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REVIEW ARTICLE

# Voice rehabilitation for laryngeal cancer after radiotherapy: a systematic review and meta-analysis

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## Abstract

**Purpose** We aimed to determine whether voice rehabilitation after radiotherapy improves the quality of life (QOL), voice function, and self-rated voice function in patients with laryngeal cancer.

**Methods** We searched CENTRAL, MEDLINE, EMBASE, PEDro, and World Health Organization International Clinical Trials Registry Platform for randomized controlled trials published between inception and October 2018. The primary outcome was QOL, adverse events and mortality. Secondary outcomes included voice function and self-rated voice function. The quality of evidence was determined using the Grading of Recommendations Assessment, Development, and Evaluation approach.

**Results** Three trials (enrolling 122 patients) compared voice rehabilitation to usual care or no intervention after radiotherapy. Voice rehabilitation did not significantly improve any QOL scores. Data on adverse events and mortality were not available in any of the trials. Voice rehabilitation did not improve any voice function scores, such as jitter (mean difference: – 0.48 [– 1.27 to 0.32]), shimmer (mean difference: – 0.04 [– 0.27 to 0.19]), maximum phonation time (mean difference: 1.54 [– 1.13 to 4.22]), and the grade, roughness, breathiness, asthenia, and strain scale (mean difference: – 0.39 [– 2.59 to 1.80]). Voice rehabilitation also did not improve the voice handicap index, which was used as a self-rated voice function score (mean difference: 5.54 [– 2.07 to 13.16]). The certainty of the evidence was graded as low for primary and secondary outcomes.

**Conclusion** Voice rehabilitation for patients with laryngeal cancer after radiotherapy might not improve QOL, voice function, and self-rated voice function. Pre-specified voice rehabilitation programs may not be necessary for all patients with laryngeal cancer after radiotherapy.

**Keywords** Laryngeal cancer · Radiotherapy · Voice rehabilitation · Quality of life · Systematic review

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00405-019-05452-2) contains supplementary material, which is available to authorized users.

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## Introduction

Laryngeal cancer is a common cancer of the head and neck [1, 2]. Patients with laryngeal cancer show several adverse events after radiotherapy, including inflammation-induced circulatory disturbances, dry throat, reduced sensation, and voice quality changes. More than half of the patients who undergo radiotherapy show these adverse events, which can reduce their quality of life (QOL) [3–5]. In recent years, therefore, greater consideration has been given to the patient's QOL post-treatment, rather than just the curative aspects of the treatment [3].

The American Cancer Society Head and Neck Cancer Survivorship Care Guideline [2] recommends that primary care clinicians should assess patients for speech disturbances and should refer them to an experienced speech-language pathologist if a communication disorder exists. However, this guideline recommendation was not based on systematic review data, and no systematic review and meta-analysis has reported the effect of voice rehabilitation after radiotherapy in patients with laryngeal cancer. Therefore, in this systematic review and meta-analysis, we investigated whether voice rehabilitation after radiotherapy can improve QOL in patients with laryngeal cancer.

## Methods

### Compliance with reporting guidelines

We conducted a systematic review using a pre-specified published protocol (PROSPERO: CRD42018081881) [6]. This systematic review was synthesized following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [7]. We assessed this systematic review using the PRISMA 2009 checklist [8] (details provided in Online Supplementary File 1).

### Research question and eligibility criteria

We posed the following research question: "In adult patients with laryngeal cancer, does voice rehabilitation after radiotherapy result in improved clinically relevant outcomes in comparison with usual care?" We included all published and unpublished prospective randomized controlled trials (RCTs) involving adult human subjects (aged ≥ 18 years), including those that were only abstracts or letters. Crossover trials and cluster-, quasi-, or non-randomized trials were excluded. Studies were included regardless of the time of follow-up. We included studies assessing patients with newly diagnosed laryngeal cancer who were to receive curatively intended radiation therapy with or without chemotherapy. We included laryngeal cancer patients diagnosed with tumor size and tumor stage (T0–T4) at the glottic, supraglottic, subglottic, and transglottic sites. Patients were included irrespective of sex, race, and setting. We excluded patients who had received surgery for laryngeal cancer or laser cordectomy, or showed cognitive dysfunction or voice disorder by other diseases except laryngeal cancer. The intervention in the review was protocolized voice rehabilitation (such as diaphragmatic breathing, coordination of breathing and phonation, control and variation of pitch, general relaxation, and vocal hygiene by speech-language pathologists). We excluded studies of interventions that focused solely on education by video-based lectures or brochures.

