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Randomized controlled single-blinded clinical trial of functional voice outcome after vascular targeting KTP laser microsurgery of early laryngeal cancer

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Abstract

Background: Local control rate (LCR) of early glottic cancer is high after radiation therapy or transoral laser microsurgery (TLM). The aim of this study was to investigate functional voice outcome after TLM using a microvessel-ablative potassium-titanyl-phosphate (KTP) laser in comparison with a gold standard cutting CO_2 laser.

Methods: The primary end point of this prospective, randomized, single-blinded, clinical phase II study with control group was voice outcome during a follow-up of 6 months assayed by Voice Handicap Index (VHI-30)-questionnaires in patients with unilateral high-grade dysplasia, carcinoma in situ or early glottic cancer undergoing TLM-KTP (n = 8) or TLM-CO_2 (n = 12). The secondary end point was LCR.

Results: Starting from the 9-week-follow-up visit, TLM-KTP yielded significantly reduced VHI scores compared to TLM-CO_2. No relapse occurred after TLM-KTP in contrast to one recurrence after TLM-CO_2 within 6 months.

Conclusion: Multicenter phase II or III studies on voice outcome or local control rate after TLM-KTP in early glottic cancer are warranted enrolling larger patient cohorts.

KEYWORDS
angiolytic therapy, CO_2 laser, local control rate, T1 glottic cancer, Voice Handicap Index (VHI-30)

1 | INTRODUCTION

Early stage glottic cancer rates of 5-year local control, overall survival, disease-free survival, and laryngeal preservation are high using established treatment modalities consisting predominantly of transoral laser microsurgery (TLM) or radiation therapy (RT).[1,2]

Tracheostomy or feeding tubes can usually be avoided after both treatments.[3,4] On the one hand, irradiation dose may have an impact on local control as well as on larynx preservation.[3,5] On the other hand, there is only little evidence of a significant advantage of TLM compared to RT.[6,7]

TLM using CO_2 lasers has become a gold standard preserving the larynx by narrow-margin resections of approximately 1-3 mm.[8,9] Hence, these cutting lasers always remove functionally relevant endolaryngeal microstructures. Although postoperative phonation appears to be acceptable

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after TLM, a detailed retrospective analysis of voice outcome reveals mild-to-moderate voice dysfunction after TLM as well as after RT.[10] Nevertheless, no significant difference was found between these 2 modalities applying perceptual analysis (grade-roughness-breathiness-asthenia-strain/GRBAS scale), acoustic (fundamental frequency range, percentage jitter, percentage shimmer, intensity) aerodynamic (phonation quotient), videostroboscopic or subjective (Voice Handicap Index, VHI) parameters.[10] Especially the VHI has become a validated self-rating measure of functional voice outcome often used in clinical trials.[11,12] The original 30-item catalog consists of multiple choice answers covering functional, physical, and emotional domains. It appears to be significantly correlated to voice-related quality-of-life assessment tools.[13]

Preservation of the delicate microstructure of phonatory mucosa consisting of superficial lamina propria and epithelium is still the key issue in phonomicrosurgery of the larynx to protect functionally relevant pliability of the vocal folds.[14] Forty years ago, first clinical experience was gathered and partial resections of the vocal cords were reported using CO_2 lasers.[9] Meanwhile it is well accepted that total cordectomy is not always oncologically necessary using a CO_2 laser.[15]

Inspired by J. Folkman's paradigm-shifting concept on the oncological potential of anti-angiogenesis[16] that has led to multiple bench-to-bedside developments in chemotherapy, Zeitels et al. pioneered a novel translational procedure of applying selective vascular ablation using pulsed potassium-titanyl-phosphate (KTP) lasers as a larynx preserving surgical technique in early glottic cancer. This new treatment idea is often referred to in the literature as "angiolytic therapy".[17] Wavelength-related (532 nm) laser effects are hemoglobin-selective and induce microvessel thermoablation. In preclinical models, KTP laser effects were studied in detail and 15- to 30-millisecond pulses with a fiber-to-tissue distance of 3 mm were shown to avoid chaotic vessel rupture and hemorrhage reliably in the chorion allantois assay.[18,19] In experimental hamster-cheek-pouch-head-and-neck-tumors of less than 2 mm in diameter, direct wavelength-specific KTP laser effects on microvessels thus affected tumor growth indirectly and efficiently.[20] Structure preserving angiolytic treatment resulted in complete early tumor remission proven by histology in these animal experiments.

Regarding glottic malignancies, so far there are only retrospective cohort studies focusing on voice outcome[21,22] and oncologic efficacy after TLM-KTP[22,23] reporting encouraging results in patients with previously untreated cT1-cT2 glottic cancer. Furthermore, treatment modalities should be compared by evidence from randomized controlled trials.[24] Pretherapeutic and posttherapeutic voice evaluation using the VHI is in line with European Board recommendations.[25,26] As less heat and carbon is generated in the normal vocal fold soft tissue by KTP lasers, the surgeon is able to recognize more easily the interface of cancer and normal vocal fold soft tissue. Enhanced visualization of sublesional normal vocal fold soft tissue allows to preserve more of the vocal folds' layered microstructure. Consequently, in the healing process, less aerodynamic incompetence during phonatory entrained vocal fold vibration appears to be possible. Therefore, the aim of this prospective, randomized, single-blinded investigator initiated trial with a control group receiving the gold standard TLM treatment was to analyze functional voice outcome after TLM-KTP in patients with early glottic cancer during a 6-month observation time. In addition, 3-year local control rates were documented.

2 | PATIENTS AND METHODS

The study protocol was approved by the Ethics Committee of Goethe-University at Frankfurt/Main with regard to the World Medical Association Declaration of Helsinki (version 2002) as well as to the European Medicines Agency Guidelines for Good Clinical Practice.

All patients were screened at the Comprehensive University Cancer Center (UCT) of the Goethe-University Hospital at Frankfurt/Main, Germany. Histological diagnosis and staging was realized by panendoscopy under general anesthesia.

Inclusion criteria were unilateral high-grade dysplasia, carcinoma in situ (cTis), or early glottic cancer (cT1a), as well as written consent for a surgical treatment. Furthermore, patients had to be older than 18 years and female patients had to provide adequate contraception.

