

Initial Surgical versus Non-Surgical treatments for advanced hypopharyngeal cancer: a meta-analysis with trial sequential analysis

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Research article

Keywords: surgical, chemoradiotherapy, advanced hypopharyngeal cancer, survival, trial sequential analysis.

Posted Date: January 8th, 2020

DOI: <https://doi.org/10.21203/rs.2.20267/v1>

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Version of Record: A version of this preprint was published at International Journal of Surgery on October 1st, 2020. See the published version at <https://doi.org/10.1016/j.ijssu.2020.04.059>.

Abstract

Background

There is no consensus whether either initial surgical or non-surgical treatments should be the standard treatment pattern to advanced hypopharyngeal cancer. The aim of the meta-analysis was systematically and quantitatively to compare the relative efficacy between initial surgical and non-surgical therapies in patients with advanced-stage hypopharyngeal carcinoma.

Methods

A comprehensive search was performed in PubMed, the ISI Web of Knowledge, the Cochrane Library, and Embase databases from inception through to April 10, 2019. Citation screening, data abstraction and quality assessment were performed in duplicate. Meta-analysis with trial sequential analysis (TSA) were used to assess the primary and secondary outcomes. In addition, we used the Grading of Recommendations Assessment Development and Evaluation (GRADE) to evaluate the certainty of the body of evidence.

Results

A total of 17 trials was appraised with 2539 patients that were in compliance with inclusion and exclusion criterion. Pooled analyses indicated patients receiving primary surgical and non-surgical therapy did not significantly differ in overall survival (OS) (relative risk [RR] = 1.04, 95% confidence interval [CI] = 0.94 to 1.15), with TSA inconclusive. Additionally, patients treated with primary surgical experienced an increased disease free survival (DFS) probability compared with non-surgical treatment (RR 1.20, 95% CI=1.05 to 1.37), while TSA is inconclusive. Notably, non-surgical management did have a beneficial efficacy on larynx preservation (RR 0.48, 95% CI=0.33 to 0.70), and TSA also provided conclusive evidence. GRADE indicated the level of evidence was low or very low for primary or secondary outcomes.

Conclusion

The results of our meta-analysis indicated compared to surgical treatments, non-surgical therapy for patients with advanced hypopharyngeal carcinoma appear to equivalent efficacy, and it offers an opportunity to preserve laryngeal function. Due to inconclusive evidence by TSA, further investigation with larger randomized clinical trials (RCTs) using modern approaches should be undertaken to verify the results of this meta-analysis.

Background

As an aggressive malignancy, hypopharyngeal cancer is less popularity than other head and neck cancers (HNC), on behalf of 3–5% of all HNC¹. According to the World Health Organization (WHO) definition, hypopharynx included four sites, namely the pyriform sinus, the post-cricoid region, the posterior wall of the hypopharynx, and the hypopharyngeal aspect of the aryepiglottic fold². Usually, these patients at diagnosis present advanced stage, due to the lack of obvious symptoms in early-stage disease and prone to extensive infiltration and growth in submucosa. In addition, more than 60% patients occurred nodal metastasis in ipsilateral³ and up to 40% of them appeared contralateral occult nodal tumor deposits⁴ on presentation, which rendered formidable therapeutic challenges to ablative and reconstructive surgeons as well as clinical oncologists. The estimated 5-year overall survival rate for treated stage III and IV hypopharyngeal cancer patients varies between approximately 15% and 40%, depending on tumor-related factors, patient-related factors, and treatment approaches⁵.

Retrospect to the 1990s, curative surgical resection followed by postoperative radiotherapy was recognized as the cornerstone treatment for advanced hypopharyngeal cancer. Over the past decade, with the advancement of radiotherapy and chemotherapy, especially the application of concurrent chemoradiotherapy and targeted drugs, organ preservation and the local control rate have been remarkably improved⁶. A vast of trials, both retrospective and prospective, have revealed that organ preservation using definitive chemoradiotherapy with surgery reserved for salvage is a receivable alternative to surgery with similar survival outcomes in HNC, including hypopharyngeal carcinoma that merely account for a smaller subgroup^{7–9}.

Regarding the preferred therapeutic option for advanced hypopharyngeal carcinoma, there is no level-one evidence even if the adoption of chemoradiotherapy as a standard of care¹⁰. The determination to treat continues to be disputable in a locally advanced setting. To resolve these knowledge gaps, we performed a comprehensive meta-analysis with trial sequential analysis (TSA), which better control type I and type II errors, to compare the outcomes of surgical management (primary surgery with either adjunctive radiotherapy or adjunctive chemoradiation) versus non-surgical modalities, including induction chemotherapy with (chemo) radiotherapy and definitive chemoradiotherapy, in patients with advanced hypopharyngeal cancer.

Methods

This meta-analysis was performed in accordance with Cochrane

Handbook for Systematic Reviews of Interventions³⁵ and PRISMA (the Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines³⁶. A pre-specified protocol registered at PROSPERO online platform in December 2018 (registry number: CRD42018118563).

Data sources

A systematic search of electronic databases was performed, including Medline (via the PUBMED interface), ISI Web of Knowledge, the Cochrane Library (via the Ovid interface), and EMBASE. All searches were conducted from inception through to April 10, 2019. All of the pertinent publications was identified by using the following terms and their combinations: (hypopharyngeal or pyriform sinus or post-cricoid), (neoplasm* or tumor* or cancer* or carcinoma* or malignanc*), (surgery or surgical) and (chemotherapy or CRT or chemoradiation or radiotherapy or RT). No language restriction was enforced. Additionally, we manually scanned references of relevant reviews of the literature and retrieved studies. To identify unpublished articles, abstracts from international conferences were inspected for additional pertinent researches.

