Factors influencing tumour relapse after total laryngectomy

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Abstract. Factors influencing tumour relapse after total laryngectomy. Objectives: To determine the prognostic factors predictive of tumour recurrence after surgical treatment for laryngeal carcinoma with total laryngectomy.

Study Design/Methods: Retrospective review of 308 patients with laryngeal carcinoma who underwent total laryngectomy in the ENT Department of AHEPA University Hospital between 01/01/1992 and 31/12/1999. In 238 patients, total laryngectomy was performed as primary treatment of laryngeal carcinoma, and in 70 others as treatment of tumour recurrence following radiotherapy or partial surgery. Follow-up was standardized, following a strict protocol, the mean follow-up time was 68 months.

Results: During post-operative follow-up, recurrences were observed in 96 of 308 patients (31%). The relapse rates were 27% (65 of 238) for patients treated with primary total laryngectomy, and 44% (31 of 70) for those treated for recurrence following previous treatment. The difference in relapse rates was statistically significant. In 39 of 238 (16%) cases treated with primary total laryngectomy cervical lymph node infiltration was present at diagnosis and radical or modified neck dissection was performed. The tumour recurrence rate in this group was 46% (18 of 39), while in metastatic node-free patients the relapse rate was 24% (47 of 199) [p < 0.05]. Primary laryngectomy was effective in 82% of glottic, 70% of supraglottic, and only 59% of transglottic carcinoma. Concerning primary tumour extension at the time of surgery, total laryngectomy proved effective in 85% of T2 tumours, 81% of T3, and only 55% for T4. The higher recurrence rates for supraglottic and transglottic tumours seem related mainly to the higher rates of cervical lymph node metastasis at diagnosis. The majority of tumour recurrences were observed during the first two years of post-operative follow-up. Thus, 76% of the 308 patients remained disease-free after the first year of post-operative follow-up, 68% after the second year, and 67% after the fifth follow-up year. Of the 96 recurrences documented until now, 91 were loco-regional (19 at the tracheostomy), and only 5 involved distant metastases. Sixteen of the 308 patients (5%) subjected to total laryngectomy have since developed second primary neoplasms, most often involving the lungs (10 patients).

Conclusions: Prognostic factors for recurrence following total laryngectomy include: performance of total laryngectomy as salvage surgery, degree of tumour extension, infiltration of cervical lymph nodes at the time of initial diagnosis, poor initial tumour differentiation and trans-glottic/sub-glottic tumour localization.

Introduction

Squamous cell carcinoma of the larynx is the most frequently occurring malignant neoplasm of the head and neck confronting the Ear, Nose and Throat specialty in Greece. According to international statistical data, laryngeal carcinoma constitutes 2-5% of all malignant neoplasms affecting mankind. While in North Europe and North America laryngeal tumours constitute 25%-40% of all head and neck tumours, in our country this incidence seems to attain rates of up to 68.4% according to accumulated data from ENT departments in Thessaloniki, Greece.

Despite constant amelioration of surgical therapeutic methods and techniques and the invaluable aid offered by radio- and chemotherapy, the necessity for a further increase in survival rates is desirable and commonly advocated, especially for more advanced-stage tumours. Recurrences of laryngeal carcinoma, usually local or loco-regional, as well as development of second primary neoplasms are the main factors that adversely influence the overall survival of patients.

Currently, therapeutic methods available for locally advanced laryngeal carcinomas are total laryngectomy, sub-total laryngectomies, radiotherapy, and combined radio- and chemotherapy. Obviously, in cases of residual disease or local recurrence after conservative treatment, total laryngectomy becomes the main solution. Advocates of the various therapeutic modalities previously listed have published comparable disease-control results, however...
random multi-centric studies comparing these varying treatment methods in an objective manner are rather uncommon.6,7 Before concluding as to the superiority of one treatment method above all others, other factors such as facility of execution, cost-effectiveness, duration of treatment and duration of hospitalization, quality of life and personal preferences of the patient need to be taken into account.

The position occupied by total laryngectomy in the therapeutic arsenal continues to remain strong, especially after the development and widespread use of phonetic prostheses that have provided a satisfactory solution to the vocal problems that arise after the operation. All of the above treatment methods are commonly used in our department. We chose however to focus our study and to report on a homogeneous patient group that was managed by total laryngectomy and subjected to long-term follow-up, and to determine the prognostic factors predictive of tumour recurrence.

