

Title: Guideline for the Treatment of Laryngeal Cancer from the Korean Society of Head and Neck Surgery

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Highlights

- The guidelines provide comprehensive, evidence-based recommendations for laryngeal cancer management, developed through a systematic literature review, meta-analysis, and expert consensus.
- In addition to oncologic control, the guidelines prioritize preserving essential functions such as voice and swallowing, considering for organ-preserving strategies when feasible.
- Recommendations are tailored to disease stage, patient condition, and treatment goals for optimal outcomes.

ABSTRACT (218 words)

Objectives: The treatment of laryngeal cancer requires clinical decision-making that balances survival outcomes with the preservation of essential functions such as voice and swallowing. The study, led by the Clinical Practice Guideline Committee of the Korean Society of Head and Neck Surgery, aims to establish evidence-based recommendations to guide optimal treatment decisions for patients with laryngeal cancer from surgeons' perspectives.

Methods: A literature search was conducted in the PubMed, Embase, Cochrane Library, and KoreaMed databases by a literature search expert and reviewed by a panel of 39 experts in the committee. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to assess the quality of evidence and to develop and report recommendations. The strength of a recommendation indicates the guideline panel's confidence that the benefits of an intervention outweigh its risks for the target population. After drafting the guidelines, Delphi questionnaires were distributed to members of the Korean Society of Head and Neck Surgery and an external reviewer panel.

Results: A total of 15 evidence-based recommendations are provided, addressing six essential aspects of laryngeal cancer treatment: early-stage treatment, locally advanced cancer treatment, neck management, adjuvant therapy, swallowing rehabilitation, and salvage treatment for recurrent tumors.

Conclusions: The guidelines provide evidence-based, validated recommendations to support clinicians in making optimal treatment decisions in laryngeal cancer.

Keywords. *Guidelines; Laryngeal cancer; Laryngectomy; Organ preservation; Neck dissection*

INTRODUCTION

According to statistical data from the Korean National Cancer Center in 2021, the prevalence rate of laryngeal cancer was reported as 24.7 cases per 100,000 individuals (1). Although the prevalence of laryngeal cancer has been gradually declining in parallel with decreasing smoking rates, it remains a significant public health concern, affecting a notable portion of the population. Treatment strategies for laryngeal cancer, as outlined in the National Comprehensive Cancer Network (NCCN) guidelines, encompass both surgical and non-surgical approaches (2). Historically, surgical treatments, particularly total laryngectomy, have significantly impacted patients' quality of life due to voice loss. In response, non-surgical, organ-preserving strategies were established as standard treatment modalities through randomized controlled studies, such as those by the Veterans Affairs Administration and the Radiation Therapy Oncology Group (RTOG 91-11) (3, 4). However, concerns regarding inferior survival outcomes with non-surgical approaches highlight the need for precise clinical decision-making (5-7).

To address these challenges, the Korean Society of Thyroid-Head and Neck Surgery (KSTHNS) developed surgical treatment guidelines for laryngeal cancer in 2017 (8). These guidelines were based primarily on narrative literature reviews and expert consensus, providing a comprehensive set of 62 recommendations across 32 categories. While these efforts significantly advanced clinical practice, the need for more robust, evidence-based guidelines became evident.

Recently, the Korean National Cancer Center launched a project to develop evidence-based clinical practice guidelines for the treatment of laryngeal cancer using systematic reviews, meta-analyses, and the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology. During the guideline development process, which incorporated strict methodological consultations, it was identified that the current clinical practice guidelines do not

comprehensively address certain specific topics which was covered in the previous guidelines (8). As such, the present guidelines should not be regarded as an update to the earlier surgical treatment guidelines but rather as a complementary resource. The systematic approach and evidence-based recommendations derived from key questions and meta-analyses from this study are expected to provide valuable support for clinical decision-making. One thing to note is that these guidelines are not intended to replace clinical judgment or resolve medico-legal issues. Instead, they should be regarded as an adjunct to, rather than a substitute for, sound clinical reasoning.

MATERIALS AND METHODS

Target population

These guidelines include patients diagnosed with laryngeal cancer, specifically those with early-stage or locally advanced disease who are eligible for curative-intent treatment, including surgery, radiation therapy, or chemoradiotherapy. However, patients with systemic metastases or unresectable disease due to extensive local progression were excluded.

Organization of the committee

The guidelines were developed by the Guideline Committee of the Korean Society of Head and Neck Surgery (KSHNS). A task force was appointed, consisting of five teams with a total of 39 experts. The task force chairman (J.O. Park) and vice-chairman (J.Y. Jang) were appointed by the President of KSHNS (K.J. Cho) with the Committee's approval. The committee members were supported by a literature search expert and a methodology expert from the Korean Cancer Management Guideline Network (KCGN) to optimize protocols for literature search, systematic review, meta-analysis (if applicable), and guideline development methodologies. Committee members participated in conference calls and regularly scheduled online or face-to-face meetings to review and evaluate each major stage of the guideline development process.

Literature search and quality assessment

A systematic literature search and retrieval were conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. A literature search was performed in the PubMed, Embase, Cochrane Library, and KoreaMed databases by a literature search expert between December 25, 2022, and April 17, 2023. Relevant text words, including MeSH and Emtree terms, were used, and Boolean operators (AND, OR, NOT) were applied to refine the search strategy. The retrieved studies underwent a screening and eligibility assessment process to exclude duplicates, irrelevant studies, or those with insufficient comparisons and descriptions. The selection process was categorized into two approaches based on the availability of systematic review studies for each Key Question (KQ): i) If an appropriate systematic review was identified for a KQ, the studies included in that review were incorporated into the guideline development. To ensure up-to-date evidence, additional original studies published after the search period of the existing systematic review were identified, screened, and selected for final analysis. ii) If no systematic review was available for a KQ, a comprehensive search was conducted for original studies covering the entire period. The final selection of studies was independently reviewed by two committee members, who determined inclusion or exclusion. The search strings used for each KQ and the number of retrieved documents are provided in Supplemental Material 1. The final PRISMA table for each KQ is provided in Supplemental Material 2.

Quality assessment of the literature, meta-analysis, and the grading of recommendations

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, an internationally recognized standard for making transparent recommendations, was used to assess the quality of evidence and to develop and report recommendations. Guideline committee members were trained on this process before the guideline meeting through a combination of online training modules, publications, and presentations, supported by the Korean

Cancer Management Guideline Network (KCGN). Among the selected studies, the quality of systematic review was assessed using A Measurement Tool to Assess Systematic Reviews (AMSTAR) II (9). The Risk of Bias for Nonrandomized Studies (RoBANS) II tool was used to evaluate non-randomized controlled trials (non-RCTs) and assess the quality of observational studies, while for randomized controlled trials (RCTs), the Cochrane Risk of Bias (RoB) 2.0 tool was applied (10, 11). The quality of evidence was assessed independently by two committee members, and in cases of disagreement, consensus was reached through discussion. The final results of the quality assessment are summarized in Supplementary Table 3.

For Key Questions where retrieved data allowed for evidence synthesis, meta-analysis was performed. The Key Question numbers for which meta-analysis was conducted were A1, A2, B1, C1, D1, and F2 (see Table 1). Meta-analysis and statistical analyses were conducted using Review Manager (RevMan) version 5.3 (The Cochrane Collaboration, London, UK). Unadjusted odds ratios (ORs) and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were used as summary statistics for dichotomous outcomes. Heterogeneity among studies was assessed using the I^2 statistic, and effect sizes were pooled using a random-effects or fixed-effects model, depending on the level of heterogeneity. A p-value < 0.05 was considered statistically significant. The level of evidence of each recommendation was assessed based on the GRADE criteria. A high level of evidence indicates strong confidence that the estimated effect closely represents the actual effect. Moderate evidence suggests that while the estimated effect is likely close to the actual effect, there remains a possibility of considerable variation. Low evidence reflects significant uncertainty, meaning the actual effect may differ substantially from the estimated value. Lastly, very low evidence, based on expert consensus, signifies that no direct evidence is available, but recommendations are derived from the formal agreement of the guideline committee.

The Delphi method was used to establish consensus, particularly regarding the balance of benefits

and harms. A panel consisting of KSHNS members and five multidisciplinary consultation experts reviewed the recommendations through an online questionnaire. A total of 16 recommendations were distributed, and panel members were asked to respond with one of the following options: “fully agree,” “agree,” “neither agree nor disagree,” “disagree,” or “totally disagree.” A recommendation was accepted if at least two-thirds of the panel members responded with “fully agree” or “agree.” In the first round, 66 responses were received, and consensus was achieved for 15 out of 16 recommendations. Recommendations that did not reach the two-thirds agreement threshold were revised based on expert feedback and redistributed for a second-round online evaluation. In the second round, 42 experts participated using the same voting method, and the remaining recommendation was finalized through panel consensus.

GUIDELINES

The organization of the Guidelines for the Treatment of Laryngeal Cancer is summarized in Table 1, and the summary of recommendations is compiled in the Supplementary Material 4.

Table 1. Organization of the KSHNS guidelines for the Treatment of Laryngeal Cancer

Location Key	Section	Item
A	Treatment for Early-stage Laryngeal Cancer (T1/T2)	
A1	What is the appropriate treatment for early-stage glottic cancer?	R1-2
A2	What is the appropriate treatment for early-stage supraglottic cancer?	R3-4
B	Treatment for Locally Advanced Laryngeal Cancer (T3/T4)	
B1	What is the role of total laryngectomy in locally advanced laryngeal cancer?	R5
B2	What is an appropriate larynx-preservation therapy in locally advanced laryngeal cancer?	R6
C	Management of the Neck	
C1	Is prophylactic neck dissection necessary for patients with clinically lymph node-negative laryngeal cancer?	R7-9
C2	What is the appropriate extent of neck dissection in patients with clinically lymph node-positive laryngeal cancer?	R10-12
D	Adjuvant Therapy	
D1	Does adjuvant therapy improve treatment outcomes in patients with laryngeal cancer following surgical resection?	R13
E	Swallowing Rehabilitation	
E1	What is the role of swallowing rehabilitation in patients with laryngeal cancer?	R14
F	Salvage Treatment for Recurrent Laryngeal Cancer	
F1	What are the salvage treatment options applicable for locally recurrent laryngeal cancer?	R15
F2	Does elective neck dissection improve oncological outcomes in salvage treatment for locally recurrent laryngeal cancer?	R16

A. Treatment for early-stage (T1/T2) laryngeal cancer

A1. What is the appropriate treatment for early-stage glottic cancer?

Recommendation 1

For early-stage glottic cancer, both surgical treatment and radiation therapy can be considered as initial treatment.

(Strong recommendation/low-quality evidence)

Recommendation 2

Transoral surgery could be considered a preferred surgical treatment method in early-stage glottic cancer.

(Conditional recommendation/low-quality evidence)

The primary goal in treating early glottic cancer (T1-T2) is to achieve local disease control while preserving the organ and its functions, particularly voice. The main treatment methods include transoral laser surgery (TOS), open partial laryngectomy and external radiation therapy (XRT) (12-15). Open partial laryngectomy, including vertical partial laryngectomy and supracricoid partial laryngectomy, has shown oncological outcomes comparable to those of TOS and XRT in early-stage laryngeal cancer (14, 16-18). However, open partial laryngectomy inevitably causes morbidity, such as dysphagia, scarring, and is primarily reserved for patients with contraindications to XRT, recurrent cases, poor larynx exposure or anterior commissure involvement. Consequently, this study excludes patients who underwent open partial laryngectomy.

Due to the anatomical structure, which has a paucity of submucosal lymphatic networks,

treatment for the lymph nodes in the neck is generally not performed in early glottic cancer, in contrast to other laryngeal subsites (19, 20). NCCN guidelines for treatment of early-stage glottic cancer recommend an organ-preserving strategy – either surgery with or without neck dissection or XRT. Many studies comparing the treatment outcomes of TOS and XRT have reported similar local control rates and survival rates between the two methods. Therefore, when selecting a treatment method for early-stage glottic cancer, post-treatment functional preservation should be considered an important factor.

Based on a review of 34 studies, we conducted a meta-analysis to compare the effectiveness of these two treatment methods (21-54). The analysis focused on oncological outcomes, post-treatment voice quality, and other post-treatment harms, such as the prevalence of secondary primary cancer and the eventual laryngeal preservation rate. From an oncological standpoint, the local control rate for early-stage laryngeal cancer is generally reported to be approximately 90% (22, 55). However, considerable debate remains in the literature regarding the oncological superiority of different treatment modalities due to lack of randomized control trials (RCTs). According to the results of our meta-analysis, TOS demonstrated better outcomes in 5-year overall survival (RR = 0.744, 95% CI 0.671-0.825; *RR, relative ratio; CI, confidential interval) (28, 29, 31, 34, 36, 37, 39, 41, 45, 46, 50, 52). However, there were no statistically significant differences between the two groups in terms of disease-specific survival (RR = 0.825, 95% CI 0.591-1.152) or disease-free survival (RR = 1.051, 95% CI 0.724-1.526). These findings are consistent with previous comparative studies, indicating that our analysis also could not establish a definitive oncological superiority between the two treatment methods.

Regarding residual voice impairment associated with treatment, TOS generally affects vocal fold vibration by leaving scars after surgery, and tissue loss can cause a glottal gap, negatively impacting the voice. This is known to be related to the extent of the excision (38). On the other hand, XRT is reported to affect vocal fold vibration by causing dryness and fibrosis (56). Previous

research has often been suggested that XRT achieves better voice outcomes than surgical treatment (12, 57, 58). Through our meta-analysis, we compared subjective assessments using Voice Handicap Index (VHI) and objective voice parameters, including fundamental frequency (F0), jitter, shimmer, noise-to-harmonic ratio (NHR), and maximal phonation time (MPT) (21, 24, 27, 31-33, 35, 38-40, 43, 45, 47, 49, 51, 53). MPT was analyzed in eight studies through a meta-analysis, and after excluding one heterogeneous study, it was found to be lower in TOS group compared to XRT group (SMD -0.748, 95% CI -1.133 to -0.364). However, no significant differences were found between the two groups in parameters other than MPT.

In relation to adverse effects post-treatment, a study was conducted to evaluate the frequency of secondary primary tumors following treatment and the need for salvage laryngectomy during the post-treatment follow-up period. A meta-analysis of six studies on the occurrence of secondary primary tumors showed no statistically significant difference in risk between the two groups (RR = 1.007, 95% CI 0.442-2.297)(35-37, 44, 46, 48). However, in the case of salvage laryngectomy, the TOS group exhibited significantly lower risk of undergoing the procedure compared to the XRT group (RR = 0.521, 95% CI 0.334-0.812), with low heterogeneity observed among the studies ($I^2 = 33\%$, $\tau^2 = 0.5088$, $p = 0.10$). These findings are consistent with previous meta-analyses (55, 59). Cernea et al. have reported that during the post-treatment observation period, individuals in the surgery group had a 1.8% probability of undergoing salvage laryngectomy, whereas those in the XRT group had an 11.8% probability (59).

We did not find convincing oncological evidence of superiority between the TOS and XRT groups. Additionally, no significant differences were observed in voice-related treatment outcomes, except for MPT. Moreover, the heterogeneity of measurement timing across studies made it challenging to derive precise conclusions regarding MPT. Notably, the frequency of salvage total laryngectomy, which reflects the laryngeal preservation rate, was statistically significantly lower in the TOS group, as confirmed through meta-analysis – consistent with

previous meta-analyses. Overall, most of the studies included in the meta-analysis were retrospective, carrying a high risk of bias. Oncologically, surgery and radiation therapy showed comparable outcomes, with each treatment option presenting distinct advantages and disadvantages concerning voice preservation and recurrence. However, since both treatments demonstrated a survival rate exceeding 90% in early glottic cancer across most studies, we recommended both treatment options with a strong recommendation.

A2. What is the appropriate treatment for early-stage supraglottic cancer?

Recommendation 3

For early-stage supraglottic cancer, both surgical treatment and radiation therapy can be considered as initial treatment.

(Strong recommendation/low-quality evidence)

Recommendation 4

Conservative laryngeal surgery (transoral surgery or open partial laryngectomy) could be considered a surgical treatment option in early-stage supraglottic cancer.

(Conditional recommendation/low-quality evidence)

For patients with early-stage supraglottic cancer (T1/T2), successful disease control can be achieved through either conservative laryngeal surgery (open partial laryngectomy or TOS) and therapeutic doses of XRT (8, 60). The most important factors to consider when deciding on initial treatment for early-stage supraglottic cancer are improved survival rate, reduced recurrence rate, and improved functional preservation of the larynx.

Regarding the comparison of the effectiveness of surgical treatment and XRT, Patel et al.

conducted a systematic literature review and meta-analysis of seven retrospective studies (60-67). This reported that disease-specific mortality (Odds ratio [OR] 0.43, 95% CI 0.31–0.60) and 5-year overall mortality (OR 0.40, 95% CI 0.29–0.55) were lower in the surgical group compared to the XRT group, while local recurrence rate was not different between the two groups (61). Among the studies included in this meta-analysis, Arshad et al. analyzed the largest sample size (2,631 patients) and found that the organ-preserving surgery with lymph node dissection group showed a significantly better survival rate than XRT-alone group, and suggested that surgical treatment is preferable as the initial treatment for early-stage supraglottic cancer (62). On the other hand, Spriano et al. reported a 5-year disease-free survival rate of 88.4% for conservative laryngeal surgery and 76.4% for radiotherapy in T1/T2 supraglottic cancer (166 patients) without significant statistical difference. This study also noted that complications related to chronic aspiration occurred in 3% of patients who underwent conservative laryngeal surgery, with a higher risk of such complications in patients who underwent more extensive surgery compared to those who received XRT (60). Since all the studies included in the meta-analysis were retrospective the level evidence is very low, making it difficult to draw definitive conclusions.

Collectively, there is no significant evidence-based difference in the oncologic outcomes of surgical treatment versus XRT for early-stage supraglottic cancer (T1/T2). Moreover, no study has yet conducted a comparative analysis of the functional outcomes of these two treatment modalities. Therefore, considering both patient factors and the benefits and risks of treatment, surgical treatment and radiation therapy are both viable initial options, and the most appropriate choice should be determined through shared decision-making between the treatment team and the patient.

B. Treatment for Locally Advanced Laryngeal Cancer (T3/T4)

B1. What is the role of total laryngectomy in locally advanced thyroid cancer?

Recommendation 5

Total laryngectomy can be selected as an initial treatment in locally advanced laryngeal cancer to achieve better locoregional control and survival.

(Conditional recommendation/low-quality evidence)

The larynx plays a crucial role in respiration, phonation, and swallowing control. Therefore, in the treatment of advanced laryngeal cancer, both ensuring survival and preserving function should be carefully considered. Total laryngectomy (TL), the primary surgical treatment modality for locally advanced laryngeal cancer, inevitably leads to a significant decline in the patient's quality of life (68, 69). Following prospective randomized trials on laryngeal preservation, including the Veteran's Affairs (VA) (70) and RTOG 91-11 (4), which reported that primary RT and combination of chemotherapy with RT were not inferior to surgery, laryngeal preservation treatment has become one of dominant treatment modality in the management of locally advanced laryngeal cancer (71, 72). However, since these laryngeal preservation treatments have not independently achieved improvements in survival (69, 71), the selection of an optimal primary treatment modality for locally advanced laryngeal cancer remains a subject of ongoing debate.

To date, a number of studies have compared the oncologic outcomes of TL and organ preservation treatments in locally advanced laryngeal cancer. We conducted a meta-analysis to evaluate oncologic outcomes, including overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS), and locoregional control (LRC). In our analysis of 17 studies that allowed for a meta-analysis of OS, we found that primary TL significantly reduced the risk compared to concurrent chemoradiation therapy (CCRT) in overall patients with T3 and T4 stages (HR 0.77; 95% CI, 0.66–0.90; $p < 0.00001$) (6, 72-84). In the subgroup analysis of T4 stage, the risk of reduced OS was significantly higher in the CCRT group compared to the TL group (HR 1.40; 95% CI, 1.20–1.57; $p < 0.00001$) (6, 71, 74, 79, 82, 83). These findings align with previous

studies, consistently demonstrating the superiority of primary TL for OS in the T4 stage disease (69, 71, 72, 79, 84). The current NCCN treatment guidelines also recommend primary surgery as the preferred treatment for T4a patients (2). Additionally, in a meta-analysis of five studies on LRC, the primary TL group demonstrated a significantly lower risk compared to the CCRT group (HR 0.58; 95% CI 0.38–0.88; $p = 0.01$) (75, 77, 78, 83, 85), although this analysis was limited by the inability to perform a stage-specific subgroup analysis. No significant difference between TL and CCRT was observed in terms of DFS and DSS, and stage-subgroup analysis was not feasible (72-75, 77, 78, 86-88).

Meanwhile, considerable controversy remains regarding the management of T3 disease. In our meta-analysis of OS in the T3 stage cases, no significant difference was found between the primary TL and CCRT groups (HR 1.19; 95% CI, 0.83–1.70; $p = 0.33$) (71, 74, 82), consistent with previous analyses, including systematic reviews (69, 71, 84). The NCCN guidelines also recommend non-surgical treatment modalities as equally feasible options for T3 cases, including those amenable to TL (89).

From a perspective of a quality of life, studies consistently highlight the loss of natural phonation due to TL and the psychological and social challenges associated with the creation of a permanent tracheostomy (68, 69, 71, 72, 79, 84, 90, 91). Additionally, during the treatment decision-making process, patients may refuse life-altering surgery or may often have comorbidities, particularly in older age, that make aggressive surgery difficult to endure (79). Conversely, non-surgical treatments also pose quality of life concerns, including dietary restrictions caused by radiation-induced oral mucositis and xerostomia (90), as well as a lower rate of improvement in dysphagia in the CCRT group compared to the surgical group (75.4% vs. 53.8%, $p < 0.001$) (91). Ganly et al. reported that when salvage TL is performed following initial CCRT failure, there is a significant increase in local complications due to delayed wound healing (45% vs. 25%, $P = 0.02$) and higher rates of pharyngocutaneous fistula (53% vs. 36%, $p = 0.08$) compared to initial TL

(92).

Collectively, although there is ongoing debate regarding the initial application of TL versus laryngeal-preserving treatments, considering the superior OS outcomes and lower local recurrence rate, TL can be selected as an initial treatment for locally advanced laryngeal cancer to achieve better locoregional control and survival especially in T4-stage disease. However, as the feasibility of surgery and tolerance for postoperative quality of life reduction vary among patients, the choice of treatment should also consider factors such as whether the disease is at T3 or T4 stage, the patient's need for voice use in social activities, age, and underlying comorbidities, making the strength of recommendation conditional. Therefore, a careful selection of initial treatment modalities, tailored to individual patient characteristics and disease burden, is crucial to achieving the optimal balance between oncologic outcomes and quality of life in the management of locally advanced laryngeal cancer.

B2. What is an appropriate larynx-preservation therapy in locally advanced laryngeal cancer?

Recommendation 6

- A) Larynx-preservation therapy (concurrent chemoradiation therapy or larynx-preservation surgery) can be applied depending on the patient's condition (T stage, age, underlying diseases, social activities, etc).

(Conditional recommendation/low-quality evidence)

- B) Larynx-preservation surgery could be performed in selected T3/T4 cancers without extensive tongue base invasion, bilateral cricoarytenoid unit impairment, or inferior extension to the cricoid cartilage, although the risk of postoperative morbidity such as dysphagia and aspiration should be carefully considered.

(Conditional recommendation/low-quality evidence)

The management of locally advanced laryngeal cancer, particularly T3 and T4 stages, presents significant challenges. This discussion is based on a comprehensive analysis of various treatment options, focusing on larynx-preservation therapies compared to TL.

TL is often considered the standard treatment for T4 tumors due to its superior outcomes in overall survival and local control. Previous studies have shown that TL reduced the risk of death compared to CCRT (93-96). Specifically, for T4 tumors, TL demonstrated significantly better OS than CCRT (93, 94, 97). On the other hand, CCRT is a viable option for T3 tumors, as it provides oncological outcomes comparable to TL. In the subgroup analysis for T3 tumors, no significant difference in OS was observed between TL and CCRT (93, 97). CCRT is particularly advantageous for patients in whom preserving laryngeal function is a priority and for those for high surgical risks. Recent meta-analysis found no significant difference in DFS between TL and CCRT with moderate heterogeneity ($I^2 = 69\%$) (93). Similarly, no significant difference in DSS was observed between TL and CCRT with high heterogeneity ($I^2 = 89\%$) (93, 95). However, TL demonstrated better local control (LC) compared to CCRT with low heterogeneity ($I^2 = 20\%$) (93).

