Original Article

Comparison of clinical outcomes of conservative treatment and surgery for esophageal cancer patients who achieve a clinical complete response following neoadjuvant chemoradiotherapy: a systematic review and meta-analysis

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Background: Although the clinical complete response (cCR) for esophageal cancer patients after neoadjuvant chemoradiotherapy (nCRT) may be related to the good survival prognosis, the choice of conservative and surgical treatments is still controversial. This study sought to compare the clinical outcomes of these two treatments.

Methods: A systematic search was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of the PubMed, Embase, and Cochrane Library databases to retrieve articles published between January 1, 2010 and March 31, 2022 on the efficacy of conservative treatment or surgery in esophageal cancer patients who had achieved a cCR after nCRT The predominant endpoints were overall survival (OS), disease-free-survival (DFS), local recurrence, and distant metastasis. Odds ratios (ORs) were generated for the dichotomous variants by meta-analysis. The software implemented was Stata 16.0 MP. This research was prospectively registered under PROSPERO (registration number: CRD42022332143).

Results: Ultimately, eight retrospective cohort studies and one randomized controlled trial, comprising 749 patients (nCRT group: 333 and nCRT + surgery group: 416), were included in the meta-analysis after two researchers independently assessed the risk of bias for all included studies. The 2-year OS [OR =1.239, 95% confidence interval (CI): 0.891 to 1.723] and 5-year OS (OR =1.369, 95% CI: 0.963 to 1.947) were comparable between the nCRT group and nCRT plus surgery (nCRT + S) group. Patients in the nCRT + S group had significantly longer DFS (2 and 5 years, OR ranging from 0.303 to 0.357) and lower local recurrence rate (OR =0.179, 95% CI: 0.104 to 0.291) than those in the nCRT group. However, the distant metastasis rate was similar between the nCRT group and the nCRT + S group.

Conclusions: Esophageal cancer patients who achieved a cCR after nCRT and received an esophagectomy had better DFS and lower local recurrence than those who received conservative treatment; however, this DFS advantage did not lead to a significant difference in OS. Salvage surgery may be a feasible option for resectable patients who have local recurrence after achieving cCR.

Keywords: Esophageal cancer; neoadjuvant chemoradiotherapy (nCRT); surgery; clinical complete response (cCR); meta-analysis

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Introduction

Esophageal cancer is the 8th most common cancer worldwide, and has an incidence of 4.7–11.5 per 100,000 persons per year (1). Most patients are at the advanced stage on their first admission to the clinic (2). The 5-year overall survival (OS) rate of esophageal cancer patients has increased from 17–19% to the present rate of 30–57%; however, due to its high-grade malignancy, the extremely poor prognosis of esophageal cancer patients has been difficult to address (3). The introduction of neoadjuvant therapy led to a revolutionary improvement in survival. Notably, neoadjuvant chemoradiotherapy (nCRT) followed by esophagectomy is widely used to treat patients with locally advanced resectable esophageal cancer (4).

In the CROSS trials, the pathologic complete response (pCR) rate of the nCRT + surgery (nCRT + S) group was 29%, and the median OS of the nCRT + S group was significantly higher than that of the surgery group [48.6 *vs.* 24.0 months; hazard ratio =0.68, 95% confidence interval (CI): 0.53–0.88; P=0.003] (5). The NEOCRTEC 5010 study in China confirmed that preoperative chemoradiotherapy significantly increased the survival of patients with locally advanced esophageal squamous cell carcinoma (ESCC), who had a pCR rate of 43.2% (6).

Thus, scholars proposed that a pCR was an independent predictor of improved survival (7). Patients who achieve pCR have been shown to have superior OS, recurrence-free survival (RFS), and disease-specific survival (DSS) than patients who do not achieve pCR (8). Most models that use clinical complete response (cCR) to predict pCR, and then patients treated with nCRT could be tried to achieve pCR from the deduction of cCR. More importantly, multiple new diagnostic procedures have been used to increase the accuracy of cCR, including positron emission tomography/computed tomography (PET/CT), magnetic resonance imaging-diffusion-weighted imaging (MRI-DWI), and endoscopic ultrasound (EUS) (9).

Castoro *et al.* found that the 5-year disease-free survival (DFS) rates were 55.5% in the nCRT + esophagectomy group and 34.6% in the nCRT group (10). However, Chao *et al.* (11) reported that there was no difference in 5-year DSS and OS between group A (surgery) and group B (non-surgery) (DSS: 44% *vs.* 45%, P=0.42; OS: 41% *vs.* 39%, P=0.99). However, due to the small sample sizes of these studies, this controversial conclusion requires further exploration.

Thus, we conducted a systematic review and meta-analysis to compare the clinical outcomes of surgical and non-surgical treatment in esophageal cancer patients who achieved a cCR after nCRT to provide evidence for clinical practice. We present the following article in accordance with the PRISMA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6186/rc) (12).

Highlight box

Key findings

- For patients with esophageal cancer who achieve cCR after nCRT, the DFS and local recurrence advantages of follow-up esophagectomy did not result in a significant difference in the OS between the conservative treatment group and surgery group.

What is known and what is new?

- Neoadjuvant chemoradiotherapy (nCRT) followed by esophagectomy is widely used to treat patients with locally advanced resectable esophageal cancer. Whether esophagectomy in patients with cCR after preoperative chemoradiotherapy will show the advantage over the non-surgery group remains controversial;
- Although esophagectomy for esophageal cancer with cCR after nCRT demonstrated improved DFS and lower local recurrence over conservative treatment, this DFS advantage did not translate to a significant OS difference.

What is the implication, and what should change now?

- The non-surgical treatment might be a feasible choice if local recurrence could be well controlled for patients with esophageal cancer who achieve cCR after nCRT.

Methods

Search strategy

We searched for relevant articles published in the PubMed, Embase, and Cochrane Library databases from January 1, 2010, to March 31, 2022. The electronic searches were independently performed by 2 authors. The search strategy for PubMed was based on a combination of the following MeSH and free text words: (((((((esophagus[Title/Abstract]) OR (esophageal[Title/Abstract])) OR (oesophageal[Title/

Abstract])) OR (oesophagus[Title/Abstract])) AND ((((cancer[Title/Abstract]) OR (neoplasm[Title/Abstract])) OR (carcinoma[Title/Abstract])) OR (tumor[Title/Abstract]))) AND ((((radiochemotherapy[Title/Abstract]) OR (chemoradiotherapy[Title/Abstract])) OR (neoadjuvant[Title/Abstract])) OR (preoperative[Title/Abstract]))) AND (((response[Title/Abstract]) OR (responder[Title/Abstract])) OR (completeresponse[Title/Abstract]))) AND (("2010/01/01"[DatePublication]:"2022/03/31"[DatePublication])).