Materials and methods

Between January 1, 1992 and December 31, 1999, 709 patients with laryngeal carcinoma were diagnosed and managed in the ENT Department of AHEPA University Hospital. In 308 of these patients total laryngectomy was deemed necessary for management of the disease or its recurrences.

As a general rule, total laryngectomy is performed in our department for the following indications: (1) as treatment of choice for the majority of tumour recurrences (salvage surgery), (2) for the majority of operable T3 and T4 laryngeal carcinomas as primary treatment, and (3) for earlier-stage neoplasms after evaluating local tumour extension, the patient’s general condition and his/her personal preferences.

The mean age of patients who underwent total laryngectomy was 61 ± 8.5 years, varying between 38 and 82 years. The vast majority of our patients (229 of 308) were in their 60s and 70s (Figure 1). Three hundred and one of the 308 patients were male, and only 7 (2.3%) were female.

In 238 patients total laryngectomy was employed as primary treatment of laryngeal carcinoma, while in the remaining 70 patients the technique was used for recurrence management following radiotherapy or conservation laryngectomy procedures. The individual characteristics of the 238 patients with laryngeal carcinoma primarily treated with total laryngectomy are presented in Table 1.

The 1988 AJCC guidelines were used for tumour classification. As the tumours in question were managed until the year 1999, a uniform classification system was maintained throughout. The relatively few patients with early α1b or α2 tumours who underwent total laryngectomy had either recurrences following previous treatment, or suffered from poor general health or severely decreased pulmonary function that precluded the choice of partial laryngectomy.

In 39 of the 238 patients (16.5%) the existence of clinical lymphatic cervical metastasis was established at the time of initial diagnosis, however a total of 59 out of 238 patients underwent therapeutic or preventive radical or modified neck dissection.

All information concerning the patients was recorded using software specially created for this purpose.

After completing initial therapy, these patients were enlisted in the oncology clinic outpatient follow-up program. The interval between visits during this follow-up was determined by the guidelines suggested by the American Cancer Society, according to which the subjects are to be reviewed once a month during the first year following diagnosis, once every two months during the second year, every three months during the third year, and every six months during the rest of their lives.

The mean follow-up time for our patients until today has been 68 months. For the purposes of this study, a retrospective review of all 308 patient files was performed, mainly concerning the effectiveness of total laryngectomy in the treatment of laryngeal carcinoma.

The Kaplan-Meyer method was used to statistically analyze the tumour recurrence data. The appearance of recurrence was considered as a terminal event for each patient. The time interval between total laryngectomy and tumour recurrence was established for each patient. For patients who did not present recurrence, the time interval between surgery and the last review, or in certain cases death by other (non-laryngeal carcinoma) independent causes, was determined.

Disease-specific survival rates at different points in time were calculated with the life-tables method. During statistical analysis, additional effort was made to analyze a series of factors possibly predisposing to the development of tumour recurrence.
Factors influencing tumour relapse after total laryngectomy

For each of the individual factors investigated, the survival curves and the recurrence rates were calculated; comparison of these rates was made by use of the Log rank test. The differences were considered statistically significant when \( p < 0.05 \).

**Results**

Until today, 96 of the 308 patients included in this study (31.2%) have developed loco-regional tumour recurrence. Nineteen of these loco-regional recurrences involved the tracheostomy orifice, while in 5 patients distant metastases were detected. The time at which these recurrences were detected or the tumour presented progression of the disease varied from 1 to 56 months, average appearance at 8.8 months. Typically, in 72 of these 96 patients (75%) tumour recurrence was recorded during the first year of post-operative follow-up. The disease-specific survival rate, as calculated with the life-tables method, for one year was 76.5%, for 3 years 67.7% and for 5 years 67.1%. The mean disease-free survival according to Kaplan-Meier was 73.9 months.

