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Oncological and functional outcome of conservative surgery for primary supraglottic cancer

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Abstract The aim of this study was to verify the oncological and functional outcome of conservative surgical treatment of primary supraglottic squamous cell carcinoma (SGSCC) and related neck disease in order to verify the effectiveness of supraglottic laryngectomy (SL) and the validity of an “observation” policy in the control of clinically negative (N0) necks. Of a total of 252 consecutive patients affected by primary SGSCC seen between 1975 and 1990 at the Department of Otolaryngology of the University of Perugia (1975–1987) and the Catholic University of the Sacred Heart of Rome (1988–1990), a subset of 132 patients treated with classical SL was evaluated after presenting sufficient clinicopathological data and a follow-up period of at least 5 years. Tumors were staged according to the 1992 UICC TNM classification and grouped into stages I-II ($n = 94$) and III-IV ($n = 38$). Comprehensive neck dissections were performed only in the clinically positive (N+) necks (25/132 cases), while in the clinically N0 ones (107/132 cases) an “observation” policy under strict follow-up conditions was adopted. After primary surgery, the 5-year relapse-free survival (RFS) was 74%. The RFS was 80% for T1-2 disease and 65% for T3. The RFS was 80% for stages I-II tumors and 71% for stages III-IV. The actual 5-year overall survival (OS) was 89% for T1-T2 tumors and 67% for T3 disease or 93% for stages I-II and 69% for stages III-IV. The OS was 89% for N0 neck and 73% for N+. The 5-year-metastasis-free survival (MFS) was 83% for N0 patients, 74% for N+, 84% for T1-T2 N0, 71% for T1-T2 N+, 81% for T3 N0 and 68% for T3 N+. In all, SL was found to be highly effective in the management of primary SGSCC. In the

presence of clinically N0 neck “observation” under strict follow-up with therapeutic comprehensive neck dissection for delayed nodal recurrence, SL was suitable for controlling the neck cancer, as well as for salvaging recurrent disease. Bilateral elective, selective or functional neck dissection in every instance of supraglottic cancer was best performed only in those SGSCC patients who were more likely to have occult nodal disease on the basis of biological factors and imaging data.

Key words Supraglottic carcinoma · Supraglottic laryngectomy · Lymph-node metastases · Neck treatment · Prognosis

Introduction

Cancer of the larynx accounts for 2% of the total cancer risk and represents the second-most-common head and neck cancer. The American Cancer Society estimated approximately 12,000 new cases of laryngeal cancer in the United States in 1995 [4]. Eighty-eight to 96% of the total laryngeal cancers consist of squamous cell carcinomas (SCC) [4, 15, 42], with the ratio of glottic to supraglottic SCC being approximately 2:1 [42].

Despite recent advances in all areas of diagnosis and treatment, the outcome of patients with supraglottic laryngeal SCC (SLSCC) has reached a plateau in the last 2 decades. Also, the slight but definite increase in advanced-staged disease indicates that efforts toward early detection have not been successful [42]. The primary goal of the treatment of SLSCC is clearly initial cancer control (i.e., local, regional and distant control, as well as the salvageability of recurrent disease and the prevention of second primary tumors) and overall and disease-free survival. However, according to current concepts of function or organ preservation, new parameters for the success of treatment such as quality of life, quality of preserved function and cost-effectiveness are now desirable secondary goals.

Prognosis is determined by age, performance status, tumor location and size, lymph-node involvement and

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stage of disease. More particularly, node-positive necks have a decisive influence on prognosis in patients with SGSSC where local recurrences are rarely observed [36, 44]. In fact, regrouping stage III and IV cases into localized disease versus regional metastasis appears to predict survival better [42].