A detailed description of the search strategy adopted in this study is provided in Appendix 1.

Inclusion criteria

Articles were included if they met the following inclusion criteria:

(I) Concerned research on esophageal cancer patients who achieved a cCR after nCRT;
(II) Comprised patients who achieved a cCR after nCRT who were further classified into surgery and non-surgery (conservative treatment) groups;
(III) Compared the treatment outcomes (OS, DFS, local recurrence, distant metastasis) of the non-surgery and surgery groups;
(IV) Randomized controlled trial/retrospective cohort study are included and have details of the scientific statistical methods adopted in the study, detailed data, and clear conclusions.

Exclusion criteria

Articles were excluded from this meta-analysis if they met any of the following exclusion criteria:

(I) Concerned studies that compared neoadjuvant radiotherapy or chemotherapy with nCRT + S;
(II) Did not include cCR patients;
(III) Comprised reviews, case reports, comments, meta-analyses, or conference proceedings; and/or
(IV) Included unclear results.

Data extraction and quality assessment

The 2 reviewers (Z Sun and J Zheng) independently assessed the quality of the articles and extracted the patient characteristics and survival data from each eligible study. A senior reviewer (Q Ye) resolved any discrepancies between the 2 reviewers. The following data were extracted: title, country, author, year of publication, trial duration, trial design, total number of patients, number of treatment groups, histology, chemoradiotherapy regimen, surgical resection information, and surveillance scheme. The primary outcomes were OS and DFS. The secondary outcome was the recurrence rate (including local recurrence and distant metastasis).

Statistical analysis

A conventional meta-analysis was conducted to determine the odds ratios (ORs) for the dichotomous variants of OS, DFS, and recurrence. If I^2<50% and P>0.01, a fixed-effects model was used; otherwise, a random-effects model was used. If there was obvious heterogeneity (i.e., an I^2>75%), subgroup, sensitivity, and other analyses were carried out as necessary. The Egger's bias test was used to examine publication bias (Appendix 2). The significance level was set at P<0.05. The Stata 16.0 MP software was used.

Patient and public involvement

No patients and or members of the public were involved in the study.

Results

Study screening and baseline characteristics and quality

In total, 6,094 articles were retrieved after the database search. After eliminating duplicate articles, the titles and abstracts of the remaining 5,075 articles were scrutinized by 2 authors (Z Sun and J Zheng). After further exclusions, 96 articles underwent full-text assessments, and an additional 87 articles were excluded for various reasons (*Figure 1*).

Ultimately, 9 articles, comprising 749 patients, were deemed eligible for inclusion in our study. Among these articles, most came from Asia [3 from Korea (8,13,14); 1 from Taiwan/China (11), and 1 from Turkey (15)], and 4 came from the West (1 each from Italy (10), the Netherlands (16), France (17), and Ireland (18)]. In total, 333 and 416 patients were categorized into the nCRT and nCRT + S groups, respectively. Of the 749 patients, 55 patients had adenocarcinoma (AC), and 694 patients had squamous cell carcinoma (SCC). The clinical data and basic characteristics of the 9 articles are shown in *Table 1*.

We summarized the risk of bias judgments across

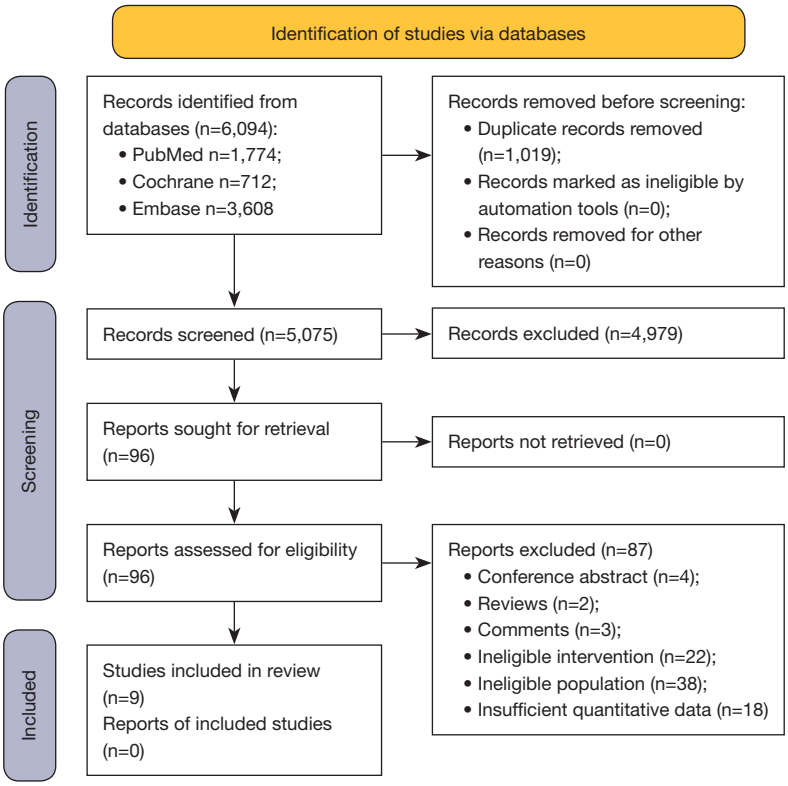

Figure 1 PRISMA flow diagram.

different studies for each domain listed and the results are sent out in our risk of bias summary table (Figure S1). We graded each prospective source of bias risk as high, low, or unclear and offered a model with a justification for our judgment.

OS

2-year OS

All of the 9 articles examined the outcomes of the 2 treatments on 2-year OS. There was slight heterogeneity among these studies (P=0.084, I^2=42.5%) but no significant publication bias (P=0.417). The 2-year OS (OR =1.24, 95% CI: 0.89–1.72) was comparable between the nCRT group and the nCRT + S group. The results are shown in *Figure 2A*.

