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REVIEW ARTICLE

Efficacy of laser surgery versus radiotherapy for treatment of glottic carcinoma: a systematic review and meta-analysis

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Abstract

Laser surgery and radiotherapy are the two most common ways to treat glottic carcinomas, which is more efficacious and remains controversial. PubMed, Embase, and Cochrane Library were searched to identify relevant studies of laser surgery versus radiotherapy in patients with glottic carcinomas through April 2017. Sensitivity analysis and subgroup analysis were performed to evaluate heterogeneity. Eighteen studies were selected, which included 2480 patients. Patients who had laser surgery had higher rates of laryngeal preservation (OR 3.852; 95% CI 1.922–7.721) and overall survival (OR 1.388; 95% CI 1.063–1.811) versus who had radiotherapy. No significant differences were observed between laser surgery and radiotherapy on local control (OR 1.186; 95% CI 0.759–1.854), recurrence (OR 0.758; 95% CI 0.445–1.289), or disease-specific survival (OR 1.597; 95% CI 0.887–2.876). There were clinical benefits for patients with glottic carcinoma after laser surgery compared with radiotherapy with respect to survival and laryngeal preservation.

Keywords Glottic carcinoma · Laryngeal preservation · Laser surgery · Meta-analysis · Radiotherapy · Recurrence · Systematic review

Introduction

Laryngeal cancer is considered to be the most common type of head and neck cancer [1]. An estimated 13,360 new cases of laryngeal cancer will be diagnosed each year, with approximately 3660 patients expected to die from the disease in 2017 [2]. Laryngeal cancer occurs more frequently in men than in women (6.2 cases per 100,000 vs 1.4 per 100,000, respectively) [2].

Glottic cancer is one of the most frequent kinds of laryngeal cancer that involves the true vocal cords and anterior and posterior commissures [3]. Because of its anatomical location, it can have profound consequences on basic voice functions in the early stages, such as persistent hoarseness symptoms. Hence, glottic carcinoma can be diagnosed early (Tis (tumor in situ) or T1-T2N0M0 (tumor 1-tumor 2 node 0 metastasis 0), based on the TNM (tumor node metastasis) staging system) [4].

The primary purpose of treating glottic cancer is to cure the disease and increase survival, while the secondary reason is to preserve the vocal cords and restore voice function. Laser surgery (LS) and radiotherapy (RT) are both effective methods for treating glottic carcinoma [5]. They can achieve a comparable high cure rate [6]. However, there are debates between the two methods with regard to survival, local control, laryngeal preservation, and voice function [7, 8].

Recently, Huang et al. published two meta-analysis regarding oncologic outcomes and voice quality after LS vs RT for the treatment of T1a glottic carcinoma. Their meta-analysis suggested that there was no significant difference in oncologic outcomes; however, better voice quality was observed in RT [9, 10]. Conversely, Mo et al. found that LS was significantly better than RT in laryngeal preservation and overall survival for T1 glottic carcinoma [11]. Because of the conflicting findings and no standard therapeutic approaches, the current meta-analysis was performed to systematically review the literature and analyze the oncologic outcomes of Tis, T1, and T2 stage glottic carcinoma patients undergoing LS or RT.

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Methods

Data sources, search strategy, and selection criteria

This study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement issued in 2009 (Checklist S1) [12].

Studies that compared the outcomes between LS and RT for the treatment of glottic carcinoma were selected for meta-analysis in this study. There is no language or publication status limitation for literature review. A systematic electronic search of PubMed, EmBase, and the Cochrane Library databases was performed for eligible studies from inception to April 2017. The following keywords and medical subject headings were used: ("glottic carcinoma" OR "glottic cancer" OR "laryngeal cancer") AND ("radiotherapy" OR "radiation therapy") AND "laser." We also reviewed the reference lists of the included studies for undetected relevant studies.

The retrieved records were independently reviewed by two investigators. If the two investigators disagreed about the eligibility of an article, it was resolved by debating with a third reviewer. The inclusion criteria were as follows: (1) patients with glottic cancer; (2) intervention was LS compared with RT; (3) outcomes data reported; and (4) article type as original research. In the current study, the outcome included tumor outcomes, such as overall survival, disease-specific survival, local control, laryngeal preservation, and recurrence.