The choice of therapy in locally advanced laryngeal cancer (T3/T4) should be individualized based on patient-specific factors and tumor characteristics. Key considerations include the patient's age, comorbidities, lung and swallowing function, and the extent of local invasion and nodal involvement (98). Partial laryngectomy can be considered for selected T3/T4 tumors that do not extensively invade critical structures. In selected cases, partial laryngectomy showed oncological outcomes similar to those of TL and CCRT (99). A recent study suggests that surgery with adjuvant therapy is the preferred initial therapy for patients with T4a tumors, whereas patients with T3 tumors can be treated with either surgery or definitive CCRT/RT to achieve

laryngeal preservation (96).

Recent advancements in transoral surgery, including laser surgery and transoral robotic surgery (TORS), have shown promise as one of the effective larynx-preserving strategies for locally advanced laryngeal cancer (100, 101). These minimally invasive techniques offer several benefits, such as reduced surgical morbidity, shorter recovery times, and the potential for better functional outcomes in terms of voice and swallowing. Laser surgery enables precise excision of tumors with minimal damage to surrounding tissues, while TORS provides enhanced visualization and dexterity. For selected patients, these approaches may serve as a useful alternative, enabling laryngeal function preservation without compromising oncologic control. However, their application should be approached with caution, as the indication and oncologic safety has not yet been fully established.

In conclusion, while TL offers superior outcomes for T4 tumors, CCRT and partial laryngectomy provide viable alternatives for T3 or selected T4 cases, allowing for laryngeal function preservation without compromising oncologic control. This tailored approach ensures optimal outcomes for patients with advanced laryngeal cancer.

C. Management of the Neck

C1. Is prophylactic neck dissection necessary for patients with clinically lymph node-negative laryngeal cancer?

The indications and extent of prophylactic neck dissection or irradiation in clinically lymph node-negative laryngeal cancer patients remain a topic of ongoing discussion. The decision to undertake prophylactic neck treatment is typically based on the primary subsite of the laryngeal cancer, the T stage, and the estimated risk of occult lymph node metastases (LNM). Direct analysis of the impact of neck dissection extent and necessity on survival in laryngeal cancer is challenging. Therefore, we sought to derive indirect evidence by analyzing the pooled incidence of LNM at

each neck level. Prophylactic treatment is generally considered when this risk is 15-20% or higher. The risk varies by primary site and stage, with the glottis typically having sparse lymphatic drainage, resulting in a lower incidence of occult LNM (102). Expected survival benefits, along with the functional and cosmetic morbidity of prophylactic treatment, are also comprehensively considered for each individual patient.

Recommendation 7

If lymph node metastasis is clinically negative in early-stage (T1/T2) laryngeal cancer confined to the glottis, prophylactic neck dissection is not mandatory.
(Conditional recommendation/low-quality evidence)

The initial search identified 868 studies on occult neck LNM in laryngeal cancer. Among them, only 10 studies specifically addressed glottic cancer, including a total of 2,192 patients (102-111). Regardless of T stage, the overall pooled incidence of occult metastasis in glottic cancer was 9% (95% CI 5.6–14.7, $I^2 = 91\%$). Five studies reported data on the T1-2 stage (102, 104-107), the pooled incidence was 6% (95% CI 0.1–12, $I^2 = 88\%$). For the subgroup with T3 stage of glottic cancer (103-107), the pooled incidence was 15.6% (95% CI 7.6–23.6, $I^2 = 30\%$). For T4 stage disease (103-107), the pooled incidence was 46.5% (95% CI 20.6–72.4, $I^2 = 67\%$).

Recently, with the introduction of non-surgical organ preservation treatments like definitive RT and transoral surgery for early-stage of glottic cancer, avoiding unnecessary neck dissection and minimizing the radiation field has become increasingly important to prevent treatment-related morbidities (112). In this context, for T1-2 glottic cancer, the probability of occult neck LNM is low, suggesting that prophylactic neck dissection may be omitted. This approach helps to avoid unnecessary procedures and potential complications, thereby preserving the patient's quality of life.

However, these results do not directly analyze the impact of prophylactic neck dissection on

survival. The decision to perform neck dissection should be based on various clinical factors, and therefore, the strength of the recommendation was designated as conditional.

Recommendation 8

If lymph node metastasis is clinically negative in early-stage (T1/T2) laryngeal cancer involving the supraglottis, prophylactic neck dissection including the levels II-III could be considered.

(Conditional recommendation/low-quality evidence)

The lymphatic drainage of the larynx differs significantly between the supraglottic and glottic regions. The supraglottis has a dense lymphatic network that drains through the thyrohyoid membrane into the first-echelon lymph nodes at levels II and III. In contrast, the glottis, particularly the free edge of the true vocal cords, has a sparse lymphatic network and is almost devoid of lymphatic vessels. Since the 1960s, several studies have highlighted these differential drainage patterns, emphasizing the rich lymphatic presence in the supraglottis compared to the minimal lymphatic structures in the vocal cords (113-115).

In our analyses, twenty-three studies specifically addressing supraglottic cancer, including a total of 2,235 patients, were reviewed (105-107, 116-135). In T1-2 tumors, the pooled incidence of occult LNM was 15.1% (95% CI 12–18.3, $I^2 = 0\%$). For the subgroup with T3 stage supraglottic cancer, the pooled incidence of occult metastasis was 23.1% (95% CI 16.6–29.7, $I^2 = 65\%$). Given the higher incidence of LNM in supraglottic cancer compared to glottic cancer at the same T classification (15.1% vs. 6% in T1-2 tumors and 23.1% vs. 15.6% in T3 tumors), prophylactic neck dissection may be warranted in early-stage (T1-2) supraglottic cancer. This increased risk of LNM highlights the importance of addressing potential lymph node involvement to ensure comprehensive treatment and improve patient outcomes.

Our analysis indicates a pooled incidence of 0.8% (95% CI 0–3.3, $I^2 = 48\%$) for level I and only

1% (95% CI 0–3.3, $I^2 = 48\%$) for level IV, suggesting that routine elective treatment of these levels may be unnecessary. Similarly, the pooled incidence for level V was 2.3% (95% CI 1.1–3.5, $I^2 = 37\%$), further supporting their exclusion from routine dissection.

Recommendation 9

If lymph node metastasis is clinically negative in advanced stage (T3/T4) laryngeal cancer, prophylactic neck dissection including the levels II-III should be considered.

(Conditional recommendation/low-quality evidence)

Twenty studies on laryngeal cancer without specifying subsite, including a total of 3,916 patients, were reviewed (107, 136-154). The pooled incidence of occult neck LNM in advanced stage (T3-4) laryngeal cancer was 20.8% (95% CI 15.5-26.1, $I^2=61\%$). This substantial risk supports the necessity of prophylactic neck dissection in patients with advanced stage laryngeal cancer who do not have clinically apparent ipsilateral neck LNM. The increasing risk of occult metastases with advancing T stage highlights the importance of this approach in ensuring comprehensive treatment and improve patient outcomes.

C2. What is the appropriate extent of neck dissection in patients with clinically lymph node-positive laryngeal cancer?

Recommendation 10

If ipsilateral lymph node metastasis is clinically apparent, comprehensive neck dissection or selective neck dissection including at least levels II, III, IV should be performed.

(Strong recommendation/low-quality evidence)

Although no large-scale randomized studies have established the optimal treatment for laryngeal cancer with clinically positive LNM, modified radical neck dissection (MRND) involving levels

I–V is commonly performed. However, studies indicate that metastasis to levels I (1.8–5%) and V (2–11%) is infrequent in laryngeal cancer (136, 155, 156). Eugenia et al. reported neck recurrence in 6 of 58 patients (10.3%) with laryngeal cancer and LNM who underwent selective neck dissection (SND) – all within previously dissected areas (157). Similarly, Lohuis et al. performed SND including II–V on 48 patients with laryngeal and hypopharyngeal cancer, reporting 6 cases of recurrence, 5 within previously dissected areas (156). Brentani et al. compared MRND and SND (II–V) in 132 patients with T2–T4N0M0 supraglottic and transglottic cancer, finding no significant differences in the 5-year survival rate, recurrence rate, complications, and hospital stay (158). However, Santos et al. reported higher neck recurrence rates after SND in patients with T3 or higher primary tumors and N2b or higher neck metastasis, suggesting caution in these cases (159). Additionally, when there is extranodal extension, resection of the spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle may be necessary.

A literature search on LNM for unilateral neck dissection in supraglottic cancer yielded a limited number of studies. In an earlier study, Candela et al. found that metastasis in laryngeal cancer was most common in levels II–IV (136). In supraglottic cancer with clinical LNM, 5% and 6% of 119 patients had metastasis in levels I and V, respectively, while postoperative confirmation showed 11% in level I and none in level V (136). Choi et al. analyzed 78 cases, 39 of which were supraglottic cancer (160). The two cases with level I metastasis were salvage surgeries, and both node-negative and node-positive patients had very low frequencies of level I involvement (160). Consistently, Buckley et al. and Gallo et al. in 2000 reported that most metastasis in laryngeal cancer occurred in levels II–V, with few cases in levels I and V. (161, 162). Multiple other studies have also indicated a low frequency of metastasis in levels I and V (163–167). However, most were retrospective studies and lacked bias assessments, making the evidences low-quality. Nevertheless, given the high probability of metastasis in levels II, III, and IV when lymph node

involvement is present, performing neck dissection that includes at least these levels is necessary, warranting a strong recommendation.

Recommendation 11

If ipsilateral lymph node metastasis is clinically apparent in laryngeal cancer confined to the glottis, contralateral prophylactic neck dissection is not mandatory.

(Conditional recommendation/low-quality evidence)

Prophylactic neck dissection in head and neck cancer is generally considered when the rate of occult metastasis is 15-20% or higher. If the tumor crosses the midline and invades the contralateral side, elective treatment may be necessary for the contralateral neck (8). Locally advanced glottic cancer (T3/T4) can extend beyond the midline, and transglottic cancer, which involves both the supraglottic and subglottic regions, may follow a lymphatic spread pattern similar to primary cancers in these areas, suggesting the need for contralateral prophylactic neck dissection.

Amar et al. studied 104 laryngeal cancer patients who underwent surgery and found that in unilateral glottic cancer without midline involvement, the contralateral occult metastasis rate was only 3.5%, suggesting that contralateral prophylactic dissection is unnecessary (168).

Böttcher et al. investigated occult metastasis rates in 28 advanced laryngeal cancer patients who underwent total laryngectomy and prophylactic neck dissection for transglottic cancer. Occult metastasis was found in 24.9% of cases—14.2% on the ipsilateral side and 10.7% on the contralateral side (152). They also noted that in previous studies, no contralateral metastasis was observed when the primary tumor did not cross the midline (169).

Given the rate of occult metastasis, current evidence does not support routine contralateral prophylactic neck dissection in glottic cancer with ipsilateral lymph node metastasis. However,

due to the lack of well-designed prospective comparative studies, the level of evidence remains low, and recommendations remain conditional.

Recommendation 12

If ipsilateral lymph node metastasis is clinically apparent in laryngeal cancer involving the supraglottis, contralateral prophylactic neck dissection including the levels II-IV should be considered.

(Conditional recommendation/moderate-quality evidence)

Studies on prophylactic contralateral neck dissection in supraglottic cancer consistently showed that surgery reduced recurrence and improved survival compared to observation, without significantly increasing complications. Specifically, Ferlito et al. found that prophylactic contralateral neck dissection improved survival and recurrence management (165). Weber et al. reported a recurrence rate of 20% in the observation group vs. 9% in the surgical group, with a 2-year survival rate of 76% vs. 72%, favoring surgery (170). Gallo et al. analyzed 24 surgical and 103 observational cases, finding 9 of 24 had pathologic lymph node metastasis, while 40 of 103 in the observation group developed local recurrence. However, 5-year survival rates did not differ (162). Chiu et al. compared 202 observational vs. 115 surgical cases, showing a lower 2-year recurrence rate (7.8% vs. 20%) and higher 2-year survival (83% vs. 72%) in the surgical group (171). Despite being retrospective, these studies included over 100 patients each, providing moderate-level evidence.

Regarding the extent of surgery, Böttcher et al. reported contralateral neck metastasis only in levels IIA, III, and IV; however, this analysis was limited to six patients, requiring cautious interpretation of the results (152). Gross et al. analyzed 65 patients and found approximately 20% of them had metastasis in contralateral level IIB, suggesting the need for surgical intervention (172). Dundar et al. analyzed 39 patients and observed that contralateral level IIB metastasis only

occurred when level IIA was also involved, making it difficult to detect during surgery as preoperative assessments showed no LNM (173). Additionally, other studies generally supported lymph node dissection in contralateral levels II–IV (134, 174, 175).

Regarding complications of contralateral prophylactic neck dissection, two retrospective studies compared complication rates in supraglottic cancer patients with unilateral neck metastasis who underwent selective dissection vs. observation. Gregor et al. found no significant differences in complications or sequelae between the surgical and observation groups (176). Similarly, Gallo et al. observed 24 surgical and 103 observational cases, reporting no significant differences in complications or 5-year survival rates between the two groups (162). The surgical procedure involved selective neck dissection of levels II–IV, with potential complications such as spinal accessory nerve injury.

D. Adjuvant Therapy

D1. Does adjuvant therapy improve treatment outcomes in patients with laryngeal cancer following surgical resection?

Recommendation 13

(A) Adjuvant therapy (radiation therapy or chemoradiation therapy) following radical surgery could be considered for patients with advanced stage (III/IV) disease and/or risk factors such as vascular invasion, perineural invasion, or multiple nodal metastases.

(Conditional recommendation/low-quality evidence)

(B) Adjuvant chemoradiotherapy should be considered for patients with laryngeal cancer and positive surgical margins or extranodal extension.

(Conditional recommendation/high-quality evidence)

Although the optimal strategy for adjuvant therapy (radiation or chemoradiation) after radical

surgery for advanced laryngeal cancer remains unclear, its benefits in stage III and IV head and neck squamous cell carcinoma (HNSCC) have been well established (177-180). We conducted a meta-analysis to assess the impact of adjuvant radiation therapy in advanced laryngeal cancer. A total of 13,359 abstracts were identified across multiple databases (Cochrane, Embase, KoreaMed, Medline) using terms related to laryngeal cancer and radiotherapy. After screening, three studies were included. Despite high heterogeneity ($I^2 = 78\%$), patients who underwent postoperative radiation therapy ($n = 596$) showed significantly improved 5-year overall survival compared to those who had surgery alone ($n = 930$) (RR 0.90, 95% CI 0.84–0.97) (181-183). Additionally, postoperative radiation therapy reduced recurrence rates (RR 0.36, 95% CI 0.14–0.90, $I^2 = 0\%$) (181, 183). These findings suggest that adjuvant radiation therapy after radical surgery improves clinical outcomes in advanced laryngeal cancer. However, in pT3N0 laryngeal cancer without other adverse pathological features, its use should be carefully weighed against potential risks (180, 182).

Previous studies have identified high-risk factors benefiting from adjuvant therapy after HNSCC surgery, including extranodal extension (ENE), positive or close margins, pT3/pT4 primary tumor, pN2/pN3 nodal disease, perineural invasion, vascular invasion, and lymphatic invasion (184). Two major RCTs investigated the optimal postoperative therapy for advanced resectable HNSCC. The RTOG 9501 trial showed that adjuvant CCRT improved locoregional control and DFS compared to adjuvant RT alone in patients with multiple lymph node metastases (>2), ENE, and microscopic positive margins (177). Similarly, the EORTC 22931 trial reported that CCRT improved progression-free and overall survival by reducing locoregional relapse in patients with pT3/pT4 tumors (except T3N0 laryngeal cancer), ENE, positive margins, perineural involvement, or vascular invasion (178). A comparative analysis of RTOG 9501 and EORTC 22931 concluded that adjuvant CCRT is most beneficial for patients with positive margins or ENE, rather than those with multiple lymph node metastases (179, 185). Based on these findings from high-quality

evidence, CCRT is recommended post-surgery for patients with ENE, with or without positive margins (184). Additionally, CCRT may be considered for vascular invasion, perineural invasion, or multiple nodal metastases when its benefits are evident (184).

Collectively, postoperative RT or CCRT may be considered for advanced (stage III/IV) laryngeal cancer with multiple nodal metastases, perineural, vascular, or lymphatic invasion. However, CCRT is preferred over RT for positive margins or ENE. Given its higher risk of severe adverse events in HNSCC, patients should be informed before choosing adjuvant therapy (177, 178).

E. Swallowing Rehabilitation

E1. What is the role of swallowing rehabilitation in patients with laryngeal cancer?

Recommendation 14

Swallowing rehabilitation may be useful for dysphagia after surgical or nonsurgical treatment for laryngeal cancer.

(Conditional recommendation/very low-quality evidence)

Swallowing difficulties are common after surgical and non-surgical treatment for laryngeal cancer, often requiring rehabilitation (186-189). After partial laryngectomy, aspiration occurs in up to 74% of patients, with recovery typically taking 4–6 weeks, while more extensive resections may require a longer recovery period (190-192). Supracricoid partial laryngectomy has a high incidence of dysphagia, but swallowing function often improves within three months post-surgery (189, 193). Total laryngectomy can affect swallowing due to reduced pharyngeal wall contraction and pharyngoesophageal pressure; however, most patients resume a normal diet within a month if no complications occur (194). Radiation therapy may cause fibrosis and radionecrosis, impairing tongue and pharyngeal muscle function, leading to dysphagia (195). Swallowing rehabilitation after laryngeal cancer treatment includes posture adjustments,

swallowing maneuvers, and bolus modification. Common techniques such as supraglottic, super-supraglottic, Masako, Mendelsohn, and Effortful swallowing maneuvers help reduce aspiration, particularly after partial laryngectomy or radiotherapy (186-188, 196). Rehabilitation strategies are tailored based on structural changes and dysphagia severity, often assessed through barium swallow tests.

We conducted a systematic literature review and identified three studies on swallowing rehabilitation (197-199). Among them, two prospective studies included head and neck cancer patients in general, rather than focusing specifically on laryngeal cancer, while one retrospective study examined swallowing rehabilitation following supracricoid partial laryngectomy. Due to significant heterogeneity in patient populations, a meta-analysis was not feasible, and a narrative literature review was conducted instead. Lewin et al. (2008) found that despite initial severe dysphagia following supracricoid partial laryngectomy, most patients regained oral intake with appropriate rehabilitation strategies (197). Hajdú et al. (2022) reported that swallowing exercises during radiotherapy improved quality of life and functional outcomes, although they had no significant effect on penetration-aspiration scores (199). Messing et al. (2017) further indicated that prophylactic swallowing exercises in patients undergoing chemoradiotherapy led to early improvements in oromotor function and swallowing efficiency (198). These findings suggest that structured swallowing rehabilitation may aid functional recovery and improve swallowing outcomes in laryngeal cancer patients.

However, several limitations were noted. Most studies included mixed cohorts of head and neck cancer patients, limiting their applicability to laryngeal cancer. Additionally, the retrospective nature of the only laryngeal cancer-specific study reduced its generalizability. Variability in treatment approaches, rehabilitation protocols, and evaluation time points further contributed to inconsistencies among studies. Given the limited availability of high-quality, controlled studies specifically focused on laryngeal cancer, the current evidence remains of very low-quality,

supporting only a conditional recommendation for swallowing rehabilitation. Despite these limitations, the existing data suggest that swallowing rehabilitation may be beneficial for dysphagia following surgical or nonsurgical treatment of laryngeal cancer. However, due to differences in dysphagia assessment tools, evaluation time points, and small sample sizes across studies, determining the precise effectiveness of swallowing rehabilitation remains challenging. Nevertheless, the available evidence supports its clinical benefit, highlighting the need for further well-designed, prospective studies to establish more definitive guidelines.

F. Salvage Treatment for Recurrent Laryngeal Cancer

F1. What are the salvage treatment options applicable for locally recurrent laryngeal cancer?

Recommendation 15

- A) Total laryngectomy should be considered for most patients with locally recurrent cancer when larynx-preserving strategy is not feasible due to patient and tumor characteristics.
(Strong recommendation/low-quality evidence)
- B) Open partial laryngectomy could be considered for selected patients with locally recurrent laryngeal cancer in whom one or two cricoarytenoid unit can be preserved.
(Conditional recommendation/very low-quality evidence)
- C) Transoral surgery may be considered for well-selected patients with localized and limited recurrent tumors, providing precise preoperative assessment to ensure adequate exposure and complete resectability
(Conditional recommendation/very low-quality evidence)
- D) RT/CCRT is an available salvage modality for eligible patients unless it was used in the initial treatment.

(Conditional recommendation/very low-quality evidence)

The larynx is more amenable to salvage surgery than other head and neck subsites, with salvage total laryngectomy (STL) remaining the primary treatment for locally recurrent, advanced-stage laryngeal cancer. STL is indicated for rT3 tumors with cricoarytenoid unit or hemilaryngeal fixation, or extension to the paraglottic/pre-epiglottic spaces, hypopharynx, or subglottis, as well as for rT4a tumors with extralaryngeal spread or cricoid cartilage infiltration. (200-203). It is also recommended for patients who are poor candidates for laryngeal conservation surgery due to advanced age or compromised cardiopulmonary function, even in cases of smaller tumors (200-203). The 5-year survival rates for STL range from 37.7% to 59% for OS, 54.9% to 68.7% for DSS, and 42.1% to 83% for DFS (200, 201, 203-205). However, STL carries a high complication rate, particularly following prior RT with or without chemotherapy. A 2017 systematic review and meta-analysis of 3,292 patients from 50 studies reported an overall complication rate of 67.5%, with pharyngocutaneous fistula being the most common complication, occurring in 5.6% to 73% of cases (pooled incidence: 28.9%) (206).

Open partial laryngectomy has gained acceptance as a salvage option in selected cases, offering acceptable survival outcomes while preserving the larynx. A 2018 meta-analysis by De Virgilio, including 251 patients from 11 studies, reported 79% 5-year OS, 80% 3-year DFS, 92% 2-year local control, and an 85.2% laryngeal preservation rate (LPR) for salvage supracricoid partial laryngectomy in recurrent laryngeal cancer (207). Notably, 27.1% of patients had rT3-T4 disease. A 2022 review by Shapira, analyzing 323 patients from 15 studies, found a 90.4% laryngectomy-free survival rate after open supracricoid partial laryngectomy, supporting open partial laryngectomy as a viable salvage option following RT failure (208). Similarly, Lucioni et al. (2016) reported 82% OS, 82% DSS, and 70% LPR after salvage partial laryngectomy for patients who failed primary transoral laser microsurgery (TLM), suggesting

its safety in this setting (209). However, most studies on salvage open partial laryngectomy are retrospective, with small patient cohorts (often <30), introducing potential selection and publication biases. Surgeons should consider these limitations when interpreting favorable outcomes.

TLM is a valuable salvage option for locally recurrent laryngeal cancer, particularly in early-stage recurrence after primary RT/CCRT or TLM. In rT1–T2 disease following RT/CCRT, salvage TLM has shown OS rates of 52.6–100.0%, DSS of 67.9–100.0%, local control rates (LCR) of 42–100.0%, and LPR of 63.0–100.0% (210-218). In rT1–T2 disease after primary TLM, outcomes include OS of 61.6–90%, DSS of 79.6–100.0%, LCR of 57.5–70.2%, and LPR of 38.5–85.0% (219-222). A 2023 systematic review and meta-analysis by Russo, including 235 and 271 patients undergoing salvage TLM after RT/CCRT and primary TLM, respectively, reported pooled 3-year LCR, DSS, and LPR rates of 53.9%, 67.8%, and 73.5% after RT/CCRT, and 53.2%, 77.0%, and 83.7% after primary TLM (223). While some studies have explored salvage TLM for rT3–T4a disease, its success depends on strict patient selection, precise preoperative assessment, and significant surgical expertise to ensure adequate exposure and complete resection.

RT/CCRT can be used as a salvage treatment for eligible patients if surgery alone was the primary treatment. However, data on the outcomes of salvage RT/CCRT after failed first-line surgical treatment remain limited. Therefore, its effectiveness for recurrent laryngeal cancer following initial surgery cannot be guaranteed. A 2021 study by Akbaba, including 75 patients who underwent salvage RT/CCRT for recurrent hypopharyngeal and laryngeal cancer after primary surgery alone, reported 5-year local progression-free survival of 75%, OS of 64%, distant progression-free survival of 82%, and LPR of 100% (224).

F2. Does elective neck dissection improve oncological outcomes in salvage treatment for

locally recurrent laryngeal cancer?

Recommendation 16

Elective neck dissection could be considered in selected patients with locally recurrent laryngeal cancer who are at high risk for regional recurrence, including those with supraglottic or transglottic involvement and advanced rT category.