Of the 238 patients who were subjected to total laryngectomy as primary treatment of laryngeal carcinoma, 65 have presented tumour recurrence until today (27.3%). The incidence of recurrence for patients who underwent total laryngectomy after previous treatment failure was 44.3% (31 of 70 patients). This difference in incidence rates proved statistically significant (Log rank, \( p = 0.0015 \); see Figure 2). The 5-year disease-specific survival was 70.9% and 54.0% respectively. No statistical relationship was established between the type of primary treatment provided and the rate of recurrence development in those patients who underwent total laryngectomy as secondary management, following another primary procedure. Specifically, of the 70 patients in that group, 13 had undergone conservative surgery as primary treatment and 57 had been subjected primarily to radiotherapy. The recurrence rates for these two sub-groups were 46% (6 of 13) and 44% (26 of 57 patients) respectively (Log rank, \( p = 0.97 \)).

**Prognostic factors that influenced the effectiveness of total laryngectomy**

Based on the objectives previously described, analysis of our data was focused mainly on the determination of the possible influence of a series of parameters on the effectiveness of total laryngectomy when applied as primary management of laryngeal carcinoma. In other words, the existence of predisposing factors for recurrence development was investigated.

Summarily, Table 2 presents the frequency of recurrence according to the prognostic factor investigated.

Significant statistical influence to the development of recurrences was proven for the following factors.
Total laryngectomy was applied as primary treatment of laryngeal carcinoma to 2 patients with T1b tumours, to 34 patients with T2 tumours, to 119 patients with T3 tumours, and to 83 patients with T4 tumours.

The recurrence rate for cases with T1b tumours was 0% (none of the 2 patients), for T2 tumours 14.7% (5 of 34 patients), for T3 tumours 19.3% (23 of 119 patients), and finally for T4 tumours the recurrence rate was 44.6% (37 of 83 patients) (Figure 3).

The recurrence rate for cases with T1b tumours was statistically higher compared to both T2 tumour patients (Log Rank, p = 0.0029) and T3 tumour patients (Log Rank, p = 0.0001). The small number of patients with T1b tumours (only 2 patients) did not allow for any conclusive data analysis. No statistically significant difference was observed in recurrence rates between patients with T2 and T3 primary tumours.
Factors influencing tumour relapse after total laryngectomy

1. 

The 5-year disease-specific survival for T2, T3 and T4 tumours was 84.8%, 78.8% and 53.0% respectively.

2. 

Recurrence was detected in 17 of 94 patients (18.1%) with laryngeal carcinomas located at the glottic region and primarily treated with total laryngectomy. The recurrence rate was significantly higher in patients with supraglottic tumours, as 34 of these 114 patients (29.8%) relapsed.

Finally, patients with trans-glottic and sub-glottic tumours suffered recurrence rates of 46.6% (14 of 30 patients). Statistical analysis revealed that patients with glottic tumours enjoyed significantly more favorable prognosis in comparison with supraglottic (Log Rank, p = 0.046) and sub-glottic tumour sufferers (Log Rank, p = 0.0008), while supraglottic tumours had a worse prognosis when compared with glottic neoplasms, but better when compared with the trans-glottic/sub-glottic tumour group (Log Rank, p = 0.04), (Figure 4). The 5-year disease-specific survival for glottic, supraglottic and trans-subglottic tumours was 80.9%, 67.8% and 50.9% respectively. Statistical analysis revealed that the difference between high and low differentiation neoplasms was statistically significant (Log rank, p = 0.02), while the medium differentiation tumour group did not present statistically significant differences when compared with the other two groups (Figure 5).

3. 

During the post-operative follow-up period, recurrence was detected in 20 of the 96 patients (21%) with well-differentiated tumours, in 32 of the 109 patients (29%) with tumours of medium differentiation, and in 13 of the 33 patients (39%) with low differentiation tumours. The 5-year disease-specific survival for high, medium and low differentiation tumours was 78.3%, 68.5% and 55.6% respectively. Statistical analysis revealed that the difference between high and low differentiation neoplasms was statistically significant (Log rank, p = 0.002) (Figure 6).

4. 