Exclusion criteria were insufficient exposure of the larynx during diagnostic suspension laryngoscopy under narcosis as well as evidence of recurrent disease or a secondary malignancy at staging. According to University Cancer Center (UCT) Frankfurt/Main standard operating procedures for early stage laryngeal cancer (T1a), a CT-scan of the larynx was performed.

All included patients had to give written informed consent referring to study participation. Withdrawal of informed consent resulted in immediate dropout. The study was designed as a prospective, randomized, single-blinded, clinical phase II investigator initiated trial with a control group (Figure 1). In addition, a retrospective chart analysis of local control, disease-free survival, and larynx preservation was performed 3 years after study termination.

All TLM procedures were performed under general anesthesia and were carried out by an experienced surgeon (S.S.) using suspension microlaryngoscopy.

Concealed allocation was performed by computer-generated simple 1:1 randomization. The control group was treated according to the surgical gold standard for unilateral high-grade dysplasia, Tis or T1a tumors with conventional TLM using a CO_2 laser (Sharplan 40 C; $\lambda = 10\,600$ nm; 4.5 W continuous mode; Lumenis, Dreieich/Germany) resecting the tumor with ultra-narrow resection margins of approximately 1 mm. The experimental arm (TLM-KTP) was treated

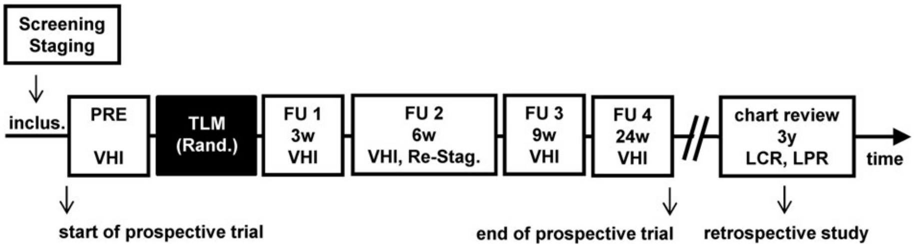

FIGURE 1 Study protocol: After screening and histological staging by panendoscopy, patients with proven unilateral high-grade dysplasia, Tis, or T1a were included after informed consent and randomized according to protocol before transoral laser microsurgery (TLM) under general anesthesia. One pretherapeutic visit (PRE) and four postherapeutic follow-up (FU) visits were scheduled for laryngoscopy and VHI acquisition after 3, 6, 9 and 24 weeks. In addition, after 6 weeks, a restaging panendoscopy with biopsy was mandatory. Without proof of recurrence, study ended after 24 weeks. Finally, a retrospective chart analysis of 3-year local control rates and larynx preservation rates was added. 3w, 3 weeks; 6w, 6 weeks; 9w, 9 weeks; 24w, 24 weeks; 3y, 3 years; VHI, Voice Handicap Index-30; LCR, local control rate; LPR larynx preservation rate

with a fiber-based KTP laser (CERALAS G5; $\lambda = 532$ nm; 4.5 W; 20-microsecond pulses; 2 pulses per second; Biolitec, Vienna, Austria) ablating the tumor as well as all angiogenic tumor microvessels surrounding the resection margin. At the time of the study, patients remained blinded to the applied laser—CO_2 or KTP—respectively (single-blinded design).

After treatment a restaging control microlaryngoscopy with mandatory biopsy at the former lesion site for histological analysis was scheduled after 6 weeks to confirm or exclude residual disease. In case of residual disease, this patient was withdrawn from further study evaluation to allow interdisciplinary tumor board-based salvage measures.

In case of negative histological findings, regular office-based follow-up visits including indirect laryngoscopy were scheduled every 4 weeks. At any time, suspected residual or recurrent disease would have led to another control microlaryngoscopy under narcosis to allow histological reevaluation.

During the follow-up, side effects were documented according to Common Terminology Criteria for Adverse Events (CTCAE version 4, according to NIH Publication No. 09-5410). All patients were seen by phoniatric specialists postoperatively. Speech therapy was offered to every patient.

The primary end point of the study was postoperative voice outcome after 6 months. Functional voice was measured by the self-rating VHI-30[25] at the time of inclusion (baseline) and at 4 time points after surgery (3, 6, 9, and 24 weeks. The secondary outcome measure was the absence of residual or recurrent disease during a 24-week postoperative period determined by indirect laryngoscopy followed by histological evaluation in case of suspicion of malignancy. Study data were reported with regard to the CONSORT 2010 Statement.[27]

After study completion, patients were resumed into standard oncological follow-up algorithms. Three-year local control rates were finally derived from a chart analysis.

2.1 | Statistical analysis

VHI-30 test-retest reliability and validation studies indicated a relevant score change of 18 or more.[11,25] The calculation of sample size was based on a power calculation using our own preliminary data (SD = 11) indicating that a minimum number of 7 subjects per group is required to achieve 80% power (type II error at 0.2) to detect a clinically relevant VHI change of 18 or more with $\alpha = 0.05$ after 6 months (primary end point). Results are presented as mean ± SD. Outcome measure data were evaluated using Mann-Whitney Rank Sum Test (SigmaStat; Jandel Scientific, San Rafael, California). *P*-values less than 5% were considered to be significant.

3 | RESULTS

3.1 | Patients

Patients were recruited for the study from September 2011 to December 2013 (last patient in). Participant flow was documented in detail according to the CONSORT 2010 Statement (Figure 2). After screening 27 patients for eligibility, 4 did not meet the inclusion criteria as histological analysis revealed only unilateral hyperplasia or mild-to-moderate dysplasia of the vocal folds. Two patients with a T1a glottic carcinoma refused to participate in the study.

Twenty-one patients were included and randomized. While 1 patient did not pass anesthesiological clearing and was referred to RT, 20 allocated subjects received TLM. Twelve patients were treated by the CO_2 laser and 8 by the KTP laser, respectively.

During the postoperative phase, 1 subject of each group withdrew his consent immediately after treatment. One patient in the TLM-KTP arm and 5 patients in the TLM-CO_2 group were lost to follow-up at different time points. But 3 patients of the latter missed only 1 of 4 scheduled follow-up time points. All recruited subjects entered analysis (Figure 2).

Medical history revealed no major discrepancies between the 2 randomly allocated groups with regard to sex, age, and histological diagnosis (Table 1).