### Outcomes of interest

Our primary outcomes were QOL, all adverse events (defined by the author), and mortality. QOL was measured by standardized questionnaires with established reliabilities and validities such as Short-Form 36 (physical component summary score and mental component summary score), the European Organization for Research and Treatment Cancer Quality of Life Questionnaire Head and Neck 35 (ERORTC QLQ-H&N35), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core30 (EORTC QLQ-C30), or Self-Evaluation of Communication Experiences after Laryngeal cancer (SECEL). Secondary outcomes were voice function (voice range profile, voice analysis, acoustic analyses) and self-rated voice function.

### Search strategy and selection of studies

We systematically searched MEDLINE via PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Excerpta Medic database via Elsevier, PEDro. and the World Health Organization international clinical trials platform search portal (WHO ICTRP) from database inception until October 18, 2018. The search was performed in October 2018 using a set of suitable search terms (details provided in Online Supplementary File 2).We also handsearched reference lists of the latest guidelines on head and neck cancers (2) as well as reference lists of extracted studies and articles citing extracted studies, using the Web of Science. If the database entry for a candidate study did not

contain the necessary information, we contacted the study author. Two reviewers (MT and ST) independently screened the title and abstract of each study returned by the search to determine whether the inclusion criteria were met. The two reviewers performed a full-text review to assess the eligibility of each candidate study. Disagreement was resolved by discussion between the two reviewers, occasionally with arbitration by a third reviewer (YT).

### Data abstraction and quality assessment

Two reviewers (MT and ST) also independently abstracted trial-level data using pre-specified forms. Disagreements in data extraction were resolved through discussions. We contacted authors of studies without sufficient information where necessary. Two reviewers (ST and MT) independently assessed the risk of bias in the included studies using the Cochrane Risk of Bias Assessment Tool. Differences in opinion following the assessment of risk of bias were resolved through discussions, and where this failed, through arbitration by YT.

All analyses were conducted using the Review Manager software (RevMan 5.3; Cochrane Community). For continuous outcomes—QOL, HNR, Jitter, Shimmer, F0, and MPT—the standardized mean difference (SMD) or mean differences (MD) with 95% CI were calculated, as recommended by the Cochrane Handbook [9]. Adverse events were narratively summarized because the definitions of these outcomes varied across studies. We used the random-effects models for all analyses.

We calculated $I^2$ as a measure of variation across studies that is due to heterogeneity rather than chance, and interpreted the values as follows: 0–40%, negligible heterogeneity; 30–60%, mild-to-moderate heterogeneity; 50–90%, moderate-to-substantial heterogeneity; 75–100%, considerable heterogeneity. If heterogeneity was identified for an outcome ($I^2 > 50\%$), we investigated the underlying reasons and conducted the $\chi^2$ test, with a $P$ value of $< 0.10$ being considered to be statistically significant.

To explore potential heterogeneity and determine whether the level of risk of bias affected the effect estimate, we planned to conduct subgroup and sensitivity analyses. However, the included studies were insufficient to perform these analyses. We investigated the reporting bias by checking the trial registers (WHO ICTRP) and detected completed but unpublished trials. $P < 0.05$ was considered statistically significant. We created a summary-of-findings table that included an overall grading of the certainty of evidence for each of the main outcomes, which was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach [10, 11].

## Results

### Results of the search

A total of 508 records were identified through database searches (Fig. 1). Duplicates ($n = 94$) were excluded. After full-text articles were assessed for eligibility, three studies (seven articles) met all inclusion criteria. One RCT [12] did not have sufficient outcome data for meta-analysis (details provided in online supplementary file 3). There was no ongoing study.

### Characteristics of the included studies

The mean or median age in the analyzed studies ranged from 57.5 to 69 years. The intervention duration was 6 weeks [13, 14] and 10 weeks [15] (Table 1). The intervention was started approximately 1 month after completion of oncologic treatment [15] or at least 6 months prior to study participation [13, 14].

### Risk of bias in the included studies

All studies showed a high or unclear risk of bias (Table 2). All three studies demonstrated adequate random sequence generation, but unclear risk of bias for allocation concealment. Moreover, participants and personnel were not blinded to the intervention. Two studies demonstrated high or unclear risk of bias for blinding of outcome assessment. All studies had unclear risk of selective reporting bias because of missing or insufficient protocol registration information.