The choice of initial treatment of the SGSCC depends on patient, tumor and physician factors [31, 39]. The standard options of treatment are conservative surgery, radiotherapy and/or chemotherapy [6, 31]. In addition to this, early lesions can be managed by endoscopic supraglottic laryngectomy (SL) using the CO₂ laser, with respectable control rates [27, 32, 55]. Most importantly, SL is a well-established voice-sparing operation for the treatment of supraglottic tumors that was first described and codified by Alonso [2] in 1947 and subsequently has been modified by Alonso [3], Bocca [5, 6], Leroux-Robert [20, 21], Ogura [33, 34] and Tapia [49]. For embryological, anatomical and oncological reasons, conservative SL produces survival rates that are virtually the same as for total laryngectomy, consistently ranging from approximately 68 to 90% [6, 8, 37]. It is now widely accepted that early-stage SGSCC can be adequately treated with single-modality therapy, using either conservative surgery or irradiation, while advanced tumors require surgery combined with radiotherapy and/or chemotherapy, as well as possibly salvage surgery [48].

Conservative surgery is indicated as initial therapy for T1 and T2 lesions in patients with N0 or N1 neck disease and is also recommended for primary tumors with extension to the base of the tongue or the hypopharynx [25, 26, 45], as well as in large, bulky, infiltrative lesions, and in cases with extensive pre-epiglottic space involvement [42].

In addition to treatment of the primary tumor, the management of cervical lymph nodes also represents an important component of the overall treatment strategy. While comprehensive neck dissection is widely reported as mandatory during initial treatment in cases with clinically positive neck nodes, no consensus exists on whether or not an elective neck dissection should be performed in SLSCC patients with clinically negative neck. Management of the N0 neck includes elective, selective or functional neck dissection or elective irradiation and observation with any statistical differences in terms of survival (overall and disease free), salvageability of recurrent disease and quality of life [40]. Elective bilateral jugular neck dissections have been advocated as both a therapeutic and staging modality and are currently the most common unsettled surgical option in SLSCC patients with clinically N0 neck [1, 7, 9, 13, 17, 24, 40, 52, 53]. However, elective bilateral jugular neck dissections in every instance of primary SGSCC could produce overtreatment with a concomitant unnecessary increase in costs, duration of treatment and treatment-related morbidity [18, 35]. On the other hand, the effectiveness of observation alone still remains unproved [47]. As the treatment of laryngeal SCC has undergone an evolution and significant progress has been made in initial cancer control as well as in the quality of life, increasing emphasis on improved function

and cosmesis is now also evident in the management of the neck [14]. The evolution of the neck dissection from Crile's radical operation through modified radical, functional and comprehensive neck dissections and selective neck dissections [7, 10, 38, 40] is representative of this trend.

This report is an update on the oncological and functional outcomes of cancer-directed primary conservative surgery as the initial single treatment of SGSCC patients in the Department of Otolaryngology of the University of Perugia (1975–1987) and at Catholic University of the Sacred Heart, Rome (1988–1990). Furthermore, the effectiveness of observation in the control of clinically N0 necks was also evaluated.

Patients and methods

In all, the results of treatment of 252 consecutive patients managed by primary supraglottic SCC were reviewed. All patients were seen from 1975 through 1990 at the Departments of Otorhinolaryngology of the University of Perugia (1975–1987) and the Catholic University of the Sacred Heart of Rome (1988–1990). Twenty-two of the patients underwent exclusive radiotherapy and 26 cases total laryngectomy because of advanced age, poor pulmonary reserve, and other related factors (occupation, preference, and ability to comply with the prescribed treatment program) were not suitable for conservative surgery. These cases were excluded from this study. Because of an inappropriate anatomic site code or an unknown or incomplete post-operative follow-up, 41 other cases were also omitted, leaving 163 cases for review. Thirty-one patients had tumors also involving the base of the tongue and the hypopharynx and underwent an extended SL. This group will be evaluated in a separate publication. The remaining 132 cases had classical SL as initial treatment, presented sufficient clinicopathological data and follow-up of at least 5 years and were suitable for the present statistical analysis.