3.2 | TLM and side effects

All patients tolerated TLM under general anesthesia well. Only limited resections were necessary in both groups

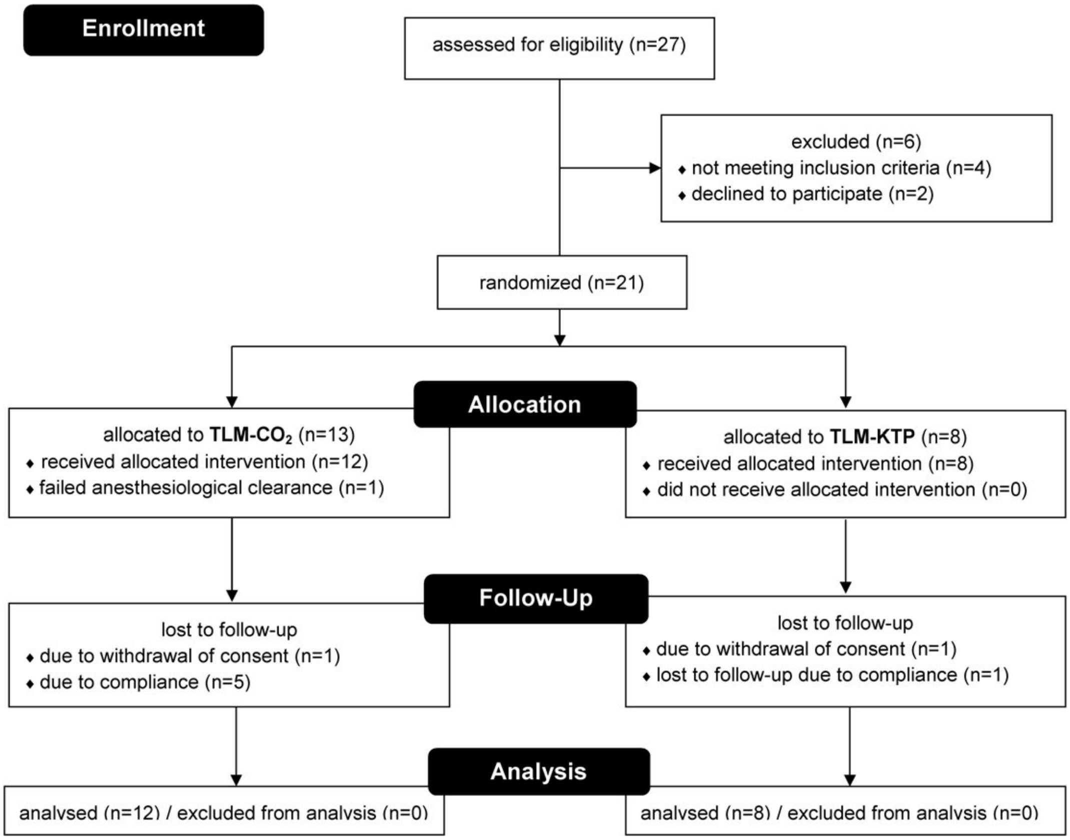

FIGURE 2 Patient participation flow diagram, according to the CONSORT 2010 statement.[27] TLM-CO_2, transoral laser microsurgery using the CO_2 laser; TLM-KTP, transoral laser microsurgery using the KTP laser

corresponding European Laryngological Society type I-III cordectomies (Figure 3). There was no need for tracheostomy or feeding tubes in any case postoperatively.

During the observation, "hoarseness" and "voice alteration" were the most common grade 1/2 side effects according to CTCAE version 4. Relevant laryngeal edema or stridor did not occur. All patients left the hospital on the first or second postoperative day and entered follow-up in the outpatient service. One patient in the TLM-CO_2 group suffered a stroke after demission. He voluntarily continued the trial due to the absence of any relevant remaining neurological expressive speech deficit (grade 1-2). Aside from this event, no further grade 3/4 side effect was documented during the 6-month observation time.

3.3 | Voice Handicap Index

The primary end point was a clinically relevant effect of TLM on functional voice measured as VHI after 6 months. Pretherapeutic voice evaluation was performed using the

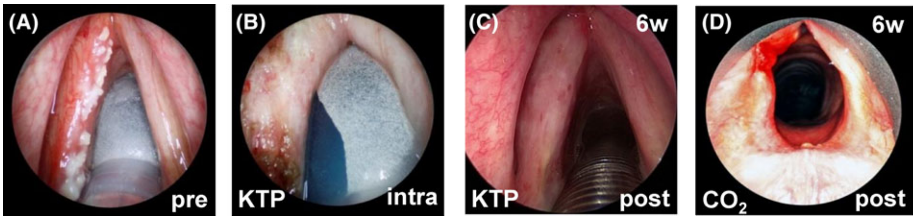

FIGURE 3 A, Preoperative T1a glottic carcinoma on the left vocal fold: Angiogenesis is clearly visible in the vicinity of the lesion reflected by tortuous fragile young vessel sprouts. In contrast, on the right vocal fold, there are only straight unactivated regular microvessels running in parallel seen by direct suspension microlaryngoscopy. B, The same T1a glottic carcinoma at higher magnification: Intraoperatively immediately after TLM-KTP treatment, the left vocal fold turns pale due to angiolytic KTP laser effects on microvessels within and around the tumor. C, Favorable postoperative microlaryngoscopic finding 6 weeks after KTP laser–based transoral microsurgery of the lesion shown in A and B. The structure preserving KTP laser application yielded regular microvessels on the left vocal fold resembling microvessels on the healthy and untreated right vocal fold. The absence of residual dysplastic or cancerous disease was proven by histological restaging. D, Unfavorable postoperative microlaryngoscopic finding 6 weeks after TLM-CO_2: The cutting laser resected a lesion of the anterior left vocal fold with ultra-narrow margins but induced significant scarring. TLM-KTP, transoral laser microsurgery using the KTP laser; TLM-CO_2, transoral laser microsurgery using the CO_2 laser; pre, preoperative microlaryngoscopy; intra, intraoperative microlaryngoscopy; post, postoperative microlaryngoscopy; 6w, 6 weeks [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Medical history data of the experimental arm (TLM-KTP) and the control group (TLM-CO_2) at baseline

	TLM-CO_2	**TLM-KTP**
Group size (patient number)	12	8
Sex		
Female (number of patients)	1	0
Male (number of patients)	11	8
Age		
Range (years)	46–87	39–87
Mean ± SD (years)	67 ± 12	68 ± 15
Histology		
High-grade dysplasia	1	0
Tis	2	3
T1a glottic carcinoma	9	5

Abbreviations: TLM-CO_2, transoral laser microsurgery using the CO_2 laser; TLM-KTP, transoral laser microsurgery using the KTP laser; Tis, carcinoma in situ; SD, standard deviation.

validated German VHI-30 version. A higher total score indicates a more serious voice handicap.

