CO_2 laser surgery for laryngeal cancer: A meta-analysis and systematic review

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► ***Review article***

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ABSTRACT

Background: To evaluate the effectiveness and safety of CO_2 laser surgery (CO_2-LS) in treating patients with laryngeal cancer (LC) by comparing it with other therapeutic modalities. ***Materials and Methods:*** The randomized controlled trials of CO_2-LS for LC from the creating day of databases to February 2023 were searched on PubMed, Embase, Web of science databases and the Cochrane library, without language restrictions. Data were extracted independently by two investigators, followed by the article quality assessment and cross-check. This meta-analysis involved five studies with good quality, covering 405 LC patients. ***Results:*** Data analysis demonstrated a higher voice handicap index (VHI) in CO_2-LS-treated patients compared to the control group at 6 months postoperatively [Odds Ratio (OR) = 1.12, 95% confidence intervals (CI) (0.19, 2.04), P = 0.02], but a lower shimmer value at 3 months postoperatively [OR = 1.04, 95% CI (0.92, 1.17), P<0.00001]. The control group exhibited a lower postoperative mucosal stability compared to the CO_2-LS group [OR = 0.41, 95%CI (0.21, 0.79), P=0.008]. The subgroup analysis showed more operation time [OR = 3.48, 95% CI (2.86, 4.10), P<0.00001] compared to the CO_2-LS group, with statistically significant difference. ***Conclusions:*** Comparing to other treatment modalities, CO_2-LS is advantageous in mucosal recovery in LC patients, but not in postoperative survival and vocal quality.

INTRODUCTION

Head and neck cancer (HNC) involves oral cavity cancer (OCC), pharyngeal cancer (PC), and laryngeal cancer (LC) [1]. Among them, LC accounts for 1% of all malignant tumors, which can be divided into glottic, supraglottic, subglottic and metastatic types, where the glottic laryngeal cancer is the most common, accounting for approximately 50% of laryngeal tumors [2, 3]. At present, it is commonly believed that the LC is related to dietary, environmental, alcohol, tobacco, and [4] occupational exposure risks [5], of which dietary factors may account for 10-15% of cases in Europe [6]. Despite the clinical progress in diagnosis and treatment of laryngeal cancer in recent years, the overall survival rate is still low. According to statistical analysis, over 80,000 people die from the laryngeal cancer each year worldwide [3], and finding a reasonable and effective treatments has been a major challenge for clinicians [7, 8].

Due to the hidden nature of LC in early stage, most of the patients diagnosed as this disease are at middle to late stage with the significant experience of discomfort such as dysphagia, breathlessness, hoarseness, etc., which, to a certain extent, will increase the difficulty in the subsequent treatment [9-12]. Selecting the reasonable and effective treatment modalities in the early stage of LC can contribute a lot to the prognosis and survival quality of patients. The available approaches mainly depend on the type of cancer and the spreading process of tumor cells, including traditional surgery, transoral robotic surgery, radiotherapy, chemotherapy, targeted drug therapy and immunotherapy [13]. Surgery is usually the premium for patients with LC, which can be categorized as minimally invasive or endoscopic surgery, vocal cord resection, laryngectomy, pharyngeal resection and cervical lymphadenectomy [14, 15]. Despite the effective clinical outcomes achieved by surgery, the transcervical or mandibular incision approach may lead to the risk of intraoperative hemorrhage, loss of pharyngeal function and

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postoperative infection. Finding new techniques to reduce the incidence of postoperative complications has become an urgent requirement.

Carbon dioxide laser surgery (CO_2 -LS) was employed to treat LC for the first time in 1975 [16], which allows for the noninvasion in the neck, high precision, small damage, fast recovery and good preservation of laryngeal function. In recent years, CO_2 -LS has been widely applied in benign tumors and benign lesions, precancerous lesions and early LC for otorhinolaryngology head and neck surgery [17, 18]. The relevant studies on CO_2 -LS for the treatment of pharyngeal cancer are most focused on small-sample studies or single-center studies, and the randomized controlled trials are lacked, while previous systematic evaluations on the efficacy are controversial. In the present study, we selected the published literature touching upon the comparative efficacy of CO_2 -LS for the treatment of pharyngeal cancer and performed a meta-analysis of the oncological and functional outcomes of the different treatment modalities. To the best of our knowledge, there are no meta-analyses that directly compare the efficacy of CO_2 -LS treatment. This study for the first time demonstrates the efficacy and safety of CO_2 -LS in the treatment of pharyngeal cancer, and provides a certain medical basis for clinical therapeutic determination.

