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HEAD & NECK

Transoral laser microsurgery in early glottic cancer involving the anterior commissure

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Abstract

Purpose Treatment modalities for glottic cancer comprise surgery, (chemo-)radiation, and combined treatment options. Glottic cancer involving the anterior commissure (AC) requires special preoperative assessment and surgical skills, as it is commonly considered a risk factor for local recurrence. The aim of this study is to analyze the oncological effectiveness of transoral laser microsurgery (TLM) in the early glottic cancer involving the AC.

Methods We retrospectively analyzed the data of all patients with primary, early staged (T1–2) glottic squamous cell carcinoma who were treated between 2004 and 2014. Patients were preferably treated by TLM (rather than open surgical techniques) if appropriated transoral exposure of the endolarynx was ensured. Voice outcomes were not assessed.

Results 186 patients with early glottic cancer were included, 143 were treated by TLM and 43 by other therapy modalities [OT open surgical techniques ($n=32$) or primary (chemo-)radiation ($n=11$)], respectively. In 84 patients (59%) of the TLM cohort, the AC was involved (OT cohort $n=29$ (73%), $p=0.143$). The 1-, 3-, and 5-year local control rates after TLM were 91%, 86%, and 81% in patients without AC infiltration and 84%, 74%, and 70% in patients with AC infiltration, respectively, showing no statistical difference ($p=0.180$). The 5-year disease-free survival and laryngeal preservation rate (LPR) did not differ with regard to AC infiltration ($p=0.215$ and $p=0.261$). Comparing the treatment modalities, the 5-year LPR was 90% for TLM and 83% for OT regardless of infiltration of the AC ($p=0{,}653$ and $p=0.267$, respectively).

Conclusion TLM is an effective surgical treatment for early glottic cancer with AC involvement in patients with adequate transoral laryngeal exposure.

Keywords Head and neck cancer · Transoral laser microsurgery · Anterior commissure · Glottic cancer

Introduction

Several treatment modalities for glottic laryngeal cancer are available such as surgery, (chemo-)radiation, and combined treatment options [1, 2]. Choosing the appropriate treatment regime in the management of anterior commissure (AC) involvement is challenging and a first-line treatment has not yet been defined. In the preoperative assessment of primary glottic cancer, it is crucial to consider multiple outcome factors in terms of voice quality and deglutition, baseline function of the patient, treatment options in case of recurrence, long-term organ preservation, and survival. In previously untreated early glottic cancer without AC involvement, transoral larynx microsurgery (TLM) has replaced open surgical techniques where applicable, whereas the role of TLM in the management of AC infiltration remains ambiguous [3, 4]. In general, TLM is associated with less morbidity compared to open surgery and radiotherapy. Further advantages of TLM comprise fast recovery, preservation of laryngeal function, and the possibility of avoiding tracheostomy [2].

In case of AC involvement, TLM is widely deemed to involve the risk of increased and severe local recurrence rates with poorer survival [5–9]. Hence, some authors even claimed a modified tumor staging classification addressing

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AC infiltration [10, 11]. To address distinct local tumor spread within the anterior commissure, TLM demands the pre-conditions of a decent transoral larynx exposure and superior surgical and anatomical skills. Beside these factors, the decision-making process is mainly dependent on the institutional preference of treatment of choice [12]. To date, no randomized, prospective study has been conducted to compare the established treatment modalities in the early glottic carcinoma with AC infiltration.

This study represents one of the largest cohorts with early glottic cancer involving the anterior commissure and aims to evaluate the long-term oncologic outcomes after transoral laser microsurgery.

Materials and methods

We screened all patients with primary early glottic carcinoma (T1a, T1b, and T2, $n=232$) who were treated in the universtiy hospital of Munich (LMU) between January 2004 and December 2014. Exclusion criteria were: synchronous malignancies/distant disease ($n=5$); non-curative treatment intention ($n=2$); refused/incomplete treatment ($n=14$); lack of complete follow-up data (at least 3 months after tumor resection, $n=25$). Accordingly, 186 patients could be included, and were first divided up according to treatment modality [TLM versus "other therapies" (OT) including open surgical techniques and primary (chemo-) radiation]. They were further grouped according to infiltration of the AC. Postoperative, pathological staging was done according to the 7th edition of the American Joint Committee on Cancer (AJCC) TNM classification system. In addition to common clinicopathological data, we collected the following parameters: adjustability of the larynx (categories: good, moderate, difficult, not possible) and detailed histopathological resection status. After receiving pathological results of biopsies from rigid panendoscopy and a computed and/or magnetic resonance tomography based staging, all cases were discussed in our multidisciplinary tumor board. TLM was advised as the first-line treatment unless there were contraindications such as limited laryngeal exposure (particularly with regard to the anterior commissure), comorbidities, age, and expected loss of follow-up.

