

Primary Surgical Treatment of T3 Glottic Carcinoma: Long-Term Results and Decision-Making Aspects

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Objectives/Hypothesis: The aim of this study was to assess the efficacy of primary surgical treatment in the management of T3 glottic carcinomas.

Study Design: Retrospective clinical study.

Methods: A retrospective evaluation of the records for all patients treated with primary surgery for T3 glottic carcinomas at a tertiary referral center between 1980 and 2005 was carried out. Data for the 5-year disease-specific survival (DSS) were assessed, as well as local control rates in relation to vocal cord immobility, N classification, choice of surgical modality, and adjuvant therapy. Patients who underwent partial laryngectomy were also evaluated in relation to organ preservation and the rate of permanent tracheotomies.

Results: The 5-year DSS in the 120 patients was 78.3%. Positive neck disease was shown to be a significant negative prognostic factor. Organ preservation was achieved in 90.1% of the patients who underwent partial laryngectomy and in 50% of the overall patient group. The occult metastasis rate was 14%.

Conclusions: Primary surgical treatment is an effective modality against T3 glottic carcinomas. Partial laryngectomy is a reliable method in carefully selected cases. Low complication rates can be expected.

Key Words: T3, glottic carcinoma, survival, laser, partial laryngectomy.

Level of Evidence: 2b

INTRODUCTION

One of the most controversial issues in the treatment of laryngeal cancers is what the best therapeutic approach is for T3 glottic carcinomas.^{1,2} Treatment options include total or partial laryngectomy (alone or in combination with adjuvant chemoradiotherapy), induction chemotherapy (followed by operation by nonresponders or concomitant chemoradiotherapy by responders), or primary chemoradiotherapy. The choice of treatment depends on several patient-related and tumor-related factors, but certainly also to a great extent on the individual surgeon's level of experience and experience in each institution.³

The purpose of the present study was to evaluate experience in the primary surgical management of T3 glottic squamous cell carcinomas at a single oncology

referral center for head and neck cancers. The study also addressed the issue of organ preservation with partial laryngectomy. An additional aim was to obtain information about the regional metastatic behavior of T3 glottic carcinomas, as this is relevant to decision-making regarding neck management.

MATERIALS AND METHODS

This retrospective study was conducted at an academic tertiary referral center (Department of Otorhinolaryngology–Head and Neck Surgery, University of Erlangen–Nuremberg, Erlangen, Germany). The records for all patients treated with primary surgery for T3 glottic carcinomas between 1980 and 2005 were evaluated. Patients with insufficient data, second primary tumors, or distant metastases at the time of diagnosis, and with histological findings other than squamous cell carcinoma, as well as patients who received primary (chemo) radiotherapy or induction chemotherapy, were excluded from the study.

Staging was conducted in accordance with the 2010 American Joint Committee on Cancer and International Union Against Cancer classification.⁴ All patients were evaluated preoperatively with a physical examination, ultrasonography of the neck, and contrast-enhanced computed tomography or magnetic resonance imaging.

The data for all the patients included were evaluated in relation to the 5-year overall survival (OS), 5-year disease-specific survival (DSS), and local control (LC) estimates in relation to vocal cord immobility, N classification, surgical modality (total laryngectomy vs. partial laryngectomy), and adjuvant

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TABLE I.
Five-Year Overall Survival, 5-Year Disease-Specific Survival, and Local Control Rates for the Study Variables Investigated.

Parameter (No. of Patients)	OS (%)	DSS (%)	LC (%)
Vocal cord immobility (96) vs. mobile vocal cord (24)	53.8 vs. 42.7 ($P > 0.05$)	71.5 vs. 82.6 ($P > 0.05$)	Not interpretable
cN0 + pN0 (95) vs. pN+ (25)	59.8 vs. 35.2 ($P = 0.003$)	84.7 vs. 55.8 ($P = 0.005$)	—
Total laryngectomy (54) vs. partial laryngectomy (66)	55.5 vs. 49.3 ($P > 0.05$)	81.0 vs. 74.9 ($P > 0.05$)	91.2 vs. 86.9 ($P > 0.05$)
Surgery (79) vs. surgery + (C)RT (41)	62.1 vs. 48.7 ($P = 0.043$)	80.9 vs. 72.9 ($P > 0.05$)	87.2 vs. 93.2 ($P > 0.05$)