### Effect of interventions

The summary of findings is presented in Table 3. Data on QOL were available in two of the three trials [13, 15], while data on adverse events and mortality were not available in any of the trials. Voice rehabilitation did not significantly improve any QOL scores. The certainty of the evidence for QOL was "low".

Data on voice function were available in three trials. Voice rehabilitation did not improve any voice function scores (jitter, shimmer, MTP, and GRBAS) (Fig. 2, Table 3). Data on self-rated voice function were available in two trials. Voice rehabilitation also did not significantly improve the voice handicap index (VHI) score, which served as a self-rated voice function score (Fig. 2). The certainty of the evidence for voice function and self-rated voice function score was "low" (Table 3).

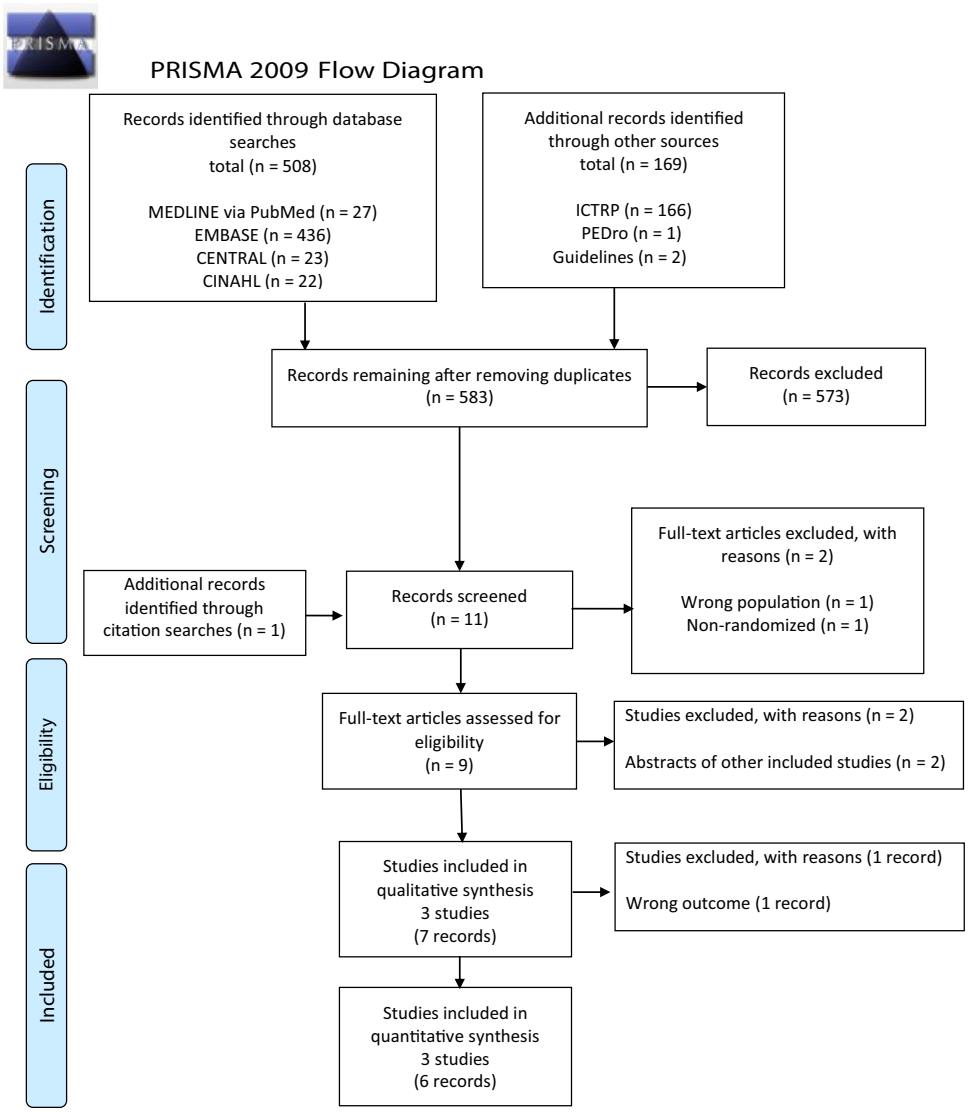



**Fig. 1** Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

## Discussion

The results of the present review covering three studies and 122 patients suggested that voice rehabilitation after radiotherapy for laryngeal cancer did not improve QOL, voice function, or self-rated voice function. We could not observe the efficacy of voice rehabilitation even though all included studies exhibited performance bias, which potentially increased the observed efficacy of the intervention. The sample size was very small in the meta-analysis for voice function and self-rated voice function, and the certainty of evidence was low.