MATERIALS AND METHODS

Writing principles and registration

This study was conducted with reference to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was completed and registered with INPLASY (INPLASY202380035). The record of this study has been published on website (inplasy.com, DOl number: 10.37766/inplasy2023.8.0035).

Study subjects and inclusion/exclusion criteria

The patients with pathologically confirmed LC without contraindications to drug use, regardless of age, gender, etiology, or ethnic group were involved in this study. The literature with publicly published controlled trials in any language and those contained abstracts with sufficient data but did not publish full information were all selected, covering the blinded and unblinded trials. Exclusion criteria for this study were (1) duplicate published literature; (2) duplicate studies or studies with incomplete data or multiple studies from the same center with duplicate data, whichever was the most recent; (3) conference abstracts, case studies, or literature that did not report relevant data; (4) literature on combination of treatments by multiple modalities; and (5) literature that was not available in the original language.

Intervention and outcome indicators

The LC patients were grouped into the experimental group and the intervention group according to whether employing CO_2 -LS or the other forms of treatment. Outcome metrics involved 3-year postoperative overall survival, 3-year postoperative recurrence, postoperative harmonics-to-noise ratio (HNR), postoperative voice handicap index (VHI), postoperative vocal gate recovery, and voice acoustic analysis (jitter and shimmer).

Retrieval and Data Organization

Search strategy

As of February 2023, we searched PubMed, Embase, and Web of science databases with no language restrictions. Combining indexed and free text terms, we searched the databases “carbon dioxide laser surgery" "pharyngeal cancer." We modified the limitations of the search terms per database. See Appendix 1- 3 for search strategies.

Additionally, we searched references of classic review articles and the WHO's International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch/) to supplement our study. The management of literature was done through the use of endnote software (EndNote X9, Australia).

Literature screening and data extraction

Literature titles and abstracts were first read by 2 researchers to eliminate literature that did not meet the criteria, and the full text was read independently, and literature that might meet the criteria was included after the initial screening; uncertain literature was discussed and a decision was made on whether to include it or not. If disagreement remained, a third researcher adjudicated. Extracts included: time of publication and authors of the included studies, basic clinical characteristics of the included subjects, parameter settings of the test and control groups, outcome indicators, and adverse reactions or adverse events. In the case of multi-arm studies, only data that met the inclusion criteria and were relevant to the purpose of this study were extracted. If there was disagreement on data extraction, the extraction was discussed again until there was a unity of opinion, and if there was still disagreement, a third investigator adjudicated.

Quality assessment of literature

Two independent researchers used the Cochrane Collaboration risk of bias tool to evaluate the quality of the articles in the included randomized controlled trial (RCTs). The Cochrane risk of bias was mainly evaluated in the following areas: blinding of investigators and subjects, blinding of study endpoints, generation of randomized sequences, concealment of allocation, completeness of outcome data, selective reporting of findings, and other biases,

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etc. The results included: low risk, unclear risk and high risk of bias. Outcomes included: low risk of bias, unclear risk of bias, and high risk of bias. If two investigators did not agree on the quality assessment, a third investigator adjudicated.

Statistical analyses

Data were analyzed using RevMan software (RevMan, version 5.4, Copenhagen). Visual Analogue Scale (VAS) or numerical rating scale (NRS) as continuous variables were expressed as Mean Difference (MD) and 95% confidence intervals (CI). Data of the same type were pooled using Standardized Mean Difference (SMD). When the literature data existed only in graphical form, we first sent an email to the original authors to request the data, and if no valid response was received, the data were extracted using the Getdata graph digitizer software. The extraction process was repeated three times and the mean value was taken for inclusion in the final analysis. When the literature data were not in the standardized mean (standard deviation) form, we converted them to the standardized mean (standard deviation) form by using the "calculator" function of the RevMan software and the online website (https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html) for conversion [35-37]. The data were first tested for skewness, and if there was no obvious skewness in the distribution, the median (range)-mean (SD) data were transformed. Transformations were performed for variables with different units.