Tumors were staged according to the 1992 UICC TNM classification [50] as follows: T1N0 (*n* = 28), T1N1 (*n* = 7), T1N2 (*n* = 2), T2N0 (*n* = 66), T2N1 (*n* = 7), T2N2 (*n* = 3), T3N0 (*n* = 12), T3N1 (*n* = 2) and T3N2 (*n* = 5). All cases were grouped as stage I–II (94 patients) and stage III–IV (38 patients). Tumors were also graded as well differentiated (G1, 30 patients), moderately differentiated (G2, 52 patients) and poorly differentiated (G3, 50 patients). Age, TNM classification, histopathological grading, early and late complications, 5-year relapse-free survival (RFS), 5-year metastasis-free survival (MFS) and 5-year overall survival (OS) were recorded and a statistical analysis performed.

All primary SGSCC patients received conservative curative surgery (supraglottic laryngectomy) of the primary tumor and comprehensive neck dissection only in clinically positive necks (stage N+; 25 cases), while in the clinically negative neck (stage N0; 107 cases) there was a wait-and-see or observation policy under strict follow-up conditions. Delayed comprehensive neck dissection was performed only when the originally clinically N0 neck nodes had become clinically positive (21 cases).

Postoperative radiotherapy to 50–70 Gy was used after primary conservative surgery in 14 out of the 25 SGSCC patients with clinically positive necks, cases with extracapsular spread (5 patients) and in cases with multiple or greater than N1 stage nodal disease (9 patients).

Statistical analysis was performed by means of a statistical package (rel. 4.5). All survival curves were examined by means of the log-rank test [23] grouping by T classification (T1–2 vs T3), lymph-node involvement (N0 vs N+), histopathological grading (G1–2 vs G3) and stage (I–II vs III–IV). Five-year RFS and MFS were calculated from the date of primary surgery to the date of local and regional clinical and pathological recurrence of disease, re-

spectively. Five-year actual OS was calculated from the date of first surgery to the date of death from disease (DOD).

RFS ($P = 0.005$ and $P = 0.03$, respectively), and shorter OS ($P = 0.05$ and $P = 0.0002$, respectively), while no significant relationships were found between MFS and the other prognostic factors evaluated. Age only significantly correlated with shorter OS ($P = 0.05$).

Results

Case-mix characteristics

Clinicopathological characteristics and univariate analysis of prognostic variable for survival in the 132 primary SGSCC patients are shown in Table 1. The majority of SGSCC patients presented with early-stage disease (94/132), clinically negative neck disease (106/132) and G1-G2 differentiated tumors (82/132). T classification and stage of disease showed a significant correlation with

Relapse-free survival

The 5-year RFS was 74%, with the residual larynx being the most frequent site of recurrence (Figs. 1, 2). The 5-year RFS according to T stage was 80% for T1-2 tumors and 65% for T3 disease, while the RFS according to stage was 80% for stages I-II and 71% for stages III-IV. Thirty-four patients underwent total laryngectomy for local tumor re-

Table 1 Univariate analysis of prognostic variables for survival in 132 primary laryngeal cancer patients

Prognostic variable	No.	Overall survival			Relapse-free survival			Metastasis-free survival		
		5-year survival (%)	RR ^a	P value	5-year survival (%)	RR	P value	5-year survival (%)	RR	P value
Age										
< 60	63	91	1		82	1		85	1	
> 60	69	81	2.2	0.05	70	1.4	0.08	77	1.4	0.2
T classification										
1-2	113	89	1		80	1		81	1	
3-4	19	67	3.2	0.005	55	2.4	0.005	83	0.9	0.5
Lymph-node involvement										
No	107	89	1		79	1		-	1	
Yes	25	73	2.3	0.03	65	1.5	0.1	-	0.4	n.a.
Histopathologic grading										
G1-G2	82	90	1		76	1		80	1	
G3	50	81	1.9	0.09	77	1.2	0.3	82	0.9	0.4
Stage										
I-II	94	83	1		80	1		81	1	
III-IV	38	69	4.5	0.0002	67	1.8	0.03	83	0.9	0.5

^aRR relative risk corresponds to the number of adverse events in one category expressed as a proportion of reference-category events

Fig. 1 Five-year RFS according to T classification in 132 laryngeal cancer patients

