Is postoperative chemotherapy necessary for resected esophageal carcinoma after neoadjuvant chemoradiotherapy? A systematic review and meta-analysis

Liang Cheng
North Sichuan Medical University
Wei Gao
North Sichuan Medical University
Hao Yang
North Sichuan Medical University
Yu Zhou
North Sichuan Medical University
Yongsheng Zhao
North Sichuan Medical University
Maoyong Fu (fumaoyongmd@163.com)
Affiliated Hospital of North Sichuan Medical College

Research

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Abstract

Background Both neoadjuvant chemoradiotherapy (NCRT) and postoperative chemotherapy (PT) are crucial treatments for esophageal carcinoma (EC). However, it is not clear whether PT is required for EC treatment after NCRT. This systematic review and meta-analysis aimed at clarifying the necessity of PT for resected EC after NCRT.

Methods We searched PubMed, Embase, and The Cochrane Library databases for relevant studies published up to March 2020, that have compared PT and non-PT for resected EC after NCRT (NCRT + PT vs. NCRT). The primary outcome of this study was overall survival (OS). Hazard risk ratio (HR) and 95% confidence interval (CI) were calculated. Subgroup and sensitivity analyses were employed to explore heterogeneity, and the random effect model was used to merge the meta-analysis data, regardless of whether the heterogeneity was large or small.

Results This study included seven retrospective cohorts, with more than 10720 patients. Most of the patients had esophageal adenocarcinomas. The Meta-analysis showed that NCRT followed by PT increased the patient OS (*HR* = 0.79, *95% CI* 0.74–0.85, *P* < 0.001). However, further subgroup analysis showed that NCRT + PT might not improve the OS of resected EC patients with a negative lymph node status (*HR* = 0.82, *95% CI* 0.67–1.01, *P* = 0.124). Further, we showed that NCRT with PT improved the survival of EC patients with a positive lymph node status who underwent resection (*HR* = 0.78, *95% CI* 0.70–0.86, *P* < 0.001).

Conclusion PT may improve the survival of lymph node-positive EC patients previously treated by NCRT. This conclusion may be more applicable to EAC patients treated with NCRT at the ypN + stage.

1. Introduction

Esophageal carcinoma (EC) is one of the most prevalent malignant tumors worldwide.[1] Compared to surgery alone, multimodality therapy results in a significant improvement in survival rates in locally advanced EC.

For EC patients who did not receive neoadjuvant therapy, the decision of whether to provide PT depends on the status of lymph nodes after surgery. Compared with surgery alone, PT does not result in significant survival benefits to EC patients with negative lymph nodes. However, PT has been proven to improve the survival of patients with locally advanced EC with positive lymph nodes.[2]

A previous cross-trial showed that NCRT significantly prolongs the overall survival (OS) of locally advanced EC and the strategy is currently the best method for the treatment of the EC.[1, 3] However, whether PT is needed in patients with locally advanced EC after NCRT and surgery should be assessed. The NCCN clinical practice guidelines recommend that resected Esophageal adenocarcinoma (EAC) patients with either lymph node-positive or negative observation need PT, while resected Esophageal squamous cell carcinoma (ESCC) patients do not need PT.

Currently, patients with locally advanced EC receive NCRT combined with surgery, which increases medical costs and requires longer recovery time. Conducting PT further increases medical costs and prolongs patient recovery. Therefore, careful consideration should be made before conducting PT on EC patients after NCRT combined with surgery. At present, no randomized controlled study outcomes have been reported on whether EC patients could benefit from PT after NCRT and surgery.

However, the results from published cohort studies show that PT improves the OS of patients who received NCRT with EC, especially for patients who showed a positive lymph node status after NCRT. This study aimed to collect substantial evidence from published cohort studies to assess the effect of conducting PT on the survival of patients with resected EC after NCRT.

2. Materials And Methods

This systematic review and meta-analysis confirmed with The Cochrane Collaboration Handbook of Interventions Systematic Reviews. Data reporting in this manuscript was done using the PRISMA Statement.