5-year OS

Of the 9 articles, 6 were included in the 5-year OS analysis. There was slight heterogeneity among these studies (P=0.163, I^2=36.5%), but no significant publication bias (P=0.270). The 5-year OS (OR =1.37, 95% CI: 0.96–1.95) was also similar between the nCRT group and the nCRT + S group. The results are shown in *Figure 2B*.

DFS

2-year DFS

Of the 9 articles, 5 analyzed the outcomes of the 2 treatments on 2-year DFS. No significant heterogeneity was found among these studies (P=0.935, I^2=0.0%), and there was no significant publication bias (P=0.710). The 2-year DFS of the nCRT + S group (OR =0.303, 95% CI: 0.195–0.471) was significantly better than that of the nCRT group. The results are shown in *Figure 3A*.

5-year DFS

Of the 9 articles, 3 were included in the 5-year DFS analysis. There was no significant heterogeneity among these studies (P=0.749, I^2=0.0%), and there was no significant publication bias (P=0.405). The 5-year DFS of the nCRT + S group (OR =0.357, 95% CI: 0.217–0.585) was significantly better than that of the nCRT group. The

Table 1 Characteristics of the included studies

Study (inclusion period)	Country/region	Study design	Patients		Histology		Chemotherapy	Radiotherapy	Response assessment	Surgical resection	Surveillance
			nCRT + S	nCRT	SCC	AC					
Furlong (18), 2013 [2000–2007]	Ireland	Retrospective	6	19	13	12	5-FU + cisplatin (2 cycles)	15*2.6 Gy (40 Gy)	Endoscopy + CT	Within 8 weeks of treatment/salvage surgery (3/19)	Endoscopy every 3 months. CT scanning every 6 months for 3 years
Castoro (10), 2013 [1992–2007]	Italy	Retrospective	39	38	77	0	5-FU + cisplatin (3–4 cycles); Taxanes for some patients	25–28*1.8 Gy (45–50 Gy)	Endoscopy + CT + PET/CT (from 2005)	4–6 weeks after treatment/salvage surgery (10/38)	Patients were examined at regularly scheduled intervals after 1, 3, 6, and 12 months, and every 6 to 12 months thereafter
Piessen (17), 2013 [1995–2009]	France	Retrospective	118	59	149	28	5-FU + cisplatin (2 cycles)	25*1.8 Gy (45 Gy)	Endoscopy + CT+ GI + PET (optional, from 2004)	All anastomoses were placed above the level of the azygos vein/salvage surgery (2/59)	Clinical examination, CT, endoscopy, and PET scans were performed serially until disease progression (every 4 months for 2 years, every 6 months for 3 years, and annually thereafter)
Chao (11), 2013 [1999–2006]	Taiwan	Retrospective	71	79	150	0	5-FU + cisplatin (2 cycles)	15*2Gy (30 Gy)	Endoscopy + EUS + CT + bone scan + esophagography	4–6 weeks after treatment/salvage surgery (7/79)	All subjects underwent chest plane radiography every 3 months and CT every 6 months
Jeong (8), 2014 [2005–2008]	Korea	Retrospective	39	31	70	0	Capecitabine + cisplatin followed by weekly cisplatin and capecitabine (2 cycles)	23*2Gy (46 Gy)	Endoscopy + EUS + CT + PET	Transthoracic esophagectomy and transhiatal esophagectomy	The interval was 3 months for the 1st 2 years, and then every 6 months until 5 years
Park (13), 2019 [2012–2016]	Korea	Randomized trial	19	18	37	0	Capecitabine + cisplatin (2 cycles)	28*1.8 Gy (50.4 Gy)	Endoscopy + CT + PET/CT	6–8 weeks after treatment/salvage surgery (6/18)	The interval was 3 months for the 1st 2 years, and then every 6 months until 5 years and endoscopy every 6 months
van der Wille (16), 2021 [2012–2018]	The Netherlands	Retrospective	29	29	43	15	Paclitaxel + carboplatin (5 weekly cycles)	23*1.8 Gy (41.4 Gy)	Endoscopy + EUS + CT + PET/CT	6 weeks after treatment/salvage surgery (14/29)	Patients in the active surveillance group underwent CRE every 3 months during the 1st year, every 4 months during the 2nd year, twice a year during the 3rd year, and annually during the 4th and 5th years
Sakin (15), 2021 [2010–2019]	Turkey	Retrospective	34	29	63	0	Paclitaxel + carboplatin (5 weekly cycles) or 5-FU + cisplatin (2 cycles)	28*1.8 Gy (50.4 Gy)	Endoscopy + CT + PET/CT	6–8 weeks after treatment	Blood analyses, chest and abdomen CT every 3–4 months for the 1st 3 years. Endoscopy every 3 to 4 months for the 1st 3 years for patients who refused surgery
Yu (14), 2022 [2005–2015]	Korea	Retrospective	61	31	92	0	Capecitabine + cisplatin, weekly or 5-FU + cisplatin (2 cycles)	46 Gy	Endoscopy + CT + PET/CT	6–8 weeks after treatment	After treatment, regular follow-up examinations were performed every 3 months during the 1st 2 years, and every 6 months thereafter until 5 years

nCRT, neoadjuvant chemoradiotherapy; nCRT + S, nCRT plus surgery; SCC, squamous cell carcinoma; AC, adenocarcinoma; 5-FU, 5-fluorouracil; CT, computed tomography; PET, positron emission tomography; GI, gastrointestinal imaging; CRE, clinical response evaluation; EUS, endoscopic ultrasound.