Voice rehabilitation programs may not improve QOL, voice function, or self-rated voice function for patients with laryngeal cancer after radiotherapy. Voice rehabilitation chosen freely according to the patient's needs is effective in patients who had voice problems after treatment for early laryngeal cancer [16]. The included studies [13–15] provided pre-specified voice rehabilitation programs for participants irrespective of tumor size, stage, and site. Various types of cancers with or without chemotherapy may lead to a variety of voice problems, and this variety can reduce the efficacy of voice rehabilitation. Additionally, the unclear allocation concealment in all included studies might have been the cause of the lower baseline score in the voice rehabilitation group than in no intervention group, and that might have resulted in the lack of significant differences between groups.

Our result did not support the recommendation of The American Cancer Society Head and Neck Cancer Survivorship Care Guideline [2]. This may be because the recommendation was not based on systematic review and meta-analysis of voice rehabilitation after radiotherapy for patients with laryngeal cancer. The best available evidence is insufficient to recommend routinely voice rehabilitation after radiotherapy for laryngeal cancer. Our results were also

**Table 1** Characteristics of included studies

| Author, Year, Country | Setting | No of participants | Characteristics of participants | Intervention (contents, frequency) | Control (standard care) | Outcomes (timing and effect measures) | Note |
|---|---|---|---|---|---|---|---|
| Tuomi (2014), Sweden | Outpatient | 79 (intervention: 41, control: 38) | | Voice rehabilitation was conducted in line with a structured protocol at the hospital in closest proximity to the patient's residence. The sessions took place 2 times/week during the first 2 weeks, once a week during weeks 3–6, and once every second week during the last 2 weeks: a total of 10 voice rehabilitation sessions were conducted with a speech-language pathologist | The control group did not receive any voice rehabilitation but were given vocal hygiene advice | QOL: S-SECEL<br>Voice function: jitter, shimmer, and HNR, F0, MPT<br>(1 month and 6 months after radiotherapy) | All patients in the western part of Sweden (Västra Götalandsregionen, VGR) were asked to participate via the weekly multidisciplinary cancer conference at the Otorhinolaryngology Clinic at the Sahlgrenska University Hospital from 2000 to 2011<br>Intervention was started approximately 1 month after completion of oncologic treatment |
| Karlsson (2015) [15], Sweden | | 89 (intervention: 47, control: 42) | Male/female: 71/18[a]<br>Tumor size: T0:1, T1:44, T2:22, T3:6, T4:1<br>with chemotherapy: 3 | | | QOL: EORTC QLQ-C30, EORTC QLQ-H&N35, S-SECEL<br>(1 month and 6 months after radiotherapy) | |
| Tuomi (2017), Sweden | | 42 (intervention: 19, control:23) | | | | QOL: S-SECEL, EORTC QLQ-C30, EORTC QLQH & N35<br>Voice function: VRP area, VRP highest Hz, VRP lowest Hz, VRP highest dB, VRP lowest dB<br>(1 month, 6 months, and 12 months after radiotherapy) | |
| Bergstrom (2016), Sweden | | 89 (intervention: 47, control: 42) | | | | Voice function: GRBAS<br>Self-rated voice function: voice perception<br>(1 month, 6 months, and 12 months after radiotherapy) | |
| Bergstrom (2017) [12], Sweden | | 89 (intervention: 47, control: 42) | | | | HADS<br>(1 month, 6 months, and 12 months after radiotherapy) | |