OS = overall survival; DSS = disease-free survival; LC = local control; (C)RT = (chemo)radiotherapy;

therapy. The regional metastatic behavior of T3 glottic carcinomas was also investigated. The patients were also evaluated for the incidence of major complications and the incidence of related (temporary or permanent) tracheotomies. Major complications were defined as those that required prolonged hospitalization, blood transfusion, additional surgery, or admission to the intensive care unit. Adjuvant treatment was decided on by an interdisciplinary tumor board and consisted of postoperative radiotherapy to the primary tumor site and both sides of the neck, either alone or in combination with chemotherapy. Adjuvant therapy was indicated when there were positive surgical margins and further surgery was not feasible, and in patients with advanced neck disease, extracapsular tumor spread, and histological evidence of infiltration of lymph vessels or nerves.

OS was estimated using the time from diagnosis to death. The 5-year DSS estimate was defined using the time from the date of diagnosis to death from the cancer or complications of treatment. Local recurrences were calculated from the date of the initial diagnosis to the date of the most recent clinical review at which local recurrence was confirmed. Local recurrence was defined as invasive carcinoma developing at the anatomic site of the primary tumor after completion of initial treatment.

Statistical analysis was performed using the log-rank test and the Kaplan-Meier method, with 95% confidence intervals. The software program SPSS version 19 for Windows (SPSS, Inc., Chicago, IL), was used for the analysis. A P value of $<.05$ was considered statistically significant.

RESULTS

Between 1980 and 2005, 142 patients with T3 glottic carcinomas were treated in our department (16 with primary radiotherapy, six with primary chemoradiotherapy, 120 with primary surgical therapy). Thus, 120 of the 142 patients (84.5%) were treated with primary surgery and were included in the study (114 males and six females; male:female ratio, 19:1). Their mean age was 61.5 years (range, 30–85 years; standard deviation, 10.94). The mean follow-up period was 72.3 months. Transoral laser resection of the tumor was performed in 23 cases (19.2%) and transcervical partial laryngectomy (frontolateral partial laryngectomy or hemilaryngectomy) in 43 cases (35.8%). Total laryngectomy was performed in 54 cases (45%). R0 resection was achieved in 116 of the 120 cases at the end of the surgical treatment (96.7%). The 5-year OS was 54% and the 5-year DSS was 78.3%, whereas the LC rate was 88.7% in this series. Table I provides details of the survival data in relation to the various parameters used in the analysis.

Of the 120 patients in the study sample, 90 underwent neck dissection (90/120, 75%). Sixty-five had pN0

status, five were pN1, 13 pN2, and seven pN3. Neck dissection was performed in 50 of the 76 patients who had a cN0 status preoperatively, and seven of these patients were staged as pN+ (one pN1, four pN2b, and two pN2c). The occult metastasis rate was therefore 14%.

Bilateral neck dissection was carried out in 39 patients, and metastases were found on the contralateral side (stage pN2c) in four (10.2%): two were cN0, one was cN2b, and one was cN2c. Clinically negative but pathologically positive contralateral lymph nodes were detected in three of these 39 patients (7.7%). Among the 12 patients with an ipsilateral clinically positive neck who underwent bilateral neck dissection, contralateral occult lymph node metastases were found in only one case (8.3%). Surgical staging altered the clinical staging in 23 of the 90 patients who underwent neck dissection (25.6%) (Table II).

In the partial laryngectomy group, seven patients had local recurrences (six after transcervical and one after transoral laser surgery). Six of these seven patients had to be treated with total laryngectomy, resulting in a larynx preservation rate of 90.9% in the partial laryngectomy group. Transcervical partial laryngectomy was possible in the seventh patient. In the total of 120 T3 glottic carcinomas, the larynx was preserved in 60 cases (50%). Of the 66 patients with partial laryngectomy, 17 patients (25.7%) required tracheostomies permanently due to persistent swallowing dysfunctions (e.g., dysphagia, aspiration) or laryngeal stenosis. In total, 19 patients had to keep their gastrostomies (two after total laryngectomies, 17 after partial laryngectomies; $P = .001$). Major complications were observed in this series in 18 of the 120 patients (15%; Table III). None of the complications was fatal.