Data collection and quality assessment

Research articles were evaluated by two independent researchers, and any inconsistencies were discussed before reaching a consensus. For each study, the following data was collected: the first author's name, publication year, country where the study was conducted, study design, number of patients, age, gender, tumor stage, treatment, and follow-up period as the baseline data. Primary outcomes were oncological outcomes, such as overall survival, disease-specific survival, local control, laryngeal preservation rate, and recurrence.

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included studies for cohort studies [13]. The NOS was based on the following three subscales: selection (four items), comparability (one item), and outcome (three items). NOS ranges were 0 to 8, and scores of 0–3, 4–6, and 7–8 were considered as low, moderate, and high quality, respectively, for these studies.

Statistical analysis

The results from each study was considered as dichotomous frequency data, and odds ratio (OR) and 95% confidence intervals (CIs) of each individual trial were calculated from event numbers in each group within the individual trials before data pooling [14]. Furthermore, ORs and 95% CIs were calculated for overall survival, disease-specific survival, local control, laryngeal preservation, and recurrence in glottic cancer patients receiving LS and RT [15]. The potential heterogeneity across the studies was examined using the Cochran's Q-statistic and I^2 statistics. If the P value for heterogeneity was < 0.1 or $I^2 > 50\%$, then it was considered as significant heterogeneity. The DerSimonian and Laird random effect model (REM) was used to combine study results when heterogeneity was high; otherwise, a fixed effect model was used [16]. Sensitivity analyses were performed to explore the sources of heterogeneity of the included studies by removing each included study subsequently [17]. Subgroup analysis was conducted by tumor stage. Publication bias was evaluated using the Egger's and Begg's test [18], and $P < 0.05$ was considered as a statistically significant publication bias; funnel plots were also conducted [19]. All reported P values were two-sided, and P values < 0.05 were considered significant for the included studies. Statistical analyses were performed with STATA software (version 10.0; Stata Corporation, College Station, TX, USA).

Results

Characteristics of the included studies

A total of 612 studies were retrieved based on our searching strategy. After reading the abstracts, 54 studies were related to our aims (Fig. 1), and 36 of them were subsequently excluded with reasons given. The remaining 18 studies were selected for our analysis (Table 1) [18, 20–37]. A total of 2480 participants were selected for the meta-analysis, of which 1239 and 1241 patients underwent laser treatment and radiation, respectively. None of the 18 studies included were completely randomized, four were prospective studies, and the remaining were retrospective. The majority of the studies were from Europe and North America. All patients were diagnosed with early glottis cancers and the tumor grading was Tis, T1 (T1a, T1b), and T2.

NOS was used to examine the quality of all included studies. Almost half of the studies (7/18) were marked as 7 in NOS as they failed to report the adequacy of follow-up. The 11 remaining studies received full scores in NOS, indicating that they were high-quality original studies. (Table 2).

Overall survival

Eleven studies provided detailed data on overall survival with 766 patients in the LS group and 900 patients in the RT group. Pooled analysis demonstrated that participants had a favorable overall survival in the laser group in comparison with the radiation group (OR = 1.388, 95% CI 1.063–1.811, $P = 0.016$; Fig. 2a). Furthermore, subgroup analysis showed significant differences only in studies with T1a glottic cancer