In 30 of the 238 patients (16.5%), the presence of infiltrated cervical lymph nodes was established clinically and radiologically at the time of diagnosis, and radical or modified neck dissection was also performed. The detection of lymphatic metastasis proved a significant predisposing factor for recurrence, as during the post-operative follow-up period for these patients, 18 out of 39 (46%) have presented loco-regional recurrence. The corresponding incidence rate for patients testing negative for lymph nodes at the time of diagnosis was 23.5% (47 of 199). The 5-year disease-specific survival was 53.4% and 74.4% respectively. This difference proved statistically significant (Log rank, p = 0.002) (Figure 6).

5. 

Emergency pre-operative tracheotomies were required in 38 of the 238 patients due to significant
stenosis of the upper airway by exorbitant tumour masses. Fifteen of the 38 patients (39%) who underwent emergency tracheotomies developed tumour recurrence. Of the remaining 200 patients, 50 presented recurrence (25%). The 5-year disease-specific survival was 58.8% and 73.2% respectively. This difference proved statistically significant (Log rank, \( p = 0.03 \)), confirming the pejorative influence exerted by emergency pre-operative tracheotomies on the prognosis of these patients.

6. Presence of a post-operative fistula

Forty of the 308 patients (13%) who underwent total laryngectomy developed a post-operative pharyngo-cutaneous fistula. This incidence rate was of the same order of magnitude in patients who had total laryngectomy as primary treatment (30 of 238 patients or 12.6%) and in patients who underwent total laryngectomy for management of tumour recurrence (10 of 70 patients or 14.3%). Further statistical analysis revealed that presence of a post-operative fistula did not negatively influence patient prognosis as far as recurrences were concerned. The recurrence incidence rate in patients who presented post-operative fistulae was 32.5% (13 of 40), while for patients who did not present fistulae the recurrence rate was 31% (83 of 268). This difference in recurrence rates did not prove statistically significant (Log rank, \( p = 0.69 \)).

7. Insertion of a Provox phonetic prosthesis

The per-operative insertion of a Provox-type phonetic prosthesis was decided upon for 45 of the 308 patients (14.5%) treated with total laryngectomy, during the primary operative procedure. Thirteen of these 45 patients (29%) developed recurrences, while among the remaining 263 patients recurrences were recorded in 83 (31.5%). Thus, the per-operative insertion of a Provox phonetic prosthesis did not appear to directly influence the development of laryngeal tumour recurrence (Log rank, \( p = 0.57 \)).

8. Development of second primary neoplasms

During the post-operative follow-up period, 16 of the 308 patients (5.2%) included in this study developed second primary neoplasms. The criteria adopted to define these tumours as second primary neoplasms, were those established by Warren and Gates. Three of the 16 cases (19%) involved a synchronous second primary tumour, which is a tumour that develops within six months from the initial diagnosis of laryngeal carcinoma. The remaining 13 cases (81%) involved metachronous neoplasms. Their most frequent localization was the lung (10 of 16 cases, or 62%), the remainder involving the urinary bladder (2 patients), the digestive system (2 patients), the mammary gland (one patient), and the testicles (one patient). The mean development period for second primary neoplasms was

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**Figure 5**

Disease-free survival as according to tumour differentiation

**Figure 6**

Disease-free survival for N(+) and N(-) patients
36 months. In 10 of 16 cases with second primary tumours, the time of detection was more than 2 years after the surgical management of the primary laryngeal tumour. It is interesting to note that of the 96 total recurrences recorded thus far in the 308 patients of the study, only 3 were observed at a time period greater than 2 years following the initial total laryngectomy. This fact concurs with the observation that second primary neoplasms constitute the most important factor of reduction of expected long-term patient survival, that is after successful management of the primary tumour and maximum reduction of the risk of tumour relapse. In the material included in this study, second primary tumours were developed by 6% of patients (14 of 238) subjected to a total laryngectomy as primary management of laryngeal carcinoma, and in 3% of patients (2 of 70) who underwent the procedure as salvage surgery after unsuccessful employment of some other initial therapeutic modality. The decreased survival time of patients in the second group explains, as previously mentioned, the difference in incidence rates of second primary neoplasm occurrence between the two groups.

**Discussion**

Despite the fact that over 120 years have passed since the first total laryngectomy was performed as treatment of choice for laryngeal carcinoma, the quest for the optimal patient-adapted therapeutic management of the disease still continues, and constitutes in our time the most disputed object of clinical research in the field of head and neck oncology. This is due on one hand to the increased frequency of the disease relative to other neoplasms, attaining rates\(^1,2\) of 25%-68.4% of all malignant tumours of the head and neck area, and on the other hand to the common observation that sufficient margins of improvement of therapeutic options still exist.

