T1 and T2 Hypopharyngeal Cancer Treatment With Laser Microsurgery

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Background and Objective: To assess the oncologic results and functional outcomes of CO_2 laser microsurgery in T1 and T2 hypopharyngeal cancer.
Methods: The files of 119 T1 and T2 hypopharyngeal carcinoma cases primarily managed with laser surgery were reviewed. Cases were assessed for 5-year disease-specific survival (DSS) as well as local control (LC) rates, with respect to T and N classification, status of surgical margins, and decision on neck management and adjuvant therapy. Cases were additionally evaluated for incidence of major complications and retention of laryngeal and pharyngeal function.
Results: DSS and LC rates of 72.6% and 85.4%, respectively, were noted overall in this series. Survival rates were found to be significantly better for cases with negative surgical margins. The presence of regional metastases was also found to significantly affect prognosis. Satisfactory retention of function and a low rate of major complications were noted.
Conclusion: Laser surgery appears to be very effective for T1 and T2 hypopharyngeal cancer treatment as long as clear surgical margins can be achieved. Oncologic results are acceptable with low incidence of complications and satisfactory retention of function. The neck must always be included in the primary treatment plan of hypopharyngeal lesions.

INTRODUCTION

Cancer of the hypopharynx is relatively rare among head and neck malignancies [1]. Despite this low incidence, hypopharyngeal carcinomas show the worst survival rates within the head and neck region [1,2]. Advanced stage of disease at the time of diagnosis seems to be mainly responsible for the poor prognosis. Interestingly, oncologic results for hypopharyngeal carcinomas have not significantly improved during recent decades regardless of the chosen management scheme including several organ preserving modalities [1,2]. However, organ preservation treatment has managed to improve functional results and laryngeal salvage rates to a certain extent [3,4]. Although organ preservation was initially used as a term to describe combined chemotherapy and radiation protocols, today it also includes various surgical techniques, such as laser microsurgery [5].

Transoral CO_2 laser microsurgery (TLM) has greatly expanded endoscopic surgical capabilities in the head and neck region. Since the introduction of laser in the treatment of hypopharyngeal carcinomas, it has been successfully utilized in early and moderately advanced as well as recurrent lesions of the hypopharynx [2,6,7]. With the use of laser, sacrifice of healthy tissue is minimized, and the need for tracheotomy and feeding through a tube is uncommon and rather lower compared to other conservation regimens as well as open surgery [2]. Due to these, as well as numerous other advantages of TLM, the technique has emerged as a very attractive alternative organ and function preserving surgical option [6].

Evaluation of available management modalities for head and neck cancer, is a complicated issue [5]. Unfortunately, definitive, prospective, randomized controlled studies comparing available treatment modalities are currently lacking [3–5]. Nonrandomized data are characterized by numerous flaws, with selection bias being the most serious. In the hypopharynx region, limited numbers of cases due to the low incidence of hypopharyngeal cancer, further hamper the significance of available studies. However, nonrandomized data remain important since they currently offer the only available basis for treatment decision-making. From this perspective, the present study aims to retrospectively assess the effectiveness of TLM in treating T1 and T2 hypopharyngeal carcinomas.

METHODS

A retrospective study was conducted at an academic tertiary referral center (Department of Otorhinolaryngology, Head and Neck Surgery, University of Erlangen-Nurembrg Medical School, Erlangen, Germany). Relevant approval from the institutional review board of the hospital was obtained. The files of all patients who underwent primary TLM for pT1 or pT2 hypopharyngeal carcinomas between 1970 and 2004 were studied. Patients with insufficient data, previous treatment for the same reason, systemic disease at the time of diagnosis, and histology other than squamous cell carcinoma, as well as patients with second primary tumors at the time of diagnosis and N3 classification were excluded from the study. All pathology reports were reviewed and staging was conducted with respect to the 2002 American Joint Committee on Cancer (AJCC) and Union Internationale Centre Contre Cancer (UICC) classification [12]. According

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to TNM staging, T classification describes the size of the primary tumor and whether it has invaded nearby tissue, while N describes any regional lymph nodes that are involved. T1 lesions are defined as those that are limited to one sub-site of the hypopharynx and have a dimension of 2 cm or less. T2 tumors involve more than one sub-site of the hypopharynx or an adjacent site or are larger than 2 cm but not larger than 4 cm at their greatest diameter without fixation of the hemilarynx.