Eligibility criteria

Literatures was independently examined by two authors to determine their eligibility for inclusion and exclusion criterion in the meta-analysis, with disagreement finally resolved by consensus. Included literatures satisfied the following PICOS standard (participants, interventions, comparators, outcomes, and study design): 1) Population: adult advanced hypopharyngeal cancer patients; 2) Intervention: surgical management (primary surgical followed by either adjuvant radiotherapy or adjuvant chemoradiation); 3) Comparison intervention: non-surgical modalities (induction chemotherapy followed by (chemo)radiotherapy and definitive chemoradiotherapy); 4) Outcome: outcomes of interest (primary or secondary endpoint) of the current meta-analysis; 5) Study design: retrospective cohorts or prospective cohorts or randomized clinical trial (RCT). Studies were excluded if they were case reports, letters to the editor, editorials, case series, review articles, and trials with insufficient data (e.g. lack of survival information), even if contacting the corresponding authors.

Data extraction

The relevant data was independently abstracted by two reviewers from the eligible studies into standardised collection tables for the evidence and outcomes, such as lead author, year of publication, nation, study design, number and percentages of man, age of patients, sample size, percentage of T4 stage, percentage of positive lymph node, percentage of stageIV, percentage of pyriform sinus, follow-up time, treatment modalities, overall survival, disease free survival, and larynx preservation.

If possible, outcome data were separately divided into each subgroup. According to the age were lower or higher than the median of the entire trials, it was classified as "low" or "high" subgroup. The predefined primary endpoint was overall survival (OS) at longest follow-up available. The predefined secondary outcomes were disease free survival (DFS) at longest follow-up available, and larynx preservation.

Quality assessment

Risk of bias of the eligible trials was independently assessed by two authors, with no affiliation with any of the eligible trials. In cases of eventual divergences by discussion to achieve a consensus or consultation with a third author. Based on the Cochrane Collaboration methods³⁷, the methodological quality of randomized controlled trials (RCTs) was assessed. The eligible studies were classified as low quality, or high quality according to the following criteria: 1) when allocation concealment or randomization was considered as a high risk of bias, regardless of the risk of other items, studies were assessed low quality; 2) if both allocation concealment and randomization were considered as a low risk of bias, and all other items were considered as low or unclear risk of bias in a study, studies were considered high quality. Based on the Newcastle-Ottawa scale, the study quality of observational studies was evaluated. The quality of trials was adjudicated on three broad perspectives: selection, comparability, and exposure/outcome, with four items (one star each), one item (up to two stars) as well as three items (one star each), respectively. In this analysis, studies were judged as high quality if they scored ≥ 7 stars.

Statistical analyses

For dichotomous outcomes, relative risk (RR) with 95% confidence interval (CI) was calculated. Between-study heterogeneity by the estimates of diversity (D^2), the inconsistency statistics (I^2) and visual inspection of the forest plots was evaluated. If a P value < 0.05 or $I^2 > 50\%$, substantial heterogeneity was considered existing. We adopted a fixed effects model and when $I^2 = 0$. If I^2 was above zero, we adopted both fixed and random effects models, and used the most conservative estimate being the estimate with the widest CI or the point estimate closest to no effect.

Pre-specified subgroups were performed based on study location (western country vs. eastern country), study design (randomized controlled trial vs. cohort), age (> 60 vs. ≤ 60), and study quality (high quality vs. low quality). Analysis was conducted to evaluate whether the difference was statistically significant between the subgroups. In addition, subgroup differences were tested by Chi-square test—that is, whether the observed differences are aligned with chance alone within the subgroups. A low P value or a large Chi-square statistic relative to its degree of freedom construct evidence of heterogeneity beyond chance.

Meta-regression analysis was conducted to explore the associations between the primary outcome and characteristics of participants. Factors considered variables included publication year, percentage of male, mean age, sample size, percentage of T4 stage, percentage of positive lymph node, percentage of stageIV, percentage of pyriform sinus, and mean follow-up time. We evaluated publication bias for primary outcomes by funnel plot inspection and the Harbord test, in which 10 or more studies provided data.

All meta-analyses were conducted with RevMan version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and Stata version 14 (StataCorp, College Station, Texas, USA). All P values are double-tailed, and the statistical significance was set at 0.05.

Grading the quality of evidence

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess the overall quality of evidence for each estimated outcome. According to study design, study quality, precision, consistency, directness and the risk of reporting bias, the overall quality of evidence is graded “high”, “moderate”, “low” or “very low” for each outcome. The analyses was performed in GRADE Pro-version 3.6 software.

Trial sequential analysis

We conducted trial sequential analysis (TSA) to explore whether cumulative data were adequately powered to assess outcomes. In this procedure, according to an alpha value set at 5% to determine significance, we established Z-curves for the primary outcome and secondary outcomes. Using the O’Brien-Fleming alpha spending method, we constructed adjusted significance trial sequential monitoring boundaries, with the hypothesis that a new study was successively added to the meta-analysis when significant testing may have been conducted each time. Based on a pre-defined relative risk reduction or increase of 15% in each outcomes, the required information size was computed, with the type I error (α) at 0.05 or 0.01 and the power ($1 - \beta$) at 0.90. TSA software version 0.9.5.9 (Centre for Clinical Intervention Research) was used for these analysis³⁸.

Results

Identification of studies

Figure 1 shows the flowchart for the research selection program. Initially, the PubMed search identified 2,341 trials, the ISI Web of Knowledge 2,760, Cochrane Library 552, and Embase 442. After 3083 were removed as duplicates, 2924 trials were further excluded after titles and abstracts reviewed, and 88 literatures were scrutinized by scanning their full texts. Ultimately, 17 researches^{11 - 27} met our predefined criteria and were included in the meta-analyses.