2.1. Criteria for considering studies for this review

The inclusion criteria were: (1) Studies that have compared the resected survival of EC patients after NCRT, with or without PT; (2) Both randomized controlled trials (RCTs) and non-randomized controlled studies (prospective and retrospective studies); (3) A follow-up time of more than one year; (4) Studies with results on hazard ratios (HRs) and analysis was done at a 95% confidence interval (CI), or the hazard ratio and 95% CI could be estimated from the data.

The Exclusion criteria were: (1) Review, editorial, and case reports, (2) Non-English language literature.

2.2. Search strategy

We conducted a systematic literature search in PubMed, Embase, and the Cochrane Library (from the inception to March 2020). Our search strategy included free words, Emtree terms and MeSH terms, such as “Esophageal carcinoma,” “Neoadjuvant chemoradiotherapy,” “Preoperative chemoradiotherapy,” “Adjuvant chemotherapy,” and “Postoperative chemotherapy.”

2.3. Selection of studies

Literature search and selection was conducted by two researchers who independently read the abstracts and full articles to evaluate whether they qualify for inclusion. Disagreements between the two researchers were solved by consensus with a third reviewer.

2.4. Quality assessment

The quality of the literature in all the cohort studies was evaluated using the Newcastle-Ottawa quality scale (NOS).[4] NOS consists of three factors: patient selection, comparability of the study groups, and

outcome assessment. A score of 0–9 was allocated to all studies. We defined the literature with a score ≥ 6 as of good quality and literature with a score 6 as of poor quality.

2.5. Outcome Measure and data extraction

We defined OS as the primary outcome. The basic information of each study was extracted, and HR and 95% CI were used as the indices for survival evaluation. We assessed the HR values for multiple follow-up time points and selected the results with the longest follow-up time. For studies that only provided survival curves (Kaplan-Meier curves) and other relevant data, HR and 95% CI were estimated using the Digitizer software.[5] For studies that provided results with multiple different correction methods, the results with the highest number of correction factors were included.

2.6. Data Analysis

The Stata software version 15.0 was used for all data analyses. Survival data were analyzed using HR at 95% CI. The random-effects model was used in all meta-analyses.

Subgroup analysis was performed to assess the survival of the two lymph node metastases status (ypN0 and ypN+) after NCRT combined with surgery.

The heterogeneity was considered to be low if I^2 50%, and high if $I^2 \geq 50\%$. We used the random effect model in all the analyses to ensure the reliability of the conclusion.

A sensitivity analysis was performed to identify the source of heterogeneity, and publication bias was evaluated using funnel plots and the Egger's test. A P value of less than 0.05 in two-tailed tests was considered statistically significant.

3. Results

3.1. Trial Flow and Characteristics

Our meta-analysis included seven eligible studies that had more than 10720 patients. [6–12] A flow chart of the procedures followed in literature retrieval and selection is shown in Fig. 1. The basic characteristics of the literature are presented in Table 1.

Table 1
Characteristic of the Included Cohorts

Study	Year	Treatment	Tumor stage	EAC	ESCC	Median follow-up (months)	R0 after surgery(%)	ypN stasus (%)	NOS score
Brescia[6]	2016	NCRT	ypT1-T3Nx	48	3	21.1	100.0	100	6
		NCRT + PT	ypT2-T4Nx	37	3		100.0	100	
Burt[7]	2016	NCRT	ypT0-T4Nx	2742	0	25.7	92.1	35.6	8
		NCRT + PT	ypT0-T4Nx	300	0		89.7	63.7	
Kim[8]	2016	NCRT	ypT1-T4Nx	61	23	60	NR	54.2	7
		NCRT + PT	ypT1-T4Nx	49	13		NR	74.2	
Saeed[9]	2017	NCRT	ypT0-T4Nx	83	9	32	84.7	66.3	6
		NCRT + PT	ypT0-T4Nx	44	2		84.7	78.2	
Mokdad[10]	2018	NCRT	ypT0-T4Nx	NR	0	27	92.0	70	7
		NCRT + PT	ypT0-T4Nx	NR	0		92.0	69	
Christopher[11]	2018	NCRT	ypT0-T4Nx	5184	1068	25.7	97.0	35.0	7
		NCRT + PT	ypT0-T4Nx	421	40		94.0	70.0	
Drake[12]	2019	NCRT	ypT1-T4Nx	295	0	25	100.0	100	8