(Conditional recommendation/very low-quality evidence)

An evaluation was conducted on the rate of occult metastasis in patients with locally recurrent laryngeal cancer who underwent salvage laryngectomy (total laryngectomy) with prophylactic neck dissection of the N0 neck. The analysis included 22 studies (225-246). The rate of occult metastasis was assessed in patients who underwent neck dissection; however, a meta-analysis was not feasible, and results were derived through quantitative synthesis. Among 981 patients who underwent neck dissection, 138 were found to have occult metastasis, yielding an occult metastasis rate of 14.1% (range: 0–31.1%).

Next, we conducted a meta-analysis to evaluate disease-specific survival (DSS) rates in relation to neck dissection performed alongside total laryngectomy. Five studies were included in the analysis (228, 229, 236, 240, 243). The DSS rate was 64.9% (range: 56.4–100%) in patients who underwent elective neck dissection, compared to 70.5% (range: 54.6–100%) in those who did not. The meta-analysis found no significant difference in DSS between the two groups (RR 0.96, 95% CI 0.78–1.19), likely due to variations in patient numbers, primary tumor site (supraglottic, transglottic, glottic), disease stage, and survival evaluation time points. Furthermore, a meta-analysis on overall survival (OS) rates was conducted using data from eight studies (226-229, 236, 240, 245, 246). The OS rate was 62.9% (range: 42.9–100%) in patients who underwent elective neck dissection, compared to 60.4% (range: 36.2–100%) in those who did not. The results

indicated no significant difference in OS between the two groups (RR 1.01, 95% CI 0.86–1.17). A meta-analysis on regional recurrence rates was conducted using data from nine studies (225–228, 232, 235, 242, 243, 246). The regional recurrence rate was 7.7% (range: 0–18.8%) in patients who underwent elective neck dissection, compared to 9.2% (range: 0–30.8%) in those who did not. This meta-analysis also found no significant difference in regional recurrence rates between the two groups (RR 0.69, 95% CI 0.40–1.21).

An analysis of complications associated with neck dissection performed alongside total laryngectomy was conducted. The most commonly evaluated complications included pharyngocutaneous fistula, wound hematoma, and infection. Additionally, some studies assessed chyle leakage and prolonged feeding tube use. Despite variations in the types of complications evaluated and the timing of assessments across different studies (225–227, 229, 231, 232, 240, 242, 246), the meta-analysis found no significant difference in complication rates between the groups with and without neck dissection (RR 1.25, 95% CI 0.84–1.87).

Two papers included in the systematic literature review reported differences in occult metastasis rates and corresponding survival rates based on the primary tumor site. Birkeland (2016) found a higher occult metastasis rate of 28% in the supraglottis compared to other subsites ($p < 0.00$) (234). Koss (2014) reported high occult metastasis rates of 60% in the supraglottis ($p = 0.02$) and 30% in the transglottis, with correspondingly lower survival rates ($p = 0.02$) (236). Birkeland (2016) also reported that higher primary tumor stages at recurrence were associated with increased occult metastasis rates: 10% for T1–T2, 15.7% for T3, and 34% for T4 ($p < 0.00$) (234). Most studies included in this review focused on cases where initial treatment involved RT or CRT. Further evaluation is needed to determine the applicability of these findings to cases where surgical management was the primary treatment.

Concluding remarks

The management of laryngeal cancer requires a balance between achieving optimal oncologic outcomes and preserving essential functions such as voice and swallowing. The Korean Society of Head and Neck Surgery, with support from the Korean Cancer Management Guideline Network (KCGN), has developed new guidelines for laryngeal cancer management. A key limitation of these guidelines is that a multidisciplinary committee was not actively involved in the development process, highlighting the need for future revisions incorporating broader expertise. Additionally, most key recommendations are based on low-quality evidence and conditional recommendations, making it difficult to provide a clear decision flow. This limitation should be addressed through the generation of high-quality evidence in future research. Nevertheless, these guidelines, developed through a systematic literature review, meta-analysis, and expert consensus, with methodological consultation based on GRADE criteria, provide evidence-based recommendations to assist clinicians in making informed treatment decisions.

Conflict of interest

No potential conflict of interest relevant to this article was reported

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Supplementary Table 1. The search string used for each key question

A. Treatment for Early-stage Laryngeal Cancer (T1/T2)

- **A1.** What is the appropriate treatment for early-stage glottic cancer?

- **A2.** What is the appropriate treatment for early-stage supraglottic cancer?

DB	no.	Search Query	Search result 2022.12.25	Note
Ovid MEDLINE	#1	Laryngeal Neoplasms/	28,846	P (patient)
	#2	((larynx* or throat) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*)).tw,kf,kw.	24,369	
	#3	((glott* or subglott* or sub-glott* or supraglott* or supra-glott*) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*)).tw,kf,kw.	3,911	
	#4	((vocal adj (cord\$1 or fold\$1 or ligament\$1)) or voice box) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*)).tw,kf,kw.	1,161	
	#5	exp "Otorhinolaryngologic Neoplasms"/ or exp "Respiratory Tract Neoplasms"/	374,673	
	#6	exp "Laryngeal Diseases"/ or exp Larynx/ or (larynx* or throat or glott* or subglott* or sub-glott* or supraglott* or supra-glott* or (vocal adj (cord\$1 or fold\$1 or ligament\$1)) or voice box).tw,kf,kw.	158,910	
	#7	5 and 6	32,773	
	#8	1 or 2 or 3 or 4 or 7	39,601	I (intervention)
	#9	Surgical Procedures, Operative/ or Otorhinolaryngologic Surgical Procedures/	62,412	
	#10	(surger* or surgical* or operation\$1 or operative or procedure\$1 or endolaryngeal or cordectomy* or (larynx* adj3 preserv*)).tw,kf,kw.	3,403,652	
	#11	Laser Therapy/ or Microsurgery/ or Endoscopy/	123,665	
	#12	(transoral or trans-oral or endoscop* or microsurg* or micro-surg* or microscop* or microscale).tw,kf,kw.	1,091,641	
	#13	(laser adj3 (therap* or treat* or surger* or surgical* or vaporization\$1 or ablation\$1 or ablative or nonablative or photoablation\$1 or scalpel\$1 or knife\$1 or knife\$1)).tw,kf,kw.	48,372	
	#14	Laryngectomy/	10,196	
	#15	((partial or subtotal or sub-total or incomplete) adj3 (laryngectomy* or resect* or remov* or surger* or surgical* or operation\$1 or operative or procedure\$1) or hemilaryngectomy* or hemi-laryngectomy*).tw,kf,kw.	36,162	
	#16	9 or 10 or 11 or 12 or 13 or 14 or 15	4,355,534	
	#17	8 and 16	17,239	P and I

	#18	(nonsurger* or non-surger* or nonsurgical* or non-surgical*).tw,kf,kw.	34,455	C (comparator)
	#19	Radiotherapy/ or "Radiotherapy, Adjuvant"/	68,396	
	#20	(radiotherap* or radio-therap* or radiation\$1 or irradiation* or hyperfractionat* or hypofractionat* or dose fractionat*).tw,kf,kw.	720,136	
	#21	18 or 19 or 20	767,155	
	#22	17 and 21	5,330	P and I and C
	#23	22 not (Case Reports.pt. or case report\$1.ti. or Comment.pt. or comment*.ti. or Letter.pt. or letter.ti. or Editorial.pt. or (animals/ not (animals/ and humans/)))	4,529	
	#24	limit 23 to yr="2016 -2022"	1,007	
	#25	limit 23 to yr="2015 -2022"	1,146	A2
EMBASE	#1	'larynx tumor'/exp	41,413	P (patient)
	#2	((larynx* OR throat) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	28,581	
	#3	((glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott*) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	4,743	
	#4	(('vocal cord\$' OR 'vocal fold\$' OR 'vocal ligament\$' OR 'voice box') NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	1,367	
	#5	'head and neck tumor'/exp OR 'respiratory tract tumor'/exp	944,484	
	#6	'larynx disorder'/exp OR 'larynx'/exp OR (larynx* OR throat OR glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott* OR 'vocal cord\$' OR 'vocal fold\$' OR 'vocal ligament\$' OR 'voice box'):ti,ab,kw	223,884	
	#7	#5 AND #6	58,791	
	#8	#1 OR #2 OR #3 OR #4 OR #7	62,866	
	#9	'surgery'/de OR 'ear nose throat surgery'/de OR 'throat surgery'/de OR 'larynx surgery'/exp	754,382	I (intervention)
	#10	(surger* OR surgical* OR operation\$ OR operative OR procedure\$ OR endolaryngeal OR cordectom* OR (larynx* NEAR/3 preserv*)):ti,ab,kw	4,606,631	
	#11	'laser surgery'/de OR 'laser therapy'/de OR 'microsurgery'/de OR 'endoscopy'/de	192,785	
	#12	(transoral OR trans-oral OR endoscop* OR microsurg* OR micro-surg* OR microscop* OR microscale):ti,ab,kw	1,379,298	
	#13	(laser NEAR/3 (therap* OR treat* OR surger* OR surgical* OR vaporization\$ OR ablation\$ OR ablative OR nonablative OR photoablation\$ OR scalpel\$ OR knife\$ OR knife\$)):ti,ab,kw	62,185	
	#14	'laryngectomy'/exp	13,816	

	#15	((partial OR subtotal OR sub-total OR incomplete) NEAR/3 (laryngectom* OR resect* OR remov* OR surger* OR surgical* OR operation\$ OR operative OR procedure\$)) OR hemilaryngectom* OR hemilaryngectom*):ti,ab,kw	49,538	
	#16	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	5,895,863	
	#17	#8 AND #16	28,080	P and I
	#18	(nonsurger* OR non-surger* OR nonsurgical* OR non-surgical*):ti,ab,kw	46,202	C (comparator)
	#19	'radiotherapy'/de OR 'adjuvant radiotherapy'/de	187,947	
	#20	(radiotherap* OR radio-therap* OR radiation\$ OR irradiation* OR hyperfractionat* OR hypofractionat* OR 'dose fractionat*'):ti,ab,kw	968,873	
	#21	#18 OR #19 OR #20	1,039,414	
	#22	#17 AND #21	9,249	P and I and C
	#23	#22 NOT ('case study'/exp OR 'case report\$':ti OR comment*:ti OR letter:it OR letter:ti OR editorial:it OR ('animal'/de NOT ('animal'/de AND 'human'/de)))	8,820	
	#24	#23 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [2016-2022]/py	1,689	A1
	#25	#23 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [2015-2022]/py	1,905	A2
Cochrane	#1	[mh ^"Laryngeal Neoplasms"]	337	P (patient)
	#2	((larynx* OR throat) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	1,267	
	#3	((glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott*) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	192	
	#4	((vocal-cord? OR vocal-fold? OR vocal-ligament? OR "voice box") NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	52	
	#5	[mh "Otorhinolaryngologic Neoplasms"] OR [mh "Respiratory Tract Neoplasms"]	10,219	
	#6	[mh "Laryngeal Diseases"] OR [mh "Larynx"] OR (larynx* OR throat OR glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott* OR vocal-cord? OR vocal-fold? OR vocal-ligament? OR "voice box"):ti,ab,kw	20,260	
	#7	#5 AND #6	414	
	#8	#1 OR #2 OR #3 OR #4 OR #7	1,405	I (intervention)
	#9	[mh ^"Surgical Procedures, Operative"] OR [mh ^"Otorhinolaryngologic Surgical Procedures"]	1,297	
	#10	(surger* OR surgical* OR operation? OR operative OR procedure? OR endolaryngeal OR cordectomy* OR (larynx* NEAR/3 preserv*)):ti,ab,kw	502,954	
	#11	[mh ^"Laser Therapy"] OR [mh ^"Microsurgery"] OR [mh ^"Endoscopy"]	4,547	

#12	(transoral OR trans-oral OR endoscop* OR microsurg* OR micro-surg* OR microscop* OR microscale):ti,ab,kw	42,799	
#13	(laser NEAR/3 (therap* OR treat* OR surger* OR surgical* OR vaporization? OR ablation? OR ablative OR nonablative OR photoablation? OR scalpel? OR knife? OR knife?)):ti,ab,kw	11,042	
#14	[mh ^"Laryngectomy"]	176	
#15	((partial OR subtotal OR sub-total OR incomplete) NEAR/3 (laryngectom* OR resect* OR remov* OR surger* OR surgical* OR operation? OR operative OR procedure?)) OR hemilaryngectom* OR hemilaryngectom*):ti,ab,kw	2,068	
#16	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	528,402	
#17	#8 AND #16	772	P and I
#18	(nonsurger* OR non-surger* OR nonsurgical* OR non-surgical*):ti,ab,kw	5,024	C (comparator)
#19	[mh ^"Radiotherapy"] OR [mh ^"Radiotherapy, Adjuvant"]	2,206	
#20	(radiotherap* OR radio-therap* OR radiation? OR irradiation* OR hyperfractionat* OR hypofractionat* OR dose-fractionat*):ti,ab,kw	56,831	
#21	#18 OR #19 OR #20	61,580	
#22	#17 AND #21	386	P and I and C
#23	#17 AND #21 with Cochrane Library publication date Between Jan 2016 and Dec 2022, in Cochrane Reviews, Trials	205	A1
#24	#17 AND #21 with Cochrane Library publication date Between Jan 2015 and Dec 2022, in Cochrane Reviews, Trials	210	A2

B. Treatment for Locally Advanced Laryngeal Cancer (T3/T4)

- **B1.** What is the role of total laryngectomy in locally advanced laryngeal cancer?
- **B2.** What is an appropriate larynx-preservation therapy in locally advanced laryngeal cancer?

DB	no.	Search Query	Search result 2022.12.25	Note
Ovid MEDLINE	#1	Laryngeal Neoplasms/	28,846	P (patient)
	#2	((larynx* or throat) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*)):tw,kf,kw.	24,369	
	#3	((glott* or subglott* or sub-glott* or supraglott* or supra-glott*) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*)):tw,kf,kw.	3,911	

	#4	((vocal adj (cord\$1 or fold\$1 or ligament\$1)) or voice box) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*).tw,kf,kw.	1,161	I (intervention)
	#5	exp "Otorhinolaryngologic Neoplasms"/ or exp "Respiratory Tract Neoplasms"/	374,673	
	#6	exp "Laryngeal Diseases"/ or exp Larynx/ or (larynx* or throat or glott* or subglott* or sub-glott* or supraglott* or supra-glott* or (vocal adj (cord\$1 or fold\$1 or ligament\$1)) or voice box).tw,kf,kw.	158,910	
	#7	5 and 6	32,773	
	#8	1 or 2 or 3 or 4 or 7	39,601	
	#9	Laryngectomy/	10,196	
	#10	(laryngectom* or (larynx* adj5 (resect* or remov*))).tw,kf,kw.	10,656	
	#11	exp Radiotherapy/ or exp Chemoradiotherapy/	205,339	
	#12	(radiotherap* or radio-therap* or radiation\$1 or irradiation* or hyperfractionat* or hypofractionat* or dose fractionat*).tw,kf,kw.	720,136	
	#13	(chemoradiat* or chemo-radiat* or chemoradiotherap* or chemo-radiotherap* or radiochemotherap* or radio-chemotherap* or CCRT).tw,kf,kw.	44,083	
	#14	Combined Modality Therapy/	185,208	
	#15	(combined modality or multimodal*).tw,kf,kw.	67,657	
	#16	((partial or subtotal or sub-total or incomplete) adj3 (laryngectom* or resect* or remov* or surger* or surgical* or operation\$1 or operative or procedure\$1)) or hemilaryngectom* or hemi-laryngectom*).tw,kf,kw.	36,162	
	#17	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	1,004,913	
	#18	8 and 17	15,166	
	#19	18 not (Case Reports.pt. or case report\$1.ti. or Comment.pt. or comment*.ti. or Letter.pt. or letter.ti. or Editorial.pt. or (animals/ not (animals/ and humans/)))	12,303	P and I
	#20	limit 19 to yr="2016 -2022"	2,400	B1, B2
EMBASE	#1	'larynx tumor'/exp	41,413	P (patient)
	#2	((larynx* OR throat) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	28,581	
	#3	((glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott*) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	4,743	
	#4	(('vocal cord\$' OR 'vocal fold\$' OR 'vocal ligament\$' OR 'voice box') NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	1,367	
	#5	'head and neck tumor'/exp OR 'respiratory tract tumor'/exp	944,484	
	#6	'larynx disorder'/exp OR 'larynx'/exp OR (larynx* OR throat OR glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott* OR 'vocal cord\$' OR	223,884	

	'vocal fold\$' OR 'vocal ligament\$' OR 'voice box'):ti,ab,kw		
	#7 #5 AND #6	58,791	
	#8 #1 OR #2 OR #3 OR #4 OR #7	62,866	
	#9 'laryngectomy'/exp	13,816	I (intervention)
	#10 (laryngectom* OR (larynx* NEAR/5 (resect* OR remov*))) :ti,ab,kw	12,988	
	#11 'radiotherapy'/exp OR 'chemoradiotherapy'/exp	664,475	
	#12 (radiotherap* OR radio-therap* OR radiation\$ OR irradiation* OR hyperfractionat* OR hypofractionat* OR 'dose fractionat*'):ti,ab,kw	968,873	
	#13 (chemoradiat* OR chemo-radiat* OR chemoradiotherap* OR chemo-radiotherap* OR radiochemotherap* OR radio-chemotherap* OR CCRT):ti,ab,kw	79,520	
	#14 'multimodality cancer therapy'/de	72,799	
	#15 ('combined modality' or multimodal* OR 'multiple modality'):ti,ab,kw	107,362	
	#16 (((partial OR subtotal OR sub-total OR incomplete) NEAR/3 (laryngectom* OR resect* OR remov* OR surger* OR surgical* OR operation\$ OR operative OR procedure\$)) OR hemilaryngectom* OR hemilaryngectom*):ti,ab,kw	49,538	
	#17 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	1,370,221	
	#18 #8 AND #17	25,539	P and I
	#19 #18 NOT ('case study'/exp OR 'case report\$:ti OR comment*:ti OR letter:it OR letter:ti OR editorial:it OR ('animal'/de NOT ('animal'/de AND 'human'/de)))	24,023	
	#20 #19 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [2016-2022]/py	4,739	B1, B2
Cochrane	#1 [mh ^"Laryngeal Neoplasms"]	337	P (patient)
	#2 ((larynx* OR throat) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	1,267	
	#3 ((glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott*) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	192	
	#4 ((vocal-cord? OR vocal-fold? OR vocal-ligament? OR "voice box") NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	52	
	#5 [mh "Otorhinolaryngologic Neoplasms"] OR [mh "Respiratory Tract Neoplasms"]	10,219	
	#6 [mh "Laryngeal Diseases"] OR [mh "Larynx"] OR (larynx* OR throat OR glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott* OR vocal-cord? OR vocal-fold? OR vocal-ligament? OR "voice box"):ti,ab,kw	20,260	
	#7 #5 AND #6	414	

#8	#1 OR #2 OR #3 OR #4 OR #7	1,405	I (intervention)
#9	[mh ^"Laryngectomy"]	176	
#10	(laryngectom* OR (laryn* NEAR/5 (resect* OR remov*))) :ti,ab,kw	679	
#11	[mh "Radiotherapy"] OR [mh "Chemoradiotherapy"]	6,706	
#12	(radiotherap* OR radio-therap* OR radiation? OR irradiation* OR hyperfractionat* OR hypofractionat* OR dose-fractionat*) :ti,ab,kw	56,831	
#13	(chemoradiat* OR chemo-radiat* OR chemoradiotherap* OR chemo-radiotherap* OR radiochemotherap* OR radio-chemotherap* OR CCRT) :ti,ab,kw	9,920	
#14	[mh ^"Combined Modality Therapy"]	15,918	
#15	("combined modality" OR multimodal* OR "multiple modality") :ti,ab,kw	25,560	
#16	((partial OR subtotal OR sub-total OR incomplete) NEAR/3 (laryngectom* OR resect* OR remov* OR surger* OR surgical* OR operation? OR operative OR procedure?)) OR hemilaryngectom* OR hemilaryngectom*) :ti,ab,kw	2,068	
#17	{OR #9-#16}	81,380	
#18	#8 AND #17	908	P and I
#19	#8 AND #17 with Cochrane Library publication date Between Jan 2016 and Dec 2022, in Cochrane Reviews, Trials	464	B1, B2

C. Management of the Neck

- C1. Is prophylactic neck dissection necessary for patients with clinically lymph node-negative laryngeal cancer?

- C2. What is the appropriate extent of neck dissection in patients with clinically lymph node-positive laryngeal cancer?

DB	no.	Search Query	Search result 2023.3.14	Note
Ovid MEDLINE	#1	Laryngeal Neoplasms/	28,926	P (patient)
	#2	((laryn* or throat) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*)) :tw,kf,kw.	24,547	
	#3	((glott* or subglott* or sub-glott* or supraglott* or supra-glott*) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*)) :tw,kf,kw.	3,937	

EMBASE	#4	((vocal adj (cord\$1 or fold\$1 or ligament\$1)) or voice box) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*).tw,kf,kw.	1,174	I (intervention)
	#5	exp "Otorhinolaryngologic Neoplasms"/ or exp "Respiratory Tract Neoplasms"/	377,490	
	#6	exp "Laryngeal Diseases"/ or exp Larynx/ or (larynx* or throat or glott* or subglott* or sub-glott* or supraglott* or supra-glott* or (vocal adj (cord\$1 or fold\$1 or ligament\$1)) or voice box).tw,kf,kw.	160,538	
	#7	5 and 6	32,889	
	#8	1 or 2 or 3 or 4 or 7	39,812	
	#9	Elective Surgical Procedures/	16,800	
	#10	Lymph Node Excision/	37,556	
	#11	Neck Dissection/	8,432	
	#12	((lymph nodal or lymph node or neck) adj5 (dissect* or excision\$1 or resect* or extirpation\$1)).tw,kf,kw.	41,312	
	#13	(lymphadenectom* or lymphadenectomy*).tw,kf,kw.	20,165	
	#14	9 or 10 or 11 or 12 or 13	93,244	P and I
	#15	8 and 14	2,613	
	#16	15 not (Case Reports.pt. or case report\$1.ti. or Comment.pt. or comment*.ti. or Letter.pt. or letter.ti. or Editorial.pt. or (animals/ not (animals/ and humans/)))	2,115	
	#17	limit 16 to yr="2019 - 2022"	211	
	#18	limit 16 to yr="1860 - 2022"	2,100	C2
EMBASE	#1	'larynx tumor'/exp	41,711	P (patient)
	#2	((larynx* OR throat) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	29,001	
	#3	((glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott*) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	4,771	
	#4	(('vocal cord\$' OR 'vocal fold\$' OR 'vocal ligament\$' OR 'voice box') NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	1,373	
	#5	'head and neck tumor'/exp OR 'respiratory tract tumor'/exp	962,158	
	#6	'larynx disorder'/exp OR 'larynx'/exp OR (larynx* OR throat OR glott* OR subglott* OR sub-glott* OR supra-glott* OR supra-glott* OR 'vocal cord\$' OR 'vocal fold\$' OR 'vocal ligament\$' OR 'voice box'):ti,ab,kw	226,501	
	#7	#5 AND #6	59,373	
	#8	#1 OR #2 OR #3 OR #4 OR #7	63,485	
	#9	'elective surgery'/de	44,720	I (intervention)
	#10	'lymph node dissection'/de	88,338	
	#11	'neck dissection'/de	19,306	

	#12	((('lymph nodal' OR 'lymph node' OR neck) NEAR/5 (dissect* OR excision\$ OR resect* OR extirpation\$)):ti,ab,kw	61,641	P and I
	#13	(lymphadenectom* OR lymphadenectom*):ti,ab,kw	32,102	
	#14	#9 OR #10 OR #11 OR #12 OR #13	177,239	
	#15	#8 AND #14	4,919	
	#16	#15 NOT ('case study'/exp OR 'case report\$':ti OR comment*:ti OR letter:it OR letter:ti OR editorial:it OR ('animal'/de NOT ('animal'/de AND 'human'/de)))	4,544	
	#17	#16 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [2019-2022]/py	701	
	#18	#16 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [1966-2022]/py	3,712	
Cochrane	#1	[mh ^"Laryngeal Neoplasms"]	386	P (patient)
	#2	((larynx* OR throat) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	1,289	
	#3	((glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott*) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	195	
	#4	((vocal-cord? OR vocal-fold? OR vocal-ligament? OR "voice box") NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	53	
	#5	[mh "Otorhinolaryngologic Neoplasms"] OR [mh "Respiratory Tract Neoplasms"]	12,043	
	#6	[mh "Laryngeal Diseases"] OR [mh "Larynx"] OR (larynx* OR throat OR glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott* OR vocal-cord? OR vocal-fold? OR vocal-ligament? OR "voice box"):ti,ab,kw	20,616	
	#7	#5 AND #6	484	
	#8	#1 OR #2 OR #3 OR #4 OR #7	1,434	I (intervention)
	#9	[mh ^"Elective Surgical Procedures"]	2,259	
	#10	[mh ^"Lymph Node Excision"]	1,509	
	#11	[mh ^"Neck Dissection"]	175	
	#12	((('lymph nodal' OR 'lymph node' OR neck) NEAR/5 (dissect* OR excision? OR resect* OR extirpation?)):ti,ab,kw	5,323	
	#13	(lymphadenectom* OR lymphadenectom*):ti,ab,kw	1,910	
	#14	#9 OR #10 OR #11 OR #12	7,571	
	#15	#8 AND #14	116	P and I
	#16	#8 AND #14 with Cochrane Library publication date from Jan 2019 to Dec 2022, in Cochrane Reviews and Trials	18	C1
	#17	#8 AND #14 with Cochrane Library publication date to Dec 2022, in Cochrane Reviews and Trials	116	C2

D. Adjuvant Therapy

- **D1.** Does adjuvant therapy improve treatment outcomes in patients with laryngeal cancer following surgical resection?