All cases were assessed for disease-specific survival (DSS) as well as local control (LC) rates, with respect to T and N classification, status of surgical margins, and decision on neck management and adjuvant therapy. Moreover, all primary tumor pathology reports were evaluated for status of surgical margins. Surgical margins were considered as positive when characterized by the presence of invasive carcinoma at the edge of resection on permanent section pathology. Five-year DSS rate was defined as the percentage of patients alive for more than 5 years divided by the total number of patients who died of the tumor of interest. This rate included only deaths specifically due to this specific tumor and excluded all other deaths in the patient group. LC, reflected the analysis of tumor recurrence in the primary site, and was calculated from the date of surgery to the date of local recurrence diagnosis or date of last follow-up. Local recurrence was defined as invasive carcinoma developing after completion of initial treatment at the anatomic site of the primary tumor.

Cases were additionally evaluated for incidence of major complications and related tracheotomies. Major complications were defined as those which necessitated prolonged hospitalization, blood transfusion, additional surgery, or admission to the intensive care unit. Tracheotomies were considered as transient when performed intraoperatively or in the immediate postoperative period but later closed. Accordingly, tracheotomies were considered as permanent in cases where closing had not been possible at any time postoperatively. Long-term swallowing inability was determined by evaluating the incidence of permanent gastrostomies.

Statistical analysis was performed using the Kaplan–Meier method and the long rank test with 95% intervals, and the Fischer exact test. Software SPSS Version 17 (SPSS, Inc., Chicago, IL) for Microsoft Windows was used for the analysis. A P-value of <0.05 was considered significant.

RESULTS

A total of 119 cases were finally included in this study. Among these, 107 were men and 12 women, with 9:1 men to women ratio. Mean age in the whole study group was 55.4 years, ranging between 34 and 83 years (SD = 11.2). Mean follow-up period was 71 months. In total, 45 T1 and 74 T2 cases were included. A detailed presentation of cases according to the affected anatomic sub-site of the hypopharynx can be found in Table I.

Five-year DSS was 72.6% overall in this series. For T1 cases DSS was 77.8% and for T2 cases 70.0%. DSS was 84.4% for stage I, 77.1% for stage II, and 68.2% for stage III cases. LC was 85.4% overall in this series. For T1 cases LC was 90% and for T2 cases 83.1%. Oncologic results according to T and N classification are presented in Table II. A more detailed presentation of N2 classification cases with respective survival rates can be found in Table III. Kaplan–Meier analysis of DSS and LC according to T classification are shown in Figure 1.

TABLE I. Detailed Presentation of All Cases According to the Affected Anatomic Sub-Site of the Hypopharynx

Anatomic sub-site	Number of cases (%)
Pyriform sinus	85 (71.4)
Postcricoid area	11 (9.2)
Posterior pharyngeal wall	14 (11.7)
Multiple sites	9 (7.5)

According to pathology reports, negative surgical margins (R0 status) had been achieved in 101/119 (84.8%) cases in this series. A single procedure had been enough in order to achieve this status in the vast majority (92 patients, 91%) of cases, while a second operation was necessary in the rest (9 cases, 9%). Conversely, 18 (15.2%) cases had positive surgical margins (R+ status) at the end of surgical treatment. Seventeen out of these 18 cases received adjuvant treatment as described later, while one case had died due to unrelated reasons before the initiation of postoperative treatment. Survival rates were found to be significantly better for cases with R0 status (DSS 77.0%) compared with R+ status cases (DSS 48.1%, $P < 0.001$). In addition, survival rates were comparable between cases where only one procedure had been necessary in order to achieve R0 status and cases that underwent a second procedure, although the number of cases in this latter group was too low for proper statistical evaluation. LC was also found to be significantly superior for cases with R0 status compared to R+ status cases (88.4% vs. 68.7%, $P = 0.008$). Kaplan–Meier analysis of DSS and LC of all cases, according to R status is presented in Figure 2.

The presence of regional metastases was found to significantly affect prognosis in this series. DSS was 83.7% for a total of 47 N0 cases, while it was 67.4% ($P = 0.047$) for 72 cases with neck metastases (N+ classification). Details regarding neck status and relevant prognosis can be found in Table II. Overall, 94 cases underwent some form of neck dissection. Conversely, in 25 cases the neck was not surgically treated. In all cN0 cases where the neck was primarily managed, either a bilateral or ipsilateral to the side of tumor, selective dissection of levels II, III, and IV was performed, depending on the exact location of the primary lesion and the T classification. In cases with known positive neck nodes, a modified radical neck dissection was typically performed. Surgery of the neck was performed simultaneously with the primary site procedure or, in some cases, within 10 days after TLM, when permanent histology results from the primary tumor had been made available.