Characteristics of the eligible studies

Table 1 present the main characteristics of selected studies. The 17 studies included two RCTs^{11,22} and fifteen retrospective cohorts^{12 - 21,23-27}, with a total of 2539 patients, and were published from 1994 to 2019. Eight trials were conducted in western countries (eg. France, USA, Croatia, Portugal, The Netherlands), eight in eastern countries (eg. Taiwan, Korea, China), one not available. The sample size varied from 47 to 857 per study, the average age of patients varied between 54.4 and 64 years. Percentages of man, percentage of T4 stage, percentage of positive lymph node, percentage of stageIV and percentage of pyriform sinus, varied widely, with ranging from 78.6–100%, ranging from 4.3–86.7%, ranging from 63.4–91.8%, ranging from 6.6–87.8%, ranging from 50.6–100%, respectively. Mean follow-up periods varied, ranged from 19–92 months. Table S1 details treatment modalities of the studies included in the meta-analysis.

Table 1
Baseline characteristics of the studies included in the meta-analysis.

Study(year)	Nation	Study design	Male, No. (%)	Age (y), average (range or SD)	Sample size	T4, No. (%)	N+, No. (%)	Stage IV, No.(%)	Pyriform sinus, No.(%)	Follow-up (m),mean (rang)
Beauvillain (1997)	France	RCT	90(97.8)	56(35–69)	92	4(4.3)	65(70.6)	NA	90(97.8)	92(64–115)
Chung (2019)	Korea	RC	249(93.6)	63.7(41–86)	266	86(32.3)	242(91%)	NA	216(81.2)	32.9(6–152)
Harris (2015)	USA	RC	59(77)	63.6(8.7)	76	36(47)	61(80)	NA	NA	30(6–120)
Huang (2010)	Taiwan	RC	45(95.7)	57(40–73)	47	26(55.3)	33(70.2)	36(76.6)	41(87.2)	19.4(NA)
Hung (2006)	NA	RC	60(100)	58(NA)	60	52(86.7)	52(86.7)	NA	35(58.3)	20(NA)
Jang (2016)	Korea	RC	NA	NA	177	NA	NA	NA	NA	19(NA)
Kim (2001)	Korea	RC	67(91.8)	58(25–79)	73	NA	NA	57(78.1)	NA	NA
Kim (2016)	Korea	RC	86(94.5)	64(36–80)	91	30(33)	79(86.8)	6(6.6)	73(80.2)	50(5–141)
Kim (2018)	Korea	RC	706(82.4)	NA	857	237(27.7)	609(71.1)	NA	434(50.6)	NA
Lajtman (2001)	Croatia	RC	52(85.2)	64(32–79)	61	24(39.3)	56(91.8)	NA	61(100)	NA
Lee (2008)	Taiwan	RC	71(95.9)	62(43–76)	74	31(41.9)	67(90.5)	65(87.8)	46(62.2)	21(3–132)
Lefebvre (1996)	France	RCT	186(95.9)	55(35–70)	194	11(5.7)	123(63.4)	71(37)	152(78)	51(3–106)
Reis (2016)	Portugal	RC	142(98.6)	54.4(34–81)	144	NA	NA	109(75.7)	117(81.3)	36.6(3–110)
Slotman (1994)	The Netherlands	RC	45(83.3)	64(43–90)	54	17(31.5)	42(77.8)	NA	54(100)	NA
Vandersteen (2015)	France	RC	86(87.8)	62.4(37–87)	98	38(38.8)	67(68.4)	NA	NA	43(NA)
Zelevsky (1996)	USA	RC	44(78.6)	61(36–80)	56	10(17.9)	44(78.6)	35(62.5)	38(67.9)	NA
Zhang (2018)	China	RC	112(94.1)	57(27–78)	119	52(43.7)	108(90.8)	86(72.3)	75(63.0)	NA

Abbreviations: NA=not available, SD=standard deviation, No.= number of participants, RC=retrospective cohort, RCT=randomized controlled trial.

Methodological quality of eligible studies

Figures S1 and S2 shows the quality assessment of the RCTs. To summarize, neither two RCTs reported the blinding of patients and personnel, or the blinding of outcome assessment. On account of other items in RCTs was low bias, two RCTs were adjudicated high quality. Table S2 displays the quality assessment of the cohorts. These results showed that five studies, which was rated as high quality, scored between 7 and 8 points, and the other ten studies, which was considered as low quality, scored below 6 points.

Primary outcomes

Results of the pooled effect indicated that the difference between non-surgical treatment and initial surgical on overall survival (OS) was not statistically of significance (relative risk [RR] 1.04; 95% confidence interval [CI] 0.94 to 1.15; $I^2 = 5\%$) (Fig. 2A), and the summary OR and 95% CI were estimated using the random effect model with the widest CI. TSA results indicated that the cumulative Z-curve did not enter the futility area

(Fig. 2B). The estimated required information size to cross the futility boundaries was 3823 randomized patients. The subgroup analysis did not find any significant differences between subgroups on the basis of study location, study design, age, and study quality (Table 2)

Table 2. Subgroup analyses comparing surgical versus non-surgical treatments for overall survival.

Subgroup		No. of studies	RR (95% CI)	P value	P values between subgroup
Study location	western country	8	1.13(0.94-1.34)	0.19	0.23
	eastern country	8	0.99(0.88-1.11)	0.85	
Study design	RCT	2	1.13(0.61-2.98)	0.46	0.51
	cohort	15	1.03 (0.92-1.15)	0.61	
Age	≤60	7	1.13(0.96-1.33)	0.15	0.73
	>60	8	1.08(0.91-1.29)	0.37	
Study quality	high quality	7	1.10(0.94-1.29)	0.25	0.29
	low quality	10	0.98(0.85-1.13)	0.77	

Abbreviations: No.= number of participants, RR= relative risk, CI=confidence interval, cohort, RCT=randomized controlled trial.