**Table 1** (continued)

| Author, Year, Country | Setting | No of participants | Characteristics of participants | Intervention (contents, frequency) | Control (standard care) | Outcomes (timing and effect measures) | Note |
|---|---|---|---|---|---|---|---|
| Angadi (2016), USA | Outpatient | 12 (Intervention: 7, Control: 5) | Male/Female: 7/3<br>Tumor size:<br>T1:6, T2:3, T3:1 with chemotherapy: 3 | Vocal function exercises are a series of isometric and endurance-based exercises aimed at strengthening and balancing the three sub-systems of voice production, specifically respiration, phonation, and resonance. Voice function exercise also aims to directly strengthen vocal fold musculature, thus improving its vibratory characteristics. The exercise program consists of a series of four exercises, including a warm-up, vocal fold stretching, vocal fold contraction, and endurance exercise<br>The Voice function exercise program for the proposed study lasted 6 weeks where the patient was required to perform the exercises twice a day, every day | The control group did not receive any voice rehabilitation but were given vocal hygiene advice | Voice function: CAPE-V, MPT, CSID, pitch range, jitter, shimmer, NHR<br>MDVP, ADSV<br>Self-rated voice function: VHI<br>(Baseline and after 6 weeks) | Participants had to have completed radiation therapy at least 6 months prior to study participation |

**Table 1** (continued)

| Author, Year, Country | Setting | No of participants | Characteristics of participants | Intervention (contents, frequency) | Control (standard care) | Outcomes (timing and effect measures) | Note |
|---|---|---|---|---|---|---|---|
| La Mantia (2018), Italy | Outpatient | 21 (Intervention: 11, Control: 10) | Male/Female: 16/3<br>Tumor size:<br>T1:5, T2:8, T3:6 with chemotherapy: 1 | Voice interventions were conducted in line with a structured protocol by a certified speech-language pathologist not involved in this study and trained specifically in the care of patients with laryngeal cancer. Treatment plans lasted for 6 weeks. Voice function exercise were designed to strengthen and rebalance the sub-systems involved in voice production through a program of systematic exercise. Voice function exercise consisted of a series of four exercises that included a warm-up exercise, stretching, contraction, and increased resistance exercises<br>The voice function exercise program was required to perform the exercises twice a day, every day | The control group did not receive any voice rehabilitation but were given vocal hygiene advice | QOL: EORTC QLQ-H&N35<br>Voice function: GRBAS, NMWA, NGG, Jitter, Shimmer, MPT, MFR<br>Self-rated voice function: VHI<br>(Baseline and after 6 weeks) | Participants had to have completed radiation therapy at least 6 months prior to study participation |

*QOL* quality of life, *EORTC QLQ-C30* The European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire, *Core-30, EORTC QLQ-H & N35* the European Organisation for Research and Treatment of Cancer quality of life Questionnaire Head and Neck 35, *S-SECEL* the Swedish version of the Self-Evaluation of Communication Experiences after Laryngeal cancer, *HNR* harmonics-to-noise ratio, *F0* fundamental frequency, *MPT* maximum phonation time, *VRP* voice range profile, *Hz* Hertz, *dB* decibel, *VHI* Voice Handicap Index, *GRBAS* the grade, roughness, breathiness, asthenia, and strain scale, *HADS* the Hospital Anxiety and Depression Scale, *CAPE-V* Consensus Auditory Perceptual Evaluation of Voice, *CSID* Cepstral Spectral Index of Dysphonia, *MDVP* Multidimensional Voice Profile, *ADSV* Analysis of Dysphonia in Speech and Voice

[a]These characteristics of participants was reported in Karlsson's study

**Table 2** Assessment of risk of bias of the included trials

| Trial | Random Sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting |
|---|---|---|---|---|---|---|
| Karlsson et al. | Low | Unclear | High | High | High | Unclear |
| Angadi et al. | Low | Unclear | High | Unclear | Low | Unclear[a] |
| La Mantia et al. | Low | Unclear | High | Low | Low | Unclear |

[a]Only primary outcome was registered in clinical trial registration

different from previous findings showing that vocal function exercise was efficacious in enhancing vocal function in individuals with normal and disordered voices, presbylaryngis, and professional voice users [17]. Meanwhile, many participants in the RCTs included in our review had glottic cancer, and radiotherapy might induce mucosal inflammation and voice impairment. The effects of voice rehabilitation may be different in these participants. Although we did not perform subgroup analysis for severity of voice impairment, pre-specified voice rehabilitation programs might be effective in patients with mild voice impairment. Further studies would be needed to reveal the efficiency for these patients.