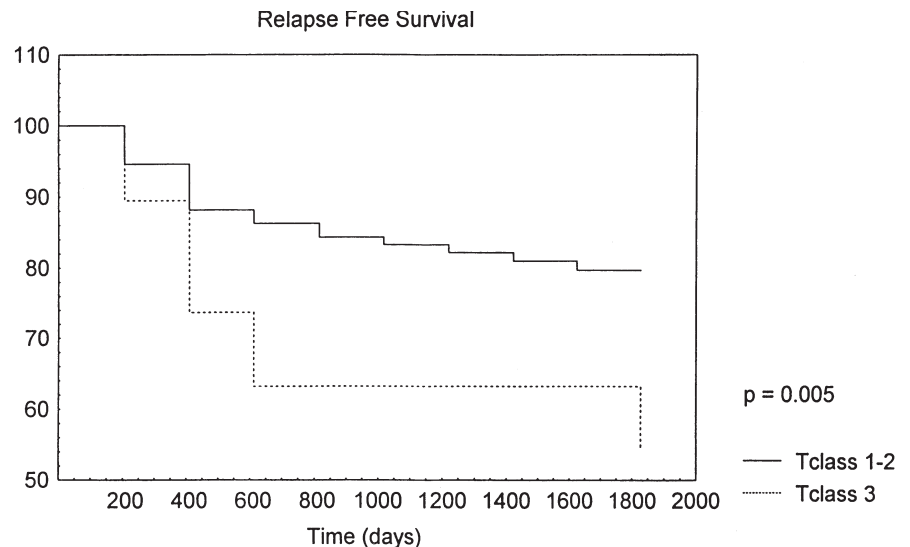


Fig.2 Five-year RFS according to stage in 132 laryngeal cancer patients

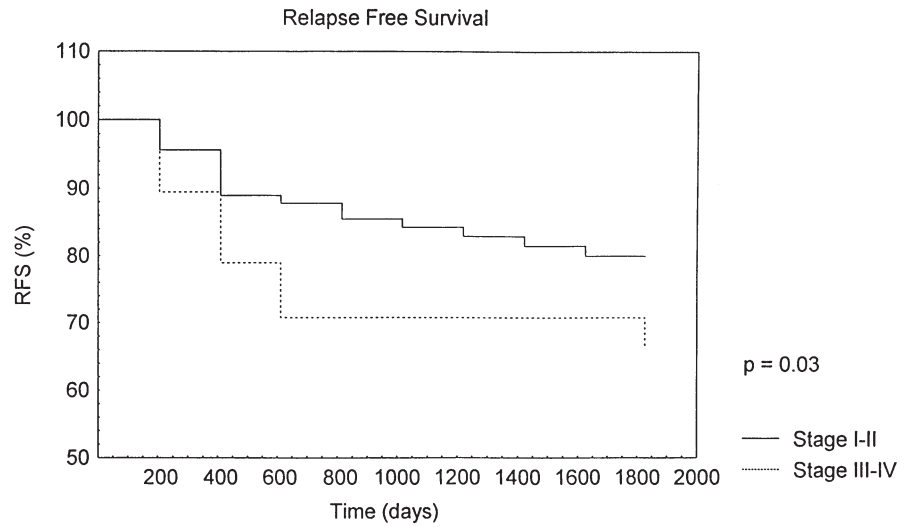


Fig.3 The actual 5-year OS for all 132 primary laryngeal cancer patients