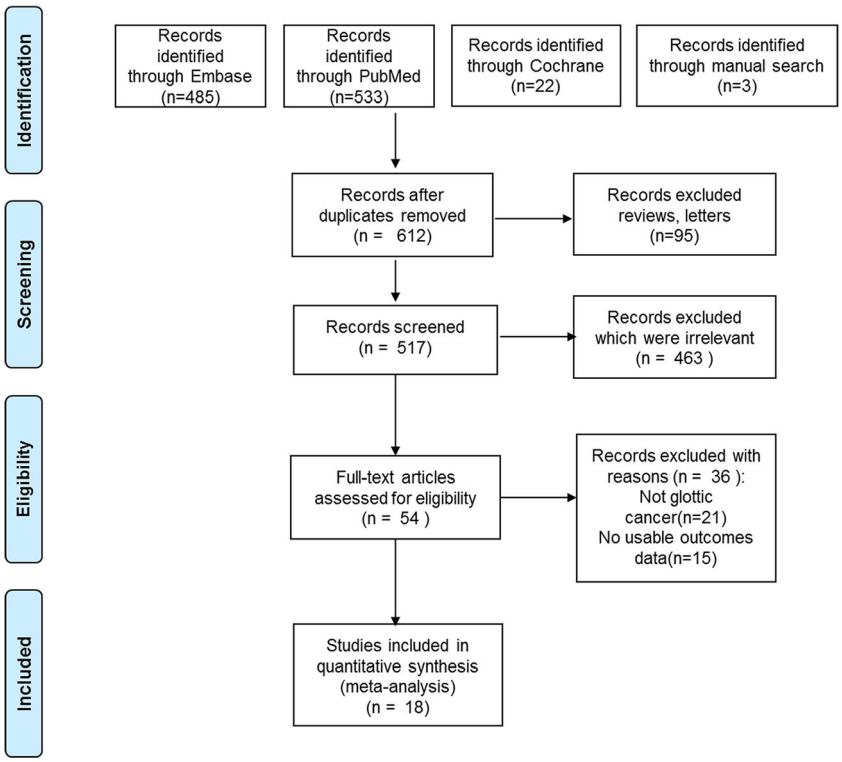

Fig. 1 Study selection process

(OR = 1.466, 95% CI 1.049–2.047, $P = 0.025$; Fig. 2b) and not in studies with T1 glottic cancer (OR = 0.978, 95% CI 0.55–1.739, $P = 0.939$). There was no heterogeneity within the groups ($I^2 = 0\%$, $P = 0.964$).

Disease-free survival

Ten studies having a total of 1561 glottic cancer patients provided the disease-specific survival after LS and RT. There was no

Table 1 Basic characteristics of the selected studies

Study, year	Country	Study types	Age (LS vs RT, years)	Gender (LS vs RT, male %)	LS participants	RT participants	Carcinoma stage	Follow-up (month)
Epstein, 1990	America	Retrospective	62 vs 63	100 vs 90	17	43	T1a	180
Rosier, 1998	Belgium	Retrospective	N/A	81 vs 85	31	41	T1	194
Spector, 1999	America	Retrospective	N/A	N/A	61	104	T1	60
Stoeckli, 2003	Switzerland	Retrospective	N/A	N/A	65	75	T1 and T2	137
Krengli, 2004	Italy	Retrospective	67.5 vs 69	97 vs 96	122	80	T1a	120
Goor, 2007	The Netherlands	Retrospective	67.4 vs 63.8	N/A	54	31	T1a	24
Sjogren, 2008	The Netherlands	Retrospective	N/A	89.0 vs 95.7	73	70	T1a	118
Thurnher, 2008	Australia	Retrospective	62.7 vs 64	91 vs 90	81	108	T1a	617
Kerr, 2012	Canada	Retrospective	67 vs 67	86 vs 90	125	62	T1 and T2	60
Mahler, 2009	Norway	Perspective	N/A	N/A	188	163	T1a	261
Schrijvers, 2009	The Netherlands	Retrospective	64 vs 67	88 vs 88	49	51	T1a	166
Kujath, 2011	Canada	Retrospective	N/A	N/A	54	25	T1 and T2	24
Van Gogh, 2012	The Netherlands	Perspective	N/A	N/A	67	39	T1a	24
Milovanovic, 2013	Serbia	Perspective	N/A	90.3 vs 90.5	72	74	Tis and T1a	107
Remmelts, 2013	The Netherlands	Retrospective	67 vs 64	88 vs 87	91	159	Tis, T1, and T2	108
Taylor, 2013	Canada	Perspective	N/A	86 vs 93	21	42	T1b	102
Kono, 2016	Tokyo	Retrospective	64 vs 69	81 vs 89	15	22	T1a	70
Low, 2016	Australia	Retrospective	65.4 vs 70.6	79 vs 85	53	52	T1a	60