Secondary outcomes

Pooled analysis demonstrated patients treated with primary surgical experienced an increased disease free survival (DFS) probability compared with non-surgical treatment, with a RR of 1.20 (95% CI = 1.05 to 1.37; $I^2 = 0\%$) (Fig. 3A). However, the results of TSA indicated that the cumulative Z-curve just reached the conventional boundary, and did not cross the trial sequential monitoring boundary (Fig. 3B). The estimated required information size to cross the boundary for conventional and trial sequential monitoring was 3367 randomized patients.

Pooled estimates indicated compared to non-surgical treatment, initial surgical significantly lowered larynx preservation, with a RR of 0.48 (95% CI = 0.33 to 0.70; $I^2 = 73\%$) (Fig. 4A). TSA analysis shown the cumulative Z-curve crossed the boundary for conventional and trial sequential monitoring (Fig. 4B).

Meta-regression analysis, publication bias, and GRADE

A meta-regression analysis shown that sample size significantly inflected effect size ($P = 0.038$) (Fig. 5D), which a trend towards a greater and more conform declines in survival probability was observed among patients received surgical management. Whereas year of publication ($P = 0.402$), percentage of male ($P = 0.931$), mean age ($P = 0.893$), percentage of T4 stage ($P = 0.941$), percentage of positive lymph node ($P = 0.556$), percentage of stage IV ($P = 0.278$), percentage of pyriform sinus ($P = 0.144$), and mean follow-up time ($P = 0.556$) did not significantly alter effect size, respectively (Fig. 5A, B, C, E, F, G, H and I). There was no evidence of publication bias for the primary outcome (OS) on inspection of the funnel plot (Figure S3) or from the Harbord test, 0.67. The GRADE level of evidence for OS and larynx preservation was very low and the level of evidence for DFS was low. The results was presented in the 'summary of findings' (Table 3).

Table 3
Summary of findings table

Outcomes for advanced hypopharyngeal cancer					
Patient or population: Patients with advanced hypopharyngeal cancer Intervention: Surgery Comparison: Non-surgery					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Outcomes			
Overall Survival	Study population		RR 1.04 (0.94 to 1.15)	2539 (17 studies)	⊕⊕⊕⊕ very low ¹
	422 per 1000	439 per 1000 (397 to 485)			
	Moderate				
	417 per 1000	434 per 1000 (392 to 480)			
Disease-free Survival	Study population		RR 1.2 (1.05 to 1.37)	1200 (11 studies)	⊕⊕⊕⊕ low
	371 per 1000	446 per 1000 (390 to 509)			
	Moderate				
	367 per 1000	440 per 1000 (385 to 503)			
Larynx Preservation	Study population		RR 0.48 (0.33 to 0.7)	1195 (10 studies)	⊕⊕⊕⊕ very low
	550 per 1000	264 per 1000 (182 to 385)			
	Moderate				
	372 per 1000	179 per 1000 (123 to 260)			
	368 per 1000	408 per 1000 (361 to 460)			
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio;					
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.					

Discussion

The current meta-analysis, which involved two RCTs, comprising 286 patients, and fifteen retrospective cohorts, including 1987 patients, compared primary surgical with non-surgical administration. The summary results confirmed that between initial surgical and non-surgical management have similar overall survival (RR 1.04, CI = 0.94 to 1.15; $I^2 = 5\%$), with TSA inconclusive. Subgroup analysis verified that the finding were generally conform, regardless of study location, study design, age, and study quality. Additionally, compared to non-surgical treatment, the primary surgical significantly improved disease free survival (RR 1.20, CI = 1.05 to 1.37; $I^2 = 0$), with TSA inconclusive. Noteworthy, non-surgical administration did have a beneficial effect on larynx preservation, with TSA conclusive.

Recently systematic reviews illustrated management of advanced hypopharyngeal carcinoma²⁸, while it did not statistically integrate available data to analyze whether there exist significant efficacy difference between primary surgical and non-surgical therapy or not. Meanwhile, it did not incorporate three additional new trials^{12,19,17}, with two of them as larger simple retrospective cohorts. In 2018, Kim et al., using the latest population-based database (Surveillance, Epidemiology, and End Results (SEER)), analyzed the comparative effectiveness of primary surgical and non-surgical therapy for advanced hypopharyngeal cancer in the contemporary era, and indicated that treatment outcomes in the chemoradiotherapy group were comparable to that of the surgical group for locally advanced hypopharyngeal cancer¹⁹. Sequentially, Chung et al. performed a multicenter trials comparing induction chemotherapy with (chemo) radiotherapy, definitive chemoradiotherapy and surgery-based therapy to assess the relative efficacy outcomes on patients with locally advanced hypopharyngeal squamous cell carcinoma, which

verified that whether induction chemotherapy followed by (chemo) radiotherapy or definitive chemoradiotherapy showed a comparable overall survival rate to surgery-based therapy¹².

To the best of our knowledge, this is first comprehensive meta-analysis to summarize all current studies focusing on comparing the relative effectiveness of between primary surgical and non-surgery therapy in advanced hypopharyngeal carcinoma. The meta-analysis and systematic review have a number of methodological strengths. Firstly, the protocol of this study was registered on PROSPERO. A prior-registered protocol may enhance the quality and transparency of meta-analyses. Secondly, predefined subgroup was performed to explore that specific patients can benefit from initial surgical or non-surgical treatment. Additionally, meta-regression was conducted to investigate the potential modifiers on outcomes. Thirdly, TSA was used to evaluate the risk of random errors (false discoveries), and its results support the contention that a 15% relative decrease or increase in incidence of events can be confidently removed. Finally, we analyzed the level of evidence using the GRADE method, which ranks evidence of clinical outcomes as high, moderate, low, or very low quality.