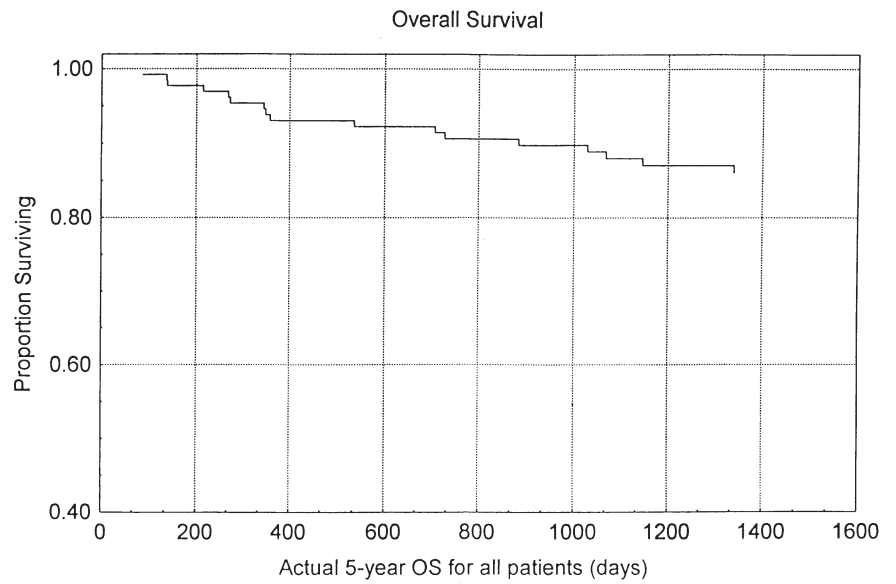


Fig.4 The actual 5-year OS according to T classification in 132 primary laryngeal cancer patients

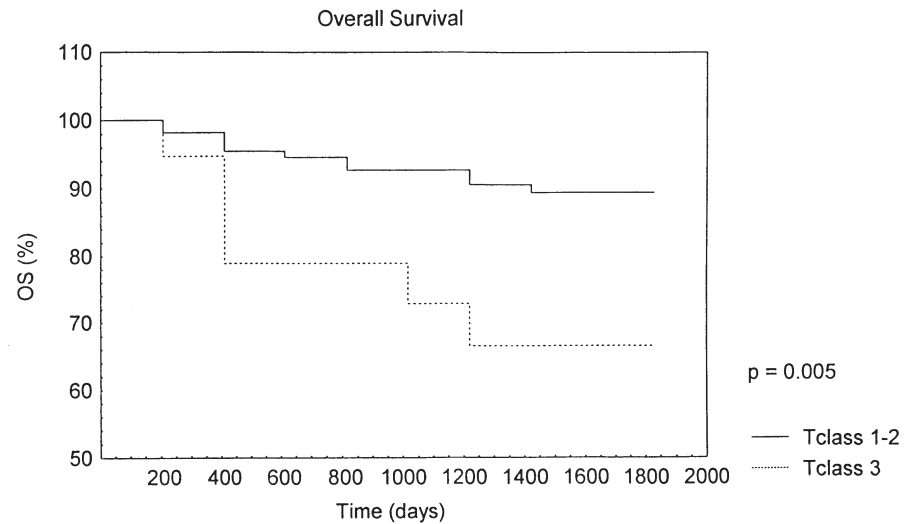


Fig.5 The actual 5-year OS according to stage in 132 primary laryngeal cancer patients