The incidence of adverse reactions as a dichotomous variable was expressed using odds ratio (OR). A chi-square test was used to test for heterogeneity at a level of P = 0.1.

If P ≤ 0.1 and I^2 > 50% indicated significant heterogeneity in the data, the random effects model was used; Whenever P > 0.1 and I2 > 50% indicated that heterogeneity was not significant, the fixed effects model was used.

Sensitivity analyses and subgroup analyses

If heterogeneity existed between similar studies, subgroup analyses would be further performed based on possible heterogeneity factors and, if required, sensitivity analyses were employed to test the stability of the results, using article-by-article exclusion and replacement effects modelling.

Publication bias test and Egger's test

If the number of included studies was exceeded 6, the publication bias of the included studies would be analyzed using the "funnel plot" function of RevMan 5.3 software. If there existed bias in the literature, an asymmetric funnel plot would appear, and the more obvious the asymmetry was, the greater the degree of bias was. The Egger's test was performed using R software (R package SIMEX, version 1.7; R Foundation for Statistical Computing, Vienna, Austria), $p<0.05$ indicated the significant publication bias.

RESULTS

Literature search

A total of 3,640 papers were obtained after the initial review, of which 1543 were duplicates, 1844 abstracts did not meet our requirements. Finally, we checked 253 articles for completeness and selected 5 for inclusion in the final analysis (figure 1).

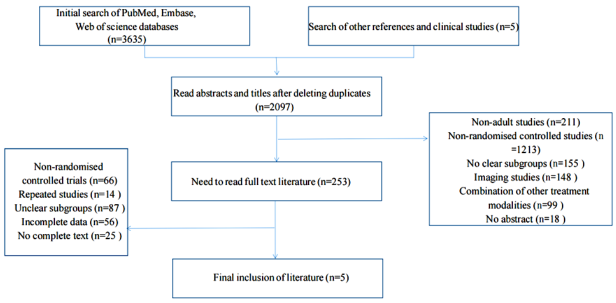

Figure 1. Map of the data retrieval process and basic information about the included studies.

Characteristics of the included studies

Among the 5 selected studies, with publication dates from 2014 to 2019, 405 LC patients were included in the study. The basic characteristics of the included literature are shown in table 1. All of the literature referred to ethnicity and interventions with a clear basis for subgrouping. The experimental group were intervened by CO_2-LS, and the control group by radiofrequency ablation (RFA), potassium-titanyl-phosphate (KTP) laser, and Radiation therapy. And no significant differences were found in gender and age between the experimental group and the control group in all covered trails (p≥0.05).

Table 1. Basic characteristics of the included literature.

No	First author and year of publication	Nation	Cancer	Control group intervention	N	Trial group intervention	N
1	Zhang 2018 [18]	China	glottic cancer	LTP-RFA	66	CO2 -LS	65
2	Sebastian 2019[19]	Germany	early glottic cancer	KTP laser	8	CO2 -LS	12
3	Yonatan 2019[20]	United States	early glottic squamous cell carcinoma	KTP-ablation surgery	12	CO2 -LS	12
4	Shuang 2016[21]	China	early glottic cancer	RFA	97	CO2 -LS	71
5	Aaltonen 2014[22]	Germany	Early Vocal Cord Cancer	Radiation therapy	31	CO2 -LS	31

Note: RFA, radiofrequency ablation;CO_2-LS, CO_2 laser surgery; KTP, potassium-titanyl-phosphate.