Our meta-analysis confirmed that the primary surgical compared to non-surgical management does not significantly improve overall survival in advanced hypopharyngeal cancer. However, our TSA presented that the Z-curve not only did not cross the conventional boundary and trial sequential monitoring boundary for benefit, but also did not enter the futility area, which show that conclusive evidence is not established and more researches were needed to affirm the results. Subgroup analysis verified that the result were generally consistent, regardless of study location, study design, age, and study quality. In additional, we found that the primary surgical can increase disease free survival probability compared with non-surgical administration, whereas TAS result showed that the cumulative Z-curve did not cross the trial sequential monitoring boundary. The result indicated that the required information size was not reached, the evidence achieving a credible conclusion was insufficient and future clinical researches were needed to affirm. It is worth mentioning that non-surgical management did have a positive effect on larynx preservation, with TSA conclusive. Regarding larynx preservation, this evidence is firm conclusion, and that further trials are not required.

A meta-regression analysis using restricted maximum likelihood estimators find that sample size had potential influence on treatments when the sample size in a trial was used as a moderating variable. Sample size possess a significant declining trend on effect size, that is to say, the primary surgical will be inferior to non-surgical treatment with the increase of sample size in advanced hypopharyngeal carcinoma. The finding may be explained that Kim et al. trial with maximum sample size in all included studies account for 22.1% overall estimate from forest plot and exert an observable impact on effect size. What's more, the result imply that further more trials are required, in accordance with the results of our TSA with regard to overall survival and disease free survival. Hence, further large and perspective RCTs were need to clarify the relative efficacy between surgery-based therapy and non-surgical treatment on survival outcome.

Currently, in the context of the global trend toward organ-preserving treatment (non-surgical treatment), definitive chemoradiotherapy has obtained increasing prevalence as the definitive therapy in hypopharyngeal cancer. Given we cannot come to a clear conclusion that non-surgical treatment is non-inferior to surgery-based therapy in terms of survival outcome, thus it is of great importance to identify reliable and convenient clinical factors/markers to screen out which subset of patients with advanced hypopharyngeal cancer is suitable to organ-preserving treatment using definitive chemoradiotherapy with surgery reserved for salvage, and optimize non-surgical therapeutic strategies. Induction chemotherapy appears to serve as mediator, as studies revealed that a response to incipient chemotherapy predicted a response to subsequent treatment in the advanced head and neck cancer, including oral cavity, oropharynx, laryngeal and hypopharynx²⁹⁻³¹. In additional, compared to non-responders, responders had significantly favorable survival. The concept was also adopted in the Veterans Affairs Laryngeal Cancer Study⁷. On account of hypopharynx cancer accounting for minor part in above trials, the effect of response to induction chemotherapy only in advanced hypopharynx cancer patients to determine organ-preserving treatment are awaited to further research. In recent years, human papilloma virus (HPV) infection have been recognized as risk factors for HNC, including hypopharynx. Several trials indicated that HPV positive patients were sensitive to radiotherapy and chemotherapy as well as showed superior survival^{32,33}. Maybe HPV status can be a predictor to select non-surgical treatment. Future larger prospective studies with adequately powered are warranted to clarify issues.

Several limitations should be noted in our study. First, the number of retrospective cohorts was relatively large, and there were only two old RCTs published in the early 1980s. As for retrospective trials, selection bias is very likely due to no randomisation between the treatment strategies. In regard to RCTs, neither trials stated blinding for participants, personnel or the outcome assessment, which augmented the bias risk of performance and detection. On the basis of above reasons, GRADE judged the certainty of the body of evidence as low or very for each outcome. Hence, there is a need for large, multi-centered RCTs to support the current results. Second, though we found that non-surgical administration can remarkably improve larynx preservation, the obvious heterogeneity was observed. This is because marked heterogeneity existed across the included studies in terms of the different types of chemotherapy received, as well as the type and doses of radiotherapy. But almost all studies there is a clear superiority with non-surgical treatments in terms of preserving a functional larynx. Third, a large proportion of eligible trials had a small sample size, with only 6 of the 17 trials containing a sample size of larger than 100 patients. Just as our findings of meta-regression analysis and TSA, the small sample sizes may have influence on treatment effects, indicating a need for large and perspective researches. Fourth, the safety of non-surgical administration cannot be detected on account of insufficient data. Most of the included studies did not thoroughly evaluated the adverse effect of organ preservation treatment in locally advanced hypopharyngeal cancer, unlike in carcinoma of the

larynx, which hindered a definite conclusion regarding optimal treatment regimen³⁴. Further well-designed researches are warranted to resolve these issues.

Conclusion

The results of our meta-analysis indicated treatment outcomes in non-surgical therapy were comparable to that of surgery-based therapy for advanced-stage hypopharyngeal cancer, which makes larynx preservation feasible. It can be served as an alternative approach in patients who are unfit for or refuse surgery. On account of inconclusive evidence from TSA, further prospective investigations comparing modern non-surgical management with modern surgical techniques remain necessary.

Abbreviations

TSA= trial sequential analysis, GRADE= The Grading of Recommendations Assessment Development and Evaluation, RR= relative risk, CI=confidence interval, OS=overall survival, DFS= disease free survival, WHO=World Health Organization, HNC=head and neck cancers, PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-analyses, PICOS =participants, interventions, comparators, outcomes, and study design, RCTs= randomized controlled trials, SEER=Surveillance, Epidemiology, and End Results, HPV= human papilloma virus, NA=not available, SD=standard deviation, No.= number of participants, RC=retrospective cohort, RT= radiotherapy, CRT= chemoradiotherapy, CT= chemotherapy, REC=representative of exposed cohort , SNC=selection of nonexposed cohort, AE=ascertainment of exposed, AOI=absence of outcome of interest.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

There is no additional data are available.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

Study concept and design: GLL, JC, LPW, XJT, JSL and HY. Acquisition of data: GLL, JSP and ZC. Analysis and interpretation of data: JC, HYH, GLL and LPW. Drafting of the manuscript: XJT and WQC. Critical revision of the manuscript for important intellectual content: GLL, JSL and HY. Statistical analysis: GLL, JSP and LPW. Administrative, technical, and material support: HY and LPW. Study supervision: GLL, JC, XJT, JSL and HY. All authors have read and approved the manuscript for publication.