Out of 42 cases with cN0 status preoperatively, 21 were treated with a neck dissection while another 21 were not. All the latter had either refused to undergo surgery of the neck or had been considered poor candidates for open surgery due to other reasons such as general health status. In those cases that were operated upon, occult metastases in the neck specimens were found in 8 out of 21, with an overall incidence of 38.0%. All cN0 cases that were not operated upon received radiotherapy, alone or combined with chemotherapy. Adjuvant radiotherapy was also administered to the majority (16/21 cases) of surgically treated cN0 necks. DSS rates were found to be comparable among cN0 cases that underwent neck surgery and those that did not (76.8% and 75.6%, respectively, $P = 0.37$).

A neck dissection was performed in all cases with known neck metastases except of four. In two of these four cases, surgery of the neck had been planned at a second stage a few days after TLM but permanent histology revealed the presence of positive surgical margins in the primary tumor site. A decision was made for them to be admitted for radiochemotherapy. When adjuvant treatment had been completed the necks were negative for disease and patients were placed on follow-up. Both died within 3 years for reasons not related to their disease. The other two cases had refused to undergo surgery of the neck and died either before the initiation or the completion of adjuvant treatment.

Adjuvant treatment in this series consisted of postoperative radiotherapy either alone or combined with chemotherapy. Typical indications for adjuvant treatment included the presence of positive surgical margins when further surgery was not feasible, advanced neck disease (N2 classification), extracapsular tumor spread that was evident in 12 cases, and infiltration of lymph vessels or nerves on permanent histology. The decision to offer adjuvant therapy was also affected by

TABLE II. Oncologic Results Found in This Series, According to T and N Classification

T classification	N0 classification	N1 classification	N2 classification	Total number of cases	DSS	LC
T1	20	6	19	45	77.8%	90%
T2	27	11	36	74	70.0%	83.1%
Total number of cases	47	17	55	119	72.6%	85.4%
DSS	83.7%	71.3%	63.3%	72.6%		

DSS, 5-year disease-specific survival; LC, 5-year local control.

the choice of surgical management of the neck. Overall, adjuvant treatment protocols were eventually administered in the majority of cases (99/119 patients, 83.2%). Irradiation typically included the primary tumor site and both sides of the neck. Various changes in treatment protocols as well as technical developments have been noted over the years. Today, however, routine adjuvant treatment in our center comprises of radiation therapy with a cumulative dosage of 64 Gy using conventional fractionation, plus concomitant cisplatinum-based chemotherapy. Interestingly, a trend towards better survival was noted for cases that received adjuvant treatment compared to those that did not (DSS 73.8% and 65.1%, respectively, $P = 0.162$).

Major complications in this series included postoperative bleeding, aspiration, fistula, and granulation tissue formation. None of these complications was fatal. A detailed presentation can be found in Table IV. Overall incidence of complications was 12.6%. A trend towards fewer complications was noted in the treatment of T1 tumors although statistical significance was not reached ($P = 0.067$). Overall incidence and type of tracheotomy is also presented in Table IV. Permanent tracheotomy was rarely necessary, with an incidence of 2.5%, including three T2 cases that presented severe postoperative aspiration. Accordingly, permanent gastrostomy tubes were necessary in only three cases, with an overall incidence of 2.5% (Table IV).

DISCUSSION

The primary aim of this study was to evaluate the oncologic and functional results of laser surgery in the treatment of T1 and T2 hypopharyngeal cancer. Hypopharyngeal lesions in general have been traditionally characterized by poor survival outcomes [2]. The use of open surgery, radiation treatment followed by surgery as salvage, and combined nonsurgical conservation regimens have all produced 5-year DSS rates ranging between 17% and 59% [1,8–14]. It is obvious that, although these studies did not specifically focus on early local lesions, they produced discouraging oncologic results. Moreover, organ preservation rates have been similarly discouraging, even with modalities that actually aimed on function retention [8–14].