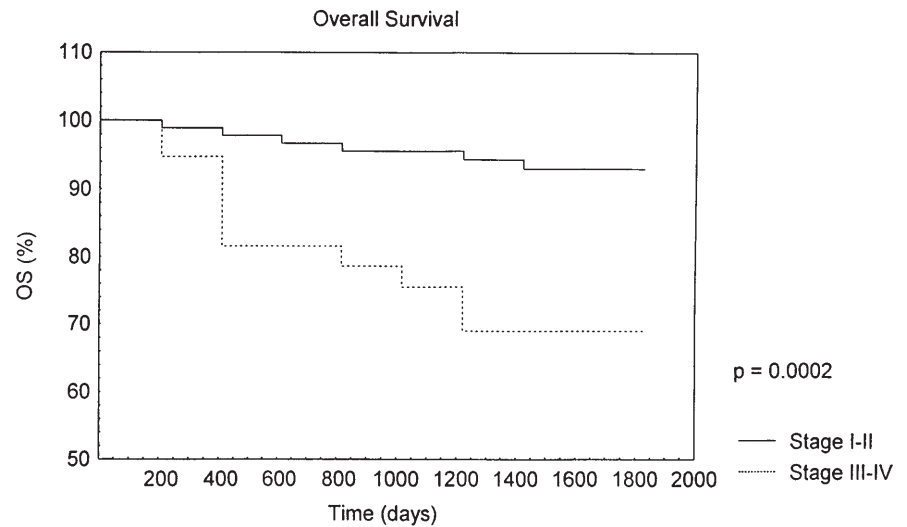
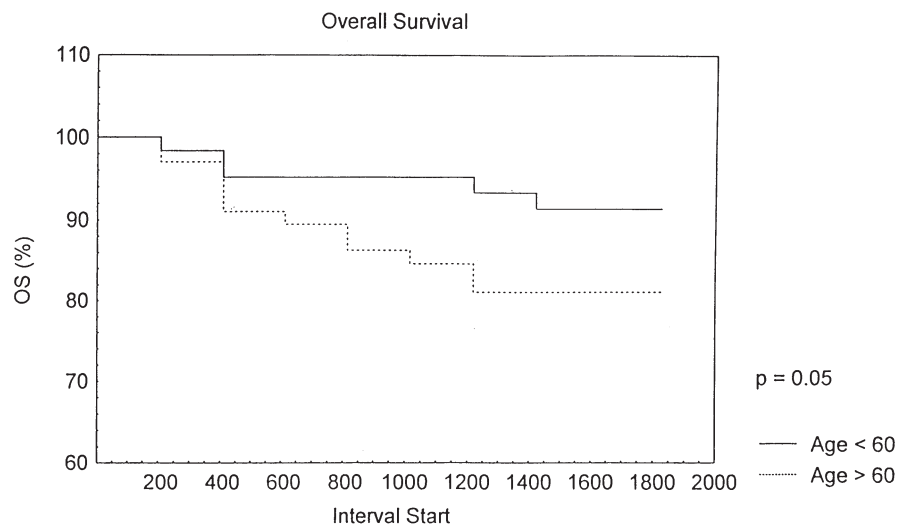


Fig.6 The actual 5-year OS according to age in 132 primary laryngeal cancer patients



lapses (3 T1, 16 T2 and 15 T3): 17 are still alive without evidence of locoregional disease, while the other 17 died as the result of extralaryngeal spread.

Survival

The 5-year actual OS was 86% (Fig.3). The OS according to T classification was 89% for T1-2 tumors and 67% for T3 ones (Fig.4). This was 93% for stages I-II and 69% for stages III-IV (Fig.5), while it was 89% for clinically negative neck (stage N0) and 73% for clinically positive one (stage N+). Actual 5-year OS according to age was 91% for patients under 60 years and 81% for older patients (Table 1, Fig.6).

Neck recurrence

The global 5-year MFS was 78% (Fig.7). The MFS according to N stage was 80% (86/107) for N0 (Fig.8) and 74% (23/25) for N+, while MFS according to T and N

stage was 84% for T1-T2 N0 and 71% for T1-T2 N+, and 81% for T3 N0 and 68% for T3 N+. The 5-year MFS was 85% for patients under 60 years and 77% for older patients. Of the 107 untreated patients with clinically N0 necks, 21 patients developed neck-node metastases in a period ranging from 3 to 52 months following initial primary surgery. Fourteen of them presented with delayed N1 metastatic neck disease and underwent therapeutic comprehensive neck dissections (salvage surgery) with adjuvant radiotherapy in only 2 cases (pN1 with extranodal spread): all are still alive without disease. Seven patients presented delayed metastatic neck disease greater than N1 and also underwent postsurgical adjuvant irradiation (five cases) and adjuvant radiochemotherapy (2 cases): all died of disease.