Of the 23 patients who received transoral laser surgery, only one had a local recurrence and had to be treated with total laryngectomy (larynx preservation rate 95.6%). Moreover, only three of these 23 patients

TABLE II.
Clinical and Surgical Staging in the Study Patients.

Clinical Stage	Surgical Stage		
	III	IVA	IVB
III	60	9	3
IVA	8	6	3
IVB	0	0	1

TABLE III.
Specific Types and Incidence of Surgical Complications.

Complication	No. of Patients (%)
Bleeding	6 (5.0)
Fistula	4 (3.3)
Wound healing disorders	2 (1.7)
Nerve lesions	1 (0.8)
Other complications	5 (4.2)

required permanent tracheostomies due to swallowing dysfunctions (13%).

DISCUSSION

T3 glottic tumors are a heterogeneous group of lesions that range from cases with vocal cord immobility but without deep infiltration into the paraglottic space to lesions with considerable invasion of the paraglottic structures and even minor thyroid cartilage erosion (e.g., on the inner cortex) with normal vocal cord mobility.⁵ Vocal cord fixation has been attributed to invasion of the cricoarytenoid joint, infiltration of the vocal or thyroarytenoid muscle, or fixation of the vocal cord to the inner perichondrium of the thyroid cartilage.^{3,6} The relative rarity of this stage of glottic cancer may be attributable to the fact that the disease is more often discovered at an earlier stage, when the patients present with hoarseness.

In the treatment of these tumors, surgical modalities (such as transoral laser resection, transcervical partial laryngectomy, and total laryngectomy) are nowadays in competition with nonsurgical forms of treatment (such as induction chemotherapy protocols or simultaneous chemoradiotherapy).⁷⁻⁹ In view of the negative impact of laryngectomy on a patient's quality of life, nonsurgical forms of treatment are being increasingly widely used. Concurrent platinum-based chemoradiotherapy is considered to be the standard nonsurgical treatment option.¹⁰ The use of induction chemotherapy is currently being investigated as means of selecting patients in whom nonsurgical treatment is effective.¹¹ Unfortunately, there is a lack of prospective studies directly comparing organ-preserving surgery with nonsurgical modalities in locally advanced glottis cancer.¹² Because retrospective studies with primary (chemo) radiotherapy protocols do not appear to offer better oncologic results,¹³⁻¹⁵ function-preserving surgery continues to have a role in primary management in this patient group. The high rates of DSS and LC, with a low rate of major complications, confirm that primary laryngeal surgery can effectively and safely provide a cure for T3 glottic cancer.

Interestingly, adjuvant chemoradiotherapy was combined with a significant decrease in OS. This may have been due to the fact that the 41 patients who received combined therapy usually had poorer prognostic factors. The fact that homogeneous criteria were not used throughout the study period (with different TNM classification systems, different diagnostic facilities, and

different adjuvant therapy protocols, indications, and techniques) means that evaluating the present findings is complicated. This could be regarded as a limitation of the study, which included patients who were treated for T3 glottic carcinomas over a period of 25 years.

The choice of the surgical modality in patients with T3 glottic carcinoma is still a matter of controversy. In view of the role of the larynx in speech and swallowing, preserving the organ and maintaining good phonation and swallowing function are important aspects in the treatment of the disease. When considering organ preservation, it is essential to realize that maintaining the local anatomy may not translate into a good functional outcome.^{16,17} As vocal cord fixation is interpreted as a sign of deep tumor invasion, total laryngectomy has traditionally been considered the optimal treatment for this group of patients.^{1,5,18} The dilemma in managing these patients has traditionally been whether long-term survival will be compromised if anything less than total laryngectomy is performed.⁵ On the other hand, there have been several literature reports advocating transcervical vertical partial laryngectomy⁵ and transoral laser partial laryngectomy¹⁹ for carefully selected T3 cases. Interestingly, Vilaseca et al. found that transoral laser surgery was associated with very good oncologic outcomes in this specific group of patients (OS, 73.1%; DSS, 86.3%).²⁰

The present analysis showed that partial surgical methods were not associated with compromises in relation to the study parameters (Table I). Preservation of the larynx was possible in more than 90% of the patients with partial laryngectomy, without local recurrences developing. In addition, decannulation was possible in almost 75% of these patients. In carefully selected patients, transoral laser surgery proved to be a method with sound oncologic outcomes and quite acceptable functional outcomes (larynx preservation in over 85%, decannulation in 87%). However, patients who received partial laryngectomies remained dependent on gastrostomy tubes significantly more often postoperatively.