Literature quality assessment

Among the 5 included studies, one did not mention the random sequence generation method [22], and one lacked the allocation scheme concealment [19]. All studies reported full findings

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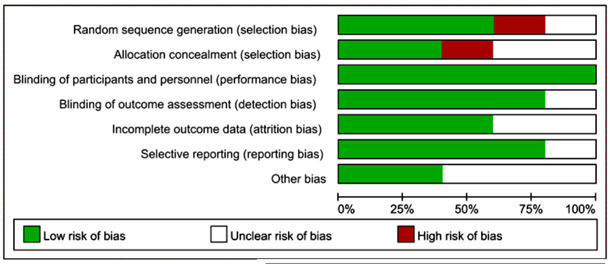
with blinded designs for subjects and investigators except for 1 study [19]. The other outcome bias was disproved in 3 studies and ignored in 2. The risk of bias evaluation of the included literature is shown in figure 2 (a, b).



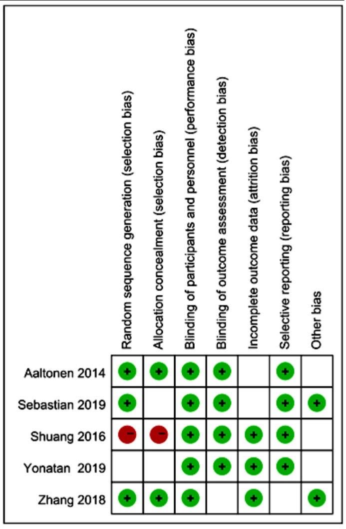


Figure 2. Results of risk of bias analyses of included studies (**a.** Risk of bias graph; **b.** Percentage of items that created risk of bias for all included studies)

Note: Random sequence generation (selection bias): random sequence generation (selection bias); Allocation concealment (selection bias): allocation concealment (selection bias); Blinding of participants and personnel (performance bias): blinding of patients, trial personnel (implementation bias); Blinding of outcome assessment (detection bias): blinding of outcome assessors (measurement bias); Incomplete outcome data (attrition bias): Incomplete outcome data (follow-up bias); Selective reporting (reporting bias): selective reporting (reporting bias); Other bias: other bias; Low risk of bias; Unclear risk of bias (Low risk of bias; Unclear risk of bias; High risk of bias.

Results of meta-analysis

The analysis was performed using a fixed-effects model (figure 3a), no significant difference was found in overall survival at 3 years postoperatively between all patients: [OR = 1.72, 95% CI (0.80, 3.69), p = 0.17]. And a significant difference (figure 3b) in VHI at 6 months postoperatively was found between all patients: [OR = 1.12, 95% CI (0.19, 2.04), p = 0.02]. No significant difference in recurrence (figure 3c) was found at 3 years postoperatively between all patients: [OR = 1.32, 95% CI (0.58, 3.02), p = 0.50]. The postoperative 3-month shimmer significantly differed (figure 3d) between all patients: [OR =0.99, 95% CI (0.87, 1.11), p<0.00001]. A random effects model was employed for analysis, and no significant difference was found (figure 3e) in HNR at 3 months postoperatively between all patients: [OR = 3.80, 95% CI (-0.16, 7.76), p=0.06], as well as the postoperative vocal fold closure (figure 3f): [OR = 0.61, 95% CI (0.32, 1.15), p = 0.13]. The results (figure 3g) showed that there was a significant difference in postoperative mucosa waving between all patients: [OR = 0.41, 95% CI (0.21, 0.79), P=0.008]. Between patients treated with CO2-LS and the other approaches, no significant difference in postoperative vocal fold symmetry (figure 3h) was found: [OR = 0.46, 95% CI (0.08, 2.59), p = 0.38].