LS: laser surgery; RT: radiotherapy; N/A: not available

Table 2 Methodological quality of the studies included in the meta-analysis

First author	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factors or additional factors	Outcome assessment	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total quality scores
Epstein	☆	☆	☆	☆	☆	☆	☆	–	7
Goor	☆	☆	☆	☆	☆	☆	☆	–	7
Kerr	☆	☆	☆	☆	☆	☆	☆	–	7
Kono	☆	☆	☆	☆	☆	☆	☆	☆	8
Krengli	☆	☆	☆	☆	☆	☆	☆	☆	8
Kujath	☆	☆	☆	☆	☆	☆	☆	–	7
Low	☆	☆	☆	☆	☆	☆	☆	☆	8
Mahler	☆	☆	☆	☆	☆	☆	☆	–	7
Milovanovic	☆	☆	☆	☆	☆	☆	☆	–	7
Remmelts	☆	☆	☆	☆	☆	☆	☆	–	7
Rosier	☆	☆	☆	☆	☆	☆	☆	☆	8
Schrijvers	☆	☆	☆	☆	☆	☆	☆	☆	8
Sjogren	☆	☆	☆	☆	☆	☆	☆	☆	8
Spector	☆	☆	☆	☆	☆	☆	☆	☆	8
Stoeckli	☆	☆	☆	☆	☆	☆	☆	☆	8
Taylor	☆	☆	☆	☆	☆	☆	☆	–	7
Thurnher	☆	☆	☆	☆	☆	☆	☆	☆	8
Van Gogh	☆	☆	☆	☆	☆	☆	☆	–	7

statistical significance (OR = 1.597; 95% CI 0.887–2.876; P = 0.119; Fig. 3a), and insignificant heterogeneity was observed (I^2 = 0%; P = 0.984). Subgroup analysis based on tumor stage suggested a difference in T1a glottic carcinoma (OR = 2.453, 95% CI 0.962–6.259; P = 0.060).

Laryngeal preservation

A total of 12 studies having 892 patients in the LS group and 947 patients in the RT group were evaluated for laryngeal preservation. Interestingly, this meta-analysis showed a strong favorable outcome for laser treatment in terms of laryngeal preservation (OR = 3.852, 95% CI 1.922–7.721, P < 0.001; Fig. 4a), with extremely high heterogeneity (I^2 = 48.1%, P = 0.031). Significant differences in only T1a was observed (OR = 4.61, 95% CI 1.634–13.005, P = 0.004) and not in T1b (OR = 7.658, 95% CI 0.411–142.746, P = 0.173) or T1 subgroup (OR = 2.939, 95% CI 0.687–12.574, P = 0.146).

Local control

Fourteen studies having 973 patients in the LS group and 1058 patients in the RT group reported local control. Results of the pooled effect demonstrated that the difference between LS and RT group on local control was not statistically significant (OR = 1.186, 95% CI 0.759–1.854, P = 0.454; Fig. 5), and in T1a subgroup (OR = 1.307, 95% CI: 0.75–2.278, P = 0.345), had high heterogeneity (I^2 = 52.3%, P = 0.014).

Recurrence

Thirteen studies reported on recurrence. No significant differences were observed in the laser group compared to radiation treatment (OR = 0.758, 95% CI 0.445–1.289, P = 0.306; Supplementary Fig. 1). There was high heterogeneity within the groups (I^2 = 64.7%, P = 0.001). Similar results were observed in the T1a subgroup (OR = 0.726, 95% CI 0.416–1.269, P = 0.261).

Sensitivity analysis

The sensitivity analysis shows that the results were not affected by the exclusion of any individual trial for outcomes including overall survival, disease-specific survival, local control, recurrence, and laryngeal reservation (Supplementary Fig. 2).

Publication bias

Review of the funnel plots could not rule out the potential for publication bias (Supplementary Fig. 3). The Begg's test showed no evidence for publication bias. However, Egger's test showed disease-specific survival (P = 0.003), and laryngeal preservation had potential publication bias (P = 0.021). A sensitivity analysis was conducted with trim and fill method, and the results were similar [38].