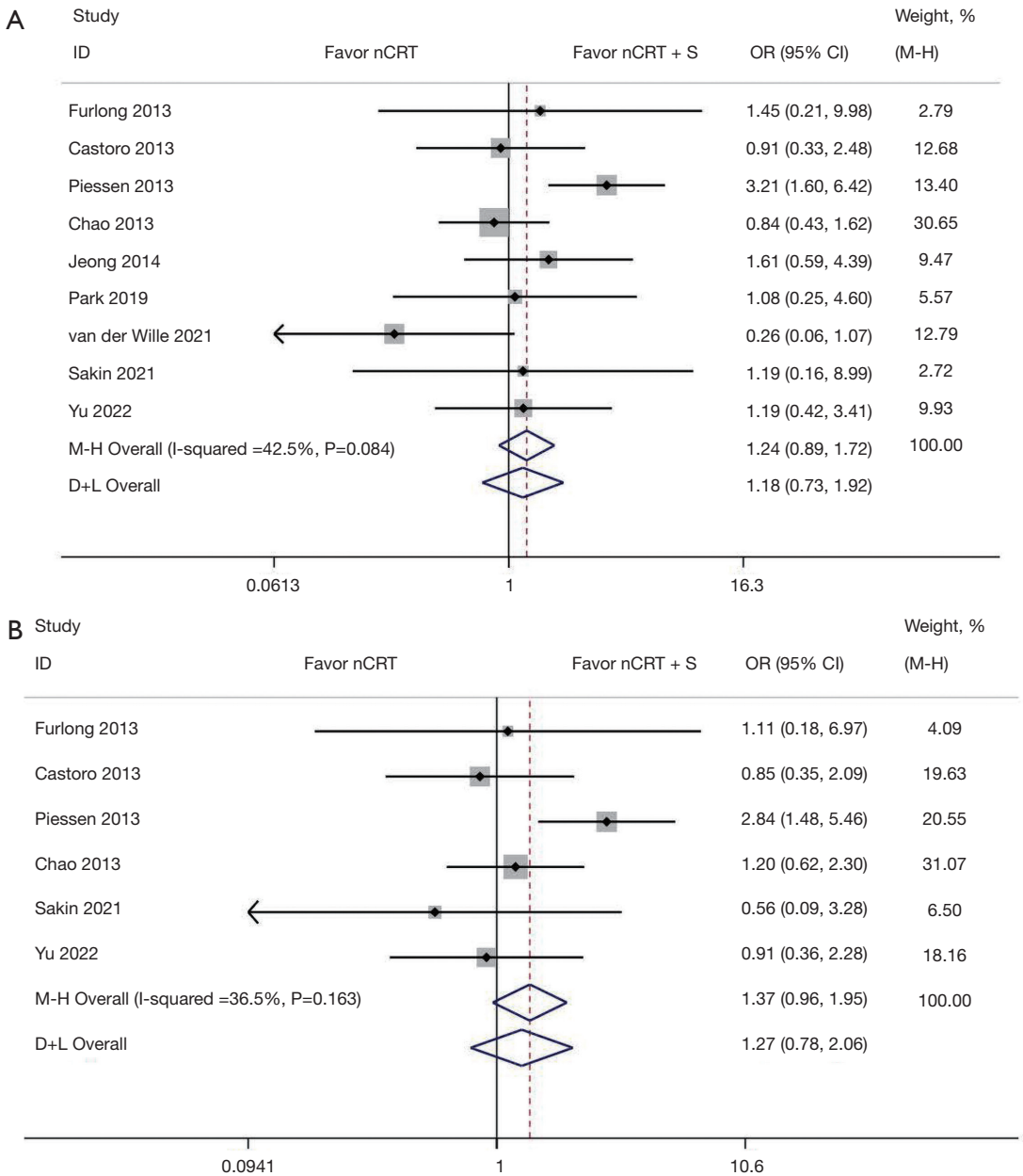

Figure 2 Forest plot of comparisons between nCRT and nCRT + S on 2-year overall survival (A) and 5-year overall survival (B). nCRT, neoadjuvant chemoradiotherapy; nCRT + S, nCRT plus surgery; OR, odds ratio; CI, confidence interval; M-H, Mantel-Haenszel test; D+L, DerSimonian-Laird.

results are shown in *Figure 3B*.

Local recurrence and distant metastasis

Of the 9 articles, 5 examined local recurrence and distant metastasis. There was no significant heterogeneity among these studies (P=0.530, I^2=0.0%) and there was no significant publication bias (P=0.579) in terms of local recurrence. The local recurrence rate of the nCRT + S group was significantly lower than that of the nCRT group (OR =0.179, 95% CI: 0.104–0.291). However, the distant metastasis rates (OR =1.466, 95% CI: 0.651–3.300) were comparable between the 2 groups. The results are shown in *Figure 4A*,*4B*.