This systematic review has three potential limitations. First, there were many different kinds of outcomes to measure QOL, voice function, and self-rated voice function. These outcomes had wide range of standard deviation (SD) or interquartile range (IQR) values. Second, we did not perform subgroup analysis and could not consider presence/absence of communication disorder, stages of cancer, time from radiotherapy to first intervention, intervention duration, and frequency.

The present review also has several strengths. The results of this review were based on the best available evidence obtained from a comprehensive search for evidence. In addition, we employed rigorous methodology that followed a written, a priori protocol developed according to the PRISMA statement [7] and Cochrane Handbook [9], duplicate assessment of eligibility, risk of bias, and data abstraction, and used the GRADE approach [10, 11] for assessing the certainty of evidence. We only included RCTs and we could conduct an intention-to-treat analysis to understand the effect of voice rehabilitation compared with usual care, which provides a pragmatic estimate of the benefit of a change in treatment policy.

## Conclusion

The findings of the present meta-analysis indicate that voice rehabilitation might not improve QOL, voice function, or self-rated voice function. Pre-specified voice rehabilitation programs may not be necessary for all patients after radiotherapy for laryngeal cancer. It may be important to develop specialized voice rehabilitation for patients with laryngeal cancer according to the patient's need. Further well-methodologically designed studies including trial registration, and appropriate allocation concealment will be needed.

**Table 3** Findings from three trials focused on voice rehabilitation after radiotherapy for laryngeal cancer

| Overview of study design | | | | | | |
|---|---|---|---|---|---|---|
| Patients or study population: adult patients with newly diagnosed laryngeal cancer who were to receive curatively intended radiation therapy<br>Setting: any<br>Intervention: protocolized voice rehabilitation<br>Comparison: no intervention or usual care | | | | | | |
| Outcome | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) | Comments |
| | Assumed risk<br>Control | Corresponding risk<br>Intervention | | | | |
| Quality of life<br>EORTC QLQ-H&N35 overall (La Mantia I. 2018)<br>Speech and social [15]<br>EORTC QLQ-C30 [15]<br>S-SECEL [15] | Study population | All studies found no difference in QOL as a result of the intervention | | Variable according to individual study and outcome measure | ⊕⊕⊖⊖ Low[ab] | Only 2 small RCTs reported data for QOL; pooling of data was inappropriate because of differences in outcome measures<br>Individual study findings are reported separately |
| Voice function<br>Jitter | Study population | MD: – 0.48 (– 1.27 to 0.32) | | 98 (3 RCTs) | ⊕⊕⊖⊖ Low[ac] | |
| Voice function<br>Shimmer | Study population | MD: – 0.04 (– 0.27 to 0.19) | | 98 (3 RCTs) | ⊕⊕⊖⊖ Low[ac] | |
| Voice function<br>MTP | Study population | MD: 1.54 (– 1.13 to 4.22) | | 98 (3 RCTs) | ⊕⊕⊖⊖ Low[ac] | |
| Voice function<br>GRBAS | Study population | MD: – 0.39 (– 2.59 to 1.80) | | 80 (2 RCTs) | ⊕⊕⊖⊖ Low[ab] | |
| Self-rated voice function<br>VHI | Study population | MD: 5.54 (– 2.07 to 13.16) | | 29 (2 RCTs) | ⊕⊕⊖⊖ Low[ab] | |

GRADE Working Group grades of evidence; *High certainty* we are very confident that the true effect lies close to that of the estimate of the effect, *Moderate certainty* we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different, *Low certainty* our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect, *Very low certainty* we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

*CI* confidence interval, *QOL* quality of life, *EORTC QLQ-H&N35* The European Organisation for Research and Treatment of Cancer quality of life Questionnaire Head and Neck 35, *EORTC QLQ-C30* The European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire, Core-30, *S-SECEL* the Swedish version of the Self-Evaluation of Communication Experiences after Laryngeal cancer, *RCT* randomised controlled trial, *MD* mean difference, *MPT* maximum phonation time, *GRBAS* the grade, roughness, breathiness, asthenia, and strain scale, *VHI* voice handicap index