With regard to normal VHI-30 values (<10; VHI range 0-120) in healthy individuals, baseline VHI total scores were comparable in the experimental arm and the control group reflecting equally relevant clinical voice impairment before treatment in both groups (Figure 4). The use of the CO_2 laser resulted in an impairment of functional voice 3 weeks after the procedure. Although additional VHI assessments revealed no further VHI-30 increase, voice function was still impaired at the end of the follow-up period after 24 weeks compared to baseline.

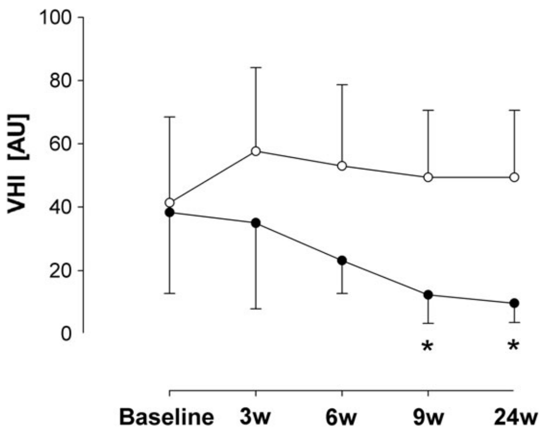

FIGURE 4 VHI after transoral laser microsurgery (TLM): TLM-CO_2 (open circle) resulted in higher total scores (3w: 57.6 ± 26.5; 6w: 53.0 ± 25.7; 9w: 49.4 ± 21.2; 24w: 50.1 ± 31.3) compared to baseline (41.8 ± 26.4). In contrast, TLM-KTP (closed circle) yielded lower VHI-30 scores (3w: 35.0 ± 27.2; 6w: 23.2 ± 10.4; 9w: 12.3 ± 9.0; 24w: 9.7 ± 6.1) compared to baseline (38.3 ± 25.5). Comparing both groups ($\Delta VHI_{baseline} = 3.5$; $\Delta VHI_{3w} = 22.6$; $\Delta VHI_{6w} = 29.8$; $\Delta VHI_{9w} = 37.0$; $\Delta VHI_{24w} = 40.5$) VHI-30 scores after TLM-KTP treatment were significantly lower after 9 weeks ($P = .006$) and after 24 weeks ($P = .008$), respectively (* $P < .05$). Abbreviations: TLM-CO_2, transoral laser microsurgery using the CO_2 laser; TLM-KTP, transoral laser microsurgery using the KTP laser; 3w, 3 weeks; 6w, 6 weeks; 9w, 9 weeks; 24w, 24 weeks; VHI, Voice Handicap Index-30

In contrast, using the KTP laser for transoral microsurgery, there was a slight tendency to improvement of functional voice comparing the 3-week time point with baseline (Figure 4). At follow-up visits, VHI-30 scores after TLM-KTP were continuously decreasing finally resulting in normal functional voice values (VHI < 10) after 24 weeks. These are VHI-30 scores usually found among healthy individuals. Comparing the VHI-30 in both postoperative groups, there were statistically significant differences between the surgical techniques on follow-up visits after 9 weeks as well as at the end of the prospective observation period after 24 weeks—the primary endpoint of the trial (Figure 4).

Analyzing in detail differences of VHI-30 scores compared to baseline (ΔVHI, Table 2), TLM-CO_2 did not deteriorate functional voice in a clinically relevant manner at any time point ($|\Delta VHI| < 18$). In contrast, an obviously clinically relevant VHI-30 reduction ($|\Delta VHI| > 18$ or $\Delta VHI < -18.0$, respectively) was already reached in the TLM-KTP arm after 9 weeks and thus even before the scheduled follow-up time point after 6 months for primary end point analysis.

Regarding functional, physical, and emotional domains separately, VHI subscale analysis revealed more and earlier significant differences between the treatment arms regarding functional and physical scores compared to the emotional set (Table 3).

Interestingly, the offer of postoperative speech therapy was appreciated by 6 patients. All of them were derived from the TLM-CO_2 group and received a varying number of speech therapy units. The number of therapeutic sessions ranged from 4 to 10 (4-7-7-9-10; for 1 subject, the number of therapeutic sessions was not determined).

Therefore, transoral microsurgery using the KTP laser appears to be functionally superior in high-grade glottic dysplasia as well as in early stage laryngeal cancer compared to the gold standard CO_2 laser–based method.

3.4 | Local control

Study-related observation period was set up for 24 weeks. During this follow-up time, 1 patient was seen with a recurrent disease after CO_2 laser treatment and was referred to

TABLE 2 VHI results given as delta from baseline (ΔVHI) at each postoperative follow-up interval (3, 6, 9, and 24 weeks) in both treatment arms (TLM-CO_2; TLM-KTP)

	ΔVHI_{3w}	**ΔVHI_{6w}**	**ΔVHI_{9w}**	**ΔVHI_{24w}**
TLM-CO_2	+15.8	+11.2	+7.6	+8.3
TLM-KTP	−3.3	−15.1	−26.0	−28.6

Obviously, primary end point referring to a clinically relevant VHI reduction ($\Delta VHI < -18.0$) was already reached in the TLM-KTP arm after 9 weeks and thus even before the scheduled primary analysis follow-up time point after 6 months / 24 weeks.
Abbreviations: TLM-CO_2, transoral laser microsurgery using the CO_2 laser; TLM-KTP, transoral laser microsurgery using the KTP laser; VHI, Voice Handicap Index-30; 3w, 3 weeks; 6w, 6 weeks; 9w, 9 weeks; 24w, 24 weeks.