For carcinomas involving the anterior commissure, usually, a "Type VI" cordectomy, according to the European Laryngological Society, was performed [13]. This type of resection includes an anterior commissurectomy with bilateral anterior cordectomy. To remove the Broyle's ligament, the incision was started above the insertion plane of the vocal folds, at the base of the epiglottic insertion, and was extended through the Broyle's ligament. During resection, the thyroid cartilage was exposed in all patients. If there was any evidence of infiltration, a part of the thyroid cartilage was removed. In some cases, resection of the petiole of the epiglottis was necessary to ensure sufficient visualization. Furthermore, to expose the anterior part of the vocal folds, partial resection of the ventricular folds was necessary in some patients. Neck dissection (levels II–IV) was only indicated in patients with clinical suspicious nodal status (cN0).

Our standard follow-up protocol consists of a microlaryngoscopic examination in general anesthesia after 6–8 weeks in all patients who were treated by TLM, as well as a clinical follow-up examination with endoscopic laryngoscopy on a regular basis (every 4–6 weeks in the first, every 2–3 months in the second and third, and every 3–6 months in the fourth and fifth year, respectively). This retrospective study was approved by the institutional review board of the university hospital of Munich (LMU).

Statistical differences between the groups according to AC infiltration status were analyzed using the Chi-square test and Fisher's exact test for categorical, and the unpaired student's t test for continuous variables.

As main endpoints, the local control rate (LCR), disease-free survival (DFS), and laryngeal preservation rate (LPR) were assessed measuring the time from surgical resection to local recurrence, loco-regional/distant metastasis, and laryngectomy, respectively. Overall (OS) and disease-specific (DSS) survival were defined measuring the time from surgical resection to death of any cause and tumor-related death, respectively. LCR, DFS, LPR, OS, and DSS were calculated using the Kaplan–Meier method and further analyzed with the log-rank test for univariate analysis. Patients with loss to follow-up were censored. Variables that revealed modifying potential on the outcome were subsequently evaluated by the proportional Cox regression for multivariate analysis. All statistics were two-sided and p values <0.05 were considered statistically significant. For statistical analysis, SPSS 25.0 (SPSS Inc., Chicago, IL) software was used.

Results

Out of 186 patients with primary early glottic cancer (T1-2), 143 patients were treated by TLM and 43 by OT [open surgical techniques ($n=32$) or primary (chemo-)radiation ($n=11$)]. Detailed treatment modalities within the OT cohort and further patient and tumor characteristics are summarized in supplementary table 1. In the TLM cohort, patients were subdivided into early glottic cancer with AC infiltration ($n=59$) and without ($n=84$) (see Table 1). The mean age was 65 years in both subgroups ($p=0.995$) with a predominance of male patients (90%). The majority of early glottic cancer without AC infiltration were staged T1a (88%). AC infiltration in the other group subsequently caused a significant different distribution of T1a (41%), T1b (29%) and T2 (31%) stages, respectively ($p<0.001$). The