DB	no.	Search Query	Search result 2023.4.17	Note
Ovid MEDLINE	#1	Laryngeal Neoplasms/	28,982	P (patient)
	#2	((larynx* or throat) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*)).tw,kf,kw.	24,637	
	#3	((glott* or subglott* or sub-glott* or supraglott* or supra-glott*) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*)).tw,kf,kw.	3,962	
	#4	((vocal adj (cord\$1 or fold\$1 or ligament\$1)) or voice box) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*)).tw,kf,kw.	1,177	
	#5	exp "Otorhinolaryngologic Neoplasms"/ or exp "Respiratory Tract Neoplasms"/	379,005	
	#6	exp "Laryngeal Diseases"/ or exp Larynx/ or (larynx* or throat or glott* or subglott* or sub-glott* or supraglott* or supra-glott* or (vocal adj (cord\$1 or fold\$1 or ligament\$1)) or voice box).tw,kf,kw.	161,169	
	#7	5 and 6	32,958	
	#8	1 or 2 or 3 or 4 or 7	39,919	I (intervention)
	#9	exp Radiotherapy/ or exp Chemoradiotherapy/	206,227	
	#10	(radiotherap* or radio-therap* or radiation\$1 or irradiation* or hyperfractionat* or hypofractionat* or dose fractionat*).tw,kf,kw.	732,117	
	#11	(chemoradiat* or chemo-radiat* or chemoradiotherap* or chemo-radiotherap* or radiochemotherap* or radio-chemotherap* or CCRT).tw,kf,kw.	45,175	
	#12	Combined Modality Therapy/	184,683	
	#13	(combined modality or multimodal* or multiple modality).tw,kf,kw.	70,857	
	#14	9 or 10 or 11 or 12 or 13	982,258	
	#15	8 and 14	9,822	P and I
	#16	15 not (Case Reports.pt. or case report\$1.ti. or Comment.pt. or comment*.ti. or Letter.pt. or letter.ti. or Editorial.pt. or (animals/ not (animals/ and humans/)))	8,175	
	#17	limit 16 to yr="1860 - 2022"	8,089	D1
EMBASE	#1	'larynx tumor'/exp	41,837	P (patient)
	#2	((larynx* OR throat) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	29,089	

	#3	((glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott*) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	4,790	
	#4	((('vocal cord\$' OR 'vocal fold\$' OR 'vocal ligament\$' OR 'voice box') NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	1,375	
	#5	'head and neck tumor'/exp OR 'respiratory tract tumor'/exp	967,110	
	#6	'larynx disorder'/exp OR 'larynx'/exp OR (larynx* OR throat OR glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott* OR 'vocal cord\$' OR 'vocal fold\$' OR 'vocal ligament\$' OR 'voice box'):ti,ab,kw	227,530	
	#7	#5 AND #6	59,609	
	#8	#1 OR #2 OR #3 OR #4 OR #7	63,722	
	#9	'radiotherapy'/exp OR 'chemoradiotherapy'/exp	676,030	
	#10	(radiotherap* OR radio-therap* OR radiation\$ OR irradiation* OR hyperfractionat* OR hypofractionat* OR 'dose fractionat*'):ti,ab,kw	987,728	
	#11	(chemoradiat* OR chemo-radiat* OR chemoradiotherap* OR chemo-radiotherap* OR radiochemotherap* OR radio-chemotherap* OR CCRT):ti,ab,kw	81,092	
	#12	'multimodality cancer therapy'/de	73,083	
	#13	('combined modality' or multimodal* OR 'multiple modality'):ti,ab,kw	111,025	
	#14	#9 OR #10 OR #11 OR #12 OR #13	1,344,649	
	#15	#8 AND #14	19,465	
	#16	#15 NOT ('case study'/exp OR 'case report\$:ti OR comment*:ti OR letter:it OR letter:ti OR editorial:it OR ('animal'/de NOT ('animal'/de AND 'human'/de)))	18,330	
	#17	#16 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [1966-2022]/py	13,373	
Cochrane	#1	[mh ^"Laryngeal Neoplasms"]	386	P (patient)
	#2	((larynx* OR throat) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	1,295	
	#3	((glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott*) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	196	
	#4	((('vocal-cord?' OR 'vocal-fold?' OR 'vocal-ligament?' OR 'voice box') NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	53	
	#5	[mh "Otorhinolaryngologic Neoplasms"] OR [mh "Respiratory Tract Neoplasms"]	12,073	
	#6	[mh "Laryngeal Diseases"] OR [mh "Larynx"] OR (larynx* OR throat OR glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott* OR vocal-cord?	20,913	

	OR vocal-fold? OR vocal-ligament? OR "voice box"):ti,ab,kw		
#7	#5 AND #6	485	
#8	#1 OR #2 OR #3 OR #4 OR #7	1,440	
#9	[mh "radiotherapy"] OR [mh "chemoradiotherapy"]	10,273	I (intervention)
#10	(radiotherap* OR radio-therap* OR radiation* OR irradiation* OR hyperfractionat* OR hypofractionat* OR dose-fractionat*):ti,ab,kw	58,221	
#11	(chemoradiat* OR chemo-radiat* OR chemoradiotherap* OR chemo-radiotherap* OR radiochemotherap* OR radio-chemotherap* OR CCRT):ti,ab,kw	10,221	
#12	[mh ^"Combined Modality Therapy"]	17,904	
#13	("combined modality" or multimodal* OR "multiple modality"):ti,ab,kw	27,176	
#14	{OR #9-#13}	81,810	
#15	#8 AND #14	830	P and I
#16	#15 with Cochrane Library publication date to Dec 2022, in Cochrane Reviews, Trials	819	D1

E. Swallowing Rehabilitation

- E1. What is the role of swallowing rehabilitation in patients with laryngeal cancer?

DB	no.	Search Query	Search result 2023.4.17	Note
Ovid MEDLINE	#1	Laryngeal Neoplasms/	28,982	P (patient)
	#2	((larynx* or throat) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*)):tw,kf,kw.	24,637	
	#3	((glott* or subglott* or sub-glott* or supraglott* or supra-glott*) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*)):tw,kf,kw.	3,962	
	#4	((vocal adj (cord\$1 or fold\$1 or ligament\$1)) or voice box) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*)):tw,kf,kw.	1,177	
	#5	exp "Otorhinolaryngologic Neoplasms"/ or exp "Respiratory Tract Neoplasms"/	379,005	
	#6	exp "Laryngeal Diseases"/ or exp Larynx/ or (larynx* or throat or glott* or subglott* or sub-glott* or supraglott* or supra-glott* or (vocal adj (cord\$1 or fold\$1 or ligament\$1)) or voice box).tw,kf,kw.	161,169	
	#7	5 and 6	32,958	
	#8	1 or 2 or 3 or 4 or 7	39,919	
	#9	Deglutition/	11,458	I

	#10	exp Deglutition Disorders/	59,020	(intervention)
	#11	(swallow* or deglutit* or dysphag* or eating or feeding or diet*).tw,kf,kw.	965,862	
	#12	9 or 10 or 11	1,003,432	
	#13	8 and 12	3,093	
	#14	13 not (Case Reports.pt. or case report\$.ti. or Comment.pt. or comment*.ti. or Letter.pt. or letter.ti. or Editorial.pt. or (animals/ not (animals/ and humans/)))	2,424	P and I
	#15	limit 14 to yr="2014 - 2022"	765	E1
EMBASE	#1	'larynx tumor'/exp	41,837	P (patient)
	#2	((larynx* OR throat) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	29,089	
	#3	((glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott*) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	4,790	
	#4	(('vocal cord\$' OR 'vocal fold\$' OR 'vocal ligament\$' OR 'voice box') NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	1,375	
	#5	'head and neck tumor'/exp OR 'respiratory tract tumor'/exp	967,110	
	#6	'larynx disorder'/exp OR 'larynx'/exp OR (larynx* OR throat OR glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott* OR 'vocal cord\$' OR 'vocal fold\$' OR 'vocal ligament\$' OR 'voice box'):ti,ab,kw	227,530	
	#7	#5 AND #6	59,609	
	#8	#1 OR #2 OR #3 OR #4 OR #7	63,722	
	#9	'swallowing'/exp	27,516	I (intervention)
	#10	'dysphagia'/exp	94,726	
	#11	(swallow* OR deglutit* OR dysphag* OR eating OR feeding OR diet*):ti,ab,kw	1,240,969	
	#12	#9 OR #10 OR #11	1,280,866	
	#13	#8 AND #12	7,139	P and I
	#14	#13 NOT ('case study'/exp OR 'case report\$:ti OR comment*:ti OR letter:it OR letter:ti OR editorial:it OR ('animal'/de NOT ('animal'/de AND 'human'/de)))	6,530	
	#15	#14 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [2014-2022]/py	2,054	E1
Cochrane	#1	[mh ^"Laryngeal Neoplasms"]	386	P (patient)
	#2	((larynx* OR throat) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	1,295	
	#3	((glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott*) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	196	
	#4	((vocal-cord? OR vocal-fold? OR vocal-ligament? OR "voice box") NEAR/5 (cancer* OR neoplas* OR	53	

	malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw		
#5	[mh "Otorhinolaryngologic Neoplasms"] OR [mh "Respiratory Tract Neoplasms"]	12,073	
#6	[mh "Laryngeal Diseases"] OR [mh "Larynx"] OR (larynx* OR throat OR glott* OR subglott* OR subglott* OR supraglott* OR supra-glott* OR vocal-cord? OR vocal-fold? OR vocal-ligament? OR "voice box"):ti,ab,kw	20,913	
#7	#5 AND #6	485	
#8	#1 OR #2 OR #3 OR #4 OR #7	1,440	
#9	[mh ^"Deglutition"]	583	
#10	[mh "Deglutition Disorders"]	3,812	
#11	(swallow* OR deglutit* OR dysphag* OR eating OR feeding OR diet*):ti,ab,kw	141,202	I (intervention)
#12	#9 OR #10 OR #11	143,331	
#13	#8 AND #12	244	P and I
#14	#8 AND #12 with Cochrane Library publication date Between Jan 2014 and Dec 2022, in Cochrane Reviews, Trials	173	E1

F. Salvage Treatment for Recurrent Laryngeal Cancer

- F1. What are the salvage treatment options applicable for locally recurrent laryngeal cancer?

DB	no.	Search Query	Search result 2022.12.26	Note
Ovid MEDLINE	#1	Laryngeal Neoplasms/	28,846	P1 (patient – larynx cancer)
	#2	((larynx* or throat) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*)):tw,kf,kw.	24,369	
	#3	((glott* or subglott* or sub-glott* or supraglott* or supra-glott*) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*)):tw,kf,kw.	3,911	
	#4	((vocal adj (cord\$1 or fold\$1 or ligament\$1)) or voice box) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*)):tw,kf,kw.	1,161	
	#5	exp "Otorhinolaryngologic Neoplasms"/ or exp "Respiratory Tract Neoplasms"/	374,673	
	#6	exp "Laryngeal Diseases"/ or exp Larynx/ or (larynx* or throat or glott* or subglott* or sub-glott* or supraglott* or supra-glott* or (vocal adj (cord\$1 or fold\$1 or ligament\$1)) or voice box).tw,kf,kw.	158,910	
	#7	5 and 6	32,773	
	#8	1 or 2 or 3 or 4 or 7	39,601	

	#9	Neoplasm Recurrence, Local/	140,330	P2 (recurrence)
	#10	(recurren* or return* or relapse* or recrudescen*).tw,kf,kw.	1,076,382	
	#11	9 or 10	1,108,294	
	#12	8 and 11	7,178	P1 and P2
	#13	Salvage Therapy/	16,293	I (intervention)
	#14	(salvage or preserv* or sparing or conservat*).tw,kf,kw.	670,172	
	#15	Laser Therapy/	40,335	
	#16	(laser adj3 (therap* or treat* or surger* or surgical* or vaporization\$1 or ablation\$1 or ablative or nonablative or photoablation\$1 or scalpel\$1 or knife\$1 or knife\$1)).tw,kf,kw.	48,372	
	#17	Laryngectomy/.	10,196	
	#18	((partial or subtotal or sub-total or incomplete) adj3 (laryngectom* or resect* or remov* or surger* or surgical* or operation\$1 or operative or procedure\$1)) or hemilaryngectom* or hemilaryngectom*).tw,kf,kw.	36,162	
	#19	13 or 14 or 15 or 16 or 17 or 18	783,017	
EMBASE	#20	12 and 19	3,225	P and I
	#21	20 not (Case Reports.pt. or case report\$1.ti. or Comment.pt. or comment*.ti. or Letter.pt. or letter.ti. or Editorial.pt. or (animals/ not (animals/ and humans/)))	2,678	
	#22	limit 21 to yr="2013 -2022"	826	F1
	#1	'larynx tumor'/exp	41,413	P1 (patient – larynx cancer)
	#2	((larynx* OR throat) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	28,811	
	#3	((glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott*) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	4,743	
	#4	('vocal cord\$' OR 'vocal fold\$' OR 'vocal ligament\$' OR 'voice box') NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	1,367	
	#5	'head and neck tumor'/exp OR 'respiratory tract tumor'/exp	944,484	
	#6	'larynx disorder'/exp OR 'larynx'/exp OR (larynx* OR throat OR glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott* OR 'vocal cord\$' OR 'vocal fold\$' OR 'vocal ligament\$' OR 'voice box'):ti,ab,kw	223,884	
	#7	#5 AND #6	58,791	P2 (recurrence)
	#8	#1 OR #2 OR #3 OR #4 OR #7	62,866	
	#9	'tumor recurrence'/de	69,771	
	#10	(recurren* OR return* OR relapse* OR recrudescen*):ti,ab,kw	1,618,812	

Cochrane	#11	#9 OR #10	1,635,758	
	#12	#8 AND #11	11,719	P1 and P2
	#13	'salvage therapy'/exp	38,009	I (intervention)
	#14	(salvage OR preserv* OR sparing OR conservat*):ti,ab,kw	890,859	
	#15	'laser surgery'/de OR 'laser therapy'/de	34,043	
	#16	(laser NEAR/3 (therap* OR treat* OR surger* OR surgical* OR vaporization\$ OR ablation\$ OR ablative OR nonablative OR photoablation\$ OR scalpel\$ OR knife\$ OR knife\$)):ti,ab,kw	62,185	
	#17	'Laryngectomy'/exp	13,816	
	#18	((partial OR subtotal OR sub-total OR incomplete) NEAR/3 (laryngectom* OR resect* OR remov* OR surger* OR surgical* OR operation\$ OR operative OR procedure\$)) OR hemilaryngectom* OR hemilaryngectom*):ti,ab,kw	49,538	P and I
	#19	#13 OR #14 OR #15 OR #16 OR #17 OR #18	1,028,373	
	#20	#12 AND #19	4,295	
	#21	#20 NOT ('case study'/exp OR 'case report\$:ti OR comment*:ti OR letter:it OR letter:ti OR editorial:it OR ('animal'/de NOT ('animal'/de AND 'human'/de)))	4,063	F1
	#22	#21 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [2013-2022]/py	1,194	
Cochrane	#1	[mh ^"Laryngeal Neoplasms"]	337	P1 (patient – larynx cancer)
	#2	((larynx* OR throat) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	1,267	
	#3	((glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott*) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	192	
	#4	((vocal-cord? OR vocal-fold? OR vocal-ligament? OR "voice box") NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	52	
	#5	[mh "Otorhinolaryngologic Neoplasms"] OR [mh "Respiratory Tract Neoplasms"]	10,219	
	#6	[mh "Laryngeal Diseases"] OR [mh "Larynx"] OR (larynx* OR throat OR glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott* OR vocal-cord? OR vocal-fold? OR vocal-ligament? OR "voice box"):ti,ab,kw	20,260	
	#7	#5 AND #6	414	
	#8	#1 OR #2 OR #3 OR #4 OR #7	1,405	P2 (recurrence)
	#9	[mh ^"Neoplasm Recurrence, Local"]	4,833	
	#10	(recurren* OR return* OR relapse* OR recrudescen*):ti,ab,kw	140,716	
	#11	#9 OR #10	140,716	
	#12	#8 AND #11	325	

#13	[mh ^"Salvage Therapy"]	645	I (intervention)
#14	(salvage OR preserv* OR sparing OR conservat*):ti,ab,kw	46,461	
#15	[mh ^"Laser Therapy"]	2,162	
#16	(laser NEAR/3 (therap* OR treat* OR surger* OR surgical* OR vaporization? OR ablation? OR ablative OR nonablative OR photoablation? OR scalpel? OR knife? OR knife?):ti,ab,kw	11,042	
#17	[mh ^"Laryngectomy"]	176	
#18	((partial OR subtotal OR sub-total OR incomplete) NEAR/3 (laryngectom* OR resect* OR remov* OR surger* OR surgical* OR operation? OR operative OR procedure?)) OR hemilaryngectom* OR hemilaryngectom*):ti,ab,kw	2,068	
#19	#13 OR #14 OR #15 OR #16 OR #17 OR #18	59,017	P and I
#20	#12 AND #19	96	
#21	#12 AND #19 with Cochrane Library publication date Between Jan 2013 and Dec 2022, in Cochrane Reviews, Trials	53	F1

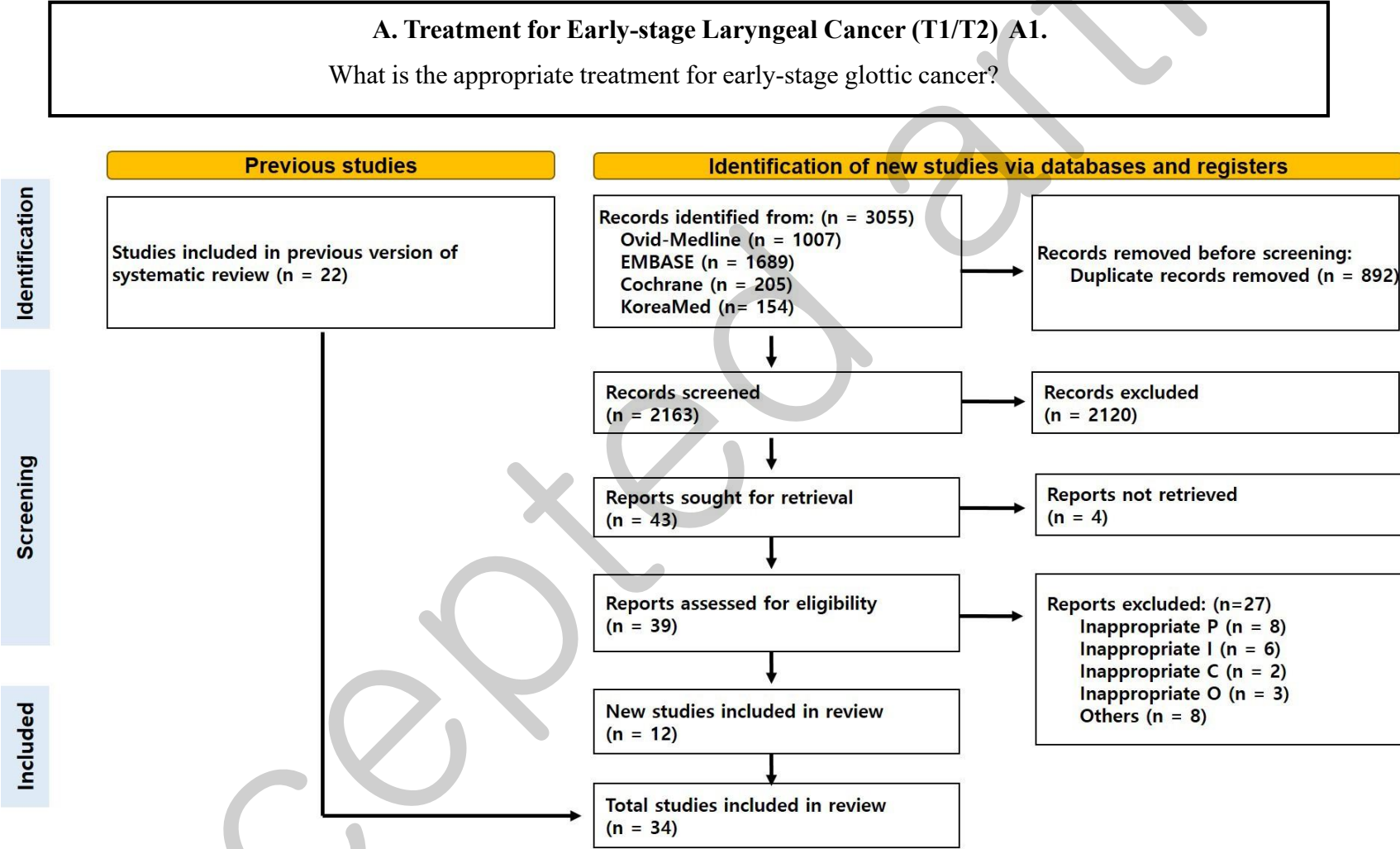
- **F2.** Does elective neck dissection improve oncological outcomes in salvage laryngectomy for locally recurrent laryngeal cancer?