Functional outcome

All patients had difficulty in swallowing. However, a feeding tube was removed between 10 and 30 days after surgery in all patients except in two who regained by-pass

Fig.7 The global 5-year MFS in 132 primary laryngeal cancer patients

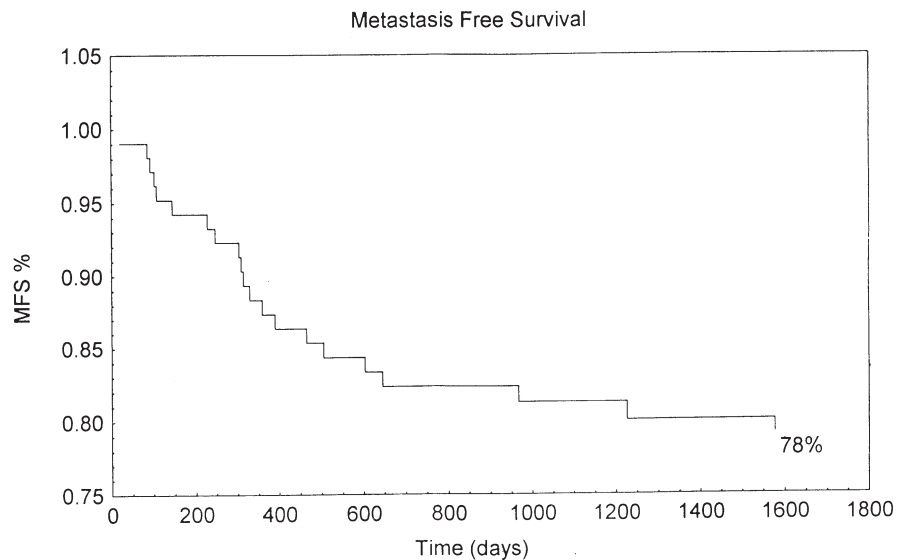
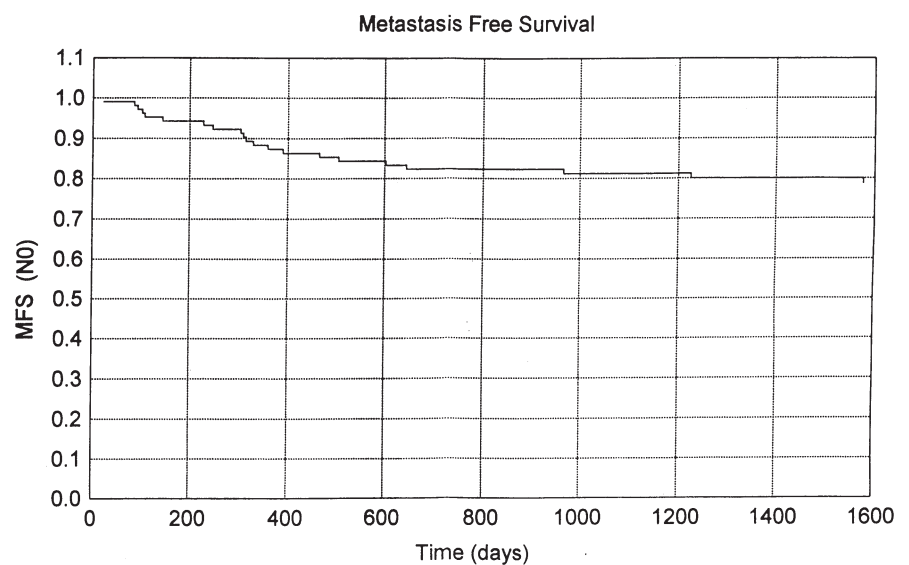


Fig.8 The MFS according to N0 stage in 132 primary laryngeal cancer patients



feeding for about 60 days after primary surgery. Immediate postoperative complications were local infection (ten patients) and pharyngocutaneous fistulas (eight patients). Minor postoperative hemorrhages occurred in five. Decannulation was possible in 120/132 of the patients over a period ranging from 2 to 6 months. Twelve patients (9%) were not decannulated, four because of laryngeal stenosis and five because of mucosal flaps. In these latter cases endoscopic CO₂ laser surgery was performed. Two patients preferred to retain their tracheostomy tubes. One patient underwent total laryngectomy because of persistent aspiration.