Table 1 Demographic and tumor characteristic

Primary glottic carcinoma treated by TLM	w/ AC involvement $n=59$ n (%)	w/o AC involvement $n=84$ n (%)	All $n=143$ n (%)	p
Age (years)				
Mean [median]	65 [65]	65 [65]	65 [65]	0.995†
Sex				0.484§
Female	7 (12)	7 (8)	14 (10)	
Male	52 (88)	77 (92)	129 (90)	
Tumor stage				< 0.001§
T1a	52 (88)	34 (41)	86 (60)	
T1b	0	24 (29)	24 (17)	
T2	7 (12)	26 (31)	33 (23)	
Nodal stage				0.512‡
N0	59 (100)	82 (98)	141 (99)	
N1	0	2 (2)	2 (1)	
M stage				
M0	59 (100)	84 (100)	186 (100)	
Grading				0.051§
G1	13 (22)	11 (13)	24 (17)	
G2	37 (63)	46 (55)	83 (58)	
G3	8 (13)	25 (30)	33 (23)	
n/a	1 (2)	2 (2)	3 (2)	
Local tumor spread				
Arytenoid cartilage	0	0	0	
Subglottic space	4 (7)	8 (10)	17 (9,1)	0.761§
Supraglottic space	5 (9)	19 (23)	24 (17)	0.029§
Vocal cord contralateral	0	24 (29)	24 (17)	< 0.001§
Transoral larynx exposure				0.060‡
Good	40 (68)	53 (63)	93 (65)	
Moderate	1 (2)	11 (13)	12 (8)	
Bad	14 (24)	18 (21)	32 (22)	
n/a	4 (7)	2 (2)	6 (4)	
Neck dissection				0.707‡
Unilateral	2 (3)	4 (5)	6 (4)	
Bilateral	0	2 (2)	2 (1)	
w/o ND	57 (97)	78 (93)	135 (94)	
Adjuvant treatment				0.057‡
RT	0	5 (6)	5 (4)	
RCT	0	2 (2)	2 (1)	
Resection status of primary lesion				0.139‡
R0	17 (29)	12 (14)	29 (20)	
Close margins	5 (8)	6 (7)	11 (8)	
R1	26 (44)	46 (55)	72 (50)	
Rx	11 (19)	20 (24)	31 (22)	
Resection status after supplemental resection margins/frozen section				0.618‡
R0	38 (64)	50 (60)	88 (61)	
R1	3 (5)	11 (13)	14 (10)	
Rx	3 (5)	6 (7)	9 (6)	
w/o	15 (25)	17 (20)	32 (22)	
Resection status after re-resection				0.464‡
R0	7 (12)	14 (17)	21 (15)	

Table 1 (continued)

Primary glottic carcinoma treated by TLM	w/ AC involvement $n=59$ n (%)	w/o AC involvement $n=84$ n (%)	All $n=143$ n (%)	p
R1	1 (2)	2 (2)	3 (2)	
Rx	0	1 (1)	1 (1)	
w/o 2. resection	51 (86)	67 (80)	118 (83)	
Microlaryngoscopic follow-up				0.195‡
Normal mucosa	38 (64)	53 (63)	91 (65)	
CIS/leukoplakia	12 (20)	10 (12)	22 (79)	
Carcinoma	2 (3)	7 (8)	9 (6)	
n/a	7 (12)	14 (17)	21 (15)	

AC anterior commissure, *w/o* without, *w/* with, *n/a* not applicable, *n* number, *TLM* transoral laser microsurgery, *OT* other therapies, *RT* radiotherapy, *RCT* radiochemotherapy, *ND* neck dissection, *Rx* presence of residual tumor cannot be assessed

†Mann–Whitney–U/Wilcoxon

‡Fisher's exact test

§Chi-Quadrat

overall rate of lymph-node metastasis (N+) was on a low level in both groups ($p=0.512$). Tumors extended more frequently to the supraglottic space in carcinoma with AC infiltration (9% vs. 23%, $p=0.029$). There was no infiltration of the posterior commissure in both cohorts. Proportions of transoral larynx exposure, performed neck dissections, and adjuvant treatment modalities were equal in both groups (see Table 1). In most cases, histopathology of the primary lesion´s margins revealed equally high rates of R1 and Rx in both cohorts [without AC infiltration: 44% and 19% and with AC infiltration: 55% and 24%, respectively ($p=0.618$)]. Most carcinoma were either evaluated as in-sano resection only after analysis of supplemental resection margins (and/or frozen sections) or after re-resection. In both cases, no statistical differences were observed (see Table 1). Tissue samples during microlaryngoscopic follow-up revealed equal rates of histopathological findings (see Table 1).