DB	no.	Search Query	Search result 2022.12.26	Note
Ovid MEDLINE	#1	Laryngeal Neoplasms/	28,846	P1 (patient – larynx cancer)
	#2	((larynx* or throat) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*)):tw,kf,kw.	24,369	
	#3	((glott* or subglott* or sub-glott* or supraglott* or supra-glott*) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*)):tw,kf,kw.	3,911	
	#4	((vocal adj (cord\$1 or fold\$1 or ligament\$1)) or voice box) adj5 (cancer* or neoplas* or malignan* or carcinoma* or tumor* or tumour*)):tw,kf,kw.	1,161	
	#5	exp "Otorhinolaryngologic Neoplasms"/ or exp "Respiratory Tract Neoplasms"/	374,673	
	#6	exp "Laryngeal Diseases"/ or exp Larynx/ or (larynx* or throat or glott* or subglott* or sub-glott* or supraglott* or supra-glott* or (vocal adj (cord\$1 or fold\$1 or ligament\$1)) or voice box).tw,kf,kw.	158,910	
	#7	5 and 6	32,773	
	#8	1 or 2 or 3 or 4 or 7	39,601	
	#9	Neoplasm Recurrence, Local/	140,330	P2 (recurrence)
	#10	(recurren* or return* or relapse* or recrudescen*):tw,kf,kw.	1,076,382	

	#11	9 or 10	1,108,294	
	#12	8 and 11	7,178	P1 and P2
	#13	Elective Surgical Procedures/	16,789	I (intervention)
	#14	Neck Dissection/	8,427	
	#15	(neck adj5 (dissect* or excision\$1 or resect* or extirpation\$1)).tw,kf,kw.	14,122	
	#16	13 or 14 or 15	33,901	
	#17	12 and 16	844	P and I
	#18	17 not (Case Reports.pt. or case report\$1.ti. or Comment.pt. or comment*.ti. or Letter.pt. or letter.ti. or Editorial.pt. or (animals/ not (animals/ and humans/)))	722	
	#19	limit 18 to yr="2019 -2022"	68	F2
EMBASE	#1	'larynx tumor'/exp	41,413	P1 (patient – larynx cancer)
	#2	((larynx* OR throat) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	28,811	
	#3	((glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott*) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	4,743	
	#4	(('vocal cord\$' OR 'vocal fold\$' OR 'vocal ligament\$' OR 'voice box') NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	1,367	
	#5	'head and neck tumor'/exp OR 'respiratory tract tumor'/exp	944,484	
	#6	'larynx disorder'/exp OR 'larynx'/exp OR (larynx* OR throat OR glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott* OR 'vocal cord\$' OR 'vocal fold\$' OR 'vocal ligament\$' OR 'voice box'):ti,ab,kw	223,884	
	#7	#5 AND #6	58,791	
	#8	#1 OR #2 OR #3 OR #4 OR #7	62,866	
	#9	'tumor recurrence'/de	69,771	P2 (recurrence)
	#10	(recurren* OR return* OR relapse* OR recrudescen*):ti,ab,kw	1,618,812	
	#11	#9 OR #10	1,635,758	P1 and P2
	#12	#8 AND #11	11,719	
	#13	'elective surgery'/de	44,036	I (intervention)
	#14	'neck dissection'/de	19,025	
	#15	(neck NEAR/5 (dissect* OR excision\$ OR resect* OR extirpation\$)):ti,ab,kw	19,524	
	#16	#13 OR #14 OR #15	70,415	
	#17	#12 AND #16	1,384	P and I
	#18	#17 NOT ('case study'/exp OR 'case report\$':ti OR comment*:ti OR letter:it OR letter:ti OR editorial:it OR ('animal'/de NOT ('animal'/de AND 'human'/de)))	1,288	

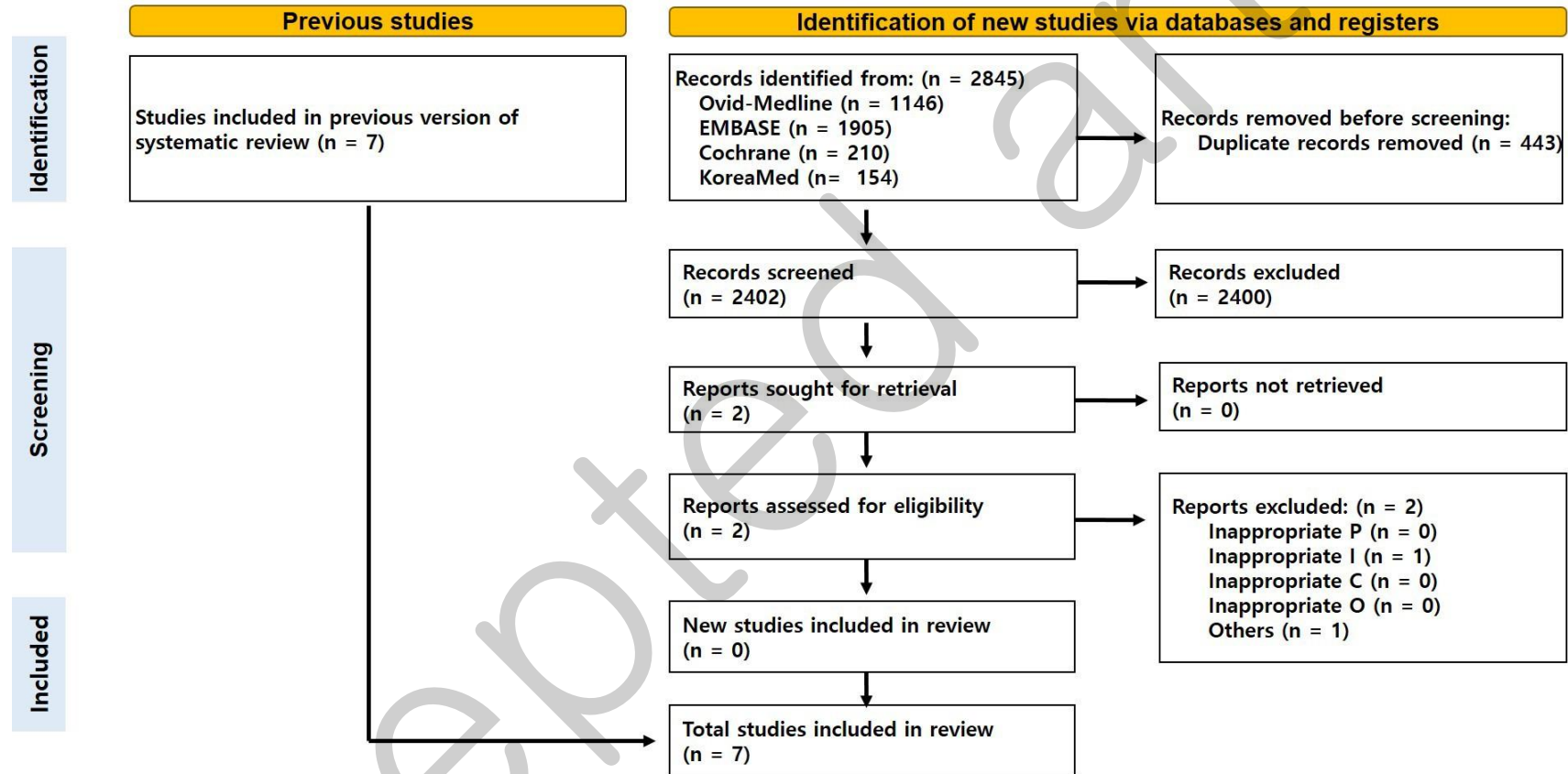
	#19	#21 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [2020-2022]/py	180	F2
Cochrane	#1	[mh ^"Laryngeal Neoplasms"]	337	P1 (patient – larynx cancer)
	#2	((larynx* OR throat) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	1,267	
	#3	((glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott*) NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	192	
	#4	((vocal-cord? OR vocal-fold? OR vocal-ligament? OR "voice box") NEAR/5 (cancer* OR neoplas* OR malignan* OR carcinoma* OR tumor* OR tumour*)):ti,ab,kw	52	
	#5	[mh "Otorhinolaryngologic Neoplasms"] OR [mh "Respiratory Tract Neoplasms"]	10,219	
	#6	[mh "Laryngeal Diseases"] OR [mh "Larynx"] OR (larynx* OR throat OR glott* OR subglott* OR sub-glott* OR supraglott* OR supra-glott* OR vocal-cord? OR vocal-fold? OR vocal-ligament? OR "voice box"):ti,ab,kw	20,260	
	#7	#5 AND #6	414	
	#8	#1 OR #2 OR #3 OR #4 OR #7	1,405	
	#9	[mh ^"Neoplasm Recurrence, Local"]	4,833	P2 (recurrence)
	#10	(recurren* OR return* OR relapse* OR recrudescen*):ti,ab,kw	140,716	
	#11	#9 OR #10	140,716	
	#12	#8 AND #11	325	P1 and P2
	#13	[mh ^"Elective Surgical Procedures"]	2,118	I (intervention)
	#14	[mh ^"Neck Dissection"]	145	
	#15	(neck NEAR/5 (dissect* OR excision? OR resect* OR extirpation?)):ti,ab,kw	894	
	#16	#13 OR #14 OR #15	3,007	
	#17	#12 AND #16	38	P and I
	#18	#12 AND #16 with Cochrane Library publication date Between Jan 2019 and Dec 2022, in Cochrane Reviews, Trials	12	F2

Supplementary Material 2. Flow diagram of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)



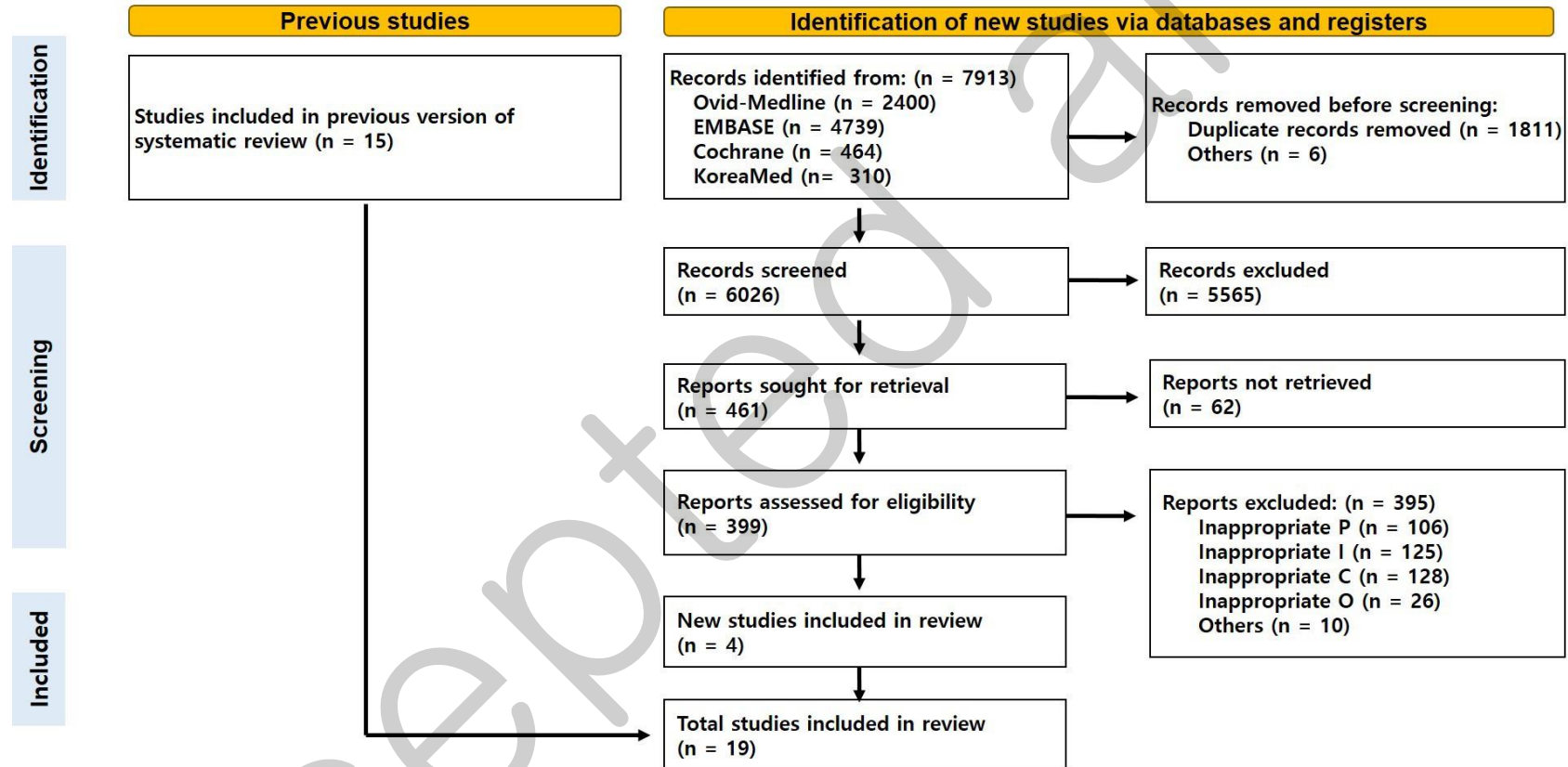
A. Treatment for Early-stage Laryngeal Cancer (T1/T2)

A2. What is the appropriate treatment for early-stage supraglottic cancer?



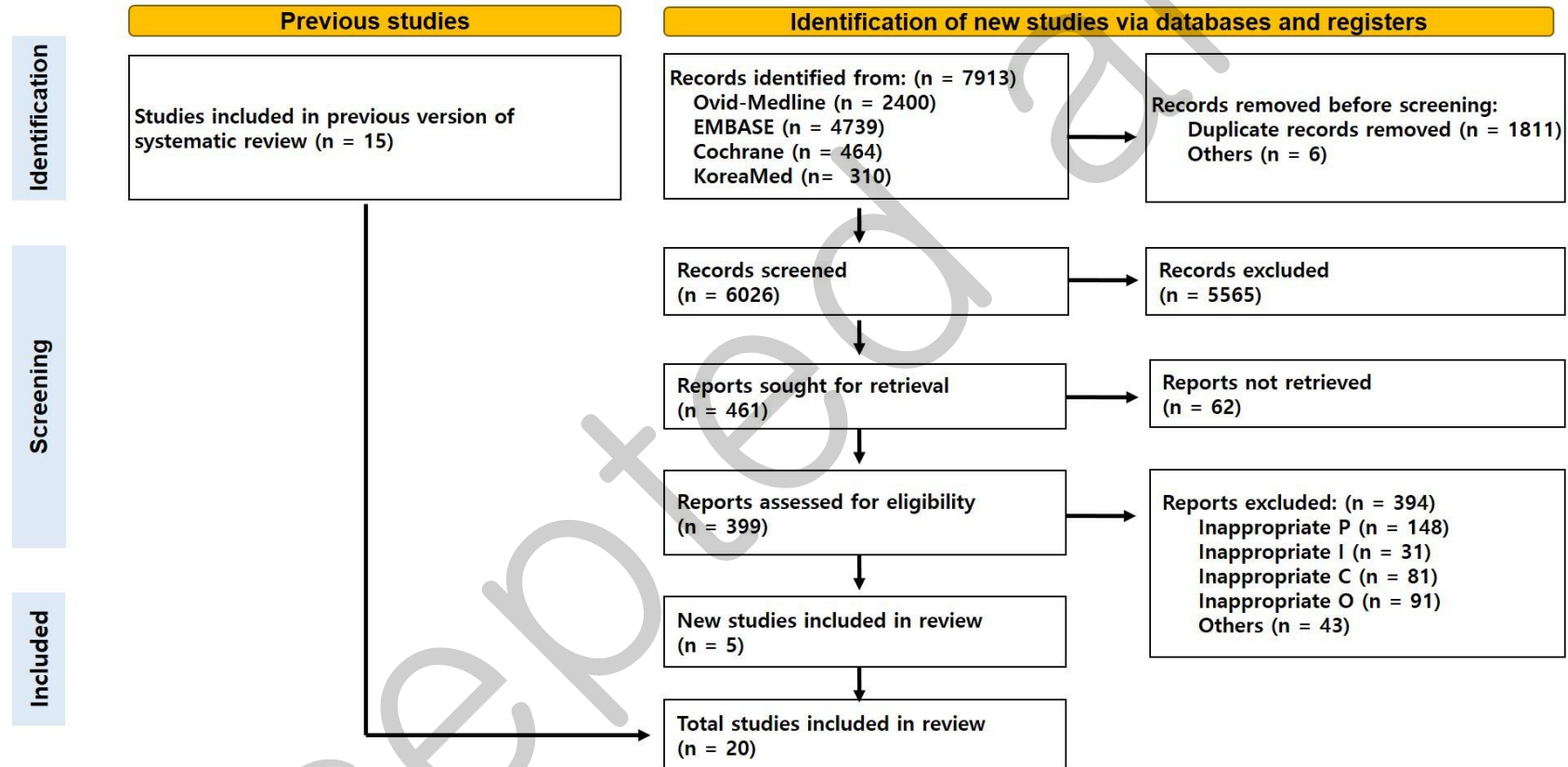
B. Treatment for Locally Advanced Laryngeal Cancer (T3/T4)

B1. What is the role of total laryngectomy in locally advanced laryngeal cancer?



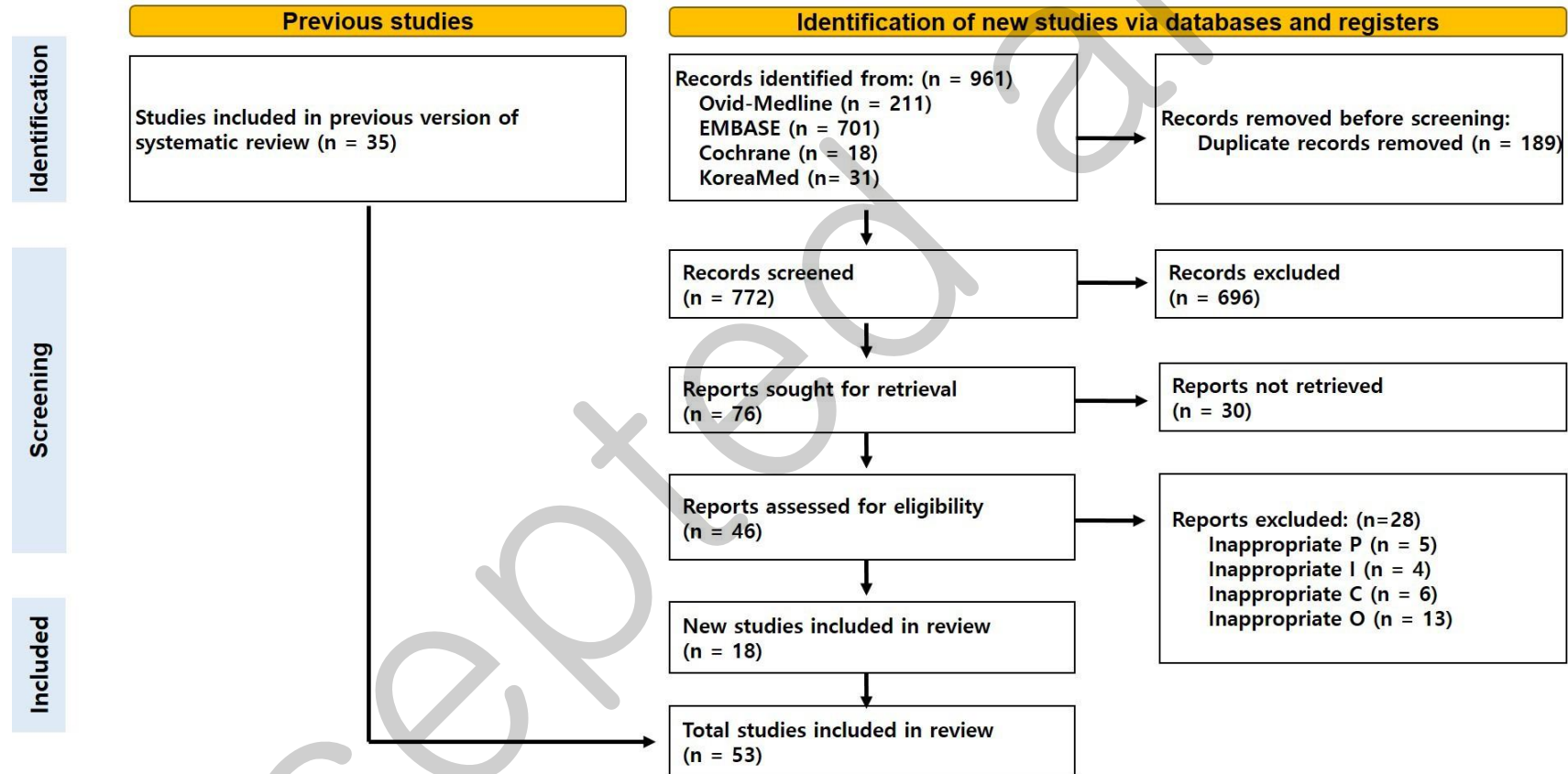
B. Treatment for Locally Advanced Laryngeal Cancer (T3/T4)

B2. What is an appropriate larynx-preservation therapy in locally advanced laryngeal cancer?



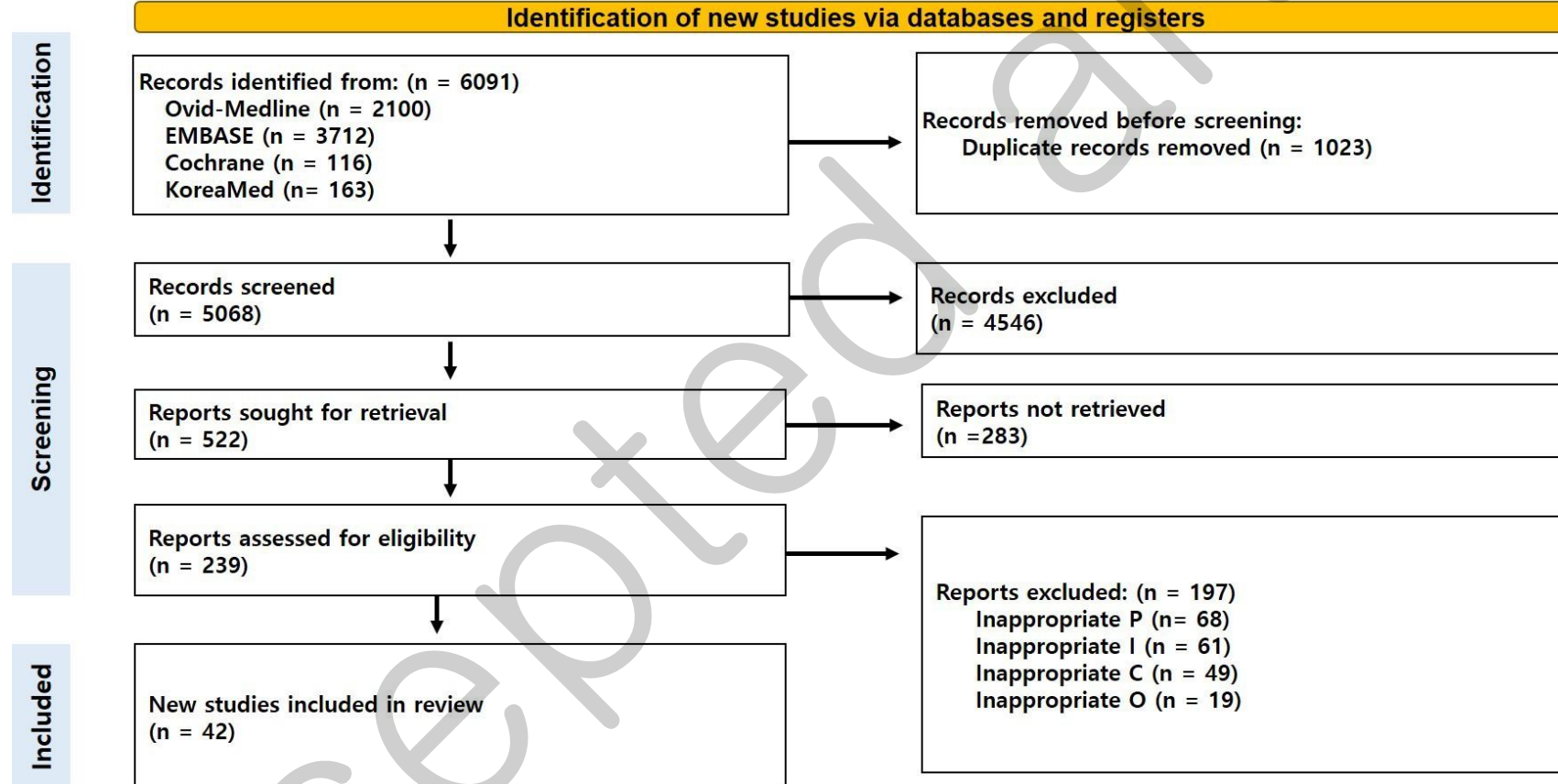
C. Management of the Neck

C1. Is prophylactic neck dissection necessary for patients with clinically lymph node-negative laryngeal cancer?