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Acknowledgements

Not applicable.

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Supplementary Figure And Table Legends

FigureS1. Risk of bias graph

FigureS2. Risk of bias summary.

FigureS3. Assessment of publication bias using a funnel plot.

TableS1. Treatment modalities of the studies included in the meta-analysis.

TableS2. Quality Assessment With Newcastle Ottawa Scale for cohort study

TableS3. Meta-regression analysis analyzing the potential confounders for outcome

Figures



Figure 1

Flow diagram of literature search and selection process of the studies

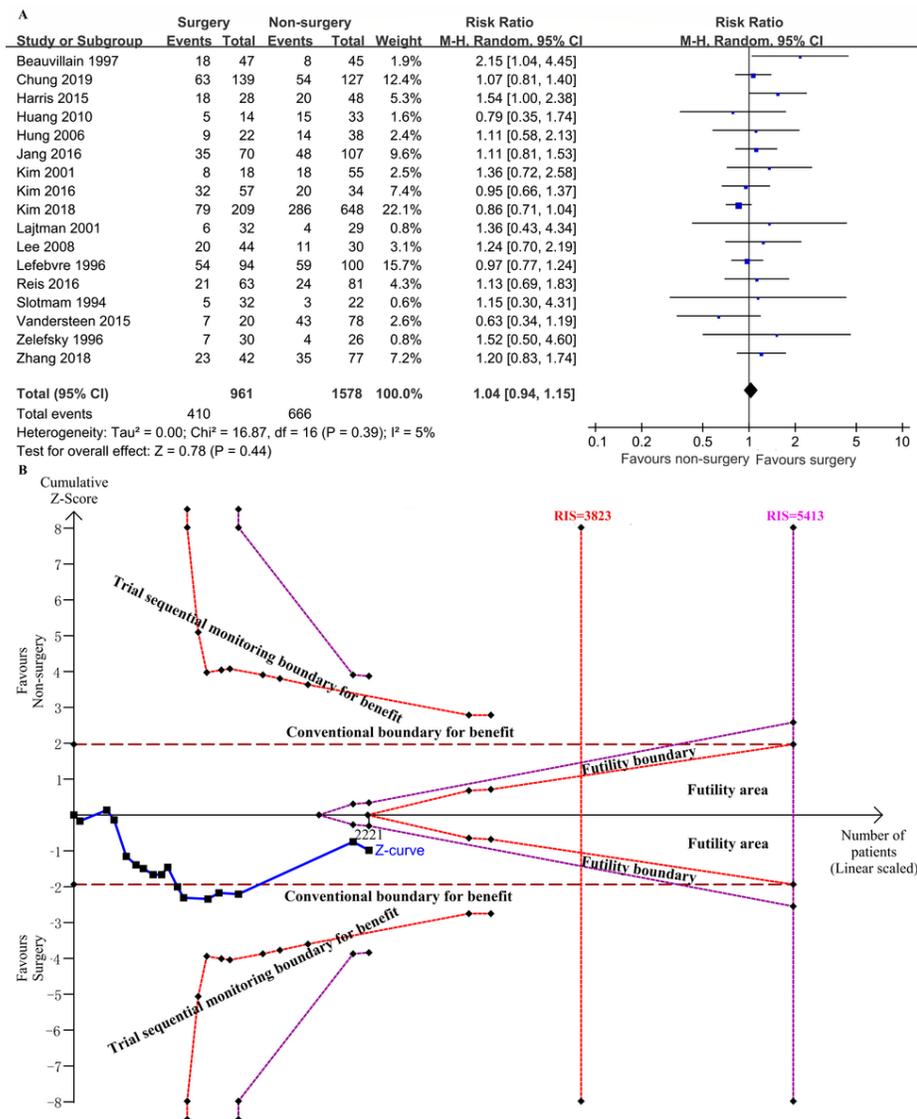


Figure 2

(A) Forest plot of studies reporting overall survival outcome. (B) Random-effect model of trial sequential analysis for overall survival outcome: a relative risk of 1.04, two-sided boundary, incidence of 40.9% in surgical group, incidence of 37.3% in non-surgical group, a low bias estimated relative risk reduction of 15%, α of 5%, power of 90% were set. The required information size was calculated as 3823. The cumulative Z-curve did not cross the conventional boundary for benefits and did not enter the futility boundary.