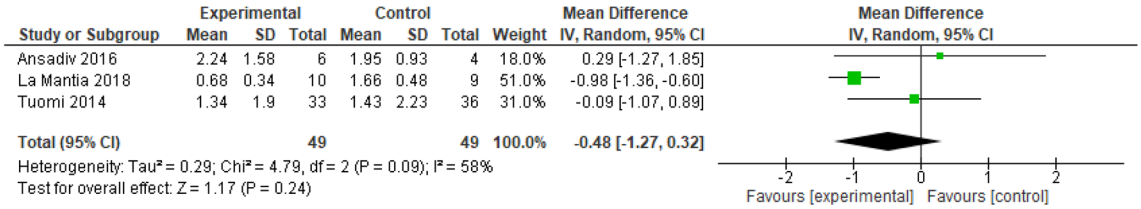
*The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect (and its 95% CI) estimated for the intervention group

[a]Downgraded because of unclear risk of bias associated with allocation concealment and selective reporting

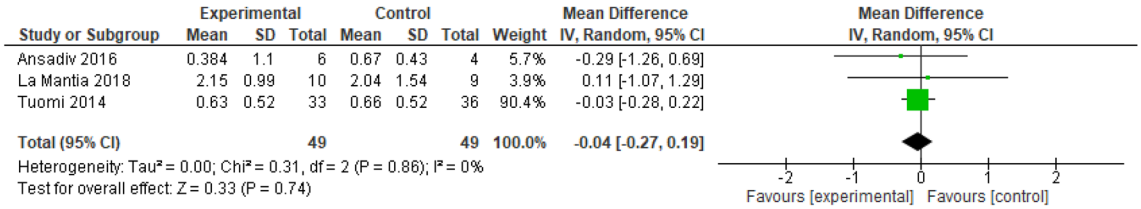
[b]Downgraded because of imprecision (only two small studies)

[c]Downgraded because of imprecision (only three small studies)

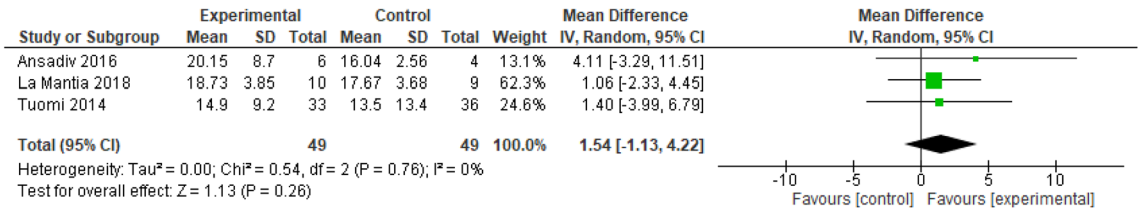
## 2-1. Jitter



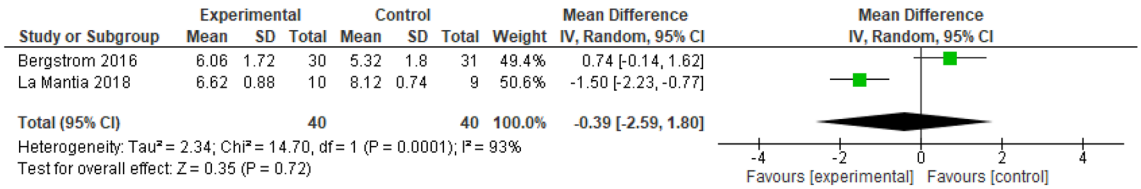

## 2-2. Shimmer




## 2-3. Maximum Phonation Time




## 2-4. The Grade, Roughness, Breathiness, Asthenia, and Strain scale




## 2-5. Voice Handicap Index

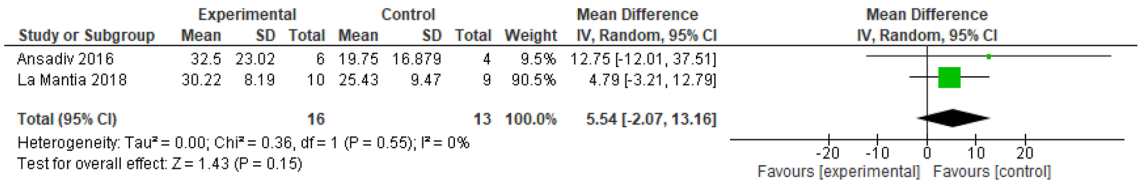



**Fig. 2** Forest plot for voice function scores and self-rated voice function score. **a** Jitter. **b** Shimmer. c Maximum phonation time. **d** The grade, roughness, breathiness, asthenia, and strain scale. **d** Voice handicap index

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they do not have any conflicts of interest.

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