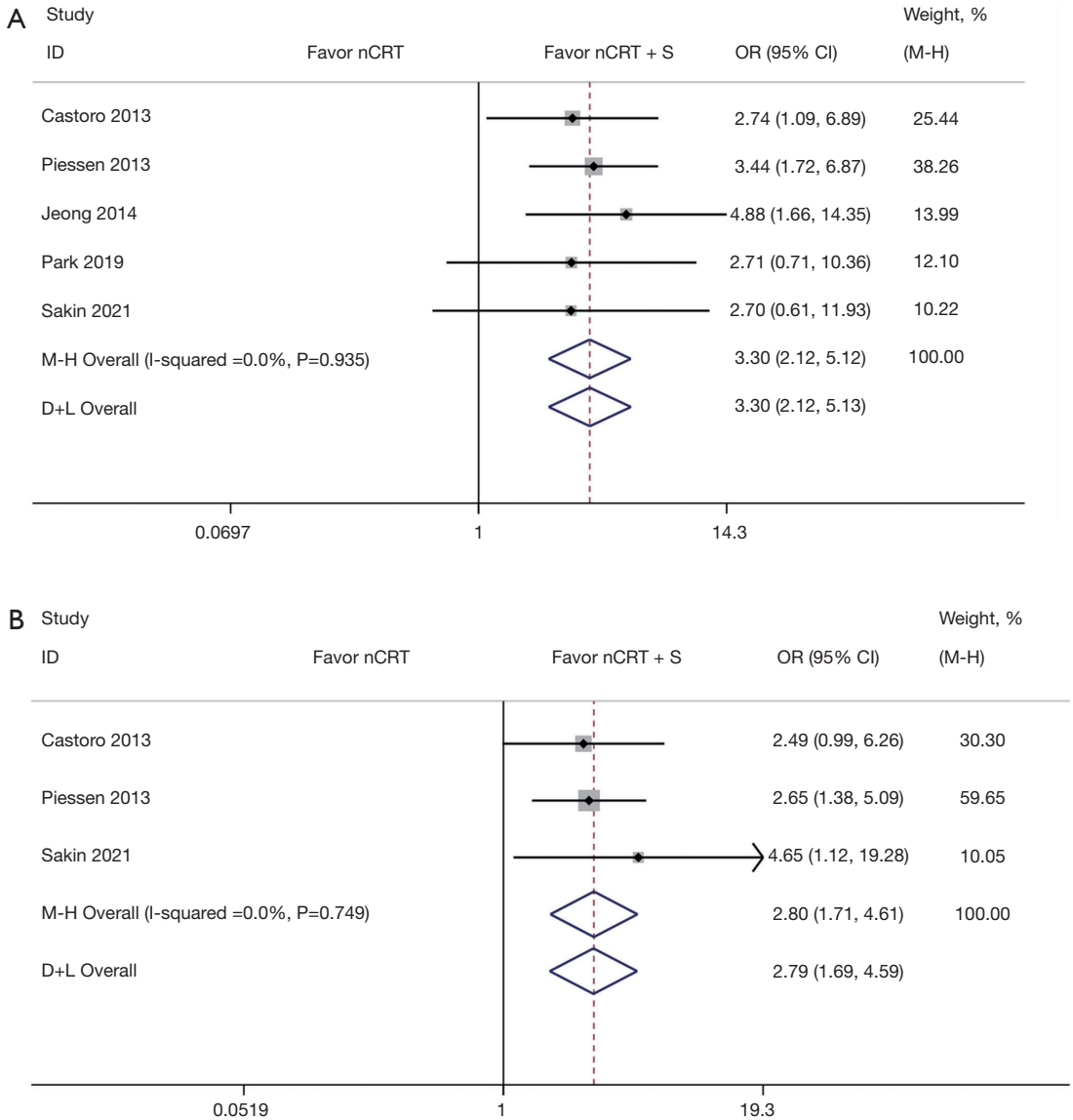

Figure 3 Forest plot of comparisons between nCRT and nCRT + S on 2-year disease-free survival (A) and 5-year disease-free survival (B). nCRT, neoadjuvant chemoradiotherapy; nCRT + S, nCRT plus surgery; OR, odds ratio; CI, confidence interval; M-H, Mantel-Haenszel test; D+L, DerSimonian-Laird.

Discussion

To the best of our knowledge, very few meta-analyses have investigated the outcomes of patients with esophageal cancer who achieved a cCR after nCRT. Further, a high proportion of articles on trials examining this issue have only been published in recent years. We explored reasonable treatments for this aggressive malignancy, which causes >400,000 deaths per year and has a poor 5-year OS rate (19,20).

Moreover, previous meta-analyses have only included 4–6 articles, which predominantly comprised articles published before 2013 and did not include long-term follow-up data (21,22). Conversely, this research included long-term survival data (i.e., 5-year OS and DFS data), and >40% of the articles included in our meta-analysis were published in the last 5 years.

Similar to van der Wilk *et al.* (16), we found that the 2-year OS and 5-year OS of patients in the nCRT + S group and those of patients in the nCRT group did not

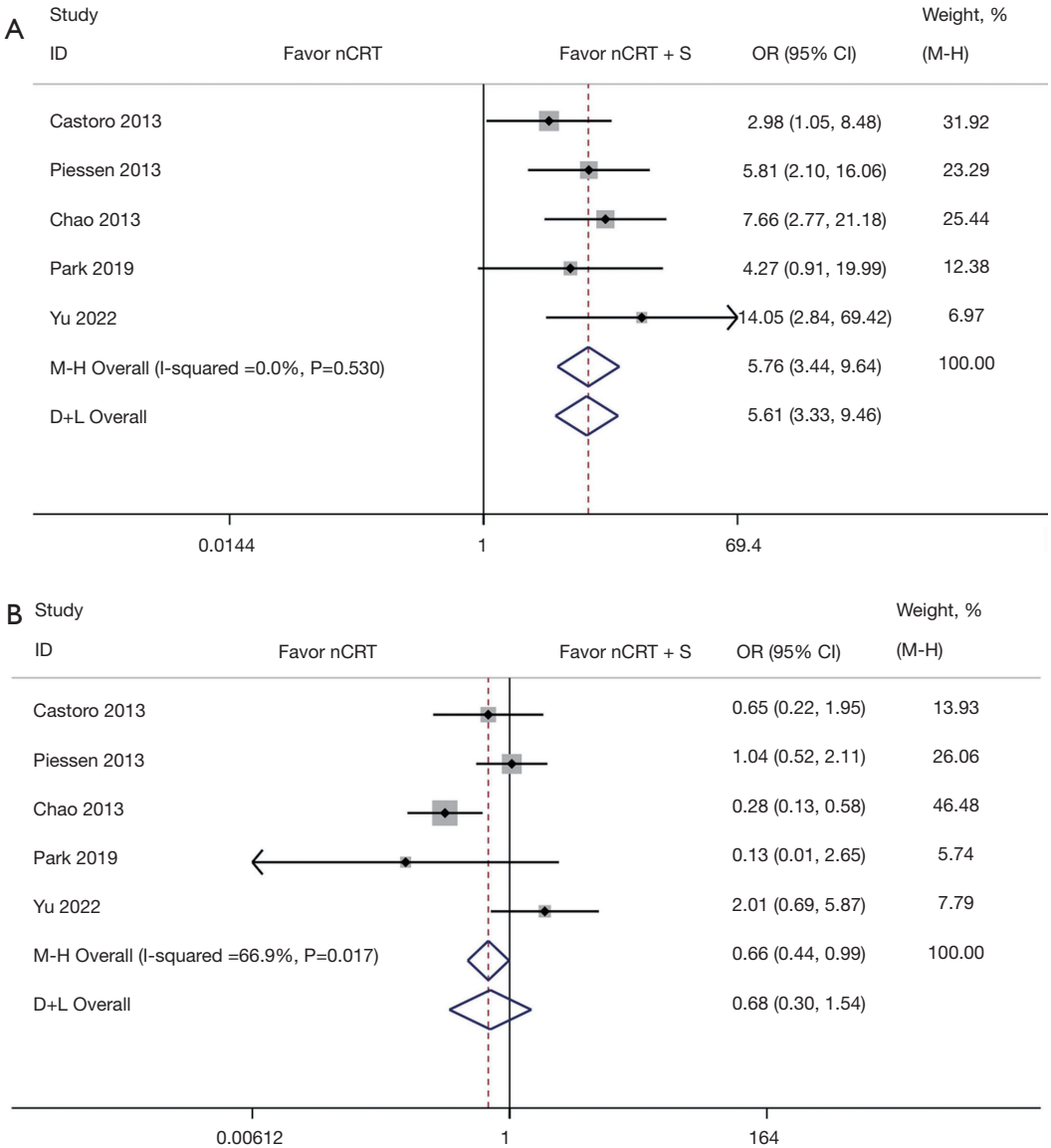

Figure 4 Forest plot of comparisons between nCRT and nCRT + S on local recurrence (A) and distant metastasis (B). nCRT, neoadjuvant chemoradiotherapy; nCRT + S, nCRT plus surgery; OR, odds ratio; CI, confidence interval; M-H, Mantel-Haenszel test; D+L, DerSimonian-Laird.

differ significantly. Of the 9 studies included in our meta-analysis, 6 included patients with ESCC, and among these 6 studies, 5 showed that conservative treatment could be adopted for patients with esophageal carcinoma who achieved a cCR after nCRT (10,11,13-15). In the following paragraphs, we interpret our OS and DFS results from a clinical perspective.