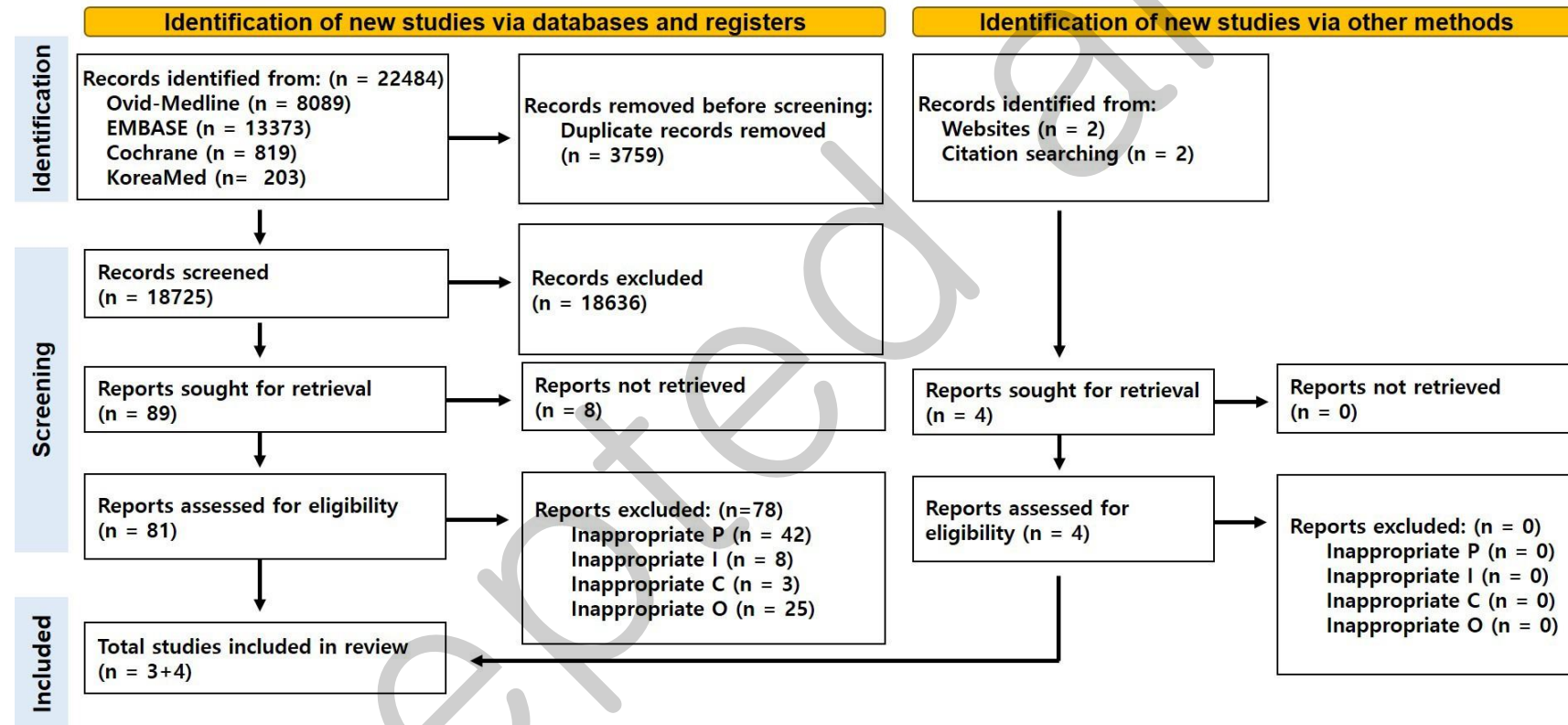
C. Management of the Neck

C2. What is the appropriate extent of neck dissection in patients with clinically lymph node-positive laryngeal cancer?



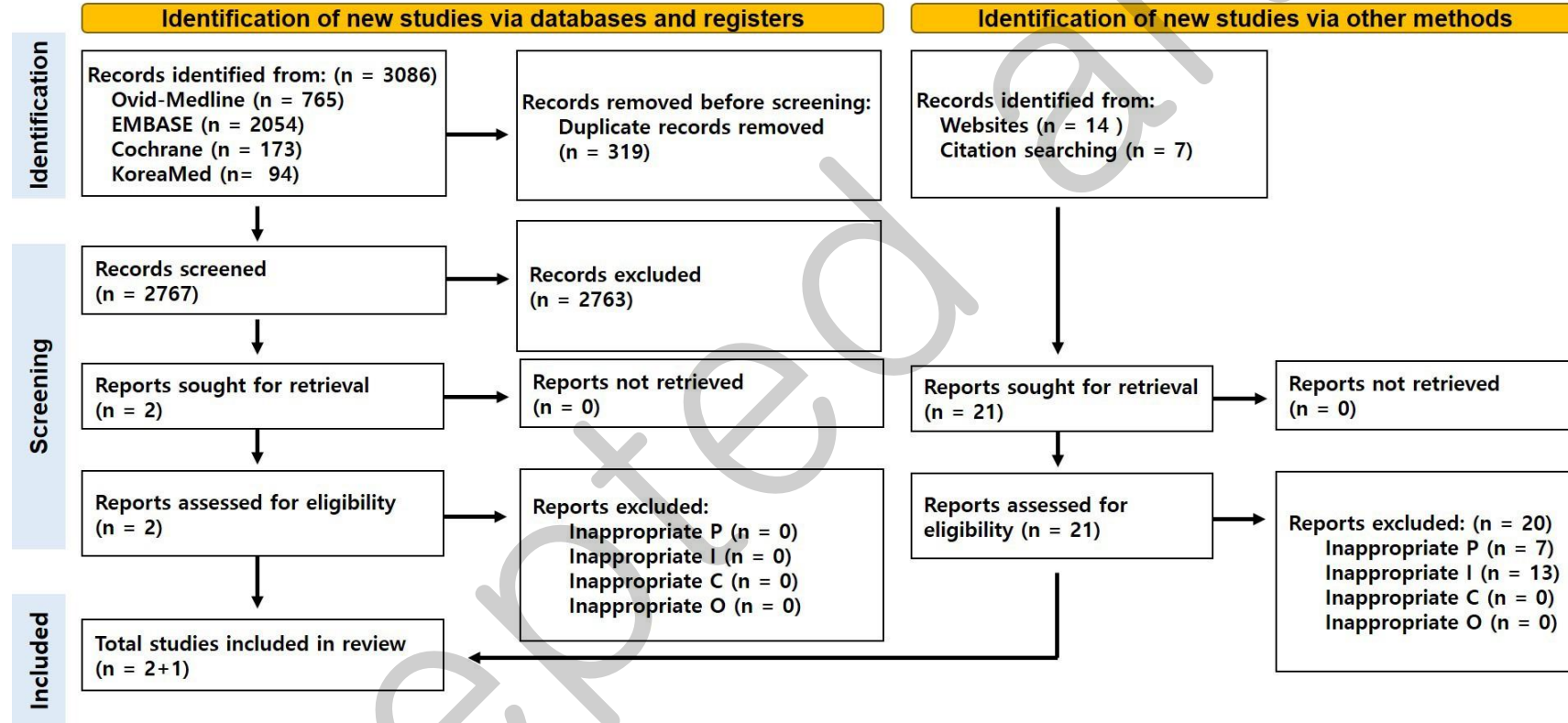
D. Adjuvant Therapy

D1. Does adjuvant therapy improve treatment outcomes in patients with laryngeal cancer following surgical resection?



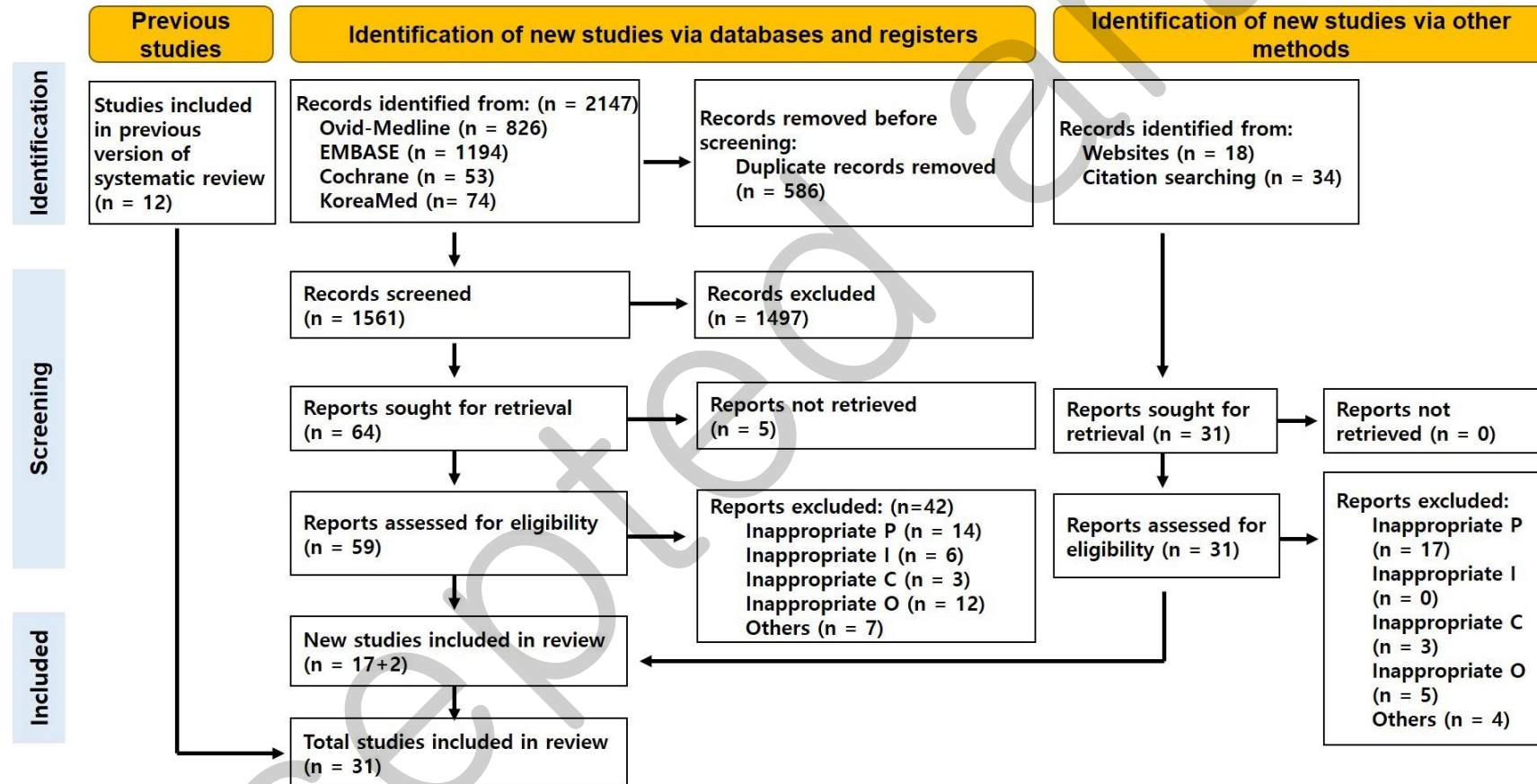
E. Swallowing Rehabilitation

E1. What is the role of swallowing rehabilitation in patients with laryngeal cancer?



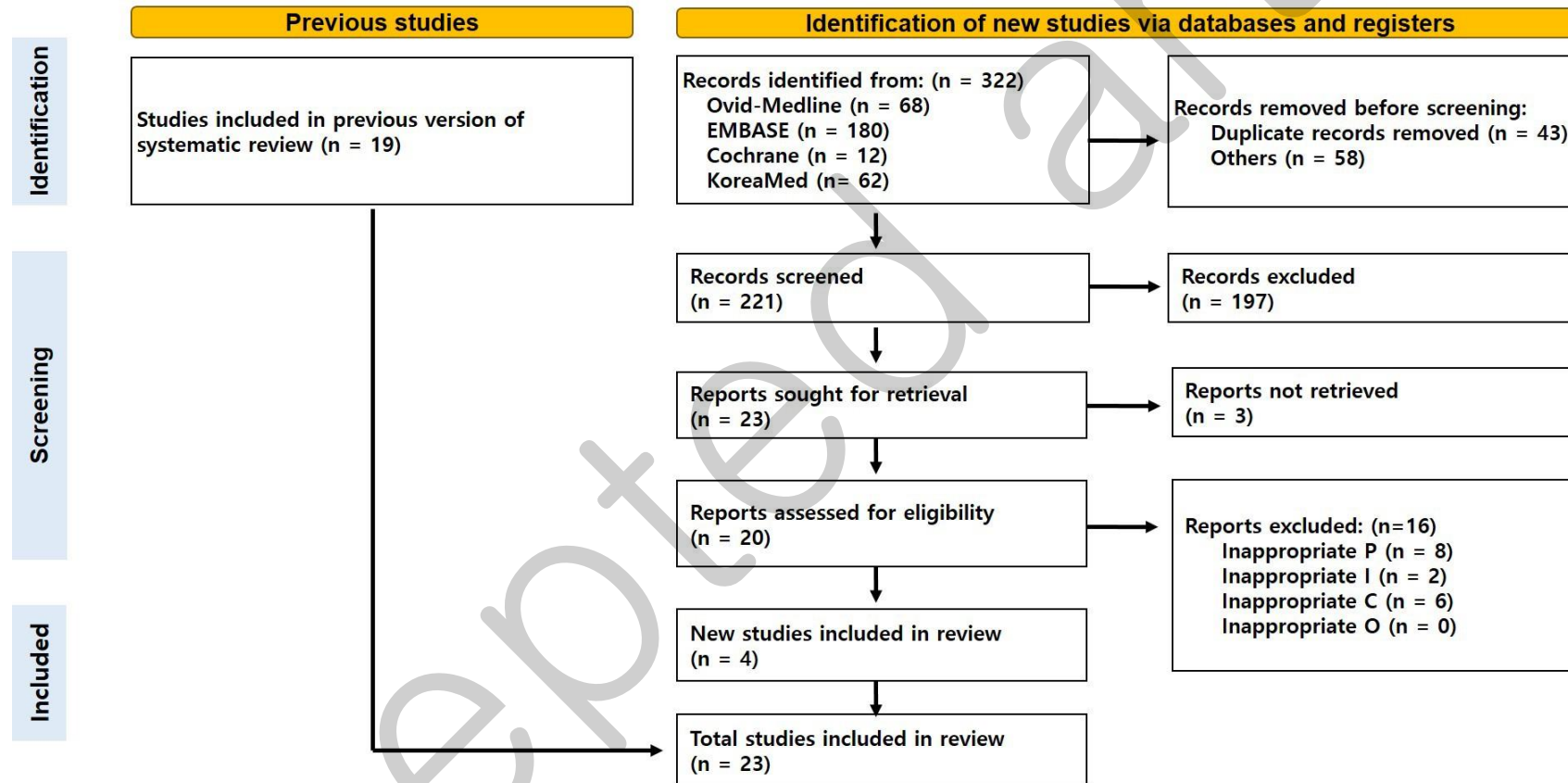
F. Salvage Treatment for Recurrent Laryngeal Cancer

F1. What are the salvage treatment options applicable for locally recurrent laryngeal cancer?



F. Salvage Treatment for Recurrent Laryngeal Cancer

F2. Does elective neck dissection improve oncological outcomes in salvage laryngectomy for locally recurrent laryngeal cancer?



Supplementary Material 3. Quality assessment of the included studies

A. Treatment for Early-stage Laryngeal Cancer (T1/T2)

A1. What is the appropriate treatment for early-stage glottic cancer?

● Final included studies

Study number	First Author (year)	Included studies
Systematic Review 1	André Vicente Guimarães (2018)	Comparison between transoral laser surgery and radiotherapy in the treatment of early glottic cancer: A systematic review and meta-analysis. <i>Sci Rep.</i> 2018 Aug 9;8(1):11900.
Non-RCT 1	Su Hyun Ahn (2012)	Comparison of Voice Outcomes in Early Glottic Cancer Patients after Laser Surgery or Radiotherapy. <i>Korean J Otorhinolaryngol-Head Neck Surg.</i> 2012;55(11):701-6.
Non-RCT 2	Jacob S Brady (2016)	Survival Impact of Initial Therapy in Patients with T1-T2 Glottic Squamous Cell Carcinoma. <i>Otolaryngol Head Neck Surg.</i> 2016 Aug;155(2):257-64.
Non-RCT 3	R J De Santis (2016)	Comparison of survival between radiation therapy and trans-oral laser microsurgery for early glottic cancer patients; a retrospective cohort study. <i>J Otolaryngol Head Neck Surg.</i> 2016 Aug 2;45(1):42.
Non-RCT 4	Tsu-Hui Hubert Low (2017)	Evaluating Organ Preservation Outcome as Treatment Endpoint for T1aN0 Glottic Cancer. <i>Laryngoscope.</i> 2017 Jun;127(6):1322-1327.
Non-RCT 5	Sachin Gandhi (2018)	A comparison of phonatory outcome between trans-oral CO2 Laser cordectomy and radiotherapy in T1 glottic cancer. <i>Eur Arch Otorhinolaryngol.</i> 2018 Nov;275(11):2783-2786.
Non-RCT 6	Cheng Zhan (2018)	Radiotherapy vs surgery for T1-2N0M0 laryngeal squamous cell carcinoma: A population-based and propensity score matching study. <i>Cancer Med.</i> 2018 Jul;7(7):2837-2847.
Non-RCT 7	Sidharth V Puram (2019)	Surgery Versus Radiation for T1 Glottic Carcinoma: Second Primary Considerations. <i>Laryngoscope.</i> 2019 Dec;129(12):2713-2715.
Non-RCT 8	Genival Barbosa de Carvalho (2022)	Survival results of 3786 patients with stage I or II laryngeal squamous cell carcinoma: a study based on a propensity score. <i>Braz J Otorhinolaryngol.</i> 2022 May-Jun;88(3):337-344.
Non-RCT 9	Kerem Ozturk (2021)	Long-term swallowing outcomes of radiotherapy and transoral laser microsurgery for T1 glottic cancer treatment. <i>Clin Otolaryngol.</i> 2021 Mar;46(2):340-346.
Non-RCT 10	Qi-Wei Liang (2022)	Comparison of survival outcomes of different treatment options for cT1-2, N0 Glottic Carcinoma: A Propensity score-weighted analysis. <i>Front Surg.</i> 2022 May 20;9:902817.
Non-RCT 11	James O'Hara (2022)	Quality of life following treatment for T1a glottic cancer with surgery or radiotherapy: outcomes from the Head and Neck 5000 cohort. <i>Clin Otolaryngol.</i> 2022 Jan;47(1):67-74.
Non-RCT 12	Wen-Lun Wang (2022)	Effect of treatment modality on the long-term survival of patients with early glottic squamous cancer: a retrospective cohort study based on the SEER database. <i>Ann Transl Med.</i> 2022 Apr;10(8):440.

RCT, randomized controlled trials.

Accepted article

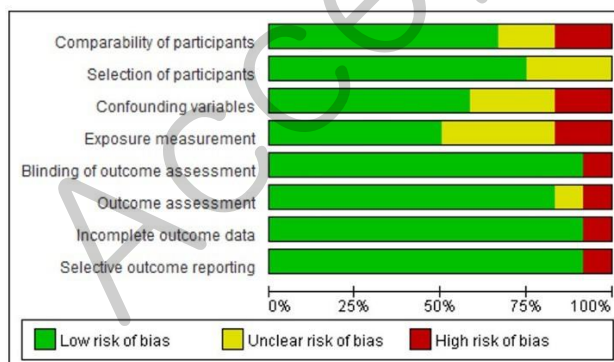
● Risk of bias

AMSTAR2 - André Vicente Guimarães (2018)

1. Components of PICO?	+
2. Review protocol?	+
3. Explanation for study design?	+
4. Comprehensive literature search strategy?	+
5. Study selection in duplicate?	-
6. Data extraction in duplicate?	-
7. List of excluded studies and justify the exclusions?	+
8. Study characteristics?	+
9. Satisfactory technique for assessing the risk of bias?	+
10. Sources of funding?	-
11. Appropriate methods?	+
12. Assess potential impact of risk of bias on the results?	-
13. Account for risk of bias when interpreting/discussing?	+
14. Satisfactory explanation for, and discussion of, any heterogeneity?	+
15. Publication bias (small study bias) assessed and discussed?	+
16. Potential sources of conflict of interest?	+

Yes"+":green, partially yes"±":orange, no"-":red, no meta-analysis(MA) conducted"n":grey

ROBANS 2.0



	Comparability of participants	Selection of participants	Confounding variables	Exposure measurement	Blinding of outcome assessment	Outcome assessment	Incomplete outcome data	Selective outcome reporting
Cheng Zhan (2018)	+	+	+	+	+	+	+	+
Genival Barbosa (2020)	+	+	+	+	+	+	+	+
Jacob S. Brady (2016)	+	+	?	+	+	+	+	+
James O'hara (2021)	+	+	+	+	+	?	+	+
Kerem Ozturk (2020)	+	?	+	?	+	+	+	+
Qi-wei Liang (2022)	+	+	+	+	+	+	+	+
R J De Santis (2016)	+	?	+	?	+	+	+	+
Sachin Gandhi (2018)	+	+	+	+	+	+	+	+
Sidharth V. Puram (2019)	+	+	+	+	+	+	+	+
Su Hyun Ahn (2012)	?	+	?	?	+	+	+	+
Tsu-Hui Hubert Low (2016)	?	+	?	?	+	+	+	+
Wen-Lun Wang (2022)	+	?	+	+	+	+	+	+

A. Treatment for Early-stage Laryngeal Cancer (T1/T2)

A2. What is the appropriate treatment for early-stage supraglottic cancer?

● Final included studies

Study number	First Author (year)	Included studies
Systematic Review 1	Krupal B Patel (2018)	Treatment of early stage Supraglottic squamous cell carcinoma: meta-analysis comparing primary surgery versus primary radiotherapy. J Otolaryngol Head Neck Surg. 2018 Mar 5;47(1):19.
Systematic Review 2	Mark S Swanson (2017)	Transoral surgery vs intensity-modulated radiotherapy for early supraglottic cancer: a systematic review. Curr Opin Otolaryngol Head Neck Surg. 2017 Apr;25(2):133-141.

RCT, randomized controlled trials.

● Risk of bias

AMSTAR2 - Krupal B Patel (2018)	
1. Components of PICO?	+
2. Review protocol?	+
3. Explanation for study design?	+
4. Comprehensive literature search strategy?	+
5. Study selection in duplicate?	+
6. Data extraction in duplicate?	-
7. List of excluded studies and justify the exclusions?	+
8. Study characteristics?	+
9. Satisfactory technique for assessing the risk of bias?	+
10. Sources of funding?	±
11. Appropriate methods?	+
12. Assess potential impact of risk of bias on the results?	-
13. Account for risk of bias when interpreting/discussing?	+
14. Satisfactory explanation for, and discussion of, any heterogeneity?	+
15. Publication bias (small study bias) assessed and discussed?	-
16. Potential sources of conflict of interest?	+

Yes"+":green, partially yes"±":orange, no"-":red, no meta-analysis(MA) conducted"n":grey

AMSTAR2 - Mark S Swanson (2017)	
1. Components of PICO?	+
2. Review protocol?	+
3. Explanation for study design?	+
4. Comprehensive literature search strategy?	+
5. Study selection in duplicate?	+
6. Data extraction in duplicate?	-
7. List of excluded studies and justify the exclusions?	+
8. Study characteristics?	+
9. Satisfactory technique for assessing the risk of bias?	+
10. Sources of funding?	±
11. Appropriate methods?	+
12. Assess potential impact of risk of bias on the results?	+
13. Account for risk of bias when interpreting/discussing?	+
14. Satisfactory explanation for, and discussion of, any heterogeneity?	-
15. Publication bias (small study bias) assessed and discussed?	+
16. Potential sources of conflict of interest?	+

Yes"+":green, partially yes"±":orange, no"-":red, no meta-analysis(MA) conducted"n":grey

B. Treatment for Locally Advanced Laryngeal Cancer (T3/T4)

B1. What is the role of total laryngectomy in locally advanced laryngeal cancer?

● Final included studies

Study number	First Author (year)	Included studies
Systematic Review 1	Zhao-Xian Tang (2018)	Efficacy comparison between primary total laryngectomy and nonsurgical organ-preservation strategies in treatment of advanced stage laryngeal cancer: A meta-analysis. <i>Medicine (Baltimore)</i> . 2018 May;97(21):e10625.
Non-RCT 1	William A Stokes (2017)	A comparison of overall survival for patients with T4 larynx cancer treated with surgical versus organ-preservation approaches: A National Cancer Data Base analysis. <i>Cancer</i> . 2017 Feb 15;123(4):600-608.
Non-RCT 2	James E Bates (2019)	Curative-dose Chemoradiotherapy Versus Total Laryngectomy For Stage T3-T4 Squamous Cell Carcinoma of the Larynx: An "Apples-to-Apples" Analysis of the National Cancer Database. <i>Am J Clin Oncol</i> . 2019 Jun;42(6):527-533.
Non-RCT 3	Hugo Fontan Köhler (2020)	Impact of treatment modality on survival in patients with stage IV laryngeal cancer: A population-based propensity score analysis. <i>Am J Otolaryngol</i> . 2020 Nov-Dec;41(6):102626.
Non-RCT 4	Aihemaiti Wushouer (2022)	Comparison of treatment modalities for selected advanced laryngeal squamous cell carcinoma. <i>Eur Arch Otorhinolaryngol</i> . 2022 Jan;279(1):361-371.

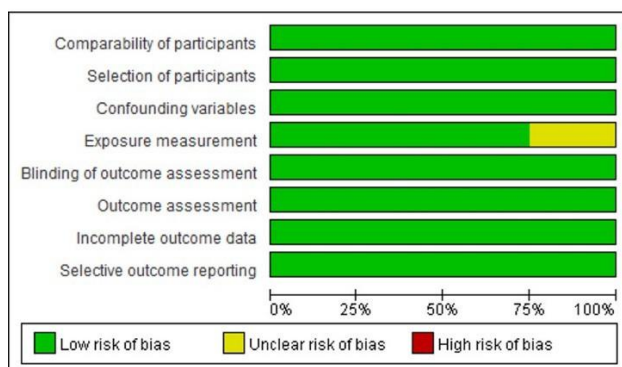
RCT, randomized controlled trials.