TABLE 3 Total and subscale VHI scores displayed at baseline and during follow-up

	$VHI_{baseline}$ (TLM-CO_2 vs TLM-KTP)	VHI_{3w} (TLM-CO_2 vs TLM-KTP)	VHI_{6w} (TLM-CO_2 vs TLM-KTP)	VHI_{9w} (TLM-CO_2 vs TLM-KTP)	VHI_{24w} (TLM-CO_2 vs TLM-KTP)
Functional score	11.9 ± 9.4 vs 10.7 ± 9.5	21.0 ± 8.9 vs 9.8 ± 9.1*	18.8 ± 9.0 vs 6.3 ± 3.1*	17.4 ± 8.4 vs 3.1 ± 3.4*	17.4 ± 9.0 vs 2.8 ± 2.3*
Physical score	14.8 ± 11.3 vs 14.6 ± 11.6	21.8 ± 9.2 vs 15.0 ± 9.2	20.3 ± 8.8 vs 9.7 ± 3.1*	19.3 ± 6.2 vs 6.3 ± 4.7*	18.7 ± 10.9 vs 4.7 ± 3.4*
Emotional score	10.5 ± 10.0 vs 8.3 ± 9.5	14.8 ± 9.3 vs 10.2 ± 9.0	13.9 ± 9.6 vs 7.2 ± 6.8	12.7 ± 8.6 vs 2.8 ± 2.5*	14.0 ± 11.7 vs 2.1 ± 1.7
Total score	41.8 ± 26.4 vs 38.3 ± 25.5	57.6 ± 26.5 vs 35.0 ± 27.2	53.0 ± 25.7 vs 23.2 ± 10.4	49.4 ± 21.2 vs 12.3 ± 9.3*	50.1 ± 31.3 vs 9.7 ± 6.1*

While total scores were significantly reduced after 9 and 24 weeks, subscale analysis revealed more and earlier significant differences between the treatment arms regarding functional and physical domains compared to the emotional set (*$P < .05$).
Abbreviations: TLM-CO_2, transoral laser microsurgery using the CO_2 laser; TLM-KTP, transoral laser microsurgery using the KTP laser; VHI, Voice Handicap Index-30; 3w, 3 weeks; 6w, 6 weeks; 9w, 9 weeks; 24w, 24 weeks.

interdisciplinary tumor board–based salvage measures. In contrast, no subject was seen with a residual or recurrent disease after TLM-KTP during observation according to the prospective protocol.

In addition, local control rates and larynx preservation rates were analyzed by a retrospective chart review 3 years after termination of the prospective trial. One patient of the TLM-KTP group was lost to retrospective follow-up, and 1 subject of each group was excluded from analysis due to withdrawn consent. All remaining 17 laser-treated and prospectively analyzed patients were found alive (TLM-CO_2: 11; TLM-KTP: 6). No recurrent disease was detected in any of the reviewed patients treated by TLM-KTP—reflecting an excellent local control rate (6/6 = 100%). In contrast, beyond the 6-month time point, there were 2 additional recurrent dysplastic or invasive recurrences among the 11 patients treated with TLM-CO_2. With regard to 1 earlier recurrence, the overall local control rate after 3 years was only 73% (8/11) for TLM-CO_2. Larynx preservation rates were 100% in both groups after 3 years.

4 | DISCUSSION

There is a fundamental difference between KTP and CO_2 laser treatment concepts. KTP laser energy is absorbed by hemoglobin resulting in selective thermoablation and occlusion of microvessels, whereas CO_2 laser light is effective against ubiquitous tissue water resulting in quite precise cuts. In contrast to the CO_2 laser beam, which has to be directed manually, the KTP laser application affords less direct microscopic targeting by the surgeon due to laser light dispersion keeping a fiber-to-tissue distance. Another key issue is that technically, high-precision tumor removals are possible using the KTP laser because the delivery system is an extremely small glass fiber that can be angulated at a tangent around the curving vocal fold. Hence, TLM-KTP appears to be more easily performed in office-based settings even under the control of flexible endoscopy visualization and local anesthesia.[17] First clinical data have been presented on the office-based KTP laser applications in patients with premalignant lesions of the glottis (e.g. papillomatosis and dysplasia).[28]

In malignancy, the ablating KTP laser pulses are deliberately not only restricted to tumor tissue but also targeted at angiogenic microvessels around resection margins.[22] The European Laryngological Society classification of cordectomies distinguishes 6 types according to the extent of resection (type I: subepithelial; type II: subligamental; type III: intramuscular; type IV: complete cordectomy; type V: extended cordectomy; type VI: anterior commissurectomy). Regarding a non-cutting KTP laser in this study, clear cutoffs between European Laryngological Society type I-III cordectomies are missing and thus it was not possible to strictly adhere to this classification in our study. On the other hand, using the CO_2 laser with ultra-narrow margins of approximately 1 mm, it appears rather difficult to claim laser effects were limited to the superficial layer of the lamina propria (type I) or the superficial portion of the thyroarytenoid muscle (type II). However, all resections in this study were definitely not reaching the inner perichondrium of the thyroid lamina (type IV) or beyond (type V). Hence, grading the extent of resection in this study was not reliably feasible by means of distinguishing between type I, type II, or type III resections in both groups, respectively. This is in line with current publications that only distinguish between limited resections (types I-III) and extended resections (type IV-V).[29,30] Moreover, Greulich et al. most recently showed in a meta-analysis that there is no significant difference in functional voice outcome comparing true European Laryngological Society type I/II resections with type III cordectomies.[31] Although CO_2 laser effects can be further modified by more or less focused beams, lower power settings, and pulsed dye mode, for comparability 4.5 W was chosen in this trial for both laser applications clearly contrasting pulsed KTP laser treatment with continuous mode CO_2 laser–based resections. However, collateral tissue damage by cutting CO_2 lasers might be reduced by altered settings that were not studied in detail in this phase II trial.

Generally, a sophisticated preoperative staging with regard to the depth of infiltration remains a challenge due to limitations of stroboscopic mucosal wave distinguishing epithelial atypia and microinvasive cancer.[32] Some phonosurgeons use laryngomicroinjection to check invasion beyond the subepithelial lamina and to protect pliable tissue during resection.[33] However, to avoid any microtrauma to the tumor stroma biasing our comparative trial between two laser applications, no microinjections were performed before resection in this study.