The comparable efficacy of non-surgery and surgery in terms of 2- and 5-year OS

First, achieving a complete response after nCRT not only had clinical benefits for the surgery group, but also improved the clinical outcomes of the non-surgical group. Complete response was defined as no evidence of tumor

residual in the primary site or lymph nodes (LNs) based on preoperative assessments or postoperative specimens. Notably pCR is considered one of the most important predictors of survival. According to the CROSS trial, SCC patients achieve a higher rate of pCR after nCRT than AC patients (49–50% *vs.* 23–29%); however, the former had the highest proportion of esophageal malignancies in that study (5). In our research, of the 749 patients, 694 had SCC and 55 had AC. The higher rate of pCR may have led to better survival in both groups, yielding a non-significant difference between these groups in terms of OS. Alnaji *et al.* (23) showed that a pCR is also an independent predictor of nCRT for esophageal AC.

Second, esophagectomy is a very enormous injury associated with mortality (1–6%) and considerable postoperative complications (>50%) (24), which may decrease the surgical benefits. Esophagectomy and digestive tract reconstruction negatively affect patients' health-related quality of life (QOL). Pneumonia, anastomotic leakage, and wound infection are common short-term postoperative complications. Gastric reflux and vocal cord palsy also affect patients' long-term QOL. In a previous study (13), Park reported that the nCRT group tended to have lower mortality than the nCRT + S group. Thus, given the complexity and limitation of the surgery, the long-term survival advantage for the surgical group may not be obvious at all.

Third, limitations in response assessments can lead to false negatives for cCR, which may interfere with the accuracy of each research result. PET/CT and EUS, which are high precision detective approaches, were not routinely implemented in the articles published before 2019 included in this study, which might have created an imprecision that cCR can be used to predict pathologic complete response. pCR has been proven to be one of the most important predictors of survival; however, inaccurate diagnoses might lead to compromised surgical outcomes.

A previous meta-analysis suggested that EUS, PET/CT, and endoscopic biopsies can precisely identify tumor residual at the primary site after nCRT with sensitivities of 96%, 74%, and 33%, respectively (25). EUS especially can improve the sensitivity of LN diagnosis of metastasis from 84.7% to 96.7% when combined with fine-needle aspiration (26). Xu *et al.* (27) reported that combining the parameters of ^{18}F-flurodeoxyglucose (^{18}F-FDG) PET/CT and MRI-DWI increased the accuracy of predictions of primary tumor responses in ESCC. A recently published prospective diagnostic preSANO trial (6) showed that combining diagnostic tests improved residual disease detection. Thus, it is very important to include more accurately evaluative cCR research in further analyses.

The surgery group had better DFS and lower local recurrence

In this study, the nCRT + S group had a longer DFS time than the nCRT group, including a better 2-year and 5-year DFS. The local recurrence rate of the nCRT + S group was also considerably lower than that of the nCRT group.

Esophageal cancer is highly malignant and likely to recur. Surgery can be used to expand the surgical region to radically remove the tumor, which can provide better local control than singular non-surgical therapy. Yu *et al.* (14) reported that the 1- and 5-year local recurrence rates were 9% and 12%, respectively, in the nCRT + S group, and 28% and 41%, respectively, in the nCRT group. A prospective study by Park *et al.* (13) showed that the surgery group tended to have better DFS than the non-surgery group (with 2-year DFS rates of 66.7% *vs.* 42.7%, respectively).

In the present research, poor DFS and local control results in the nCRT group did not appear to produce any significant OS differences, which should be further explored in the future. We found that among the 9 included studies, in 6 articles, the non-surgery group included some cases of local recurrence followed by salvage surgery (*Table 1*). Generally, conservative treatment is available for patients who are unfit for surgery or refuse surgery. Castoro *et al.* (10) found that in a group of SCC patients who achieved a cCR after nCRT, waiting for recurrence and then undergoing salvage surgery did not compromise their survival compared to patients treated directly with surgery. van der Wilk *et al.* (16) concluded that postponing surgery and instead undertaking active surveillance was not associated with more postoperative adverse events or a higher rate of distant dissemination in recurrent cases. Thus, the use of salvage surgery in selected patients may positively affect their long-term survival. However, more research needs to be conducted to explore the risks and long-term treatment results associated with salvage surgery.

The research sought to explore whether cCR can accurately predict pCR, which is the premise to ensure the accuracy of this study. Cheedella *et al.* (28) examined the use of PET/CT and endoscopy biopsy in evaluating the response rates of patients after nCRT, and found that the sensitivity of cCR to predict pCR was 97.1%. In addition, experts (29) have noted the benefits of PET/MRI over PET/CT in the staging of non-small cell lung

cancer, and its greater sensitivity in the staging of non-enlarged but suspicious metastatic LNs. This advanced technology combines PET physiologic information with the quantitative strengths of MRI. There are limited reports on the application of PET/MRI in the accurate restaging of esophageal cancer after nCRT; however, the value of its further application should be considered.

In addition, no consensus has been reached as to the adjuvant treatment for esophageal cancer patients who remain at high risk for recurrence after nCRT + S, and the standard of care is surveillance. However, it should be noted that even among patients that achieved a complete response after esophagectomy, 24% of patients with AC and 9% of patients with SCC developed distant metastasis (30). Xi *et al.* (31) followed-up ESCC patients who achieved a pCR (pCR rate: 44.9%) and reported an overall recurrence rate of 34.3% within 5 years. Thus, the recurrence rate is an important factor affecting the clinical outcome of patients.