Since the introduction of CO_2 laser in the treatment of laryngeal cancer, this method has significantly developed and its indications widely expanded within the upper aerodigestive tract [7,15]. Eventually, indications have come to include early and moderately advanced, as well as recurrent hypopharyngeal carcinomas [2,6,7]. TLM has been popularized in the surgical treatment of the upper aerodigestive system due to many distinctive advantages. This method essentially represents a minimally invasive surgical approach which allows tumors to be removed with minimal sacrifice of healthy tissue and acceptable retention of function [7]. Additional advantages of TLM include low morbidity and mortality, avoidance of tracheostomy, shorter periods of hospitalization, and low costs [6,7].

TABLE III. Detailed Presentation of N2 Classification Cases With Respective Survival Rates

T classification	N2a classification	N2b classification	N2c classification
T1	3	10	6
T2	3	18	15
Total number of cases	6	28	21
DSS	62.3	73.4	50.1

DSS, 5-year disease-specific survival.

It has been previously shown that selected hypopharyngeal cancers of all classifications can be successfully treated with TLM [2,16]. This has been especially evident in cases with early disease. Martin et al. [2] recently presented a 5-year DSS rate of 68% for 22 cases with early stage disease. Vilaseca et al. [16] had previously published survival rates of 100% for early stage disease but included a very small number of such cases, that is, six. LC rates were quite high in both prementioned studies. Martin et al. presented 84% for pT1 and 70% for pT2, while Vilaseca et al. showed LC rates of over 90%, again including a small case sample (only two T1 and 16 T2 cases). In the present study, a total of 57 stages I and II cases were included with a DSS rate of 79.5%. Accordingly, LC rates were 90% for 45 T1 and 83.1% for 74 T2 cases. The previously shown oncologic effectiveness of TLM is therefore confirmed in this study (Table II).

The relatively high survival and LC rates presented here may strike as odd when referring to a disease that has been traditionally linked with dismal prognosis [1,2]. However, it must be emphasized that, in addition to a timely diagnosis, the selection process of cases most likely to benefit from laser surgery is of outmost importance, contributing significantly to the successful treatment outcomes of TLM. The success becomes more evident after comparing the results of TLM with results of other treatment modalities for similarly staged tumors in our center: according to data not presented here, for a total of 260 T1 and T2 hypopharyngeal carcinomas that had been managed with any form of treatment during the same time period, DSS (58.5%) and LC (66.7%) were found to be considerably lower ($P < 0.001$). When open surgical techniques that have been used in our department are separately evaluated—75 early T cases overall, showing DSS of 66.4%, and LC of 80.6%—oncologic results may be comparable to TLM ($P = 0.327$ and $P = 0.798$, respectively), but pharyngolaryngeal function is certainly diminished compared to laser surgery (data not shown). Therefore, TLM seems to provide better oncologic or at least functional results compared to other treatment modalities in the treatment of early hypopharyngeal lesions.

As previously mentioned, increased experience in patient selection and treatment decision-making, as can be found in centers with expertise in head and neck oncology and laser surgery, certainly contributes to the satisfactory outcome of TLM. Among treating physicians that may be involved in the patient selection process, including medical oncologists and radiotherapists, the head and neck surgeon should always play a key role. It is also emphasized that during the selection process, every case must be individualized and a thorough diagnostic work-up must be followed in order to decide which surgical procedure can lead to maximum tumor control and functional outcome. This decision should always be then carefully reassessed according to the intraoperative findings, when the maximum depth of tumor invasion, which is of critical importance, can be more readily evaluated.