● Risk of bias

AMSTAR2 - Zhao-Xian Tang (2018)	
1. Components of PICO?	+
2. Review protocol?	+
3. Explanation for study design?	-
4. Comprehensive literature search strategy?	+
5. Study selection in duplicate?	+
6. Data extraction in duplicate?	+
7. List of excluded studies and justify the exclusions?	+
8. Study characteristics?	+
9. Satisfactory technique for assessing the risk of bias?	+
10. Sources of funding?	-
11. Appropriate methods?	+
12. Assess potential impact of risk of bias on the results?	+
13. Account for risk of bias when interpreting/discussing?	+
14. Satisfactory explanation for, and discussion of, any heterogeneity?	+
15. Publication bias (small study bias) assessed and discussed?	+
16. Potential sources of conflict of interest?	-

Yes"+":green, partially yes"±":orange, no"-":red, no meta-analysis(MA) conducted"n":grey

ROBANS 2.0



	Comparability of participants	Selection of participants	Confounding variables	Exposure measurement	Blinding of outcome assessment	Outcome assessment	Incomplete outcome data	Selective outcome reporting
Aihemaiti Wushouer (2022)	+	+	+	?	+	+	+	+
Hugo Fontan Köhler (2020)	+	+	+	+	+	+	+	+
James E Bates (2019)	+	+	+	+	+	+	+	+
William A Stokes (2017)	+	+	+	+	+	+	+	+

B. Treatment for Locally Advanced Laryngeal Cancer (T3/T4)

B2. What is an appropriate larynx-preservation therapy in locally advanced laryngeal cancer?

● Final included studies

Study number	First Author (year)	Included studies
Systematic Review 1	Zhao-Xian Tang (2018)	Efficacy comparison between primary total laryngectomy and nonsurgical organ-preservation strategies in treatment of advanced stage laryngeal cancer: A meta-analysis. <i>Medicine (Baltimore)</i> . 2018 May;97(21):e10625.
Non-RCT 1	Evan M Graboyes (2017)	Effect of postoperative radiotherapy on survival for surgically managed pT3N0 and pT4aN0 laryngeal cancer: Analysis of the National Cancer Data Base. <i>Cancer</i> . 2017 Jun 15;123(12):2248-2257.
Non-RCT 2	Giovanni Succo (2018)	Treatment for T3 to T4a laryngeal cancer by open partial horizontal laryngectomies: Prognostic impact of different pathologic tumor subcategories. <i>Head Neck</i> . 2018 Sep;40(9):1897-1908.
Non-RCT 3	James E Bates (2019)	Curative-dose Chemoradiotherapy Versus Total Laryngectomy For Stage T3-T4 Squamous Cell Carcinoma of the Larynx: An "Apples-to-Apples" Analysis of the National Cancer Database. <i>Am J Clin Oncol</i> . 2019 Jun;42(6):527-533.
Non-RCT 4	Sagar A Patel (2019)	Comparing surgical and nonsurgical larynx-preserving treatments with total laryngectomy for locally advanced laryngeal cancer. <i>Cancer</i> . 2019 Oct 1;125(19):3367-3377.
Non-RCT 5	Aihemaiti Wushouer (2022)	Comparison of treatment modalities for selected advanced laryngeal squamous cell carcinoma. <i>Eur Arch Otorhinolaryngol</i> . 2022 Jan;279(1):361-371.

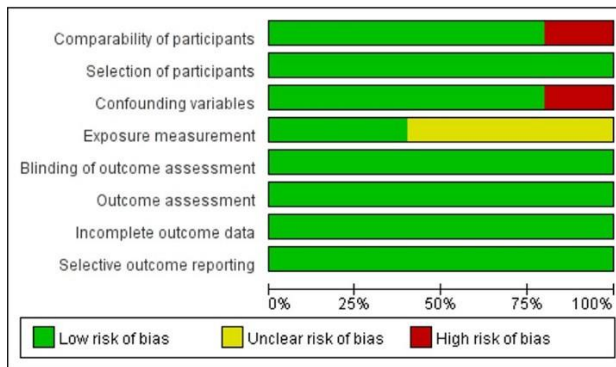
RCT, randomized controlled trials.

● Risk of bias

AMSTAR2 - Zhao-Xian Tang (2018)	
1. Components of PICO?	+
2. Review protocol?	+
3. Explanation for study design?	-
4. Comprehensive literature search strategy?	+
5. Study selection in duplicate?	+
6. Data extraction in duplicate?	+
7. List of excluded studies and justify the exclusions?	+
8. Study characteristics?	+
9. Satisfactory technique for assessing the risk of bias?	+
10. Sources of funding?	-
11. Appropriate methods?	+
12. Assess potential impact of risk of bias on the results?	+
13. Account for risk of bias when interpreting/discussing?	+
14. Satisfactory explanation for, and discussion of, any heterogeneity?	+
15. Publication bias (small study bias) assessed and discussed?	+
16. Potential sources of conflict of interest?	-

Yes"+":green, partially yes"±":orange, no"-":red, no meta-analysis(MA) conducted"n":grey

ROBANS 2.0



	Comparability of participants	Selection of participants	Confounding variables	Exposure measurement	Blinding of outcome assessment	Outcome assessment	Incomplete outcome data	Selective outcome reporting
Aihemaiti Wushouer (2022)	+	+	+	?	+	+	+	+
Evan M Graboyes (2017)	+	+	+	?	+	+	+	+
Giovanni Succo (2018)	+	+	+	+	+	+	+	+
James E Bates (2019)	+	+	+	+	+	+	+	+
Sagar A Patel (2019)	+	+	+	?	+	+	+	+

C. Management of the Neck

C1. Is prophylactic neck dissection necessary for patients with clinically lymph node-negative laryngeal cancer?

● Final included studies

Study number	First Author (year)	Included studies
Systematic Review 1	Alvaro Sanabria (2020)	Incidence of Occult Lymph Node Metastasis in Primary Larynx Squamous Cell Carcinoma, by Subsite, T Classification and Neck Level: A Systematic Review. <i>Cancers (Basel)</i> . 2020 Apr 24;12(4):1059.
Non-RCT 1	Melih Cayonu (2019)	Lymph node yield and lymph node density for elective level II-IV neck dissections in laryngeal squamous cell carcinoma patients. <i>Eur Arch Otorhinolaryngol</i> . 2019 Oct;276(10):2923-2927.
Non-RCT 2	D Riviere (2019)	Nodal metastases distribution in laryngeal cancer requiring total laryngectomy: Therapeutic implications for the N0 Neck. <i>Eur Ann Otorhinolaryngol Head Neck Dis</i> . 2019 Jun;136(3S):S35-S38.
Non-RCT 3	Yong Shi (2019)	Management of the N0 neck in patients with laryngeal squamous cell carcinoma. <i>Acta Otolaryngol</i> . 2019 Oct;139(10):908-912.
Non-RCT 4	Shi-Xu Wang (2019)	Predictors of Occult Lymph Node Metastasis and Prognosis in Patients with cN0 T1–T2 Supraglottic Laryngeal Carcinoma: A Retrospective Study. <i>ORL J Otorhinolaryngol Relat Spec</i> . 2019;81(5-6):317-326.
Non-RCT 5	Ye Zhang (2020)	Rational choice of neck dissection in clinically N0 patients with supraglottic cancer. <i>Head Neck</i> . 2020 Mar;42(3):365-373.
Non-RCT 6	Arne Böttcher (2021)	Rational surgical neck management in total laryngectomy for advanced stage laryngeal squamous cell carcinomas. <i>J Cancer Res Clin Oncol</i> . 2021 Feb;147(2):549-559.
Non-RCT 7	Cornelius H L Kürten (2021)	Patterns of cervical lymph node metastasis in supraglottic laryngeal cancer and therapeutic implications of surgical staging of the neck. <i>Eur Arch Otorhinolaryngol</i> . 2021 Dec;278(12):5021-5027.
Non-RCT 8	Tirth R Patel (2021)	Occult Lymph Node Metastasis in Early-Stage Glottic Cancer in the National Cancer Database. <i>Laryngoscope</i> . 2021 Apr;131(4):E1139-E1146.
Non-RCT 9	Eric M Anderson (2023)	Predicting Pathologic Lymph Node Positivity in cN0 Pharynx and Larynx Cancers. <i>Laryngoscope</i> . 2023 Jul;133(7):1660-1666.
Non-RCT 10	Ömer Bayır (2022)	Occult lymph node metastasis in patients with laryngeal cancer and relevant predicting factors: a single-center experience. <i>Tumori</i> . 2022 Oct;108(5):439-449.
Non-RCT 11	Zhimou Cai (2022)	Improving Survival of T3cN0M0 Glottic Squamous Cell Cancer With Elective Neck Dissection. <i>Laryngoscope</i> . 2022 Sep;132(9):1807-1816.
Non-RCT 12	Ahmad Mohamed Elteley (2022)	Assessment of Occult Nodal Micrometastases to the Clinically Negative Contralateral Neck in Locally Advanced Supraglottic Squamous Cell Carcinoma. <i>Indian J Otolaryngol Head Neck Surg</i> . 2022 Sep;74(3):369-374.

Non-RCT 13	Yu Heng	Management of clinically node-negative glottic squamous cell
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	(2022)	carcinoma patients according to risk-scoring model for occult lymph node metastases. Laryngoscope Invest Otolaryngol. 2022 Mar 30;7(3):715-722.
Non-RCT 14	Shenshan Jia (2022)	Efficacy of superselective neck dissection (IIA and III) for supraglottic laryngeal cancer with clinically negative neck. J Cancer Res Clin Oncol. 2022 Jun;148(6):1457-1463.
Non-RCT 15	Khairnar PS (2022)	Role of Elective Neck Dissection in Clinically Negative Neck Nodes in Head and Neck Malignancies. Int J Pharmaceutical Clin Res. 2022.
Non-RCT 16	Kuauhyama Luna-Ortiz (2022)	Role of Neck Dissection in Organ-Preservation for Glottic Squamous Cell Carcinoma. Indian J Otolaryngol Head Neck Surg. 2022 Dec;74(Suppl 3):5865-5870.
Non-RCT 17	Mehel DM (2022)	Neck metastasis in transglottic laryngeal carcinomas. J Experimental Clinical Med (Turkey). 2022.
Non-RCT 18	Stephanie Nga-Sze Wong (2022)	Retrospective Review on Role of Neck Dissection in Laryngectomy of Patients With N0 Laryngeal Carcinoma. OTO Open. 2022 Sep 23;6(3):2473974X221127903.

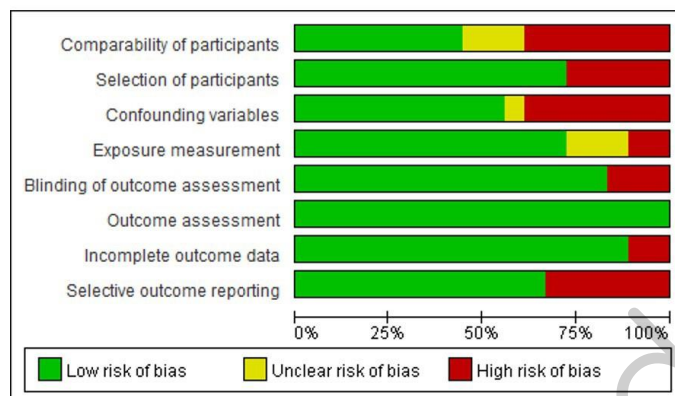
RCT, randomized controlled trials.

● Risk of bias

AMSTAR2 - Alvaro Sanabria (2020)	
1. Components of PICO?	+
2. Review protocol?	±
3. Explanation for study design?	+
4. Comprehensive literature search strategy?	+
5. Study selection in duplicate?	-
6. Data extraction in duplicate?	-
7. List of excluded studies and justify the exclusions?	+
8. Study characteristics?	+
9. Satisfactory technique for assessing the risk of bias?	+
10. Sources of funding?	-
11. Appropriate methods?	n
12. Assess potential impact of risk of bias on the results?	n
13. Account for risk of bias when interpreting/discussing?	+
14. Satisfactory explanation for, and discussion of, any heterogeneity?	-
15. Publication bias (small study bias) assessed and discussed?	n
16. Potential sources of conflict of interest?	+

Yes"+":green, partially yes"±":orange, no"-":red, no meta-analysis(MA) conducted"n":grey

ROBANS 2.0



	Comparability of participants	Selection of participants	Confounding variables	Exposure measurement	Blinding of outcome assessment	Outcome assessment	Incomplete outcome data	Selective outcome reporting
Ahmad Mohamed Elteley (2022)	+	+	+	+	+	+	+	+
Arne Böttcher (2021)	+	+	+	+	+	+	+	+
Cornelius H L Kürten (2021)	+	+	+	+	+	+	+	+
D Riviere (2019)	+	+	+	+	+	+	+	+
Eric M Anderson (2023)	+	+	+	+	+	+	+	+
Khairnar PS (2022)	+	+	+	+	+	+	+	+
Kuauhyama Luna-Ortiz (2022)	+	+	+	+	+	+	+	+
Mehel DM (2022)	+	+	+	+	+	+	+	+
Melih Cayonu (2019)	+	+	+	+	+	+	+	+
Ömer Bayır (2022)	+	+	+	+	+	+	+	+
Shenshan Jia (2022)	+	+	+	+	+	+	+	+
Shi-Xu Wang (2019)	+	+	+	+	+	+	+	+
Stephanie Nga-Sze Wong (2022)	+	+	+	+	+	+	+	+
Tirth R Patel (2021)	+	+	+	+	+	+	+	+
Ye Zhang (2020)	+	+	+	+	+	+	+	+
Yong Shi (2019)	+	+	+	+	+	+	+	+
Yu Heng (2022)	+	+	+	+	+	+	+	+
Zhimou Cai (2022)	+	+	+	+	+	+	+	+

C. Management of the Neck

C2. What is the appropriate extent of neck dissection in patients with clinically lymph node-positive laryngeal cancer?

● Final included studies

Study number	First Author (year)	Included studies
Non-RCT 1	F C Candela (1990)	Comparison between transoral laser surgery and radiotherapy in the treatment of early glottic cancer: A systematic review and meta-analysis. Arch Otolaryngol-Head Neck Surg 1990;116(4): 432-435.
Non-RCT 2	B J Davidson (1993)	Posterior triangle metastases of squamous cell carcinoma of the upper aerodigestive tract. Am J Surg 1993;166(4): 395-398.
Non-RCT 3	P C Weber (1994)	The impact of bilateral neck dissection on pattern of recurrence and survival in supraglottic carcinoma. Arch Otolaryngol-Head Neck Surg 1994;120(7): 703-706.
Non-RCT 4	R T Gregor (1996)	Management of cervical metastases in supraglottic cancer. Ann Otol Rhinol Laryngol 1996; 105(11): 845-850.
Non-RCT 5	C Y Yang (1998)	Nodal disease in purely glottic carcinoma: is elective neck treatment worthwhile? Laryngoscope 1998;108(7): 1006-1008.
Non-RCT 6	R R Brentani (1999)	End results of a prospective trial on elective lateral neck dissection vs type III modified radical neck dissection in the management of supraglottic and transglottic carcinomas. Head Neck 1999;21(8): 694-702.
Non-RCT 7	E C Choi (1999)	Is it Necessary to Dissect Level I in Laryngeal and Hypopharyngeal Squamous Cell Carcinoma? Korean J Otolaryngol-Head Neck Surg 1999;42(7): 482-485.
Non-RCT 8	Hicks WL Jr (1999)	Patterns of nodal metastasis and surgical management of the neck in supraglottic laryngeal carcinoma. Otolaryngol-Head Neck Surg 1999;121(1): 57-61.
Non-RCT 9	J G Buckley (2000)	Cervical node metastases in laryngeal and hypopharyngeal cancer: a prospective analysis of prevalence and distribution. Head Neck 2000;22(4): 380-385.
Non-RCT 10	Ferlito A (2000)	Surgical treatment of the neck in cancer of the larynx. ORL 2000;62(4): 217-225.
Non-RCT 11	O Gallo (2000)	Treatment of the contralateral negative neck in supraglottic cancer patients with unilateral node metastases (N1-3). Head Neck 2000;22(4): 386-392.
Non-RCT 12	P Ambrosch (2001)	Efficacy of selective neck dissection: a review of 503 cases of elective and therapeutic treatment of the neck in squamous cell carcinoma of the upper aerodigestive tract. Otolaryngol-Head Neck Surg 2001;124(2): 180-187.
Non-RCT 13	C R Dos Santos (2001)	Involvement of level I neck lymph nodes in advanced squamous carcinoma of the larynx. Ann Otol Rhinol Laryngol 2001;110(10): 982-984.
Non-RCT 14	Alfio Ferlito (2002)	The use and misuse of level IA dissection for head and neck cancer. Acta Oto-Laryngologica 2002;122(5): 553-555.
Non-RCT 15	Ahmet Koybasioğlu	Lymphatic metastasis to the supraretrospinal recess in laryngeal squamous cell carcinoma. Annals of Otology, Rhinology &

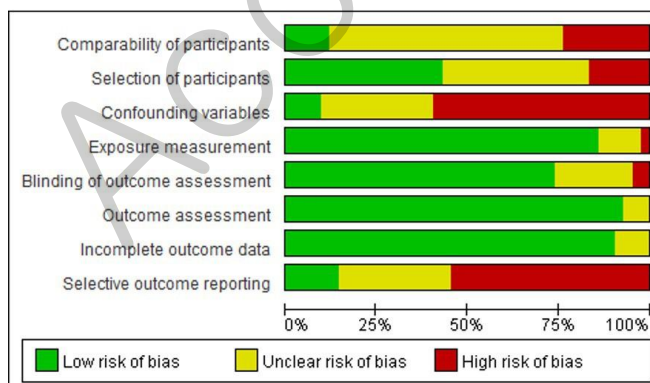
	(2002)	Laryngology 2002;111(1): 96-99.
Non-RCT 16	Robert J Chiu (2004)	Efficacy of routine bilateral neck dissection in the management of supraglottic cancer. Otolaryngology - Head & Neck Surgery 2004; 131(4): 485-488.
Non-RCT 17	Christine G Gourin (2004)	Is selective neck dissection adequate treatment for node-positive disease? Archives of Otolaryngology - Head and Neck Surgery 2004;130(12): 1431-1434.
Non-RCT 18	Peter J F M Lohuis (2004)	Effectiveness of therapeutic (N1, N2) selective neck dissection (levels II to V) in patients with laryngeal and hypopharyngeal squamous cell carcinoma. American Journal of Surgery 2004;187(2): 295-299.
Non-RCT 19	Toby H Corlette (2005)	Neck dissection of level IIb: Is it really necessary? Laryngoscope 2005;115(9): 1624-1626.
Non-RCT 20	André Bandiera de Oliveira Santos (2006)	Selective neck dissection for node-positive necks in patients with head and neck squamous cell carcinoma: A word of caution. Archives of Otolaryngology - Head and Neck Surgery 2006;132(1): 79-81.
Non-RCT 21	Young Chang Lim (2006)	Level IIb lymph node metastasis in laryngeal squamous cell carcinoma. Laryngoscope 2006;116(2): 268-272.
Non-RCT 22	Hüseyin Katılmış (2007)	Is dissection of levels 4 and 5 justified for cN0 laryngeal and hypopharyngeal cancer? Acta Oto-Laryngologica 2007;127(11): 1202-1206.
Non-RCT 23	Ozan Seymen Sezen (2007)	Frequency of metastases at the area of the supraretrospinal (level IIB) lymph node in laryngeal cancer. Head & Neck 2007;29(12): 1111-1114.
Non-RCT 24	Alfio Ferlito (2008)	Neck dissection for laryngeal cancer. Journal of the American College of Surgeons 2008;207(4): 587-593.
Non-RCT 25	Roberto Santoro (2008)	Nodal metastases at level IIb during neck dissection for head and neck cancer: clinical and pathologic evaluation. Head & Neck 2008;30(11): 1483-1487.
Non-RCT 26	Sedat Oztürkcan (2009)	Occult contralateral nodal metastases in supraglottic laryngeal cancer crossing the midline. European Archives of Oto-Rhino-Laryngology 2009;266(1): 117-120.
Non-RCT 27	Sandra Schmitz (2009)	Results of selective neck dissection in the primary management of head and neck squamous cell carcinoma. European Archives of Oto-Rhino-Laryngology 2009;266(3): 437-443.
Non-RCT 28	M Mnejja (2010)	Occult lymph node metastasis in laryngeal squamous cell carcinoma: Therapeutic and prognostic impact. European Annals of Otorhinolaryngology, Head and Neck Diseases 2010;127(5): 173-176.
Non-RCT 29	Ali Amar (2012)	Neck dissection in squamous cell carcinoma of the larynx. Indication of elective contralateral neck dissection. Brazilian Journal of Otorhinolaryngology 2012;78(2): 7-10.
Non-RCT 30	Riza Dünder (2012)	The necessity of dissection of level IIb in laryngeal squamous cell carcinoma: A clinical study. Otolaryngology - Head and Neck Surgery 2012;146(3): 390-394.
Non-RCT 31	S Wiegand (2012)	Relevance of level I and IIB neck dissection in laryngeal cancer. Journal of Laryngology & Otology 2012;126(8): 795-799.
Non-RCT 32	Brian C Gross (2013)	Level IIB lymph node metastasis in laryngeal and hypopharyngeal squamous cell carcinoma: single-institution case series and review of the literature. Laryngoscope 2013;123(12): 3032-3036.
Non-RCT 33	Eugenia	Effectiveness of therapeutic selective neck dissection in laryngeal

	Allegra (2014)	cancer. ORL; Journal of Oto-Rhino-Laryngology & its Related Specialties 2014;76(2): 89-97.
Non-RCT 34	Şenol Çomoğlu (2016)	Paratracheal lymph node dissection, in which patients should it be performed? The Turkish Journal of Ear Nose and Throat 2016;26(4): 213-218.
Non-RCT 35	Ben Green (2016)	Current surgical management of metastases in the neck from mucosal squamous cell carcinoma of the head and neck. British Journal of Oral and Maxillofacial Surgery 2016;54(2): 135-140.
Non-RCT 36	Arne Böttcher (2017)	A novel classification scheme for advanced laryngeal cancer midline involvement: implications for the contralateral neck. Journal of Cancer Research and Clinical Oncology 2017;143(8): 1605-1612.
Non-RCT 37	D Rivière (2018)	Lymph-node metastasis following total laryngectomy and total pharyngolaryngectomy for laryngeal and hypopharyngeal squamous cell carcinoma: Frequency, distribution and risk factors. European annals of otorhinolaryngology, head & neck diseases 2018;135(3): 163-166.
Non-RCT 38	Fernando López (2020)	Selective neck dissection in the treatment of head and neck squamous cell carcinoma patients with a clinically positive neck. Oral Oncology 2020;102: 104565.
Non-RCT 39	Arne Böttcher (2021)	Rational surgical neck management in total laryngectomy for advanced stage laryngeal squamous cell carcinomas. Journal of Cancer Research & Clinical Oncology 2021;147(2): 549-559.
Non-RCT 40	Ruihua Fang (2021)	The survival benefit of lymph node dissection in resected T1-2, cN0 supraglottic cancer: A population-based propensity score matching analysis. Head & Neck 2021;43(4): 1300-1310.
Non-RCT 41	Andrea Castellucci (2021)	Patterns of cervical lymph node metastasis in supraglottic laryngeal cancer and therapeutic implications of surgical staging of the neck. European Archives of Oto-Rhino-Laryngology 2021;278(12): 5021-5027.
Non-RCT 42	Ahmad Mohamed Elteley (2022)	Assessment of Occult Nodal Micrometastases to the Clinically Negative Contralateral Neck in Locally Advanced Supraglottic Squamous Cell Carcinoma. Indian Journal of Otolaryngology & Head & Neck Surgery 2022;74(3): 369-374.

RCT, randomized controlled trials.