According to Checkmate 577 (32), the DFS of patients with resected esophageal cancer after nCRT was significantly longer in those who received nivolumab adjuvant therapy than those who received a placebo. For patients who achieve a cCR after nCRT, it is worth exploring whether the programmed cell death protein 1 (PD-1) antibody can improve their DFS and local recurrence rate and be used as maintenance therapy for high-risk cases. The PALACE-1 trial (33) showed the safety of preoperative chemoradiotherapy with pembrolizumab, and this strategy produced a 55.6% pCR rate for resected tumors. Thus, we also intend to examine whether PD-1 combined with nCRT leads to better clinical outcomes.

Under French national guidelines (34), it is an option for patients who achieved a cCR to refuse surgery after definite CRT. A recent article reported that omitting surgery may lead to better OS in patients who achieve a cCR after nCRT, as surgery can decrease the QOL and increase postoperative mortality (22). Two important prospective randomized controlled studies (35,36) (the ESOSTRATE and SANO trials) compared the clinical results of immediate esophagectomy with active surveillance in patients who achieved a cCR after nCRT. All of the above-mentioned studies also confirmed that a conservative treatment strategy is not inferior to immediate esophagectomy in patients with accurately evaluated cCR.

Limitations

This study had a number of limitations. First, most of the enrolled studies were retrospective studies, which might weaken the strength of our results; however, the publication time of the literature is comprehensive (from 2013 to 2022). Since most of the studies comprised Asian patients, ESCC accounted for the majority of esophageal cancer, but SCC and AC were not analyzed separately. The selection bias may have been inevitable in the 2 groups. In this research, the chemotherapy regimens differed slightly among the enrolled studies, and the radiotherapy dosages ranged from 30 to 50.4 Gy. The diagnostic criteria for cCR also differed, and EUS and PET/CT were not performed in all cases. Finally, not all of the studies include long-term survival data, especially DFS and objective response rate (ORR) results, which weakens the clinical value of our research results.

Conclusions

For patients with esophageal cancer who achieve cCR after nCRT, the DFS and local recurrence advantages of follow-up esophagectomy did not result in a significant difference in the OS between the conservative treatment group and surgery group. Salvage surgery may be a feasible option for resectable patients who have local recurrence after achieving cCR.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-6186/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6186/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Appendix 1

Search strategy and MeSH terms in each database

PubMed [1,774]

(((((((esophagus[Title/Abstract]) OR (esophageal[Title/Abstract])) OR (oesophageal[Tit le/Abstract])) OR (oesophagus[Title/Abstract])) AND ((((cancer[Title/Abstract])OR(neo plasm[Title/Abstract])) OR (carcinoma[Title/Abstract])) OR (tumor[Title/Abstract])))) AND ((((radiochemotherapy[Title/Abstract]) OR (chemoradiotherapy[Title/Abstract])) OR (neoadjuvant[Title/Abstract]))OR(preoperative[Title/Abstract])))) AND (((response[Title/Abstract])OR(responder[Title/Abstract])) OR (completeresponse[Title/Abstract])))) AND (("2010/01/01"[DatePublication]:"2022/03/31"[DatePublication])) Filters: English

Embase [3,608]

((((esophagus) OR (esophageal)) OR (oesophageal)) OR (oesophagus)):ti,ab,kw AND (((((cancer) OR (neoplasm)) OR (carcinoma)) OR (tumor)):ti,ab,kw) AND (((((radiochemotherapy) OR (chemoradiotherapy)) OR (neoadjuvant)) OR (preoperative)):ti,ab,kw) AND ((((response) OR (responder)) OR ('complete response')):ti,ab,kw) AND ((English):la) AND [2010- 2022]/py

Cochrane [712]

709 Trialsmatching (((esophagus) OR (esophageal)) OR (oesophageal)) OR (oesophagus) in Title Abstract Keyword AND (((cancer) OR (neoplasm)) OR (carcinoma)) OR (tumor) in Title Abstract Keyword AND (((radiochemotherapy) OR (chemoradiotherapy)) OR (neoadjuvant)) OR (preoperative) in Title Abstract Keyword AND ((response) OR (responder)) OR (complete response) in Title Abstract Keyword-with Cochrane Library publication date Between Jan 2010 and Mar 2022 (Word variations have been searched)

3 Cochrane Reviews matching (((esophagus) OR (esophageal)) OR (oesophageal)) OR (oesophagus) in Title Abstract Keyword AND (((cancer) OR (neoplasm)) OR (carcinoma)) OR (tumor) in Title Abstract Keyword AND (((radiochemotherapy) OR (chemoradiotherapy)) OR (neoadjuvant)) OR (preoperative) in Title Abstract Keyword AND ((response) OR (responder)) OR (complete response) in Title Abstract Keyword-with Cochrane Library publication date Between Jan 2010 and Mar 2022 (Word variations have been searched)

Appendix 2: Publication bias and plot

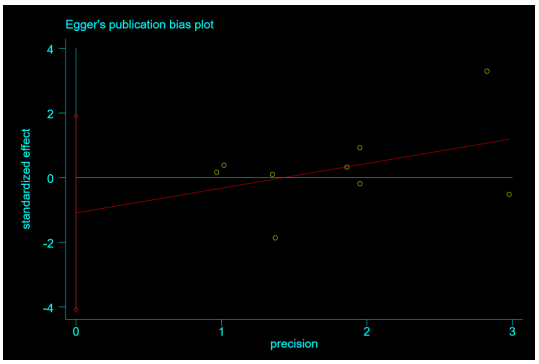
Publication bias

	Egger's bias test (P value)
2-year OS	0.417
5-year OS	0.270
2-year DFS	0.710
5-year DFS	0.405
Local recurrence	0.579
Distant metastasis	0.870

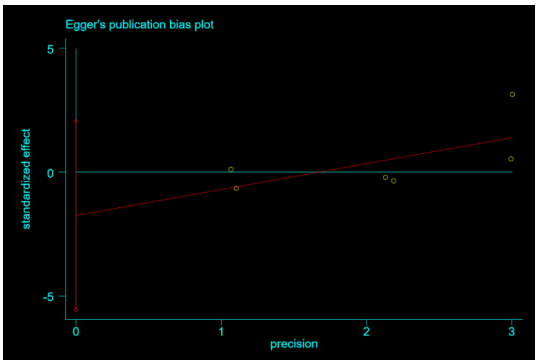
OS, overall survival; DFS, disease-free survival.

