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 CO2 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-CO2 (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-CO2. No relapse occurred after TLM-KTP in contrast to one recurrence after TLM-CO2 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, CO2 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 CO2 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...
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 phonosurgery 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 CO2 lasers.9 Meanwhile it is well accepted that total cordectomy is not always oncologically necessary using a CO2 laser.15

Inspired by J. Folkman’s paradigm-shifting concept on the oncological potential of anti-angiogenesis16 that has led to multiple bench-to-bedside developments in chemotherapy, Zeitels et al. pioneered a novel translational procedure of selecting 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 “angio-lytic 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 outcome21,22 and oncologic efficacy after TLM-KTP22,23 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 CO2 laser (Sharplan 40 C; λ = 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...
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 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.

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 $\pm$ 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...
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-CO2 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

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**FIGURE 2**  Patient participation flow diagram, according to the CONSORT 2010 statement.27 TLM-CO2, transoral laser microsurgery using the CO2 laser; TLM-KTP, transoral laser microsurgery using the KTP laser.

| Enrollment | assessed for eligibility (n=27) |
|------------|----------------------------------|
|            | excluded (n=6)                   |
|            | • not meeting inclusion criteria (n=4) |
|            | • declined to participate (n=2)   |
|            | randomized (n=21)                |
|            | allocated to TLM-CO2 (n=13)      |
|            | • received allocated intervention (n=12) |
|            | • failed anesthesiological clearance (n=1) |
|            | allocated to TLM-KTP (n=8)       |
|            | • received allocated intervention (n=8) |
|            | • did not receive allocated intervention (n=0) |
|            | lost to follow-up                 |
|            | • due to withdrawal of consent (n=1) |
|            | • due to compliance (n=5)         |
|            | analyzed (n=21) / excluded from analysis (n=0) |

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**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-CO2: 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-CO2, transoral laser microsurgery using the CO2 laser; pre, preoperative microlaryngoscopy; intra, intraoperative microlaryngoscopy; post, postoperative microlaryngoscopy; 6w, 6 weeks [Color figure can be viewed at wileyonlinelibrary.com]
Abbreviations: TLM-CO₂, transoral laser microsurgery using the CO₂ laser; TLM-KTP, transoral laser microsurgery using the KTP laser; Tis, carcinoma in situ; SD, standard deviation.

TLM-KTP, transoral laser microsurgery using the KTP laser; 3w, 3 weeks; 6w, 6 weeks; 9w, 9 weeks; 24w, 24 weeks. 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-CO₂ did not deteriorate functional voice in a clinically relevant manner at any time point (| ΔVHI | <18). In contrast, an obviously clinically relevant VHI-30 reduction (| ΔVHI | >18 or ΔVHI < −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-CO₂ 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 CO₂ 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 CO₂ laser treatment and was referred to

| TABLE 1 | Medical history data of the experimental arm (TLM-KTP) and the control group (TLM-CO₂) at baseline |
|----------|------------------------------------------------------------------------------------------------|
|          | TLM-CO₂ | 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 |

| 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-CO₂; TLM-KTP) |
|----------|------------------------------------------------------------------------------------------------|
|          | Δ VHI₃w | Δ VHI₆w | Δ VHI₉w | Δ VHI₂₄w |
| TLM-CO₂  | +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 (ΔVHI < −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.
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 withdrawal consent. All remaining 17 laser-treated and prospectively analyzed patients were found alive (TLM-CO2: 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-CO2. With regard to 1 earlier recurrence, the overall local control rate after 3 years was only 73% (8/11) for TLM-CO2. Larynx preservation rates were 100% in both groups after 3 years.

### DISCUSSION

There is a fundamental difference between KTP and CO2 laser treatment concepts. KTP laser energy is absorbed by hemoglobin resulting in selective thermoablation and occlusion of microvessels, whereas CO2 laser light is effective against ubiquitous tissue water resulting in quite precise cuts. In contrast to the CO2 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. 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). In malignancy, the ablating KTP laser pulses are deliberately not only restricted to tumor tissue but also targeted at angiogenic microvessels around resection margins. 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 cut-offs 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 CO2 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). 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 II/II resections with type III cordectomies. Although CO2 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 CO2 laser–based resections. However, collateral tissue damage by cutting CO2 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. Some phonosurgeons use laryngomicroinjection to check invasion beyond the subepithelial lamina and to protect pliable tissue during resection. However, to avoid any microtrauma to the tumor.

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

|          | VHI<sub>base</sub> (TLM-CO2 vs TLM-KTP) | VHI<sub>phys</sub> (TLM-CO2 vs TLM-KTP) | VHI<sub>em</sub> (TLM-CO2 vs TLM-KTP) | VHI<sub>dif</sub> (TLM-CO2 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).
stoma 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 symptoms4 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 phonsurgery 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. Differrentiating between noninvasive (high-grade dysplasia, Tis) and invasive lesions (T1a glottic carcinoma), proportions were comparable between both groups (TLM-CO$_2$: 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. Zeilets 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-CO2 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-CO2. In larger retrospective studies of outcome after TLM-CO2–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 CO2 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 angioytic KTP laser resulted in superior functional voice outcomes in early stage laryngeal cancer compared to TLM using the gold standard CO2 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-CO2 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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