The mean follow-up time was 47 months. The 1-, 3-, and 5-year local control rates in patients without AC infiltration were 91%, 86%, and 81%; in patients with AC infiltration 84%, 74%, and 70%, respectively ($p=0.180$, see Fig. 1a). Therefore, no significant differences between the groups were found. Equally, the 5-year DFS and LPR in patients without AC infiltration were 79% and 92%; in patients with AC infiltration 68% and 86%, respectively ($p=0.215$ and $p=0.267$, see Fig. 1b, c). Multivariate analysis was adjusted for potential independent risk factors and could not reveal further prognostic parameters on DFS (see supplementary table 2). Recurrence occurred in 21% ($n=30$) of the TLM cases, with a rate of 97% relapsing within the glottis (see Fig. 2). The AC was involved in 69% of the glottic recurrences ($n=29$). 62% of the local recurrences could be treated by larynx preserving modalities, such as a repeated TLM (28%), partial laryngectomy (14%), transcervical chordectomy (3%), and definitive R(C)Tx (17%). Laryngectomy was performed in 38% of the cases. Six patients relapsed again, requiring laryngectomy in 50% of the cases ($n=3$).

Both mean DSS and median OS were similar in carcinoma with AC infiltration [DSS: 123 months (95% CI 117–129); OS: 111 months (95% CI 97–125)], and without AC infiltration [DSS: 134 months (95% CI 124–146); OS: 74 (95% CI 52–96), $p=0.479$ and $p=0.288$], respectively.

In the OT subgroup, the anterior commissure was clinically infiltrated in 67% ($n=29$) of the cases ($p=0.143$). To control further selection bias, we compared the treatment outcomes. The 5-year DFS was 71% in the entire TLM and 68% in the OT cohort ($p=0{,}682$, see Fig. 3). Analogous to the TLM group, AC infiltration was not associated with poorer DFS and DSS in the OT cohort ($p=0.672$ and $p=0.549$, respectively).

Discussion

Long-term organ preservation combined with favorable functional outcome is crucial in the treatment of early laryngeal cancer. Both these major objectives can be effectively addressed with transoral laser microsurgery [4, 12, 14–16]. In our cohort of early glottic cancer treated by TLM, the overall 5-year DFS and DSS were 71% and > 90%—which is in accordance with the current literature [5, 17–21]. Recurrence rates typically range from 17 to 24% depending on the follow-up time. Accordingly, the recurrence rate in the TLM cohort is 20% [15, 22–24]. Laryngeal preservation rates after TLM are most relevant in the long-term follow-up. Our overall LPR after TLM was 89% in line with rates