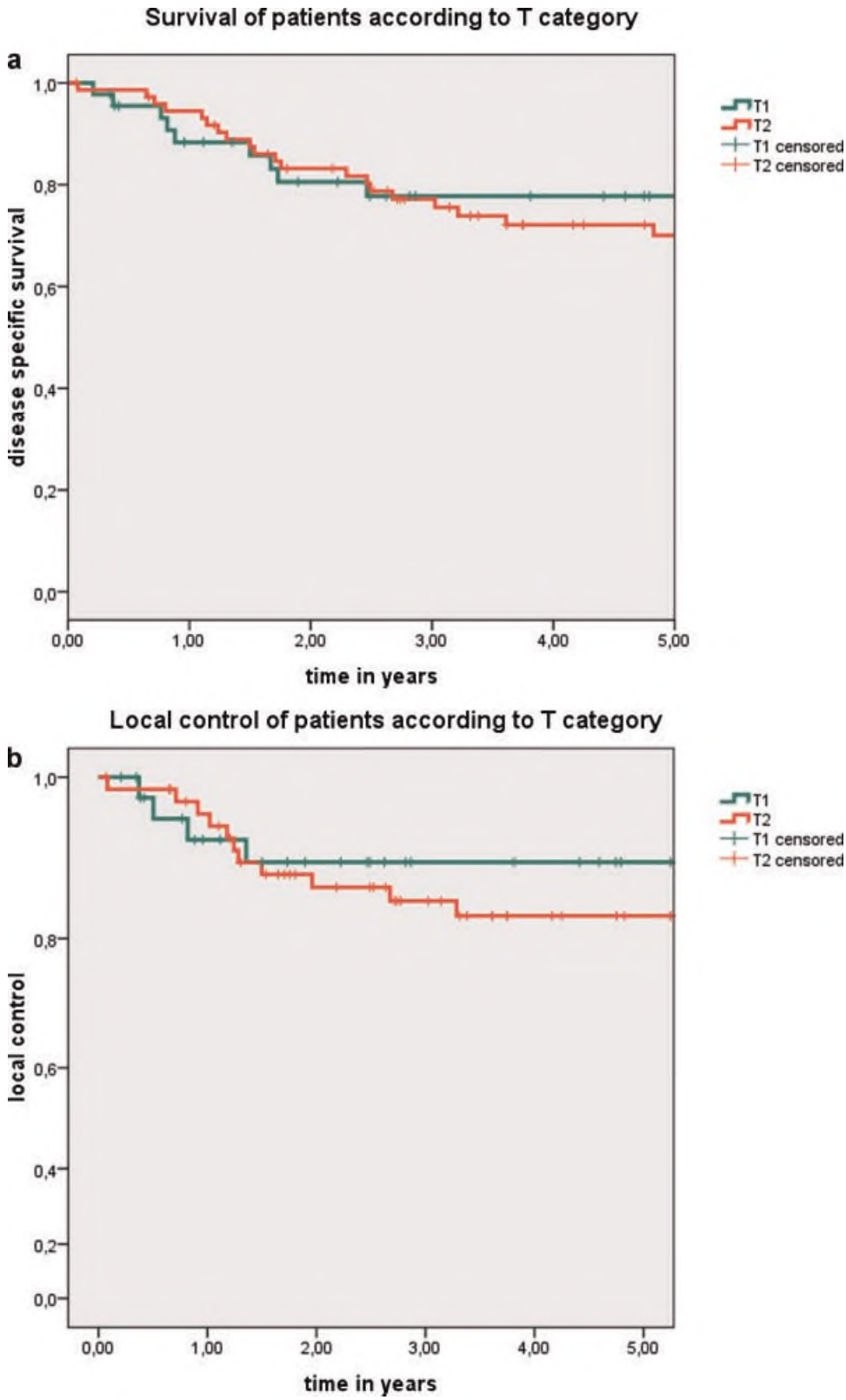

Fig. 1. Kaplan–Meier analysis of (**a**) disease-specific survival (DSS), and (**b**) local control (LC), according to T classification.