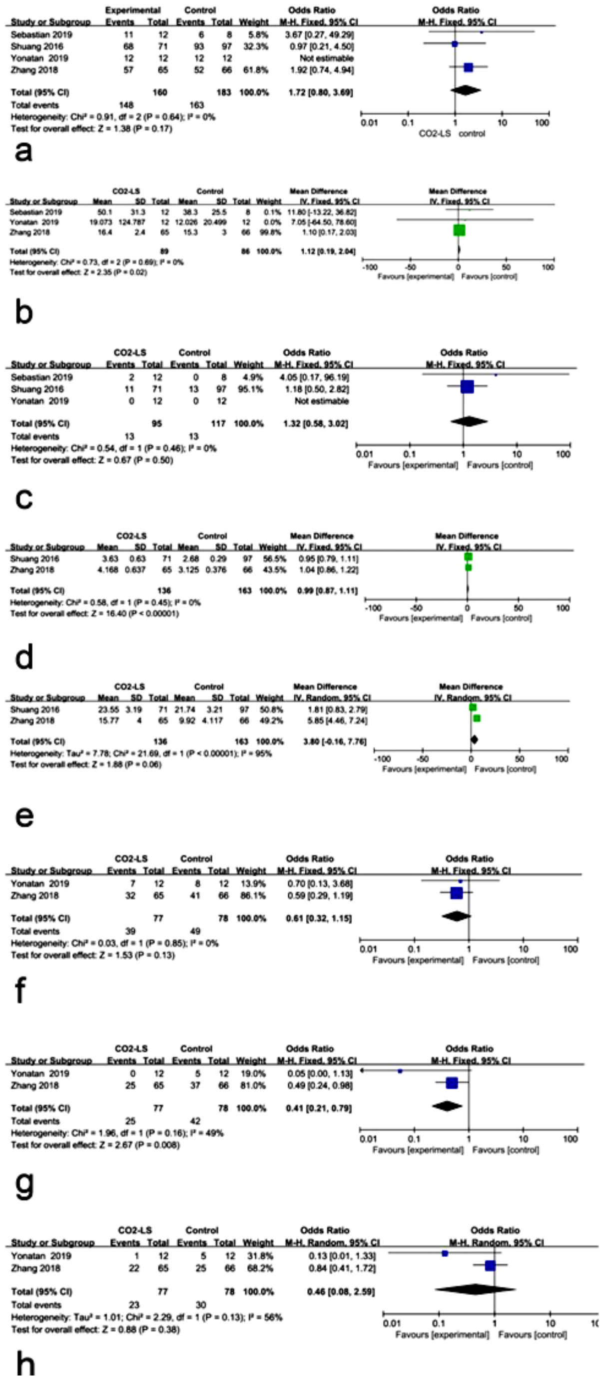


Figure 3. Forest plot of meta-analyses of included studies (**a.** 3 -year overall survival; **b.** VHI 6 months after surgery; **c.** recurrence 3 years after surgery; **d.** 3 months post-op shimmer; **e.** 3 months post-op HNR; **f.** Postoperative vocal fold closure; **g.** postoperative mucosa waving; **h.** postoperative vocal fold symmetry).

Note: VHI, voice handicap index; HNR, Harmonics-to-Noise ratio.

Subgroup analyses

Time to surgery

Three studies reported the time of patients' surgery. The result of the test of heterogeneity

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between the three studies: I^2 = 52%, P = 0.13.The analysis using the random effect model (figure 4a) showed that there was a significant difference in the time of surgery between the patients treated with CO_2-LS and the patients in the control group: [OR = 3.48, 95% CI (2.86, 4.10), P<0.00001], suggesting that the time of surgery in the operative time in the control group was less than that in the CO_2-LS group.

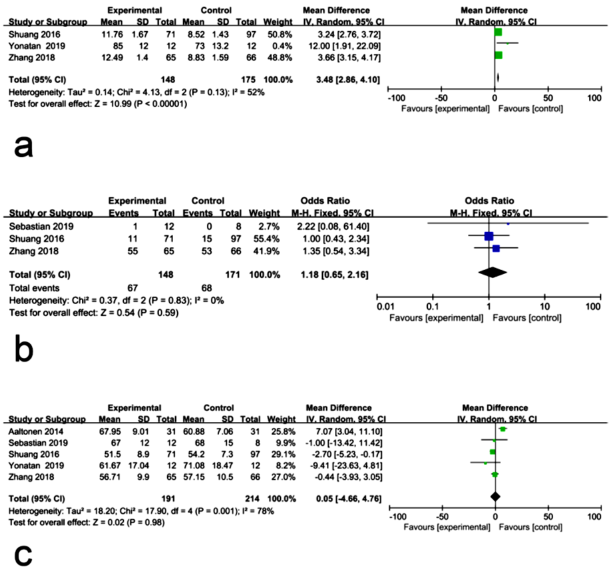

Figure 4. Results of analyses of indicator subgroups in the included studies (**a.** operating time; **b.** gender; **c.** age ;).