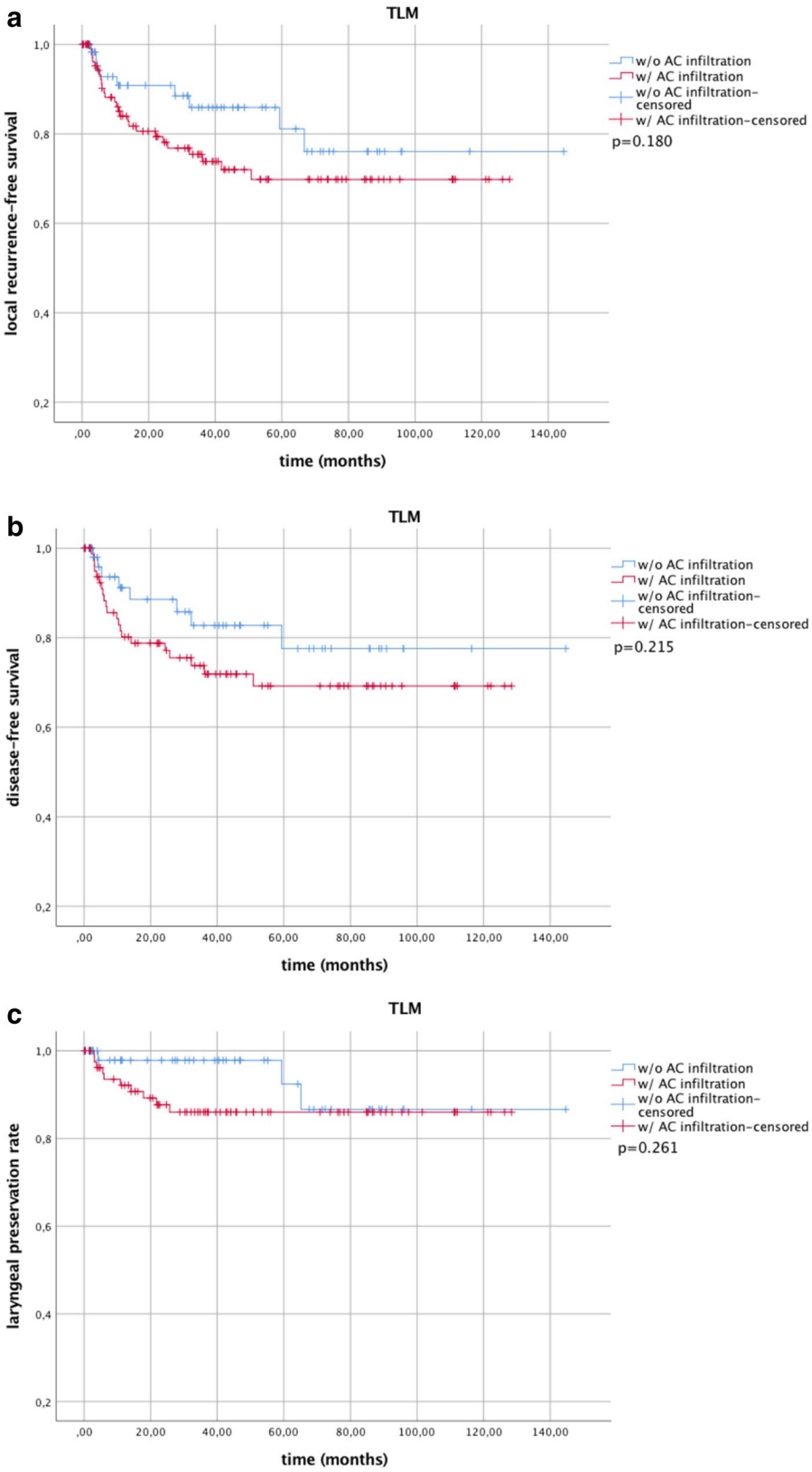

Fig. 1 **a** Kaplan–Meier estimates of local recurrence rate after TLM in dependence of AC infiltration. **b** Kaplan–Meier estimates of DFS after TLM in dependence of AC infiltration. **c** Kaplan–Meier estimates of LPR after TLM in dependence of AC infiltration

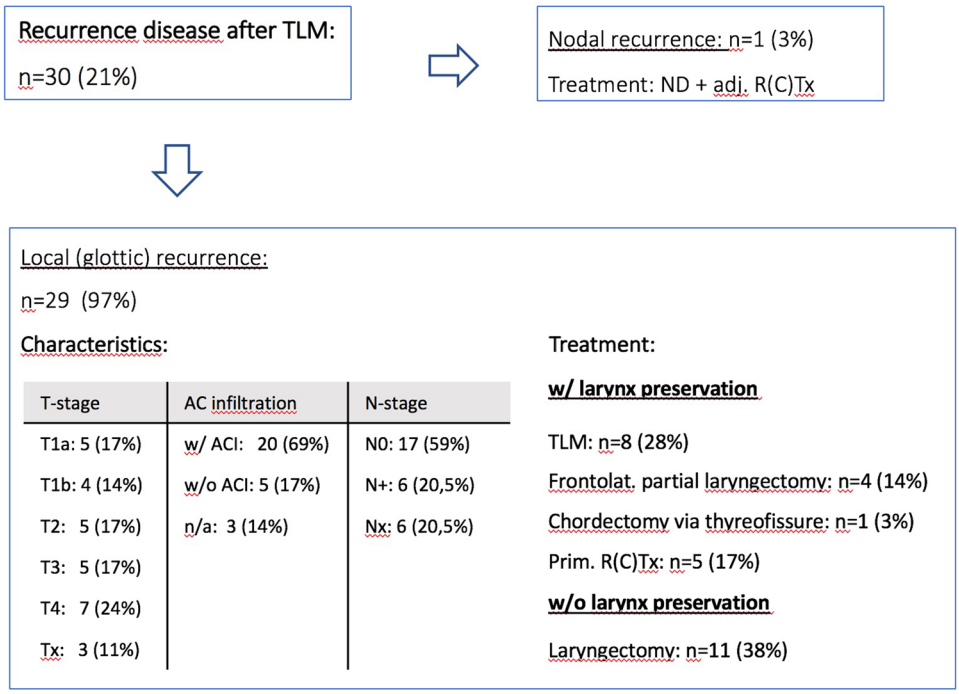

Fig. 2 Overview of recurrence disease after TLM and the subsequent therapy strategies