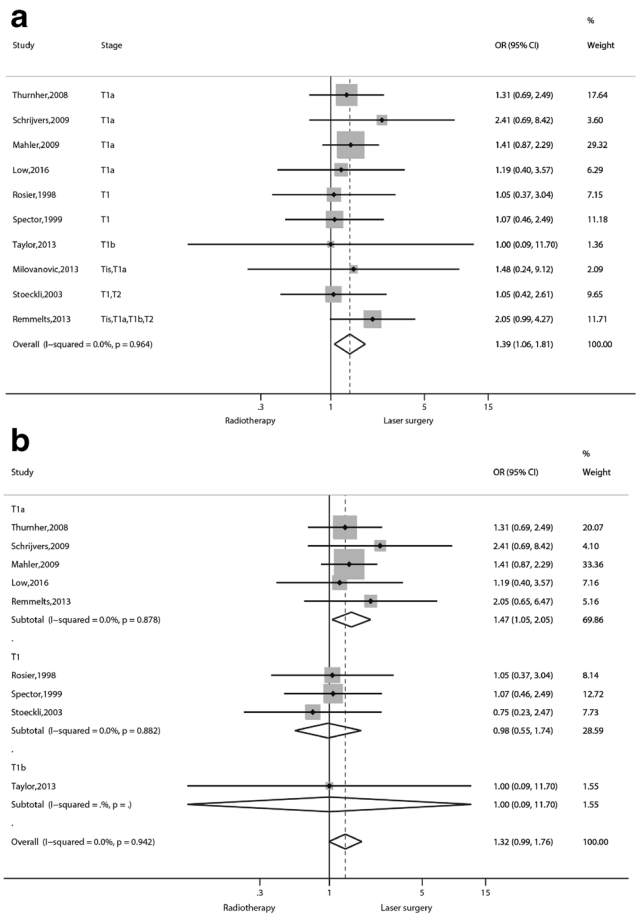

Fig. 2 Effect of laser surgery on overall survival compared to radiotherapy

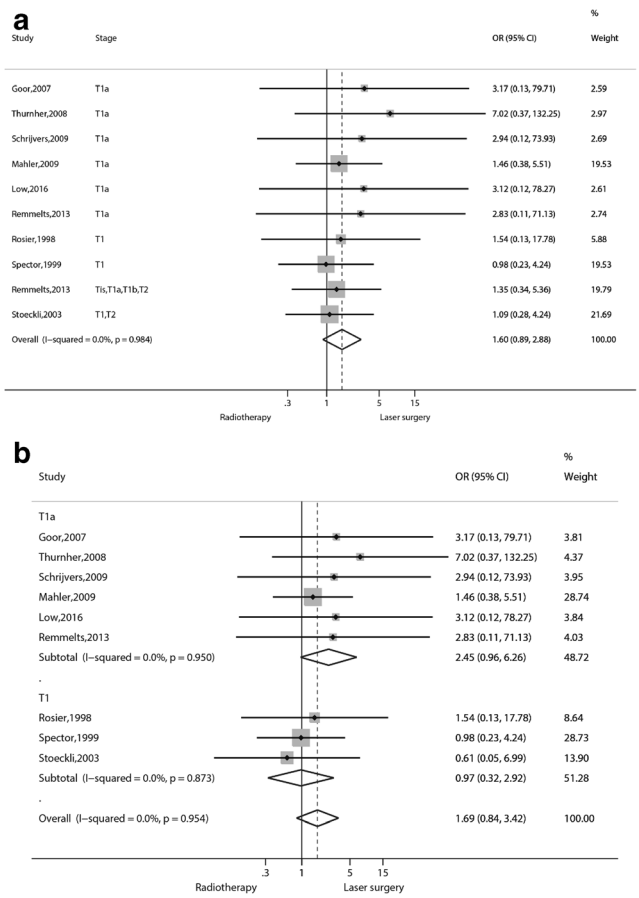

Fig. 3 Effect of laser surgery on disease-specific survival compared to radiotherapy

Discussion

Our meta-analysis was based on 18 studies and investigated the efficacy of LS compared to RT. Results demonstrate that LS significantly increased laryngeal preservation and overall survival in patients with early glottic carcinoma compared to RT. There was no statistically significant evidence to demonstrate that LS was better than RT on local control, disease-specific survival, and recurrence.

Larynx preservation was significantly higher in patients treated with LS than those treated with RT. This conclusion was unchanged after sensitive analysis and subgroup analysis. Several previous meta-analyses have reported similar results, which suggested that LS was superior for treating glottic carcinoma patients to preserve the larynx [9, 11, 39, 40].