It can therefore be concluded that organ-preserving surgical methods can be chosen as the primary treatment method in a very carefully selected group of patients with T3 glottic carcinomas. When there is adequate surgical experience and the tumors can be exposed and have a small volume (endoscopically and radiographically), with no infiltration of the thyroid or cricoid cartilage, the interarytenoid region, or invasion into the cervical soft tissue, an attempt at transoral laser resection is acceptable and is associated with very good oncologic results, regardless of the number of procedures required to obtain negative surgical margins,²¹ and quite acceptable functional prospects. When there is poor endoscopic exposability, transcervical partial laryngectomy (vertical partial laryngectomy or hemilaryngectomy) with protective tracheotomy can be performed. Total laryngectomy continues to have a place in the treatment of T3 glottic carcinomas as a method that can be used when there is an inadequate response to induction chemotherapy, as salvage surgery after primary chemoradiotherapy or partial laryngectomy, or as

a primary surgical option for patients with multiple morbidity and large tumors that cannot be treated with partial surgical methods. Primary chemoradiotherapy should be retained as an organ-preserving method of treatment for patients in whom the only surgical option would otherwise be total laryngectomy. Invasion of the cervical soft tissue and infiltrative (as opposed to exophytic) tumor growth (both reflecting a large tumor volume), as well as infiltration into the thyroid cartilage (which appears as sclerosis on pretreatment computed tomography), are considered to be unfavorable predictive factors for the local response to radiotherapy.²² The ideal patient for this form of treatment might be one who has a lesion involving one cord, adequate airways, and who is willing to have close follow-up after the completion of treatment.²³

To analyze the role of the different surgical modalities over time in our department, we divided the period 1980 to 2005 into two time frames (1980–1992 and 1993–2005). The analysis showed that 11 of 23 transoral laser resections were performed up to 1992 and the other 12 in the period 1993 to 2005. This shows that transoral laser surgery held its place over time, but that the indication for the procedure was kept quite strict as a matter of principle. The lack of any increase in the number of patients treated with laser modalities might be attributable to the following factors: laser surgery was introduced in our department in the late 1970s. The learning curve for laser surgery and the limitations of the method, as well as our personal clinical experience over time, showed that the indication for this modality in such locally advanced tumors with infiltration of deep endolaryngeal structures should be considered extremely carefully. Moreover, many patients, especially in the more recent period, with smaller-volume tumors and without cartilage infiltration (which may be favorable factors for management with laser surgery) took part in organ-preserving protocols and were therefore not included in the study sample. In addition, 43 of 54 total laryngectomies were performed up to 1992 (79.6%). Subsequently, the data show a chronological trend rather away from ablative total laryngectomy, with transoral laser resection preserving its role over the years, and transcervical partial laryngectomy gaining an increasing role in T3 glottic carcinomas.

Correct decision-making requires a thorough analysis of each individual case on the basis of data obtained from the physical examination, ultrasound, and magnetic resonance imaging or computed tomography, direct microlaryngoscopy, and in many cases intraoperative tumor (re)evaluation after laryngofissure. Tumor-related factors (e.g., tumor volume, site, pattern of invasion, exosability) and patient-related factors (e.g., age, comorbidities) should be thoroughly assessed preoperatively.²⁴ The level of experience of the person performing the endoscopic examination, in relation to the possibility of organ-preserving tumor resection, is of major importance in this field. Precise radiographic evaluation of the pattern of tumor spread, with examination of the paraglottic space, the inner cortex of the thyroid cartilage, and the cricoarytenoid joint appears to be crucial. In