● Risk of bias

ROBANS 2.0



	Comparability of participants	Selection of participants	Confounding variables	Exposure measurement	Blinding of outcome assessment	Outcome assessment	Incomplete outcome data	Selective outcome reporting
Ahmad Mohamed Elteley (2022)	?	?	?	?	?	?	?	?
Ahmet Koybasioğlu (2002)	?	?	?	?	?	?	?	?
Alfio Ferlito (2002)	?	?	?	?	?	?	?	?
Alfio Ferlito (2008)	?	?	?	?	?	?	?	?
Ali Amar (2012)	?	?	?	?	?	?	?	?
Andrea Castellucci (2021)	?	?	?	?	?	?	?	?
André Bandiera de Oliveira Santos (2006)	?	?	?	?	?	?	?	?
Arne Böttcher (2017)	?	?	?	?	?	?	?	?
Arne Böttcher (2021)	?	?	?	?	?	?	?	?
Beri Green (2016)	?	?	?	?	?	?	?	?
B J Davidson (1993)	?	?	?	?	?	?	?	?
Brian C Gross (2013)	?	?	?	?	?	?	?	?
Christine G Gourin (2004)	?	?	?	?	?	?	?	?
C R dos Santos (2001)	?	?	?	?	?	?	?	?
C Y Yang (1998)	?	?	?	?	?	?	?	?
D Rivière (2018)	?	?	?	?	?	?	?	?
E C Choi (1999)	?	?	?	?	?	?	?	?
Eugenila Allegra (2014)	?	?	?	?	?	?	?	?
F C Candela (1990)	?	?	?	?	?	?	?	?
Ferlito A (2000)	?	?	?	?	?	?	?	?
Fernando López (2020)	?	?	?	?	?	?	?	?
Hicks WL Jr (1999)	?	?	?	?	?	?	?	?
Hüseyin Katılmış (2007)	?	?	?	?	?	?	?	?
J G Buckley (2000)	?	?	?	?	?	?	?	?
M Mnejja (2010)	?	?	?	?	?	?	?	?
O Gallo (2000)	?	?	?	?	?	?	?	?
Ozan Seymen Sezen (2007)	?	?	?	?	?	?	?	?
P Ambrosch (2001)	?	?	?	?	?	?	?	?
P C Weber (1994)	?	?	?	?	?	?	?	?
Peter J F M Lohuis (2004)	?	?	?	?	?	?	?	?
Riza Dündar (2012)	?	?	?	?	?	?	?	?
Robert J Chiu (2004)	?	?	?	?	?	?	?	?
Roberto Santoro (2008)	?	?	?	?	?	?	?	?
R R Brentani (1999)	?	?	?	?	?	?	?	?
R T Gregor (1996)	?	?	?	?	?	?	?	?
Ruihua Fang (2021)	?	?	?	?	?	?	?	?
Sandra Schmitz (2009)	?	?	?	?	?	?	?	?
Sedat Öztürkcan (2009)	?	?	?	?	?	?	?	?
Şenol Çomoğlu (2016)	?	?	?	?	?	?	?	?
S Wiegand (2012)	?	?	?	?	?	?	?	?
Toby H Corlette (2005)	?	?	?	?	?	?	?	?
Young Chang Lim (2006)	?	?	?	?	?	?	?	?

D. Adjuvant Therapy

D1. Does adjuvant therapy improve treatment outcomes in patients with laryngeal cancer following surgical resection?

● Final included studies

Study number	First Author (year)	Included studies
RCT 1	Cooper JS (2004)	Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med. 2004;350(19):1937-44.
RCT 2	Bernier J (2004)	Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med. 2004;350(19):1945-52.
RCT 3	Bernier J (2005)	Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck. 2005;27(10):843-50.
RCT 4	Cooper JS (2012)	Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys. 2012;84(5):1198-205.
Non-RCT 1	Ampil FL (2007)	Total laryngectomy and T3-T4 laryngeal cancer without other adverse histopathology. Otolaryngol Head Neck Surg. 2007;136(2):296-300.
Non-RCT 2	Graboyes EM (2017)	Effect of postoperative radiotherapy on survival for surgically managed pT3N0 and pT4aN0 laryngeal cancer: Analysis of the National Cancer Data Base. Cancer. 2017;123(12):2248-57.
Non-RCT 3	Deng K (2022)	The effect of surgery plus intensity-modulated radiotherapy on treatment in laryngeal cancer: A clinical retrospective study. J Cancer Res Clin Oncol. 2022;148(2):517-25.

RCT, randomized controlled trials.

● Risk of bias

ROB 2.0

	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall bias
Bernier J (2004)	+	+	+	+	+	+
Bernier J (2005)	+	+	+	+	+	+
Cooper JS (2004)	+	+	+	+	+	+
Cooper JS (2012)	+	+	+	+	+	+

ROBANS 2.0

	Comparability of participants	Selection of participants	Confounding variables	Exposure measurement	Blinding of outcome assessment	Outcome assessment	Incomplete outcome data	Selective outcome reporting
Ampil FL (2007)	⊖	+	+	+	⊖	+	?	+
Deng K (2022)	?	+	+	+	?	+	+	+
Graboyes EM (2017)	+	+	+	+	+	+	+	+

E. Swallowing Rehabilitation

E1. What is the role of swallowing rehabilitation in patients with laryngeal cancer?

● Final included studies

Study number	First Author (year)	Included studies
RCT 1	Sara Fredslund Hajdú (2022)	Swallowing exercise during head and neck cancer treatment: results of a randomized trial. <i>Dysphagia</i> 2022;37: 749-762.
RCT 2	Xuewei Zhu (2021)	Effect of swallowing training combined with nutritional intervention on the nutritional status and quality of life of laryngeal cancer patients with dysphagia after operation and radiotherapy. <i>J Oral Rehabil</i> 2022;49: 729-733.
Non-RCT 1	Sophie A C Kraaijenga (2017)	Efficacy of a novel swallowing exercise program for chronic dysphagia in long-term head and neck cancer survivors. <i>Head Neck</i> 2017;39: 1943-1961.

RCT, randomized controlled trials.

● Risk of bias

ROB 2.0

	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall bias
Sara Fredslund Hajdú (2022)	+	+	?	+	+	+
Xuewei Zhu (2021)	?	+	+	+	+	+

ROBANS 2.0

	Comparability of participants	Selection of participants	Confounding variables	Exposure measurement	Blinding of outcome assessment	Outcome assessment	Incomplete outcome data	Selective outcome reporting
Sophie A C Kraaijenga (2017)	●	+	●	+	?	+	+	+

F. Salvage Treatment for Recurrent Laryngeal Cancer

F1. What are the salvage treatment options applicable for locally recurrent laryngeal cancer?

● Final included studies

Study number	First Author (year)	Included studies
Systematic Review 1	Shapira U (2022)	Laryngectomy-free survival after salvage partial laryngectomy: a systematic review and meta-analysis. <i>European Archives of Oto-Rhino-Laryngology</i> . 2022;279:3021-3027
Systematic Review 2	Virgilio A (2018)	Supracricoid partial laryngectomy for radiorecurrent laryngeal cancer: a systematic review of the literature and meta-analysis. <i>European Archives of Oto-Rhino-Laryngology</i> . 2018;275(7):1671-1680.
Non-RCT 1	Casiano RR (1991)	Laser cordectomy for T1 glottic carcinoma: a 10-year experience and videostroboscopic findings. <i>Otolaryngology-Head and Neck Surgery</i> . 1991;104(6):831-7
Non-RCT 2	Steiner W (2004)	Transoral carbon dioxide laser microsurgery for recurrent glottic carcinoma after radiotherapy. <i>Head & Neck: Journal for the Sciences and Specialties of the Head and Neck</i> . 2004;26(6):477-84.
Non-RCT 3	Ansarin M (2007)	Endoscopic carbon dioxide laser surgery for glottic cancer recurrence after radiotherapy: oncological results. <i>Archives of Otolaryngology-Head & Neck Surgery</i> . 2007;133(12):1193-7.
Non-RCT 4	Kim JK (2007)	Salvage Surgery for Radiation Failures in Early(T1N0, T2N0) Glottic Cancer. <i>Korean Journal of Otolaryngology-Head and Neck Surgery</i> . 2007;50(9): 795-799
Non-RCT 5	Choi SH (2007)	Laser Salvage Surgery for Recurrent Glottic Cancer after Radiotherapy. <i>Korean Journal of Otolaryngology-Head and Neck Surgery</i> . 2007;50(2): 139-144.
Non-RCT 6	Lee SW (2008)	Recurrence Risk Factors after Radiotherapy in Early Glottic Cancer and Outcome of Salvage Treatment. <i>Korean Journal of Otolaryngology-Head and Neck Surgery</i> . 2008;51(3): 261-265
Non-RCT 7	Roedel RM (2010)	Repeated transoral laser microsurgery for early and advanced recurrence of early glottic cancer after primary laser resection. <i>Auris Nasus Larynx</i> . 2010;37(3):340-6.
Non-RCT 8	Han YJ (2012)	Transoral laser microsurgery of recurrent early glottic cancer after radiation therapy: clinical feasibility and limitations. <i>Annals of Otology, Rhinology & Laryngology</i> . 2012;121(6):375-82.
Non-RCT 9	Gigot M (2022)	Salvage Partial Laryngectomy after Failed Radiotherapy: Oncological and Functional Outcomes. <i>J Clin Med</i> 2022;11(8);5411
Non-RCT 10	Pellini R (2008)	Supracricoid partial laryngectomies after radiation failure: A multi-institutional series. <i>Head Neck</i> 2008;30(3):372-379
Non-RCT 11	Vincentiis M (2015)	Oncologic results of the surgical salvage of recurrent laryngeal squamous cell carcinoma in a multicentric retrospective series: Emerging role of supracricoid partial laryngectomy. <i>Laryngoscope</i> 2015;37(1);84-91
Non-RCT 12	Bertolin A (2020)	Salvage Open Partial Horizontal Laryngectomy After Failed Radiotherapy: A Multicentric Study. <i>Laryngoscope</i> 2020;130 :431-436

Non-RCT 13	Sullivan C (2020)	Primary Laryngectomy Versus Salvage Laryngectomy: A Comparison of Outcomes in the Chemoradiation Era. <i>Laryngoscope</i> 2020;130:2179-2185
Non-RCT 14	Bertolin A (2021)	Oncological and Functional Outcomes of Primary and Salvage Total Laryngectomy. <i>Laryngoscope</i> 2021;131(2):569-575
Non-RCT 15	Huang J (2013)	Salvage transoral laser microsurgery for early recurrent glottic carcinoma after primary laser treatment. <i>Acta otolaryngologica</i> .2013;133(5):531-7.
Non-RCT 16	Lucioni M (2016)	Open partial horizontal laryngectomy for salvage after failure of CO2 laser-assisted surgery for glottic carcinoma. <i>European Archives of Oto-Rhino-Laryngology</i> 2016;273:169-175
Non-RCT 17	Forner D (2020)	Oncological and functional outcomes after repeat transoral laser microsurgery for the treatment of recurrent early glottic cancer. <i>The Journal of Laryngology & Otology</i> . 2020;134(2):169-73.
Non-RCT 18	Virgilio A (2016)	Salvage total laryngectomy after conservation laryngeal surgery for recurrent laryngeal squamous cell carcinoma. <i>Acta Otorhinolaryngologica</i> 2016;36(5):373-380
Non-RCT 19	Weiss B (2017)	Transoral laser microsurgery or total laryngectomy for recurrent squamous cell carcinoma of the larynx: Retrospective analysis of 199 cases. <i>Head Neck</i> 2017;39(6):1166-1176

RCT, randomized controlled trials.

● Risk of bias

AMSTAR2 – Shapira U (2022)	
1. Components of PICO?	+
2. Review protocol?	±
3. Explanation for study design?	+
4. Comprehensive literature search strategy?	±
5. Study selection in duplicate?	+
6. Data extraction in duplicate?	+
7. List of excluded studies and justify the exclusions?	±
8. Study characteristics?	+
9. Satisfactory technique for assessing the risk of bias?	-
10. Sources of funding?	-
11. Appropriate methods?	+
12. Assess potential impact of risk of bias on the results?	-
13. Account for risk of bias when interpreting/discussing?	+
14. Satisfactory explanation for, and discussion of, any heterogeneity?	+
15. Publication bias (small study bias) assessed and discussed?	-
16. Potential sources of conflict of interest?	+

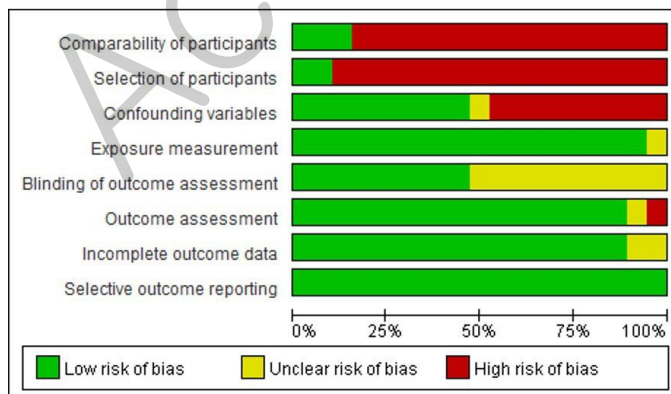
Yes"+":green, partially yes"±":orange, no"-":red, no meta-analysis(MA) conducted"n":grey

AMSTAR2 - Virgilio A (2018)

1. Components of PICO?	+
2. Review protocol?	±
3. Explanation for study design?	+
4. Comprehensive literature search strategy?	+
5. Study selection in duplicate?	+
6. Data extraction in duplicate?	+
7. List of excluded studies and justify the exclusions?	±
8. Study characteristics?	+
9. Satisfactory technique for assessing the risk of bias?	±
10. Sources of funding?	+
11. Appropriate methods?	+
12. Assess potential impact of risk of bias on the results?	+
13. Account for risk of bias when interpreting/discussing?	+
14. Satisfactory explanation for, and discussion of, any heterogeneity?	+
15. Publication bias (small study bias) assessed and discussed?	-
16. Potential sources of conflict of interest?	+

Yes"+":green, partially yes"±":orange, no"-":red, no meta-analysis(MA) conducted"n":grey

ROBANS 2.0



	Comparability of participants	Selection of participants	Confounding variables	Exposure measurement	Blinding of outcome assessment	Outcome assessment	Incomplete outcome data	Selective outcome reporting
Ansarin M (2007)	+	+	+	+	?	+	+	+
Bertolin A (2020)	+	+	+	+	+	+	+	+
Bertolin A (2021)	+	+	+	?	+	?	+	+
Casiano RR (1991)	+	+	+	+	+	+	+	+
Choi SH (2007)	+	+	+	+	?	+	+	+
Forner D (2020)	+	+	+	+	?	+	+	+
Gigot M (2022)	+	+	?	+	?	+	+	+
Han YJ (2012)	+	+	+	+	+	+	+	+
Huang J (2013)	+	+	+	+	?	+	+	+
Kim JK (2007)	+	+	+	+	+	+	?	+
Lee SW (2008)	+	+	+	+	+	+	?	+
Lucioni M (2016)	+	+	+	+	?	+	+	+
Pellini R (2008)	+	+	+	+	+	+	+	+
Roedel RM (2010)	+	+	+	+	?	+	+	+
Steiner W (2004)	+	+	+	+	?	+	+	+
Sullivan C (2020)	+	+	+	+	+	+	+	+
Vincetiis M (2015)	+	+	+	+	+	+	+	+
Virgilio A (2016)	+	+	+	+	?	+	+	+
Weiss B (2017)	+	+	+	+	?	+	+	+

F. Salvage Treatment for Recurrent Laryngeal Cancer

F2. Does elective neck dissection improve oncological outcomes in salvage laryngectomy for locally recurrent laryngeal cancer?

● Final included studies

Study number	First Author (year)	Included studies
Systematic Review 1	Cameron R. Davies-Husband (2020)	Elective neck dissection for salvage total laryngectomy: A systematic review, meta-analysis and "decision-to-treat" approach. Clin Otolaryngol. 2020 Jul;45(4):558-573
Non-RCT 1	Eda Yirmibesoglu (2013)	Incidence of subclinical nodal disease at the time of salvage surgery for locally recurrent head and neck cancer initially treated with definitive radiation therapy. Am J Clin Oncol 2013;36(5):475-480
Non-RCT 2	Farlow JL (2019)	Elective paratracheal lymph node dissection in salvage laryngectomy. Ann Surg Oncol 2019;26: 2542-2548
Non-RCT 3	Gouzos M (2019)	Elective neck dissection for the node-negative neck during salvage laryngectomy: an analysis of survival outcomes and complication rates. J Laryngol Otol 2019;133(9):788-791
Non-RCT 4	Romain Dassé (2022)	Proposal for an algorithm to avoid neck dissection during salvage total laryngectomy. A GETTEC multicentric study. Oral Oncol 2022;133:106026

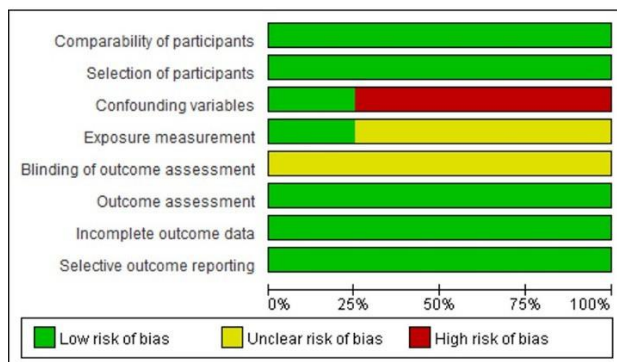
RCT, randomized controlled trials.

● Risk of bias

AMSTAR2 - Cameron R. Davies-Husband (2020)	
1. Components of PICO?	+
2. Review protocol?	+
3. Explanation for study design?	+
4. Comprehensive literature search strategy?	+
5. Study selection in duplicate?	+
6. Data extraction in duplicate?	-
7. List of excluded studies and justify the exclusions?	+
8. Study characteristics?	+
9. Satisfactory technique for assessing the risk of bias?	+
10. Sources of funding?	-
11. Appropriate methods?	+
12. Assess potential impact of risk of bias on the results?	+
13. Account for risk of bias when interpreting/discussing?	+
14. Satisfactory explanation for, and discussion of, any heterogeneity?	+
15. Publication bias (small study bias) assessed and discussed?	-
16. Potential sources of conflict of interest?	-

Yes"+":green, partially yes"±":orange, no"-":red, no meta-analysis(MA) conducted"n":grey

ROBANS 2.0



	Comparability of participants	Selection of participants	Confounding variables	Exposure measurement	Blinding of outcome assessment	Outcome assessment	Incomplete outcome data	Selective outcome reporting
Eda Yirmibesoglu (2013)	+	+	+	+	?	+	+	+
Farlow JL (2019)	+	+	+	?	?	+	+	+
Gouzos M (2019)	+	+	+	?	?	+	+	+
Romain Dasse (2022)	+	+	+	?	?	+	+	+

Guideline for the treatment of laryngeal cancer

Korean Society of Head and Neck Surgery

Recommendations

KQ1. What is the appropriate treatment for early-stage (T1/T2) glottic cancer?

KQ2. What is the appropriate treatment for early-stage (T1/T2) supraglottic cancer?

KQ3. What is the role of total laryngectomy in locally advanced (T3/T4) laryngeal cancer?

KQ4. What is an appropriate larynx preservation therapy in locally advanced (T3/T4) laryngeal cancer?

KQ5 Is prophylactic neck dissection necessary for patients with clinically lymph node-negative laryngeal cancer?

KQ6 What is the appropriate extent of neck dissection in patients with clinically lymph node-positive laryngeal cancer?

KQ7 Does adjuvant therapy improve treatment outcomes in patients with laryngeal cancer following surgical resection?

KQ8 What is the role of swallowing rehabilitation in patients with laryngeal cancer?

KQ9. What are the salvage treatment options applicable for locally recurrent laryngeal cancer?

KQ10. Does elective neck dissection improve oncological outcomes in salvage laryngectomy for locally recurrent laryngeal cancer?

KQ1. What is the appropriate treatment for early-stage (T1/T2) glottic cancer?

Recommendation 1

For early-stage glottic cancer, both surgical treatment and radiation therapy can be considered as initial treatment.

(Strong recommendation/low-quality evidence)

Recommendation 2

Transoral surgery could be considered a preferred surgical treatment method in early-stage glottic cancer.

(Conditional recommendation/low-quality evidence)

KQ2. What is the appropriate treatment for early-stage (T1/T2) supraglottic cancer?

Recommendation 3

For early-stage supraglottic cancer, both surgical treatment and radiation therapy can be considered as initial treatment.

(Strong recommendation/low-quality evidence)

Recommendation 4

Conservative laryngeal surgery (transoral surgery or open partial laryngectomy) could be considered a surgical treatment option in early-stage supraglottic cancer.

(Conditional recommendation/low-quality evidence)

KQ3. What is the role of total laryngectomy in locally advanced (T3/T4) laryngeal cancer?

Recommendation 5

Total laryngectomy can be selected as an initial treatment in locally advanced laryngeal cancer to achieve better locoregional control and survival.

(Conditional recommendation/low-quality evidence)

KQ4. What is an appropriate larynx-preservation therapy in locally advanced (T3/T4) laryngeal cancer?

Recommendation 6

A) Larynx-preservation therapy (concurrent chemoradiation therapy or larynx-preservation surgery) can be applied depending on the patient's condition (T stage, age, underlying diseases, social activities, etc).

(Conditional recommendation/low-quality evidence)

B) Larynx-preservation surgery could be performed in selected T3/T4 cancers without extensive tongue base invasion, bilateral cricoarytenoid unit impairment, or inferior extension to the cricoid cartilage, although the risk of postoperative morbidity such as dysphagia and aspiration should be carefully considered.

(Conditional recommendation/low-quality evidence)

KQ5 Is prophylactic neck dissection necessary for patients with clinically lymph node-negative laryngeal cancer?

Recommendation 7

If lymph node metastasis is clinically negative in early-stage (T1/T2) laryngeal cancer confined to the glottis, prophylactic neck dissection is not mandatory.

(Conditional recommendation/low-quality evidence)

Recommendation 8

If lymph node metastasis is clinically negative in early-stage (T1/T2) laryngeal cancer involving the supraglottis, prophylactic neck dissection including the levels II-III could be considered.

(Conditional recommendation/low-quality evidence)

Recommendation 9

If lymph node metastasis is clinically negative in advanced stage (T3/T4) laryngeal cancer, prophylactic neck dissection including the levels II-III should be considered.

(Conditional recommendation/low-quality evidence)

KQ6. What is the appropriate extent of neck dissection in patients with clinically lymph node-positive laryngeal cancer?

Recommendation 10

If ipsilateral lymph node metastasis is clinically apparent, comprehensive neck dissection or selective neck dissection including at least levels II, III, IV should be performed.

(Strong recommendation/low-quality evidence)

Recommendation 11

If ipsilateral lymph node metastasis is clinically apparent in laryngeal cancer confined to the glottis, contralateral prophylactic neck dissection is not mandatory.

(Conditional recommendation/low-quality evidence)

Recommendation 12

If ipsilateral lymph node metastasis is clinically apparent in laryngeal cancer involving the supraglottis, contralateral prophylactic neck dissection including the levels II-IV should be considered.

(Conditional recommendation/moderate-quality evidence)

KQ7. Does adjuvant therapy improve treatment outcomes in patients with laryngeal cancer following surgical resection?

Recommendation 13

(A) Adjuvant therapy (radiation therapy or chemoradiation therapy) following radical surgery could be considered for patients with advanced stage (III/IV) disease and/or risk factors such as vascular invasion, perineural invasion, or multiple nodal metastases.

(Conditional recommendation/low-quality evidence)

(B) Adjuvant chemoradiotherapy should be considered for patients with laryngeal cancer and positive surgical margins or extranodal extension.

(Conditional recommendation/high-quality evidence)

KQ8. What is the role of swallowing rehabilitation in patients with laryngeal cancer?

Recommendation 14

Swallowing rehabilitation may be useful for dysphagia after surgical or nonsurgical treatment for laryngeal cancer.

(Conditional recommendation/very low-quality evidence)

KQ9. What are the salvage treatment options applicable for locally recurrent laryngeal cancer?

Recommendation 15

- A) Total laryngectomy should be considered for most patients with locally recurrent cancer when larynx-preserving strategy is not feasible due to patent and tumor characteristics.
(Strong recommendation/low-quality evidence)
- B) Open partial laryngectomy could be considered for selected patients with locally recurrent laryngeal cancer in whom one or two cricoarytenoid unit can be preserved.
(Conditional recommendation/very low-quality evidence)
- C) Transoral surgery may be considered for well-selected patients with localized and limited recurrent tumors, providing precise preoperative assessment to ensure adequate exposure and complete resectability
(Conditional recommendation/very low-quality evidence)
- D) RT/CCRT is an available salvage modality for eligible patients unless it was used in the initial treatment.
(Conditional recommendation/very low-quality evidence)

KQ10. Does elective neck dissection improve oncological outcomes in salvage laryngectomy for locally recurrent laryngeal cancer?

Recommendation 16

Elective neck dissection could be considered in selected patients with locally recurrent laryngeal cancer who are at high risk for regional recurrence, including those with supraglottic or transglottic involvement and advanced rT category.
(Conditional recommendation/very low-quality evidence)