Gender

Three studies reported the gender of the patients. The results of the test of heterogeneity between the three studies: I^2 = 0%, P = 0.83. The analysis using the fixed effects model (figure 4b) showed that there was no significant difference in the proportion of gender distribution between patients treated with CO_2-LS and control patients: [OR = 1.18, 95% CI (0.65, 2.16), P = 0.59].

Age

There were 5 studies that reported the gender of the patients. The results of the test of heterogeneity between the 5 studies: I^2 =78%, P=0.001.The analysis using the random effects model (figure 4c) showed that there was no significant difference in the age of the patients treated with CO_2-LS and the control patients: [OR =0.05, 95% CI (-4.66, 4.76), P=0.98].

Sensitivity analysis

As a result of excluding the included studies one by one, the combined effect values did not change significantly , suggesting that the results of this study are basically robust (figure 5a-b). When modifying the effects model to a random effects model, the combined effects values did not change significantly, suggesting that the results of this study are basically robust (figure 5c).

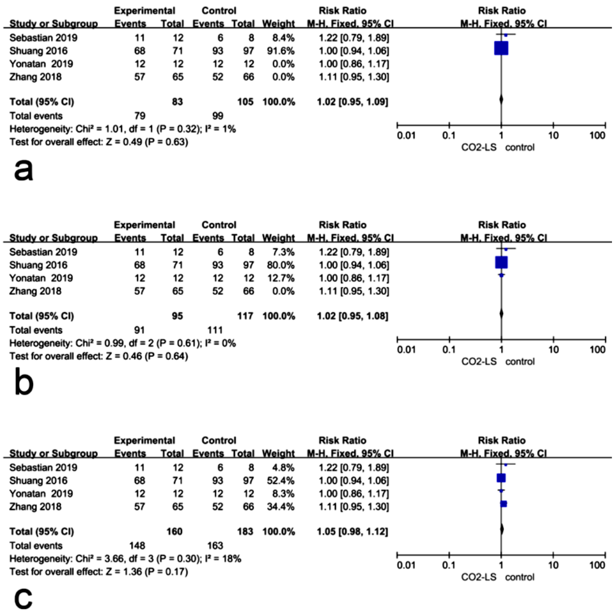

Figure 5. Sensitivity analyses of included studies (**a.** elimination of 2 papers; **b.** elimination of 1 paper; **c.** modification of the effects model to a random model).

DISCUSSION

Benefiting from the advancement in precision medicine and endoscopic, microscopic and minimally invasive techniques are rapidly developed, and the individualized surgical treatment for some laryngeal cancers can be minimally invasive, such as CO_2-LS, cryogenic plasma radiofrequency ablation, and transoral robotic surgery, etc. Due to the straightness of the cuts and the inadequate exposure, the efficacy of the CO_2 laser has been controversial. Our results showed no statistical significance in postoperative survival, recurrence, vocal fold closure/symmetry, and the HNR were different between LC patients treated with CO_2-LS and those of other treatment modalities, while the postoperative VHI and SHIMMER were higher in the experiment group compared to the other treatment groups, accompanied by the superior postoperative mucosal fluctuation.

The effectiveness of CO_2-LS in treating laryngeal cancer has been widely validated by clinical analysis, Grant [24] *et al.* performed the transoral laser surgery on 114 previously treated patients with LC, and the results demonstrated the significantly improved outcomes by the laser. Cai *et al.* [25] conducted a retrospective analysis on 55 patients with locally recurrent squamous cell carcinoma of the vocal folds at early stage, and confirmed the efficacy of laser for surgery. In addition to the efficacy, postoperative recurrence rate has been a critical indicator for cancer treatment. Horwich *et al.* [26] showed that laser treatment did not change the site of recurrence or decrease the localized recurrence rate in patients

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using a survival analysis of 15 patients who underwent TLM for head and neck malignancies, which is consistent with our findings regarding LC recurrence rates, but we did not analyze the local control rate metrics. Zhang *et al.* [27] investigated the predictors of recurrence in laser-treated LC and concluded that factors such as previous micro-laryngoscope surgery, positive surgical margins, and endogenous tumors may intensify the risk of recurrence. The references to relevant risk factors provided by the articles we included are far from adequate, so more articles for confirmation are expected.