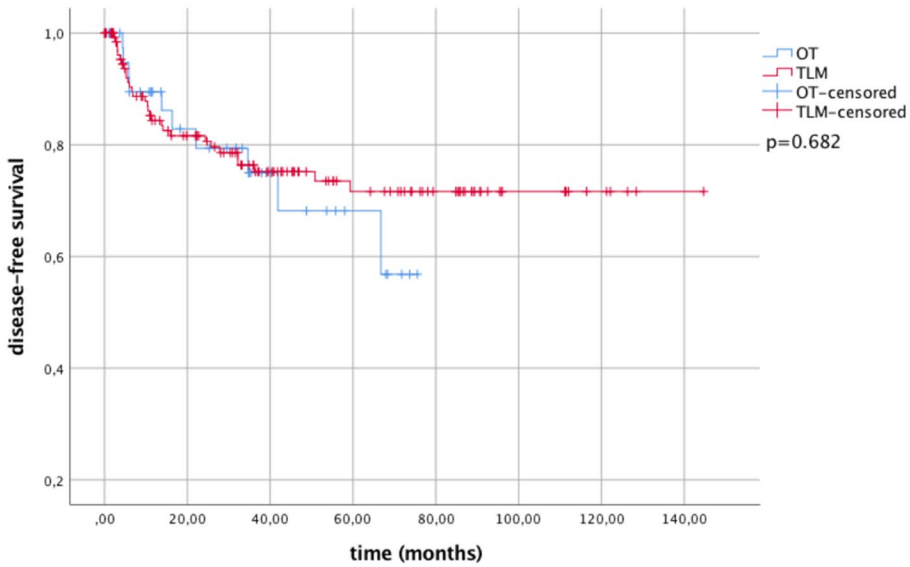

Fig. 3 Kaplan–Meier estimates of DFS in T1–2 glottic carcinoma in dependence of TLM versus OT

of 83–100% in systematic literature reviews of early glottic carcinoma [25–27].

While the early stage glottic carcinoma without AC infiltration treated by laser chordectomy shows excellent oncologic and functional outcomes, and result in equal to better outcomes than the ones treated with primary radiotherapy, carcinoma with AC infiltration is often associated with a worse clinical course. This might be due to a higher rate of local recurrence compared to the carcinomas that are solely placed on the vocal chords [6–9, 12, 18, 28]. In this respect, AC infiltration of the glottis shows distinct anatomical features compared to vocal chords neoplasms. The Broyles's ligament is a weak structure of the AC resulting in peculiar progression pathways of cartilage invasion due to local dehiscence of perichondrium at its insertion point [5, 29, 30]. Since AC tumors usually occur in immediate contact with the thyroid cartilage, sophisticated surgical skills are evident [5]. Therefore, the early carcinoma of the AC may rapidly transform into circumscribed T4a tumors which represents a contraindication for TLM [5, 18, 31]. Piazza et al. emphasized the need for more detailed staging of early glottic cancer into six subcategories to better cope with the wide

spectrum of distinct local tumor spread. For this purpose, they classified the range from tumors infiltrating one vocal cord, to those with horizontal spread to the vocal muscle/paraglottic space, or those with a vertical trans-AC extension with invasion of the anterior preepiglottic/paraglottic space [11]. To avoid understaging, preoperative assessment should at least contain multislice laryngeal computed tomography scan to exclude erosion of the thyroid cartilage.