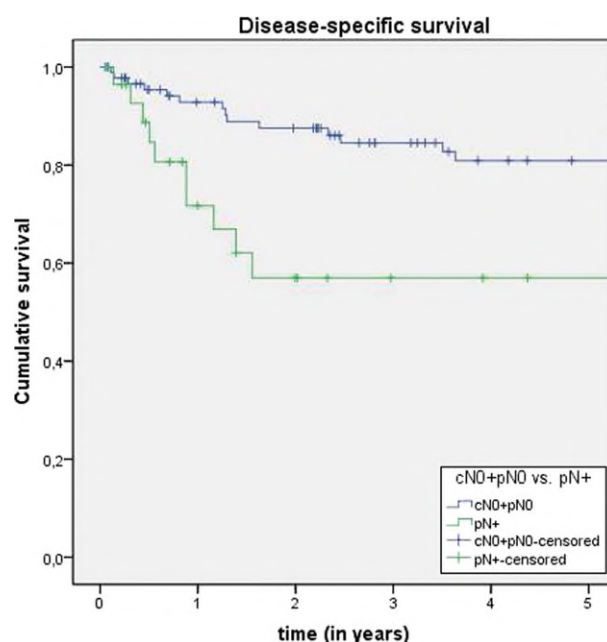


Fig. 1. Kaplan-Meier analysis of the disease-specific survival according to N status. Cum = cumulative. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

addition, direct inspection of the tumor during microlaryngoscopy plays a major role in the choice of surgical treatment. Important areas to consider are the contralateral true vocal cord, the cricoid and thyroid cartilage, and the ipsilateral arytenoid cartilage.

Nodal metastases are regarded as being one of the most influential prognostic factors in patients with head and neck carcinoma.^{25–28} This was confirmed in the present analysis. Positive neck disease (which was detected in 20.8% of the patients) affected OS and DSS (Fig. 1) to a significant extent. Remarkably, only one-fifth of the patients were found to have lymph node metastases, despite the advanced local stage of the disease. This is consistent with the common observation that the glottis is a favorable tumor location in relation to metastatic behavior, as the disease is far less aggressive in comparison with other locations,^{27,29} even in advanced T stages.

According to the relevant literature, the rate of occult metastasis in T3 glottic carcinomas can vary from 5.8%³⁰ to as much as 21.4%.²⁵ Consistent with this, a relatively low but not inconsiderable occult metastasis rate of 14% was observed in the present analysis. This may be below the 20% law described by Weiss et al.,³¹ but still remains marginal as far as the decision on elective neck management in cN0 cases is concerned.³² A 10.2% rate of contralateral metastasis was also observed. The rate of occult contralateral metastasis was 8.3%. Among the 90 patients who underwent neck dissection, 15 were upstaged and eight were downstaged. Data deriving from surgical management of the neck altered the staging and thus the prognosis in more than a quarter of the patients (25.5%).

Elective treatment of the ipsilateral neck in patients with stage cN0 may be considered, but this

would require optimized patient counseling to ensure that the patients receive sufficient information on the prognosis of the disease and the need for adjuvant therapy. From this point of view, the morbidity in the individual patient has to be weighed against the need for staging optimization. Management of the contralateral neck in patients with T3 glottic carcinomas may possibly be reserved for those with clinical N2c status. Patient compliance should always be taken into consideration, and regular follow-up is essential.

In agreement with the findings reported by Vilaseca et al.,²⁰ the presence of vocal cord fixation was not found to influence survival outcomes in the present study. By definition, a T3 glottic carcinoma infiltrates the deep endolaryngeal structures (due to vocal cord fixation, invasion of the paraglottic structures, or even minor thyroid cartilage erosion), and this feature was therefore present in all of the patients. This may possibly explain the fact that the presence of vocal cord immobility alone did not negatively affect survival rates in the present study.

CONCLUSION

One of the most controversial issues in the treatment of laryngeal cancers is what the best therapeutic approach is in patients with T3 glottic carcinoma. In many centers, total laryngectomy is still considered to be the surgical treatment of choice. The present analysis shows that partial laryngectomy can be performed with acceptable oncologic and functional outcomes in a carefully selected group of patients. Total laryngectomy may be reserved for patients with multiple morbidity (those who are unable to undergo chemotherapy) and those with large tumor volumes, or can be used as a salvage treatment after neoadjuvant chemotherapy or primary chemoradiotherapy. Correct patient selection requires a thorough analysis of each individual case on the basis of data obtained from the physical and additional diagnostic examinations. This study also shows the value of neck management as a staging procedure in patients with T3 lesions, and the importance of improved patient counseling with regard to the prognosis, particularly because positive nodal disease was found to influence survival rates to a significant extent.

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