The first remarkable conclusion drawn from analysis of this study’s patient data is the quasi-complete dominance of the male gender. Indeed, only 2.3% of the patients in this study were women, a significantly lower percentage compared to those published internationally. It is worth mentioning that the male-female ratio in international studies ranges between 5:1 and 20:1, with a marked trend for an increase in women’s rates over time. In the USA this ratio is now 5:1 compared to 12:1 twenty years ago, while in Europe male-female rates average 7:1 with women occupying a 15% share of the total patient numbers.\(^9\) Contrary to these figures, lower female prevalence continues to be observed in countries such as Japan, with a 12:1 male-female ratio,\(^10\) Turkey with a 8.7% female rate,\(^11\) Finland with 5% and no variation in this rate over the past 30 years,\(^12\) and Poland where the male-female ratio\(^13\) is 8.5:1.

Another important conclusion derived from the present study is that a large percentage of patients consult for treatment at a significantly advanced stage of the disease, although this tendency is slightly lower than in the past. Fifty percent of our patients were diagnosed when the tumour was already classified as T3 or T4, at which point total laryngectomy remained the sole possible option. We assigned prime significance to a parameter analyzed in our study group, that of frequency of tumour relapse after performance of total laryngectomy, in conjunction with the presence or absence of previous therapeutic intervention. Following analysis, we concluded that the recurrence rate was 27.3% in patients who underwent total laryngectomy as primary treatment option, while patients for whom total laryngectomy was the chosen therapeutic option following recurrence after radiotherapy or primary conservative surgery, presented a 44.3% relapse rate. This difference was statistically significant (\(p = 0.008\)). A correspondingly similar difference was observed in the survival between the two groups. The type of treatment primarily applied to the second group played no part in the recurrence rate. These findings lead to two possible conclusions. The first is that total laryngectomy is safer as a primary treatment option than either radiotherapy or conservative surgery. The second is that when tumour relapse occurs, even if successfully treated, the possibility of further recurrence is increased. The validity of either one of these two conclusions will only be established with certainty when randomized clinical trials designed for this specific purpose are carried out. Jorgensen et al.\(^14\), in a retrospective study of tumour recurrences on 1005 cases of laryngeal carcinoma primarily treated with radiotherapy, conclude that previous radiotherapy does not increase the recurrence rate and does not weigh against the overall prognosis, however their study did not include a control group composed of patients primarily treated with surgery.

Concerning the role played by local extension of the primary tumour in the prognosis after total
laryngectomy, we reached the conclusion that higher values of T (as per the tumour classification system) are associated with an increasingly poorer prognosis, both in tumour recurrence and in overall patient survival.

Also confirmed was the internationally accepted view that supraglottic and sub-glottic tumours are notoriously poor in their prognosis compared to glottic tumours,\textsuperscript{15,16} with recurrence rates of 29.8%, 46.6% and 18.1% respectively. The corresponding mean disease-free survival was 74.4 months for supraglottic, 51.8 months for sub- and trans-glottic, and 86.9 months for glottic tumours.

The histological differentiation of the tumour seemed to intervene in the prognosis, with a statistically significant difference detectable only between well-differentiated and poorly-differentiated tumours. The recurrence rates were 21% and 39%, and the mean disease-free survival periods were 83.8 months and 57.3 months respectively (p = 0.02), in accordance with previous literature reports.\textsuperscript{17,18}

The presence of metastatic cervical lymph node infiltration proved to be a significant pre-disposing factor for the development of tumour recurrence. The mean disease-free survival time for patients according to Kaplan-Meier testing was 53.5 months for N0 patients and 81 months for N+ patients. This difference proved statistically especially significant (Log Rank test, p: 0.002 < 0.05). The presence of infiltrated lymph nodes has proven to be a relevant independent factor influencing both prognosis and survival in other literature reports.\textsuperscript{19,20,21}

Based on the above findings we attempted to statistically assess the possibility of a relationship between tumour localization and possible presence of lymphatic metastasis, in conjunction with the development of recurrence in each of the individual patient subgroups.