Although high heterogeneity was observed in local control, following sequential exclusion of each study, these conclusions did not change. Our results are in-line with studies performed by Huang and Mo [9, 11]. The present meta-analysis investigated local control rates between LS and RT based on stage T1, T1a, and T1b subgroup. However, there was no significant difference in any of the subgroups. Thus, LS and RT have the same local control rate for early glottic carcinoma.

Survival is a key index for the prognosis of cancer. There were 11 and 10 original articles that reported on overall survival and disease-specific survival, respectively. There was a significant difference for overall survival between LS and RT for the total pooled effect and T1a stage subgroup. This result differs from Huang et al. [9], which reported a meta-analysis which included six studies on T1a glottic cancer for overall survival and showed no significant difference. The reason may be that the included studies in Huang et al.'s meta-analysis were different from ours. Stoeckli et al.'s results were based on T1 or T2 stage instead of T1a and should not have been included in Huang et al.'s meta-analysis due to the ambiguous disease stage. In addition, Remmelts et al.'s study involving T1a stage patients was excluded from Huang et al.'s meta-analysis [28]. Our study classified the data correctly based on different disease stages of the included studies. Moreover, the overall survival data from Schrijvers et al.'s research was extracted differently in Huang et al.'s meta-analysis compared to ours (LS group: alive 45 instead of 47, death 4 instead of 9; RT group: alive 42 instead of 39, death 9 instead of 6) [30]. Data extraction errors

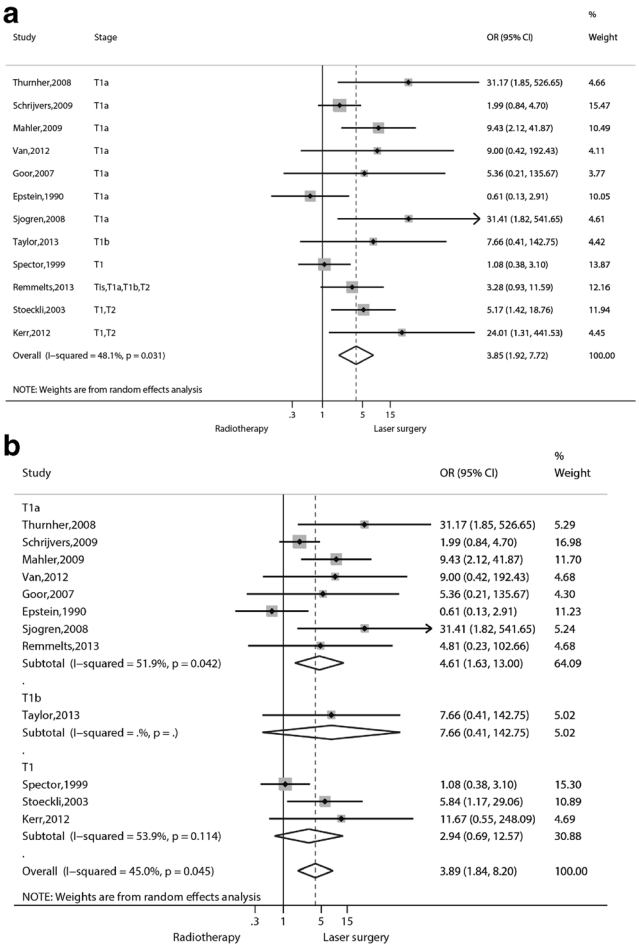

Fig. 4 Effect of laser surgery on laryngeal preservation compared to radiotherapy