Discussion

In our series the 5-year actual OS of 86% was comparable to that reported in other surgical series, ranging from approximately 68 to 90% and depending mainly on the duration of follow-up [6, 8, 29, 37]. Conservative SL as ini-

tial surgery was highly curative in the management of our SGSCC patients and did as well as total laryngectomy if the indication for surgery was properly established. Also, our 5-year RFS rate of 74% is comparable to data on local recurrence rates reported in the literature, ranging from approximately 1 to 30% [22, 34, 37, 46]. On univariate analysis, T classification and clinical stage of the disease were significant independent prognostic factors for both OS and RFS. The prognostic value of the clinical neck status was not related to OS and RFS, probably because N+ necks were fewer than N0 ones.

The global 5-year MFS was 78% and had no significant correlation with all prognostic variables considered. More particularly, the SGSCC patients with clinically N0 neck supraglottic laryngectomies and observation with therapeutic neck dissection (surgical salvage) performed if neck node metastastasis became clinically apparent was considered to be an effective available option for initial locoregional cancer control as well as for salvageability of recurrent neck disease and quality of life. However, simi-

lar to the findings by Shah [41], we observed a considerable number of patients with delayed clinically metastatic neck disease greater than N1, in whom surgical salvage failed both for survival as well as for salvageability of recurrent disease.

Although elective ipsilateral or bilateral jugular neck dissection has been advocated as both a therapeutic and staging modality, it is currently the most common unsettled surgical option in SGSCC patients where occult neck metastatic disease has been proven in about 16 to 37% of patients with no palpable nodes [6, 7, 22, 46]. The management of the clinically N0 neck is still controversial.

In fact, it is not possible to document a statistically significant difference in regional control rate and survival between patients who underwent elective neck dissection and showing occult micrometastasis and those who underwent therapeutic neck dissection for the delayed appearance of N1 disease [16, 42]. Furthermore, selective or more functional neck dissection in every instance of primary SGSCC in N0 necks was felt to represent overtreatment and created unnecessary treatment-related morbidity for patients who do not have occult lymph-node metastasis (true-negative cases) [18, 19, 35]. Additionally, selective or functional neck dissection was felt to remove or destroy a barrier to cancer spread that might be particularly important if recurrence at the primary site should occur later [43].

The effectiveness of observation with surgical salvage for delayed nodal recurrence remains unproved [47]. Despite several reports about the incidence of occult cervical lymph nodes metastases in primary SGSCC, the risk in any individual patient cannot be determined absolutely. More information is needed to select those patients with clinically negative necks who are most likely to benefit from elective selective neck dissection, thus to avoid overtreatment.

Patterns of care are influenced by advances in technology that modify diagnostic capabilities and therapeutic interventions. Although the translation of these advances from research studies to clinical practice generally occurs slowly, the improvement in imaging diagnostic tools, such as magnetic resonance studies [51], positron emission tomography [56], radioimmunosciintigraphy [11, 12] and a better understanding of molecular biology of the primary tumor for detecting or predicting the presence of propensity of neck node metastasis [28, 30] might contribute to lessen the indications for elective neck dissection in the future.

Although wider multi-institutional and multidisciplinary studies are needed before more specific conclusions can be drawn, our results suggest the possibility of limiting elective (selective or functional) neck dissections to more selected SGSCC patients who are most likely to have occult nodal disease or high regional metastatic propensity on the basis of imaging data and biological markers.

Concerning functional outcome, although aspiration was the most frequent postoperative complication, most of our patients were able to eat satisfactorily within 2 or

3 postoperative weeks [54]. Aspiration is probably the result of the combined effects of more than one single factor. The effects on swallowing of superior laryngeal nerve preservation, cricopharyngeal myotomy and hyoid bone sparing are yet to be proven. This kind of complication should be contemplated when selecting patients for supraglottic laryngectomy, and age and pulmonary conditions must be carefully evaluated. Another complication, which can delay decannulation, was related to airway obstruction due to arytenoid edema, mucosal flaps and/or laryngeal stenosis [6, 26]. In these cases steroids and CO₂ laser microsurgery were sometimes required.

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