Of the 94 cases of glottic neoplasms treated with total laryngectomy as primary therapy, cervical lymph node infiltration at the time of initial diagnosis was detected in only 6 (6.5%). Four of these six patients presently remain disease-free (67%). Of the 88 patients without cervical lymphatic metastasis at the time of initial diagnosis, 75 remain free of disease (83%). Although this difference was not proven as statistically significant, nevertheless it reflects the worse prognosis associated with lymphatic metastasis, as far as patient survival is concerned.

As expected, supraglottic neoplasms were associated with cervical lymphatic metastasis at the time of initial diagnosis at a rate attaining 23% (25 of 114 patients). Prognosis for the patients in that group was especially worse, seeing as until now 13 of the 25 have presented recurrence (52%), with a mean disease-free survival time of 47.5 months. Of the 89 patients free of cervical lymph node infiltration at the time of initial diagnosis, statistical analysis revealed certain interesting facts. Of the 27 cases of trans-glottic tumours studied, 8 (30%) presented lymphatic metastasis at the time of diagnosis. Three of these 8 patients presented recurrence during post-surgical follow-up (37.5%). The interesting fact however is that of the 19 patients without initial lymphatic infiltration, recurrence was detected in 8 (42%), with the majority of these recurrences involving local lymphatic glands. We should add at this point that the recurrence rate for glottic neoplasms without initial lymphatic infiltration was only 17% (15 of 88) and for supra-glottic neoplasms without lymphatic infiltration 23.5% (21 of 89). We would therefore formulate the view that for trans-glottic neoplasms, the increased rate of post-operative lymphatic recurrence should seriously be taken into account when planning their management, even when lymphatic infiltration is absent at the time of initial diagnosis. We believe that in these cases prophylactic neck dissection, as well as possible complementary therapy (radio- or chemotherapy), rightly deserves consideration.

Either as an emergency due to dyspnea or as an elective procedure for larger tumours during a biopsy-oriented direct laryngoscopy for assessment of tumour size and extent, the performance
of a tracheotomy worsens the prognosis leading to recurrence rates of 39% instead of 25% and a mean disease-free survival time of 53.6 months instead of 80 months in patients not tracheotomized before the definitive total laryngectomy procedure ($p = 0.03$). Lundgren et al.\textsuperscript{22} reached the same conclusion in 1988, and Lassaleta et al.\textsuperscript{21} in 2001. We conclude that in cases requiring performance of an emergency tracheotomy, total laryngectomy should immediately follow the tracheotomy, if possible in the same operative session, with a positive histological confirmation of the neoplasm as a pre-requisite to removal of the larynx.

As expected, the development of a post-operative fistula did not exert an influence on either tumour recurrence rate or patient survival. The same was true for phonetic valve insertion. Meriting mention however is that the rate of fistula development was higher in patients inserted with a phonetic prosthesis than in those not inserted with one. If future trials show this to be significant, it will likely be the result of the local inflammatory reaction due to the prosthesis acting as a foreign body.

Finally, the observations we formulated above concerning second primary neoplasms in addition to those published in a previous study we conducted,\textsuperscript{24} are not unique as several researchers have already presented their experience on the subject.\textsuperscript{14,25} The incidence rates vary to a large extent, all agree however that they are considerable, that they constitute a major factor in decreased patient survival, and that they should be methodically looked for in all stages of post-operative follow-up.

### Conclusion

In light of this study’s initial objectives, positive identification of the following factors influencing tumour recurrence after total laryngectomy was established, and includes performance of total laryngectomy as secondary treatment, following other primary treatment in the same patient, degree of local tumour extension, trans-glottic/sub-glottic tumour localization, poor initial tumour differentiation, infiltration of cervical lymph nodes at the time of initial diagnosis, and performance of an emergency pre-operative tracheotomy.

Additionally, factors such as the per-operative insertion of a phonetic valve and a major complication of the procedure, fistula development, were analyzed and found irrelevant to tumour recurrence, although possibly related pending further conclusive proof.

Second primary neoplasms were detected in 5.2% of the patients, and constitute an important factor in decreased patient survival.

### References