EAC: Esophageal adenocarcinoma, ESCC: Esophageal squamous cell carcinoma

NCRT: Neoadjuvant chemoradiotherapy, PT: Postoperative chemotherapy

NR: Not reported

R0: complete resection

Study	Year	Treatment	Tumor stage	EAC	ESCC	Median follow-up (months)	R0 after surgery(%)	ypN stasus (%)	NOS score
		NCRT + PT	ypT1-T4Nx	295	0		100.0	100	
EAC: Esophageal adenocarcinoma, ESCC: Esophageal squamous cell carcinoma									
NCRT: Neoadjuvant chemoradiotherapy, PT: Postoperative chemotherapy									
NR: Not reported									
R0: complete resection									

Table 1. **Characteristic of the included cohorts**

3.2. A meta-analysis of the OS in NCRT + PT vs. NCRT

The meta-analysis of OS included seven studies, [6–12] and there was low heterogeneity between the included studies (I^2 = 0, *PH* = 0.730). Relative to NCRT alone, NCRT + PT significantly improved the survival time of EC patients (*HR* = 0.79, *95% CI* 0.74–0.85, *P* < 0.001). (Fig. 2)

Studies of esophageal adenocarcinoma alone and studies combining esophageal adenocarcinoma with a few squamous cell carcinomas were analyzed. PT improved the survival of patients in the EAC group (*HR* = 0.80, *95% CI* 0.74–0.87, *P* < 0.001)[7, 10, 12] and patients in the EAC mixed with a few ESCC groups (*HR* = 0.77, *95% CI* 0.68–0.88, *P* < 0.001).[6, 8, 9, 11]

3.3. A meta-analysis of the OS in ypN0 patients receiving NCRT + PT versus NCRT

Two studies compared OS in patients with negative lymph nodes (ypN0).[7,11] There was considerable heterogeneity among the studies (I^2 = 49.9%, *PH* = 0.136). The random-effect model was used. The results showed that NCRT with PT had a better OS compared with NCRT (*HR* = 0.82, *95% CI* 0.67–1.01, *P* = 0.124). (Fig. 3)

3.4. A meta-analysis of the OS in ypN + patients received NCRT + PT vs. NCRT

Only four studies compared the OS of lymph node-positive patients (ypN+) after NCRT and surgery. [6, 7, 11, 12] There was low heterogeneity between included studies (I^2 = 0, *PH* = 0.450). The results showed that NCRT + PT had a better OS as relative to NCRT alone (*HR* = 0.78, *95% CI* 0.70–0.86, *P* < 0.001). PT improves the OS of patients who receive NCRT and surgery. (Fig. 4)

3.5. Sensitivity analysis

Analysis of study sensitivity was performed by excluding one study at a time and incorporating the effect sizes of the remaining studies. The results of the meta-analysis for the OS in NCRT + PT vs. NCRT revealed the stability of the combined total effect value, and exclusion of any of the studies did not affect the overall estimation.

3.6. Publication bias

No potential publication bias among the included studies was identified by both funnel plots and Egger's test ($P = 0.278$). (Fig. 6)

4. Discussion

NCRT is the standard treatment strategy for advanced esophageal cancer, and PT is also an important treatment for esophageal cancer. Currently, it is not clear whether esophageal cancer (EC) patients who receive NCRT and esophagectomy need further postoperative chemoradiotherapy. Therefore, it is worth assessing whether conducting a PT after NCRT improves the OS of resected EC patients. However, there are no published RCTs that address this question.

