ($P$=.002; Fig. 2C; the presence of comorbidities presented a quasi-significant association ($P$=.055; Fig. 2D). There was no significant association with the T classification ($P$=.117), age ($P$=.29), tumour location ($P$=.45) or histological grade ($P$=.97). In the multivariate analysis the only variable which had a significant relationship to overall survival was the extra-capsular spread of the lymph node metastases ($P$=.002; relative risk: 3.44; confidence interval of 95%: 1.6–7.4).

Discussion

After publication of the studies which indicated that the combination of chemotherapy and RT enabled preservation of laryngeal function in a large number of patients with advanced laryngeal carcinoma (specifically T3) without compromising survival, the use of TL as the initial treatment for these patients has significantly reduced. However, in T4 tumours laryngeal preservation rates are much lower and often present complications which compromise laryngeal function, which is why in these cases TL continues to be recommended. This change in the treatment paradigm for advanced laryngeal cancer has led to the majority of patients in recent years being treated with chemo and radiotherapy, even in a substantial number of patients for whom it would not be indicated, such as patients with T4 tumours. Consequently there are scarcely any recently published series on laryngeal carcinomas treated with TL, and the majority of cases include a high percentage of rescue TL surgery after RT or chemo-radiotherapy. It is therefore of interest to find out the current outcomes regarding TL as initial treatment of locally advanced (T3–T4) laryngeal cancer. In our hospital we have included the conservative non-surgical treatment of the larynx relatively recently (2006), and we therefore have an extensive series of patients who have been treated with TL in the last few years, which reflects the reality of these patients at a time when non-surgical treatment was already widespread, and could serve as a reference to compare the oncological results with those of this treatment. This is of particular importance due to the reduced survival of patients with laryngeal cancer who were observed over the last 2 decades, to which this change in treatment patterns could have contributed.

Our results show a specific survival for the disease and an overall survival rate of 5 years (72% and 55%, respectively) similar to those described in the recent series of patients treated with TL. These survival rates may be considered appropriate for an advanced stage cancer, but show that no advances have been made in the prognosis of these patients over the last 3 decades. These figures also favourably compare with those obtained by chemo-radiotherapy-based treatments; in the VALCSG study, estimated survival at 2 years was 68% (77% in our series), and in the RTOG 91-11 study, overall survival was 55% at 5 years (equal to that of our series), bearing in mind that in these series, stage III patients predominated (in contrast to our series), that the percentage of patients classified as T4 was very low, and that patients classified as T2 were also included. This means to say that survival was similar although it included patients with a better prognosis. Another noteworthy aspect is that a third of our patients were over 70, who were not usually included in the chemo-radiotherapy protocols due to the poor tolerance of this treatment in older patients. Furthermore, it should be noted that only 25% of our patients received postoperative RT, which indicates the effectiveness of surgical treatment in these tumours.

Although there are no randomised studies which compare TL (plus RT when indicated) with chemo-radiotherapy, a paired study showed similar efficacy for both therapeutic strategies. Notwithstanding, in the said study, patients with hypopharyngeal carcinoma were also included, which could have had an effect on the results. In other retrospective studies of advanced laryngeal cancer, survival was not influenced by the therapy used, whether it was surgery plus RT or chemo-radiotherapy. However, in a recent, extensive retrospective study of the population, survival was greater in cases treated with surgery, particularly in cases classified as T4. Given that in cases classified as T4 the majority of studies indicate better survival for patients treated with...
Figure 1  Specific survival graphs for the disease according to the Kaplan–Meier method in accordance with the N (A) classification, the presence of extra-capsular invasion (B), and stage (C) and T classification (D).

...surgery, the selection biases of the patients for each type of treatment may be responsible for the different outcomes.

The prognostic factors found in our series were the same as those traditionally described for these tumours: classification T, classification N, extra-capsular lymph node invasion, and also for overall survival, the presence of comorbidities. As is well known, the most important prognostic factor in laryngeal carcinoma is the presence of lymph metastasis; however, in our study there were no differences in survival among patients classified as pN0 and those classified as pN1, the prognosis being much worse for those classified as pN2 or above. A similar result was recently described by Pezier et al. in a group of patients with advanced laryngeal cancer, similar to ours, treated with TL, cervical dissection and occasional RT. These results indicate that surgical treatment (with occasional postoperative RT) is highly effective in the control of the limited lymph disease (N1). Furthermore, in our series none of the patients classified as pN1 received complementary RT, demonstrating the effectiveness of surgical treatment alone. The presence of extra-capsular lymph node invasion is an additional factor for a poor prognosis among patients with lymph node metastases, the main determinant being overall survival.

With regard to complications, TL (and cervical dissection) may be considered a safe treatment, as there were no deaths...
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or serious complications attributable to the procedure. The main complication continues being the appearance of pharyngeal-cutaneous fistulae. The percentage of patients who presented with this complication in our series (27%) may be considered high, bearing in mind that these were primary tumours with direct closure. In a recent meta-analysis the incidence of fistulae after primary TL was 14%. However, another meta-analysis which compared the incidence of fistulae after conventional closure or autosuture describes an incidence of fistulae for conventional closure (as with our series) of 23%, closer to our figures. Similarly, an extensive series of patients treated in a time period similar to ours (2000–2006) presented with fistula incidence rate of 25%. These data indicate that, despite technical advances and the use of prophylactic antibiotics, postoperative fistulae continue to be a major problem in these patients, representing the main cause of prolongation of hospital stay and postoperative morbidity.

To conclude, TL (with occasional complementary RT) offers good oncological results in terms of loco-regional control of the disease and survival in advanced laryngeal cancer. In order to be considered valid, any alternative treatment

Figure 2  Overall survival graphs for the disease according to the Kaplan–Meier method in accordance with the N (A) classification, the presence of extra-capsular invasion (B), and stage (C) and the presence or non-presence of comorbidities (D).
which attempts to preserve laryngeal function should show similar oncological outcomes to those of this surgical technique.

Conflict of Interests

The authors have no conflict of interests to declare.

References