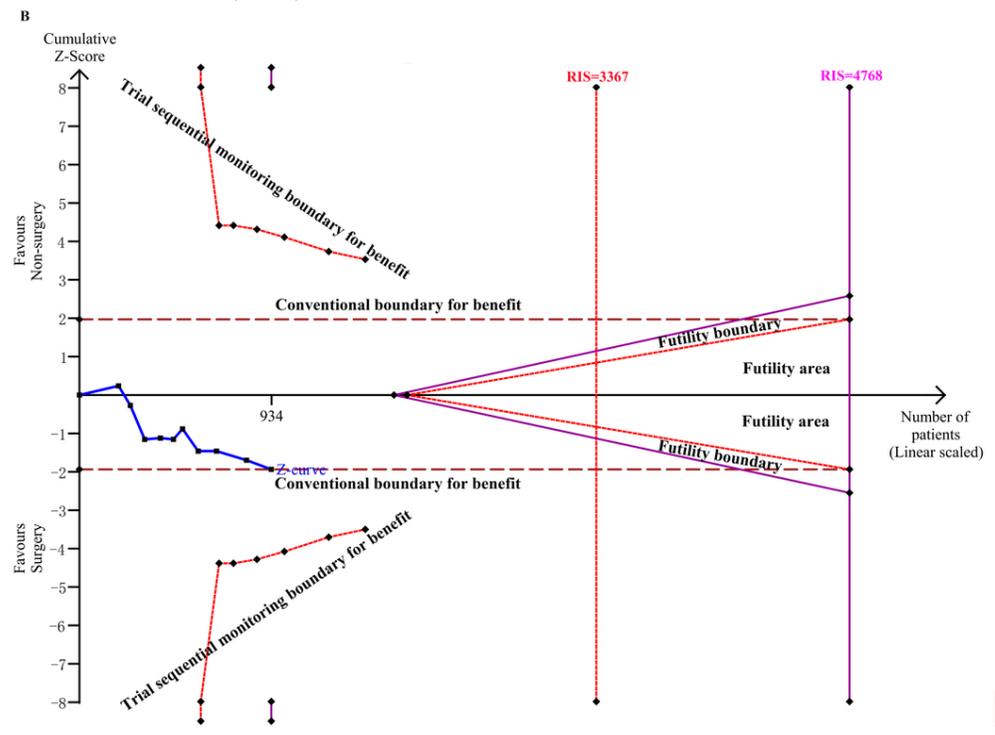
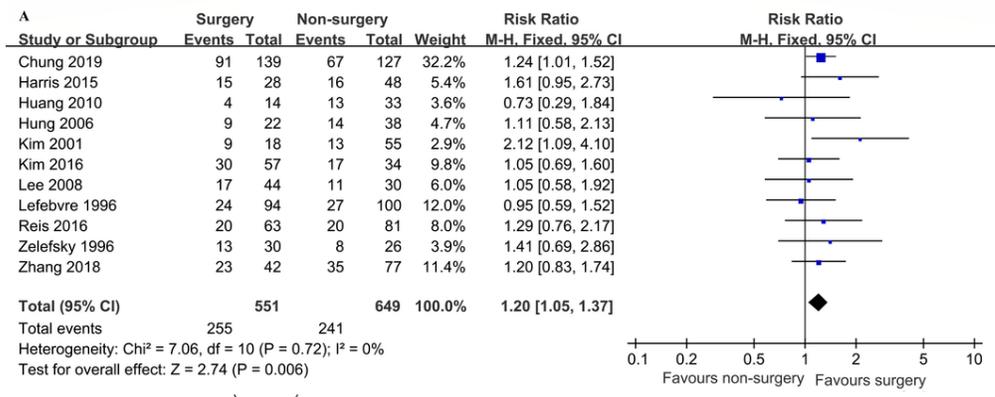


Figure 3

(A) Forest plot of studies showing disease free survival outcome. (B) Random-effect model of trial sequential analysis for disease free survival outcome: a relative risk of 1.20, two-sided boundary, incidence of 44.1% in surgical group, incidence of 34.8% in non-surgical group, a low bias estimated relative risk reduction of 15%, α of 5%, power of 90% were set. The required information size was calculated as 3367. The cumulative Z-curve just reached the conventional boundary and did not cross the trial sequential monitoring boundary.

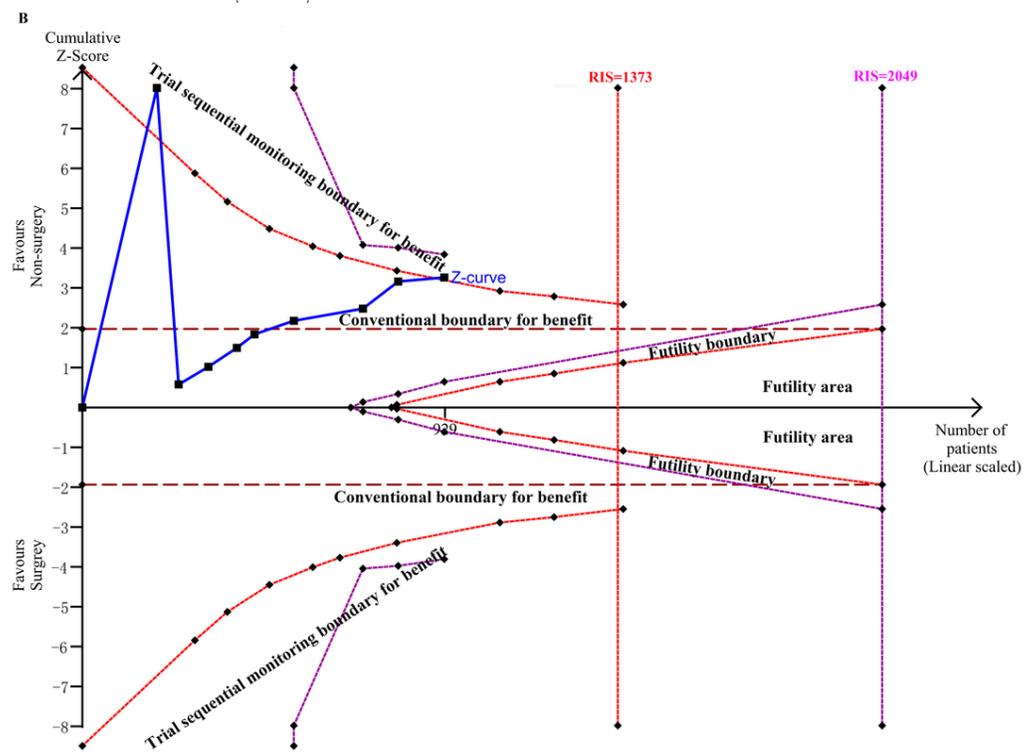
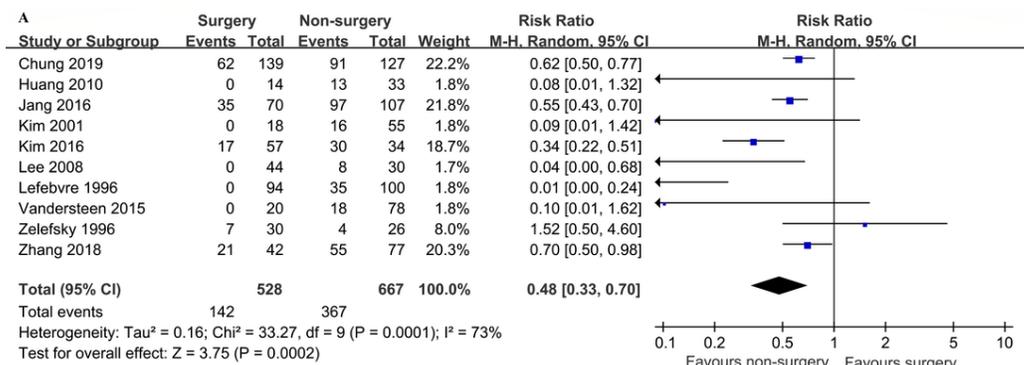