In our study that represents one of the largest AC cohorts treated by TLM, we could not find a statistical difference in the rates of local recurrence and laryngeal preservation in carcinoma with or without infiltration of the AC. Hoffmann et al. analyzed all the studies including more than 30 patients (mean 60, 4) with TLM in AC infiltration and stated poorer outcomes compared to tumors sparing the AC in most of the reviewed studies (independently from *T* stage and Rucci´s classification as far as applied) [5, 15, 22–24, 32]. This finding is reported regardless of the respective therapeutic modality applied such as radiotherapy or extended surgical procedures comprising partial laryngectomy [18, 25, 31, 33, 34]. However, comparable large sample-sized studies are rare. Hoffmann et al. (96 patients) and Carta et al. (105 patients) revealed a significant increased risk only for local recurrences in patients with extensive infiltration of the AC (AC3 in terms of Rucci´s classification system) but not for AC infiltration as a whole [5, 10, 33]. AC3 means extensive involvement of the whole subsite on both sides of the AC midline representing the combination of an AC involvement and a clinical cT1b stage [10]. We could not confirm this finding (data not shown) in our cT1b subgroup. However, our sample size is probably too small to detect potential differences. Paradoxically, Hoffman et al. described better outcomes in carcinoma with AC2 infiltration than AC1 and could, therefore, not reproduce Rucci´s results in general what makes the author to suggest that the validity of their proposed AC classification remains to be elucidated [5]. In comparison, our correspondent large-sampled T1a cohort with AC infiltration showed similar treatment outcomes (LCR, DFS and LPR) after TLM. Therefore, it may be assumed that the more aggressive behavior of cT1b tumors is adequately reflected by its distinct T stage and is subsequently addressed by more extensive treatment in respect to their higher propensity to relapse.

As long as different treatment strategies seem to result in equal clinical outcomes, the matter of peritherapeutic morbidity as well as treatment options in case of recurrence should be emphasized even more within the decision-making process in primary cases. TLM remains a safe surgical option with excellent organ preservation rates. Furthermore, it can be repeated once the tumor recurred and radiotherapy can still be applied [19, 35]. Accordingly, in case of local tumor recurrence after the initial TLM, we could perform microsurgery and other open, laryngeal preserving surgery techniques again in almost half of the patients. In contrast to microsurgery, tumor resection techniques exposing the laryngeal cartilage via transcervical approach (such as thyroid fissure and frontolateral partial laryngectomy) typically result in an unphysiological postoperative configuration of the larynx due to wound healing and scarring. The recurrent carcinoma may subsequently grow along prior scar tissue leading to increased tumor stages and requiring laryngectomy. Therefore, both radiotherapy and partial laryngectomy in primary glottic carcinoma may lead to treatment limitations in tumor relapses making organ preservation more unlikely [25]. In contrast, transoral laser resection preserves these physiological cartilage barriers. However, there are major disadvantages deriving from the laser resection technique as such: histopathological assessment is often limited by unclear margins due to vaporization and carbonization. In addition, piece-meal laser resection may be required in cases of poor transoral larynx exposition making a final statement of margins impractical [36, 37]. The technique of TLM has, therefore, challenged the conventional principle of en bloc resection. Despite of sectioned tumor blocs, resection status is commonly not deemed an independent prognostic factor after TLM, a finding that we can confirm with our data in the TLM cohort [5, 26, 38, 39]. To sufficiently cope with these distinctive features, we advise microlaryngoscopic follow-up examination 6–8 weeks after tumor resection with blind probes of the former tumor bed combined with a long-term follow-up with short intervals.

Major limitations of this study are the missing functional outcome assessments after TLM and the unequal treatment cohorts reflecting TLM as the first-line therapy in patients with early glottic cancer. Moreover, the early glottic carcinoma with extensive AC infiltration is underrepresented within the TLM subgroup. A few patients were treated by the other treatment modalities than TLM although the laryngeal exposure was assessed good and moderate ($n = 17$) hinting towards a certain degree of pretreatment selection bias. These patients might have missed further crucial selection criteria for TLM such as age, comorbidities, or conceivable noncompliance to the standard follow-up protocol. Moreover, selection bias may have be reinforced by applying the exclusion criteria (see in "Material and Methods" section). Despite this given selection bias in retrospective studies in general, large-sampled cohorts comprising a high percentage of AC infiltration may provide at least a basis for choosing the appropriate AC treatment modality as long as RCTs are missing.

Conclusion

TLM showed similar treatment outcomes in patients with early glottic cancer regardless of AC infiltration. As far as the pre-condition of an appropriate transoral exposure of

the endolarynx is assured, TLM is a safe and reliable surgical technique with less morbidity that can be repeated in selected tumor recurrence.

Compliance with ethical standards

Conflict of interest All authors state no funding and no financial disclosures.

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