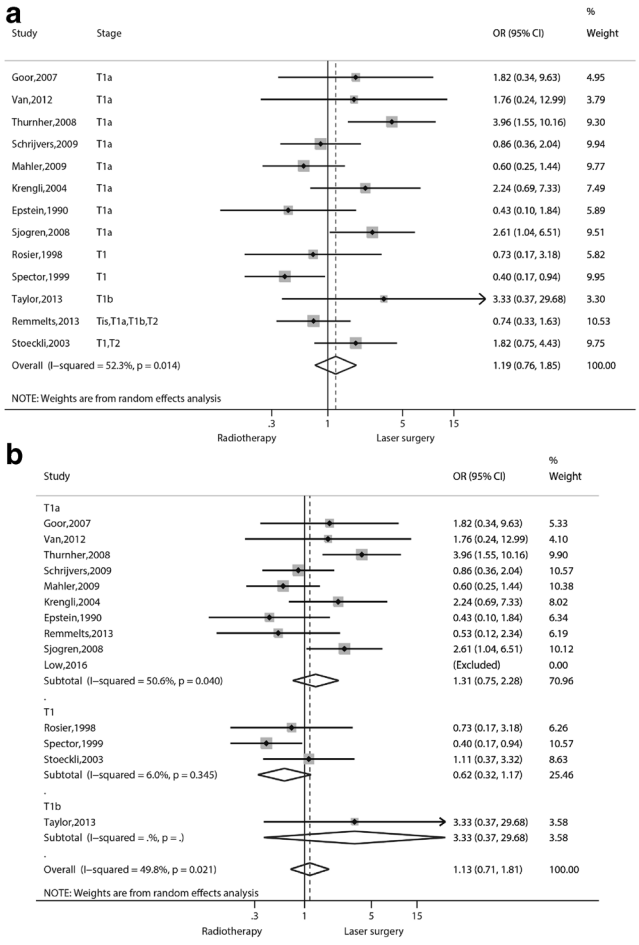

Fig. 5 Effect of laser surgery on local control compared to radiotherapy

may have resulted in incorrect conclusions in Huang et al.'s meta-analysis. We have corrected the data and have made the correct analysis in our meta-analysis.

The present meta-analysis is the first to report the summary effect of glottic cancer recurrence. The pooled effect in our meta-analysis showed no significant differences in recurrence. Both Thurnher et al. [36] and Kujath et al. [25] reported a lower recurrence in the LS group compared to the RT group, while Spector et al. [32] had a different conclusion. These conflicting conclusions may be affected by tobacco and/or alcohol consumption or other possible confounders. Nonetheless, these differing conclusions needs further study. Spector et al. [32] also indicated that salvage therapy for recurrence after primary LS surgical therapy preserved more unaided laryngeal voice function compared to RT. These results seem to indicate that LS surgical therapy was beneficial in preventing recurrence of glottic cancer.

The present meta-analysis had a few limitations. First, all the included studies were non-randomized and patient's allocation was conducted based on the physician's or patient's preference, which introduced selection bias. Secondly, several studies were published before 2000, and since then, the technology has advanced, which may lead to heterogeneity in the meta-analysis. Thirdly, the lack of detailed information on RT and LS methods also increased the heterogeneity observed. Fourthly, the number of patients included in each study was relatively small in the majority of the trials, which might affect the statistical power to detect differences between LS and RT in glottic cancer patients. Therefore, the comparison between LS and RT requires further confirmation using larger cohorts and large-scale RCTs. And lastly, the limitations of the current research data limit us to conduct more innovative research. We will conduct further research, as more original research published.

Each modality has its complications. Complications of RT include xerostomia and hyposalivation because of damage to the salivary glands, [41] erythema of and telangiectasia formation on the skin, increased skin's sensitivity to the sun, and damage to the surrounding structures of neck. [42] In the long-term, there is a risk of gastrostomy tube dependence due to acute dysphagia. [43] The complications of LS include edema requiring tracheostomy, surgical emphysema, pharyngeal bruising, endotracheal

tube cuff perforation, anterior glottic web, and intraoperative or postoperative hemorrhage [42]. It is known that the complication rate of LS is influenced by surgeon experience and size of the tumor [44]. An Australian institutional study indicated that the intraoperative and postoperative complications were low [42].

Early stage glottic carcinoma patients who underwent LS had increased larynx preservation and overall survival, especially in T1a stage patients compared to RT patients. LS and RT had comparable local control, disease-specific survival, and recurrence. This indicates that LS may be a better option for glottic cancer treatment. When doctors and patients choosing treatment modality for glottic carcinoma, they should take survival, local control, laryngeal preservation, voice function, and complications of treatment into account. Studies show that LS is a safe and effective treatment modality that can be used for treating glottic carcinoma. However, large-scale and well-designed RCTs are required before a conclusive statement could be made regarding the efficacy of laser surgery and radiotherapy for glottic carcinoma.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Not applicable.

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