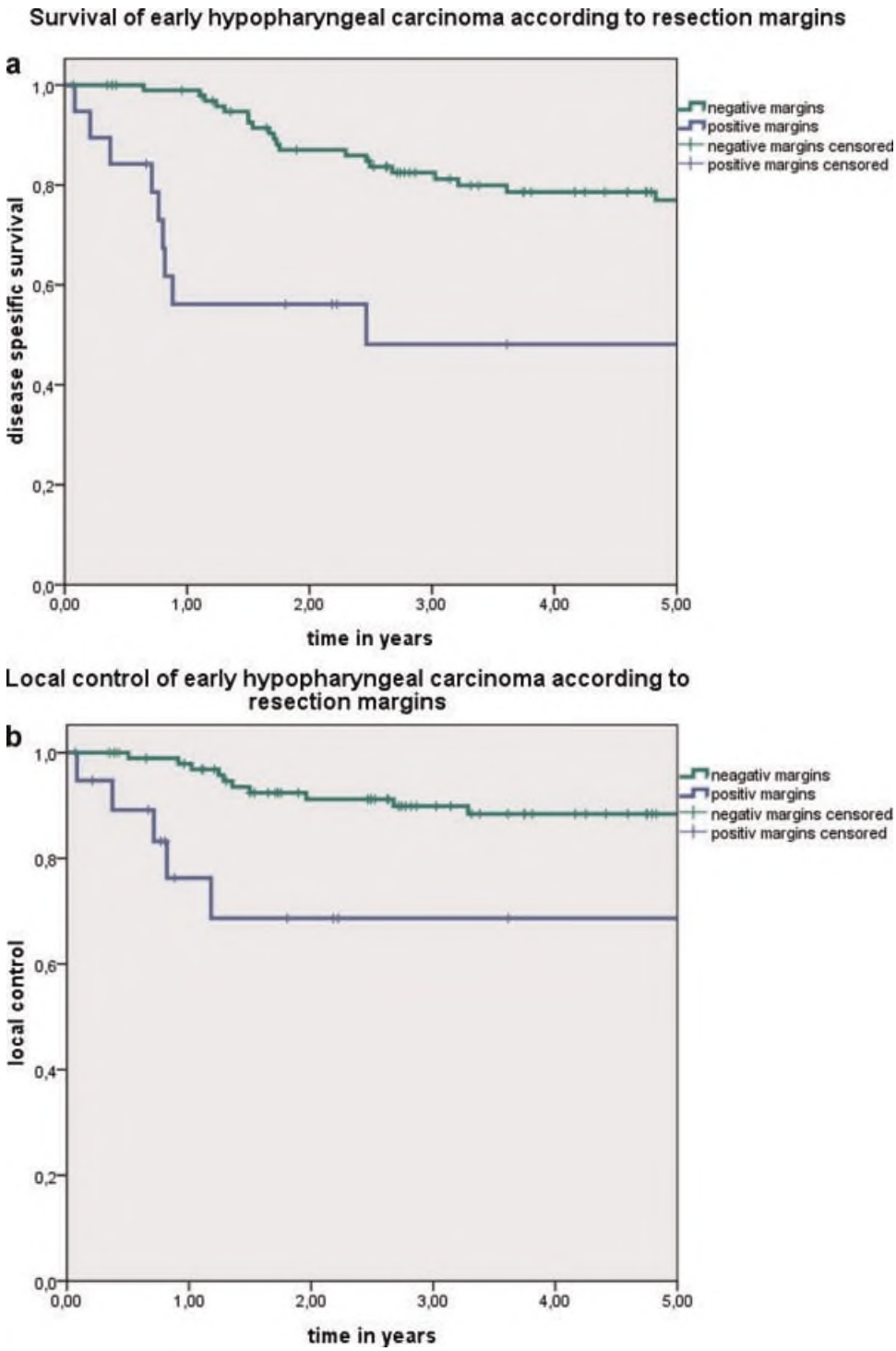

Fig. 2. Kaplan–Meier analysis of (**a**) disease-specific survival (DSS), and (**b**) local control (LC), according to status of surgical margins. R0, cases with free surgical margins; R+, cases with compromised surgical margins.

A standard piecemeal technique for laser excision is routinely utilized in our institution [7]. This technique allows narrow margin control with maximum preservation of function [2,7,17]. The CO_2 laser is typically used as a cutting instrument rather than one to vaporize the tumor. Frozen section control is necessary as an indicator for further resection, although frozen sections do not always correlate with permanent pathology [18]. The significance, nevertheless, of achieving tumor-free surgical margins cannot be overstressed. It has been previously established that patients with head and neck cancer exhibiting positive resection margins have significantly higher rates of local or regional recurrence and even show decreased survival [19–21]. This study confirms the importance of surgical margins in

TABLE IV. Incidence and Type of Complications as Well as Incidence and Type of Tracheotomies and Gastrostomies, According to T Classification

T classification	No. of (incidence) of complications	No. of cases according to type of complication				No. of (incidence) of transient tracheotomies	No. of (incidence) of permanent tracheotomies	No. of (incidence) of permanent gastrostomies
		Bleeding	Granulation	Aspiration	Fistula			
T1	4 (8.8%)	1	2	1	0	7 (15.5%)	0	0
T2	11 (14.8%)	5	1	4	1	9 (12.1%)	3 (4%)	3 (4%)
Total	15 (12.6%)	6	3	5	1	16 (13.4%)	3 (2.5%)	3 (2.5%)

laser surgery, since significantly higher survival and LC rates were found in cases where free surgical margins could be achieved (Fig. 1). This was eventually possible in the vast majority of cases after usually one or seldom two operations (101 cases, 84.7%). It should be emphasized here that laser offers significant advantages with regard to margin control, as it allows for easy, repeated, and direct access to the tumor site [5,19]. On the other hand, laser surgery may pose increased difficulties in order for pathologists to reliably assess the status of tumor resection margins [6,19]. Reasons for this discrepancy are related to the nature of CO_2 laser itself and include tissue contraction and evaporation, heat artifacts, or even small size of samples [19]. Such difficulties often result in surgical margins falsely assessed as positive or undetermined on permanent histology [6,19]. In any case, an acceptable incidence of 15.3% for positive margins was noted in this study [19].