Figure 4

(A) Forest plot of studies displaying larynx preservation outcome. (B) Random-effect model of trial sequential analysis for larynx preservation outcome: a relative risk of 0.40, two-sided boundary, incidence of 19.8% in surgical group, incidence of 46.5% in non-surgical group, a low bias estimated relative risk reduction of 15%, α of 5%, power of 90% were set. The required information size was calculated as 1373. The cumulative Z-curve crossed conventional boundary and the trial sequential monitoring boundary the boundary

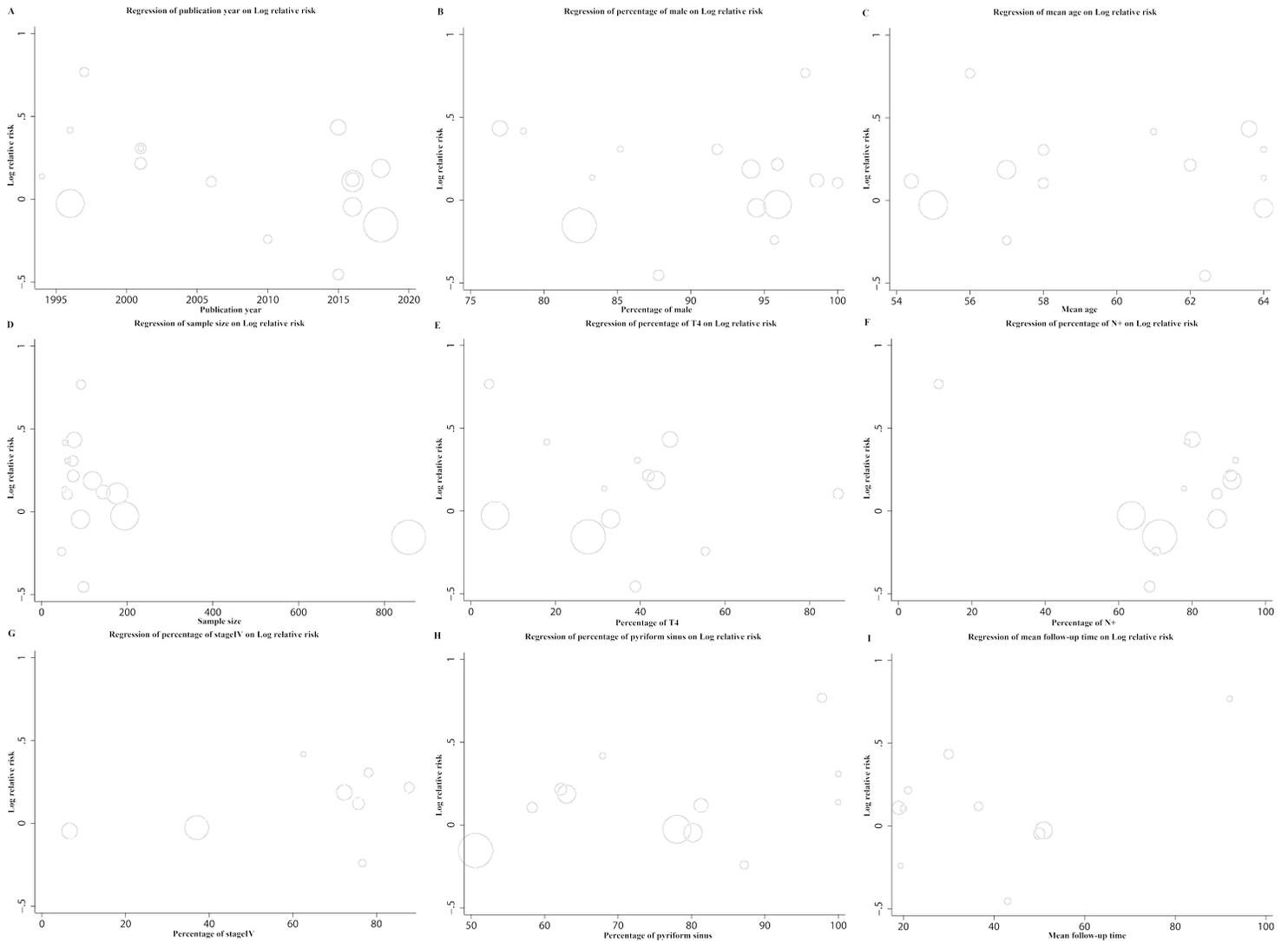


Figure 5

Random-effects meta-regression analyses showing the relationship between the study effect size and (A) publication year, (B) percentage of male, (C) mean age, (D) sample size, (E) percentage of T4, (F) percentage of N+, (G) percentage of stageIV, (H) percentage of pyriform sinus, (I) mean follow-up time. The size of the circles is inversely proportional to the size of the result study variance, so that more precise studies have larger circles.

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