https://dx.doi.org/10.21037/atm-22-6186

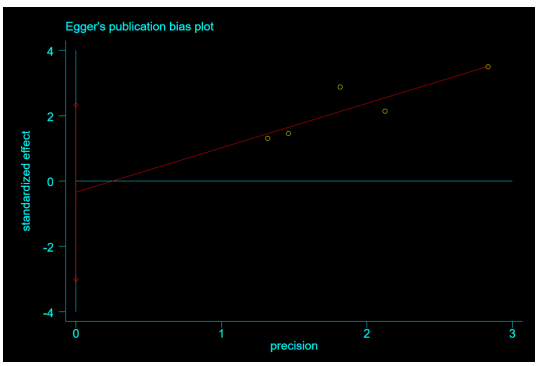
Publication bias and plot (2-year OS)



Publication bias and plot (5-year OS)

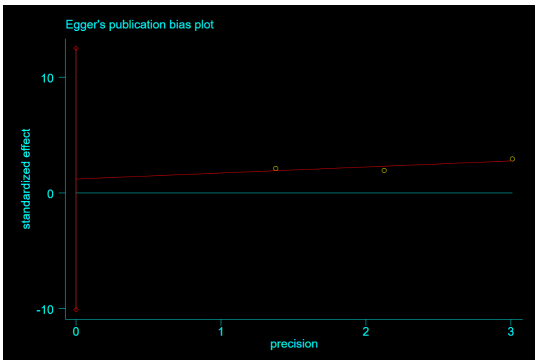


Publication bias and plot (2-year DFS)

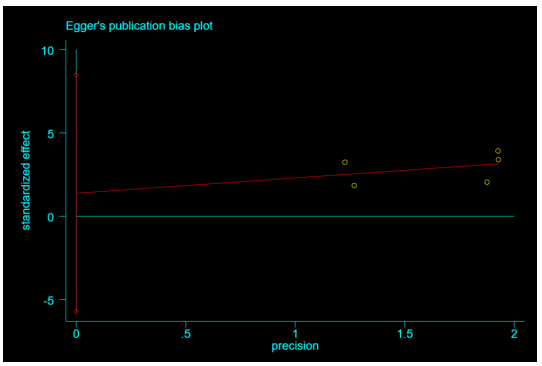


https://dx.doi.org/10.21037/atm-22-6186

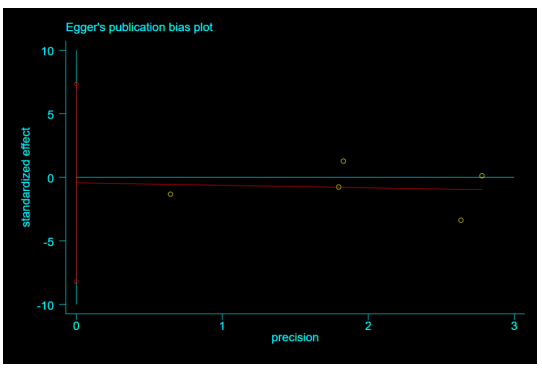
Publication bias and plot (5-year DFS)



Publication bias and plot (local recurrence)



Publication bias and plot (distant metastasis)



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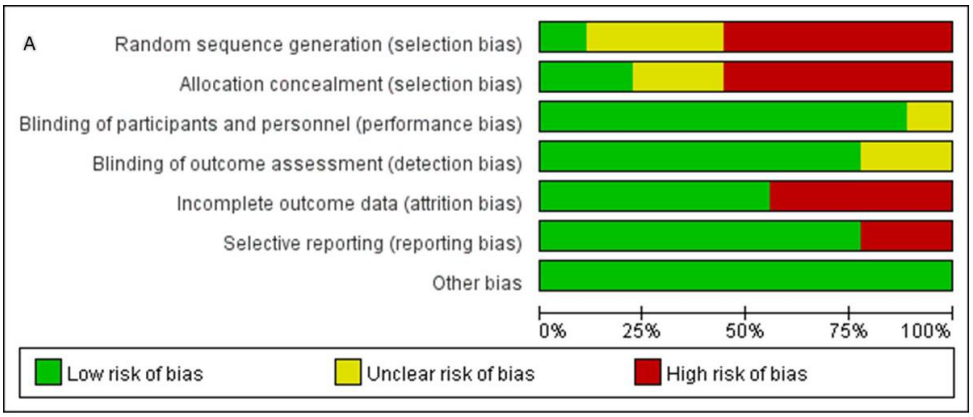

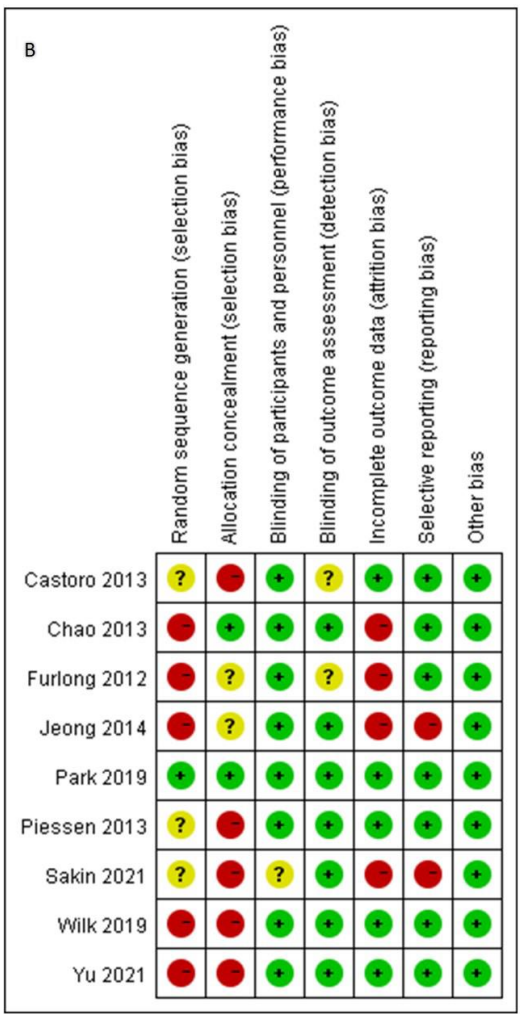

Figure S1 Risk of bias graph (A) and risk of bias summary (B).

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