The presence of neck metastases was found to significantly worsen prognosis in this series (Table II). Furthermore, in cases with cN0 classification preoperatively, performance of neck dissection revealed a 38% incidence of occult metastases with permanent histology. These two findings suggest that surgeons should adopt an aggressive management strategy for the neck, even in cases with early hypopharyngeal lesions and clinical absence of regional disease. On the other hand, cN0 cases that were not surgically addressed in this series showed comparable survival rates with those that were. However, it is emphasized that the large majority of cN0 cases (36/42 patients) received adjuvant therapy thus making the interpretation of the results rather difficult. Nevertheless, it may be suggested that, due to the high incidence of microscopic regional disease in even early hypopharyngeal lesions with cN0 classification, primary treatment of the neck is imperative. A neck dissection should be offered in every case and if refused by the patient or is not possible for other reasons, adjuvant radiotherapy that includes the neck should be administered. This tactic has been previously proposed by others [2,16]. Performance of neck surgery can either take place at the same time with TLM, or at a second stage after permanent histology results for the primary tumor are available. This delay might allow for laser re-resection at the primary site using the same anesthesia, in cases where surgical margins were found to be compromised during the first operation [2].

The traditionally poor oncologic results found for hypopharyngeal carcinomas suggest that treating physicians should adopt combined treatment modality schemes. This is already the preferred treatment strategy for cases with advanced disease [12–14]. Results from the present study suggest that even cases with early local disease might benefit from this tactic. Although statistical significance was not reached, cases that received adjuvant therapy in this series showed a trend towards better prognosis compared to cases treated with surgery alone. Interestingly, this result was found despite the fact that the adjuvant treatment group included all cases bearing negative prognostic factors. However, proper interpretation remains difficult, since, as previously mentioned, selection bias is an inherent weakness of retrospective studies. In addition, adjuvant treatment protocols have repeatedly changed over the years, thus further hampering the retrospective evaluation of adjuvant treatment effectiveness. The need for randomized prospective studies in order to more accurately evaluate the efficacy of adjuvant treatment in surgically treated early hypopharyngeal lesions is therefore emphasized.

Safe use of CO_2 laser mandates increased awareness and training on behalf of the surgeon and operating room personnel [2,5,22]. Airway fire is perhaps the most feared complication and strict caution against it cannot be overemphasized. Other potential complications include bleeding, granulation tissue formation, and aspiration pneumonia [2,16,22]. A low incidence of major complications was found for TLM cases in this series (Table IV). Fortunately, none of these complications proved to be fatal. The most common complication was postoperative bleeding which typically occurred within the first 24 hr postoperatively. All cases with hemorrhage were led back to the operation table and were endoscopically managed successfully under general anesthesia. Other isolated types of complications were in fact too rare to be separately commented upon. Moreover, TLM showed a very low incidence of permanent tracheotomy. However, a relatively high transient tracheotomy rate was found. This was mostly related to the fact that during the first years of laser application a tracheotomy was very often performed for safety purposes. This has largely changed in more recent times as more experience with the use of laser has accumulated. Finally, a very low need for permanent gastrostomy was found (Table IV). These results suggest a good functional outcome for TLM.

CONCLUSION

TLM appears to be a very effective treatment modality for T1 and T2 hypopharyngeal cancer, as long as clear surgical margins can be achieved. This technique offers acceptable oncologic results with a low incidence of complications and satisfactory retention of function. Prospective, double-blinded, randomized studies are still necessary in order to objectively compare all available treatment modalities for early local hypopharyngeal cancer. The prementioned outcomes, nevertheless, place TLM in the first line of management options for such cases, at least as part of a combined treatment strategy. Moreover, management of the neck must always be included in the primary treatment plan of all hypopharyngeal lesions.

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