With regard to functional voice outcome, it is important to mention that also RT results in acute (7.7%) or late (3.5%) CTCAE grade 3/4 dysphonic symptoms[4] defined as "severe voice changes including predominantly whispered speech that may even require frequent repetition or face-to-face contact for understandability or even assistive technology" (CTCAE version 4 according to NIH Publication No. 09-5410). Hence, late dysphonia at least as grade 1 (mild) or 2 (moderate) side effect appears as the most frequent and most serious side effect even after nonsurgical treatment of early glottic cancer.[10] Among other voice-affecting side effects of RT is laryngeal edema.[34,35] This can often be avoided using lasers for microsurgical treatments. On the other hand, surgical measures in early glottic lesions almost inevitably result in loss of pliable functional lamina propria of the glottis responsible for vibration and thus phonatory sound formation.[10] Wound healing and scarring usually does not adequately compensate the loss of vibrating tissue. Hence, Greulich et al. reported in a meta-analysis referring the lack of randomized trials that VHI scores appear not to be significantly different after TLM-CO_2 and RT, respectively.[31] Although voice outcome after CO_2-based TLM is likely to remain affected to some extent, functional deficits are often considered to be acceptable in early glottic cancer.[36]

Functional voice is rarely measured by validated instruments in prospective studies, let alone applying all phonosurgical parameters proposed according to the Guideline elaborated by the Committee on Phoniatrics of the European Laryngological Society for phonosurgery of benign lesions.[26,37] Concerning malignant lesions, a German interdisciplinary Delphi consensus conference gathering head and neck surgeons, phoniatric specialists, speech therapists, and radiotherapists was held to establish a guideline for a standardized outpatient-based functional follow-up in patients with head and neck cancer. Self-rating VHI evaluation was identified as a relevant and recommended outcome parameter for functional voice.[38] Accordingly, Keilmann et al. reported varying long-term functional outcome values including VHI self-ratings at postoperative follow-ups for 3-6 months after CO_2 laser resection of T1-T2 glottic cancer.[29] Consequently, the primary end point of our study was functional voice outcome during a 6-month follow-up by a VHI version validated in German.[25]

To our knowledge, this is the first randomized, prospective, single-blinded, and controlled trial regarding TLM-KTP effects on functional voice in early glottic cancer. Differentiating between noninvasive (high-grade dysplasia, Tis) and invasive lesions (T1a glottic carcinoma), proportions were comparable between both groups (TLM-CO2: 69.2% vs TLM-KTP: 62.5%). However, regarding the lack of clear cutoff lines for pathologists usually working with small vocal fold biopsies to prove malignancy, inclusion was limited to the mentioned criteria of early glottic malignancy without further differentiation. Zeitels et al. reported in a retrospective series of 92 patients with early glottic cancer (T1: 64; T2: 28) favorable improvements of objective acoustic (perturbation, noise-to-harmonics ratio) and aerodynamic (subglottic pressure, vocal efficiency) parameters of functional voice, respectively.[21] In addition, subjective voice-related Quality of Life (QOL) assessments confirmed functional benefits of KTP laser–based angiolytic treatment as well. Comparably, Murono et al. reported favorable voice outcomes according to a single self-rating evaluation of voice-related QOL and VHI-10 after 6 months.[22]

As involvement of the anterior commissure and potential postoperative anterior webbing are known to be independent risk factors for postoperative voice quality,[39] T1b tumors with obvious anterior commissure invasion were explicitly excluded in this study.

So far, there is no clear evidence of the benefit of postoperative speech therapy after TLM: Sittel et al. found that phonetograms as well as investigator-independent ratings of communication abilities did not differ significantly comparing groups after TLM-CO_2 with or without postoperative speech therapy.[40] However, in our prospective study, postoperative speech therapy was not mandatory, but it was offered to every included patient. Probably, only patients with relevant speech problems decided to see a speech therapist. The poorer voice results after CO_2 laser surgery therefore also resulted in higher claims of speech therapy in this group. Nevertheless, VHI scores after TLM-CO_2 remained significantly worse comparing with patients after TLM-KTP. In contrast, no patient of the TLM-KTP group felt the necessity of postoperative speech therapy. Finally, the favorable voice outcome after TLM-KTP resulted in a significant VHI decrease after TLM-KTP almost comparable to scores usually found in healthy voice users. In a detailed VHI-30 subscale analysis, reduced total VHI scores were reflected especially by lower functional and physical domain scores as well.

Although the sample size did not allow a multivariate analysis, usual confounding factors (age, sex, stage/site) were documented and did not reveal obvious differences between both groups. However, these factors including smoking habits may be more relevant for oncological survival rate end points in phase III studies than for functional voice outcome analysis in this phase II trial. A subsequent large-scale multicenter phase III trial in the future will allow adequate multivariate analysis with regard to these confounders in a more reliable manner.

Concerning oncological outcome a 6-month observation would have been rather short. Day et al. recently reported a rate of 5-year local control of 83% in T1 glottic carcinoma using TLM-CO_2.[41] Although our prospective trial was not powered to measure local control rate, we added a retrospective chart analysis after termination of the prospective trial. So, we were able to report 3-year local control rate for TLM-KTP. Interestingly, no recurrent disease was documented after TLM-KTP reflecting a remarkable 100% local control rate after 3 years. In comparison, 5-year local control rate using RT applying 60-70 Gy are ranging from 86% to 96% as reported by Robert et al. most recently.[4]

In contrast, we detected additional recurrent high-grade dysplastic or invasive findings following TLM-CO_2 resulting in a total of 3 recurrences including 1 case already documented in the prospective trial. Thus, in our analysis, local control rate was only 75% after TLM-CO_2. In larger retrospective studies of outcome after TLM-CO_2–based resections of T1a glottic carcinomas, higher 5-year local control rates are possible but recurrence appeared also in approximately 14.4%.[36]

Our encouraging local control rate data after TLM-KTP are in line with previous data of a noncontrolled retrospective analysis based on a larger series showing disease control rates of 79/82 (96%) 3 years after KTP laser application in T1 lesions.[23] Independently, Murono et al. found in a retrospective analysis of 24 patients with T1a glottic cancer treated with TLM-KTP, a local control rate of 91.7%.[22]

Short treatment duration, no risk of irradiation-induced malignancy, the possibility of repetitive applications, and more remaining salvage options favor laser-based TLM compared to RT especially in vocal fold leukoplakia.[42] In a recent retrospective study, oncological outcome after TLM-KTP and RT appears to be comparable in T1 glottic squamous cell carcinoma.[43] In a small cohort of 20 patients with recurrent glottic cancer (rT1-rT2), TLM-KTP was even used as a salvage measure in failed RT.[44] Although 80% of the treated patients were reported free of disease after 2 years, the concept of TLM-KTP should currently only be applied within GCP-ICH-conform clinical trials.