The VHI, a self-rating scale to assess vocal function, physiological characteristics and affective disorders is now widely employed, with lower overall scores indicating less severe voice disorders [28, 29]. Abie *et al.* [30] performed a cortical resection on 11 patients with squamous cell carcinoma (SCC) of the vocal hilum, and VHI index indicated significant postoperative improvement, concluding that endoscopic laser surgical resection could be the primary treatment for vocal hilum carcinoma. Kujath *et al.* [31] followed up 76 patients with stage 1 and 2 vocal hilar carcinoma and found a higher VHI of patients who underwent CO_2 laser resection, but no statistically significant difference was found in the postoperative survival, which is in agreement with our findings. Previous studies have shown that the significantly improved VHI index in patients with primary early-stage vocal fold carcinoma in 12-24 months after transoral laser microsurgery, and younger patients were more likely to show greater voice improvement [32]. Our study examined changes in VHI values in patients only up to a few months postoperatively and may not have reached the point of improvement in VHI values.

Jitter is related to the regularity of the vibratory cycle (roughness). Shimmer, on the other hand, denotes the amplitude perturbation of the vocal folds vibration, which depends on the breathiness and intensity variations of the voice [33]. Nicola Lombardo *et al.* [33] reviewed 56 T1a-b patients with early-stage vocal cancer and found the better jitter and shimmer improvement in CO_2 resected patients and chemotherapy group compared to the radiotherapy group, and recommended the priority to CO_2 laser resection. Benninger *et al.* [34] carried out a prospective study covering 21 patients with superficial lesions on the free edge of the vocal folds, and found no differences in terms of acoustic and aerodynamic measures as well as video and perceptual audio recordings between laser resection and microdissection, and they explained it that most of the values were normal preoperatively. We obtained the different results, which may be related to the fact that the included studies did not address information related to preoperative acoustic metrics. Rzepakowska *et al.* [35] suggested the limited or disappearing mucosal waves as the strongest indicator of malignancy, and the results of our study showed the superior mucosal recovery in patients treated with laser therapy compared to the other treatments, which could be a future advantage of laser therapy.

In terms of the indicators in LC patients who underwent CO_2 laser resection, we obtained some differed results, some were superior and some not, which made it less reliable to conclude which treatment modality should be more clinically replicated. Andrea Colizza *et al.* [36] compared the phonological outcomes after TOLMS and RT in the treatment of LC, but did not get a uniform conclusion. Del Mundo *et al.* [37] studied the patients with type III cordectomy and found that the postoperative shimmer profile was superior to the preoperative values (14.7 vs 9.3, P=0.007), which is contrary to the results of our study. Meanwhile, Yin *et al.* [38] showed superior postoperative speech outcomes (shimmer) by laser treatment on patients with early acoustic cancer. To the best of our knowledge, this is the first study to compare the performance and safety of CO_2 laser resection with other treatment modalities in patients with LC. We suspected that the large variability between the results of the different studies may be related to the different tumor stages of the patients. In addition to the limited number of studies, the extent and depth of laser resection also differed, as well as the dosage of other treatments, such as radiation therapy and the duration of follow-up, which may have affected the final evaluation of the meta-analysis. We look forward to studies with longer postoperative follow-up to fully demonstrate the clinical benefits of CO_2 laser surgery.

CONCLUSIONS

CO_2-LS can achieve a superior postoperative mucosal recovery in LC patients, but there was no significant advantage in terms of postoperative survival, recurrence and vocalization.

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Conflicts of interest: All authors unanimously declare that there is no conflict of interest in this study.

Ethical consideration: Not applicable.

Authors' contributions: SY Z and Y Z conceived and designed the study; FW B and MM S conducted the literature search and data collection; T G analyzed the data; T G and MM S wrote the paper and SY Z reviewed and edited the manuscript. All authors read and approved the final manuscript.

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