With regard to the gold standard CO_2 laser for TLM, we here present data of excellent voice outcome and adequate oncological safety using the KTP laser for treatment of early glottic cancer.

Besides malignant transformation of papillomatosis, there is an ongoing controversial debate about a non-smoking-related and possibly virally induced subentity in laryngeal cancer.[45,46] Although stratification of the study was not performed according to Human Papillomavirus (HPV)- status, TLM-KTP may also provide numerous advantages compared to “single-use” RT considering HPV-associated multifocal malignant transformation and metachronous lesions.

5 | CONCLUSIONS

In this prospective, randomized, single-blinded investigator initiated trial with a control group, TLM using an angiolytic KTP laser resulted in superior functional voice outcomes in early stage laryngeal cancer compared to TLM using the gold standard CO_2 laser. In addition, KTP laser–based TLM appeared oncologically safe, at least reflected by a favorable retrospective 3-year follow-up analysis.

In conclusion, this study provides preliminary evidence to suggest that, in selected cases of Tis and early T1a squamous cell carcinoma of the glottis, TLM-KTP may be able to offer improved voice preservation and similar oncological control compared to TLM-CO_2 at least in the first 6 months after treatment.

Further functional and outcome evaluation of KTP laser application enrolling patients with early laryngeal cancer in larger phase II or III multicenter trials is warranted.

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REFERENCES

1. Rosier JF, Gregoire V, Counoy H, 7et al. Comparison of external radiotherapy, laser microsurgery and partial laryngectomy for the treatment of T1N0M0 glottic carcinomas: a retrospective evaluation. *Radiother Oncol.* 1998;48(2):175–83.
2. Stoeckli SJ, Schnieper I, Huguenin P, Schmid S. Early glottic carcinoma: treatment according patient's preference? *Head Neck.* 2003;25(12):1051-1056.
3. Spector JG, Sessions DG, Chao KS, et al. Stage I (T1 N0 M0) squamous cell carcinoma of the laryngeal glottis: therapeutic results and voice preservation. *Head Neck.* 1999;21(8):707-717.
4. Robert A, Pointreau Y, Janoray G, et al. A large French multicenter retrospective series of T1-T2N0 vocal cords carcinomas treated with exclusive irradiation. *Cancer Radiother.* 2017;21(4):286-290.
5. Lyhne NM, Johansen J, Kristensen CA, et al. Pattern of failure in 5001 patients treated for glottic squamous cell carcinoma with curative intent - a population based study from the DAHANCA group. *Radiother Oncol.* 2016; 118(2):257-266.
6. Abdurehim Y, Hua Z, Yasin Y, Xukurhan A, Imam I, Yuqin F. Transoral laser surgery versus radiotherapy: systematic review and meta-analysis for treatment options of T1a glottic cancer. *Head Neck.* 2012;34(1):23-33.
7. Schrijvers ML, van Riel EL, Langendijk JA, et al. Higher laryngeal preservation rate after CO2 laser surgery compared with radiotherapy in T1a glottic laryngeal carcinoma. *Head Neck.* 2009;31(6):759-764.

8. Steiner W. Results of curative laser microsurgery of laryngeal carcinomas. *Am J Otolaryngol.* 1993;14(2):116-121.
9. Vaughan CW, Strong MS, Jako GJ. Laryngeal carcinoma: transoral treatment utilizing the CO2 laser. *Am J Surg.* 1978;136(4):490-493.
10. Sjogren EV, van Rossum MA, Langeveld TP, et al. Voice outcome in T1a midcord glottic carcinoma: laser surgery vs radiotherapy. *Arch Otolaryngol Head Neck Surg.* 2008;134(9):965-972.
11. Rosen CA, Murry T, Zinn A, Zullo T, Sonbolian M. Voice handicap index change following treatment of voice disorders. *J Voice.* 2000;14(4):619-623.
12. Loughran S, Calder N, MacGregor FB, Carding P, MacKenzie K. Quality of life and voice following endoscopic resection or radiotherapy for early glottic cancer. *Clin Otolaryngol.* 2005;30(1):42-47.
13. Portone CR, Hapner ER, McGregor L, Otto K, Johns MM III. Correlation of the voice handicap index (VHI) and the voice-related quality of life measure (V-RQOL). *J Voice.* 2007;21(6):723-727.
14. Ledda GP, Grover N, Pundir V, Masala E, Puxeddu R. Functional outcomes after CO2 laser treatment of early glottic carcinoma. *Laryngoscope.* 2006; 116(6):1007-1011.
15. Goor KM, Peeters AJ, Mahieu HF, et al. Cordectomy by CO2 laser or radiotherapy for small T1a glottic carcinomas: costs, local control, survival, quality of life, and voice quality. *Head Neck.* 2007;29(2):128-136.
16. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med.* 1971;285(21):1182-1186.
17. Zeitels SM, Burns JA, Lopez-Guerra G, Anderson RR, Hillman RE. Photoangiolytic laser treatment of early glottic cancer: a new management strategy. *Ann Otol Rhinol Laryngol Suppl.* 2008;199:3-24.
18. Broadhurst MS, Akst LM, Burns JA, et al. Effects of 532 nm pulsed-KTP laser parameters on vessel ablation in the avian chorioallantoic membrane: implications for vocal fold mucosa. *Laryngoscope.* 2007;117(2):220-225.
19. Burns JA, Kobler JB, Heaton JT, Anderson RR, Zeitels SM. Predicting clinical efficacy of photoangiolytic and cutting/ablating lasers using the chick chorioallantoic membrane model: implications for endoscopic voice surgery. *Laryngoscope.* 2008;118(6):1109-1124.
20. Burns JA, Lopez-Guerra G, Kobler JB, Faquin W, LeClair M, Zeitels SM. Pulsed potassium-titanyl-phosphate laser photoangiolytic treatment of mucosal squamous cell carcinoma in the hamster cheek pouch. *Laryngoscope.* 2011;121(5):942-946.
21. Friedman AD, Hillman RE, Landau-Zemer T, Burns JA, Zeitels SM. Voice outcomes for photoangiolytic KTP laser treatment of early glottic cancer. *Ann Otol Rhinol Laryngol.* 2013;122(3):151-158.
22. Murono S, Endo K, Kondo S, Wakisaka N, Yoshizaki T. Oncological and functional outcome after transoral 532-nm pulsed potassium-titanyl-phosphate laser surgery for T1a glottic carcinoma. *Lasers Med Sci.* 2013; 28(2):615-619.
23. Zeitels SM, Burns JA. Oncologic efficacy of angiolytic KTP laser treatment of early glottic cancer. *Ann Otol Rhinol Laryngol.* 2014;123(12):840-846.
24. van Loon Y, Sjogren EV, Langeveld TP, Baatenburg de Jong RJ, Schoones JW, van Rossum MA. Functional outcomes after radiotherapy or laser surgery in early glottic carcinoma: a systematic review. *Head Neck.* 2012;34(8):1179-1189.
25. Nawka T, Wiesmann U, Gonnermann U. Validation of the German version of the voice handicap index. *HNO.* 2003;51(11):921-930.
26. Dejonckere PH, Bradley P, Clemente P, et al. A basic protocol for functional assessment of voice pathology, especially for investigating the efficacy of (phonosurgical) treatments and evaluating new assessment techniques. Guideline elaborated by the Committee on Phoniatrics of the European Laryngological Society (ELS). *Eur Arch Otorhinolaryngol.* 2001;258(2):77-82.
27. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *PLoS Med.* 2010; 7(3):e1000251.
28. Zeitels SM, Akst LM, Burns JA, Hillman RE, Broadhurst MS, Anderson RR. Office-based 532-nm pulsed KTP laser treatment of glottal papillomatosis and dysplasia. *Ann Otol Rhinol Laryngol.* 2006;115(9): 679-685.
29. Keilmann A, Napiontek U, Engel C, Nakarat T, Schneider A, Mann W. Long-term functional outcome after unilateral cordectomy. *ORL J Otorhinolaryngol Relat Spec.* 2011;73(1):38-46.
30. Bahannan AA, Slavicek A, Cerny L, et al. Effectiveness of transoral laser microsurgery for precancerous lesions and early glottic cancer guided by analysis of voice quality. *Head Neck.* 2014;36(6):763-767.
31. Greulich MT, Parker NP, Lee P, Merati AL, Misono S. Voice outcomes following radiation versus laser microsurgery for T1 glottic carcinoma: systematic review and meta-analysis. *Otolaryngol Head Neck Surg.* 2015;152(5): 811-819.
32. Colden D, Zeitels SM, Hillman RE, Jarboe J, Bunting G, Spanou K. Stroboscopic assessment of vocal fold keratosis and glottic cancer. *Ann Otol Rhinol Laryngol.* 2001;110(4):293-298.
33. Burns JA, Friedman AD, Lutch MJ, Zeitels SM. Subepithelial vocal fold infusion: a useful diagnostic and therapeutic technique. *Ann Otol Rhinol Laryngol.* 2012;121(4):224-230.
34. Khan MK, Koyfman SA, Hunter GK, Reddy CA, Saxton JP. Definitive radiotherapy for early (T1-T2) glottic squamous cell carcinoma: a 20 year Cleveland Clinic experience. *Radiat Oncol.* 2012;7:193.
35. Smee RI, Meagher NS, Williams JR, Broadley K, Bridger GP. Role of radiotherapy in early glottic carcinoma. *Head Neck.* 2010;32(7):850-859.
36. Canis M, Ihler F, Martin A, Matthias C, Steiner W. Transoral laser microsurgery for T1a glottic cancer: review of 404 cases. *Head Neck.* 2015;37(6): 889-895.
37. DeJonckere PH, Crevier-Buchman L, Marie JP, Moerman M, Remacle M, Woisard V. Implementation of the European laryngological society (ELS) basic protocol for assessing voice treatment effect. *Rev Laryngol Otol Rhinol.* 2003;124(5):279-283.
38. Tschiesner U, Stier-Jarmer M, Strieth S, et al. Development of an ICF-based clinical practice guideline for the assessment of function in head and neck cancer. *Laryngorhinootologie.* 2013;92(5):314-325.
39. Peretti G, Nicolai P, Redaelli De Zinis LO, et al. Endoscopic CO2 laser excision for tis, T1, and T2 glottic carcinomas: cure rate and prognostic factors. *Otolaryngol Head Neck Surg.* 2000;123(1 Pt 1):124-131.
40. Sittel C, Eckel HE, Eschenburg C. Phonatory results after laser surgery for glottic carcinoma. *Otolaryngol Head Neck Surg.* 1998;119(4):418-424.
41. Day AT, Sinha P, Nussenbaum B, Kallogjeri D, Haughey BH. Management of primary T1-T4 glottic squamous cell carcinoma by transoral laser microsurgery. *Laryngoscope.* 2017;127(3):597-604.
42. Koss SL, Baxter P, Panossian H, Woo P, Pitman MJ. Serial in-office laser treatment of vocal fold leukoplakia: disease control and voice outcomes. *Laryngoscope.* 2017;127(7):1644-1651.
43. Ahmed J, Ibrahim ASG, Freedman ML, Rosow DE. Oncologic outcomes of KTP laser surgery versus radiation for T1 glottic carcinoma. *Laryngoscope.* 2018;128(5):1052-1056.
44. Barbu AM, Burns JA, Lopez-Guerra G, Landau-Zemer T, Friedman AD, Zeitels SM. Salvage endoscopic angiolytic KTP laser treatment of early glottic cancer after failed radiotherapy. *Ann Otol Rhinol Laryngol.* 2013;122(4):235-239.
45. Lee SY, Cho NH, Choi EC, Kim WS, Kim SH. Is human papillomavirus a causative factor of glottic cancer? *J Voice.* 2011;25(6):770-774.
46. Zeitels SM. Glottic cancer: a metamorphosing disease. *Ann Otol Rhinol Laryngol.* 2016;125(6):452-456.

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