In esophagogastric cancer, evidence has demonstrated that patients treated with both neoadjuvant and PT could have a significantly improved OS than patients who do not receive PT. However, the patients received neoadjuvant chemotherapy (not NCRT), and the present study has explored gastric and gastroesophageal junction carcinomas.[13–15]

Samson et al. retrospectively analyzed 3100 patients with pathologic positive nodes (ypN+) after neoadjuvant therapy and esophagectomy. Out of these, 2625 patients (84.7%) did not receive postoperative chemotherapy, while the remaining 475 patients (15.3%) did. The OS of ypN + stage patients who received postoperative chemotherapy was significantly improved. Therefore, postoperative chemotherapy was shown to be independently associated with decreased mortality hazard ($HR = 0.69$, 95% CI 0.57–0.83, $P < 0.001$). More than 80% of the patients in the study had a pathological adenocarcinoma. Of the patients receiving neoadjuvant therapy alone, 2279 (86.8%) received neoadjuvant chemoradiotherapy while only 346 (13.2%) received neoadjuvant chemotherapy. Among the patients receiving neoadjuvant therapy combined with PT, 344 (72.4%) received neoadjuvant chemoradiotherapy, while 131 (27.6%) received neoadjuvant chemotherapy.[16] Our results show that PT may improve the survival of positive lymph node patients after neoadjuvant chemoradiotherapy and resection for EC, especially esophageal adenocarcinoma.

This meta-analysis included seven retrospective cohort studies.[6–12] The pathological type of the subjects in the studies by Mookdad and Drake was esophageal adenocarcinoma.[10,12] Meanwhile, the study subjects of Burt were mainly esophageal adenocarcinoma, mixed with a few squamous cell carcinomas.[7] However, the study by Burt has independent survival data of esophageal adenocarcinoma in the

subgroup analysis, and the survival status of esophageal adenocarcinoma could be extracted separately. The most prevalent pathological type among the subjects of the four included studies was adenocarcinoma (≥ 80%), and squamous cell carcinoma (20%). However, the survival status of adenocarcinoma patients could not be extracted from the original text.

The ypN + lymph node status of patients after neoadjuvant chemoradiotherapy is directly correlated to a poor prognosis, while ypN0 has an inverse correlation.[17] Burt et al. separately analyzed the survival of patients depending on the lymph node status, with the postoperative staging of ypN0 and ypN+. [7] However, Brescia et al and Drake et al only included patients with postoperative ypN + .[6, 12] Christopher et al. conducted separate survival analysis on patients under four conditions according to the different preoperative clinical staging (ycN)/ postoperative lymph node pathological staging [(ypN),: ycN + / ypN +, ycN + / ypN0, ycN0 / ypN +, and ycN0 / ypN0].The other studies have did not distinguish between the lymph node status (ypN0 or ypN+).[11] We further analyzed the survival of patients with esophageal cancer according to the different states of ypN0 and ypN+. The analysis results showed that PT might not significantly improve the OS of resected EC patients who received NCRT and had the ypN0 pathological staging. Although we showed that the NCRT + PT group have a similar or even higher ypN + patients' ratio with NCRT alone (see Table 1), the NCRT + PT group generally had a better OS. It also indirectly suggests that PT could improve the prognosis of EC patients with ypN +.

Several limitations of this meta-analysis need to be considered with caution. First, all the studies included were retrospective cohort researches. Second, the chemotherapy and radiotherapy regimens of NCRT in the various studies were not similar, and some of the studies have not detailed the PT regimens followed. Third, almost all the patients included in the meta-analysis had esophageal adenocarcinoma. Therefore, our conclusion may only apply to esophageal adenocarcinoma cases.

In conclusion, PT may improve the survival of NCRT patients with resected esophageal cancer. However, subgroup analysis showed administration of PT to ypN0 patients did not improve the OS, while the OS of ypN + patients was improved after receiving PT. Considering that the study included an absolute advantage for adenocarcinoma patients. This conclusion may be more applicable to EAC patients treated with NCRT at the ypN + stage. Combined with the current NCCN guidelines, it could be necessary to procure PT for lymph node-positive esophageal adenocarcinoma patients who undergo NCRT combined with surgery. Considering that the researches we included are all retrospective studies, this conclusion should be confirmed by further high-level prospective studies.

Declarations

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Authors' contributions

Manuscript writing: Liang Cheng, Wei Gao

Reference literature review: Liang Cheng, Hao Yang, Yongsheng Zhao

Literature search and Data extraction: Hao Yang, Yu Zhou, Yongsheng Zhao

Program design: Liang Cheng, Maoyong Fu

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Figures

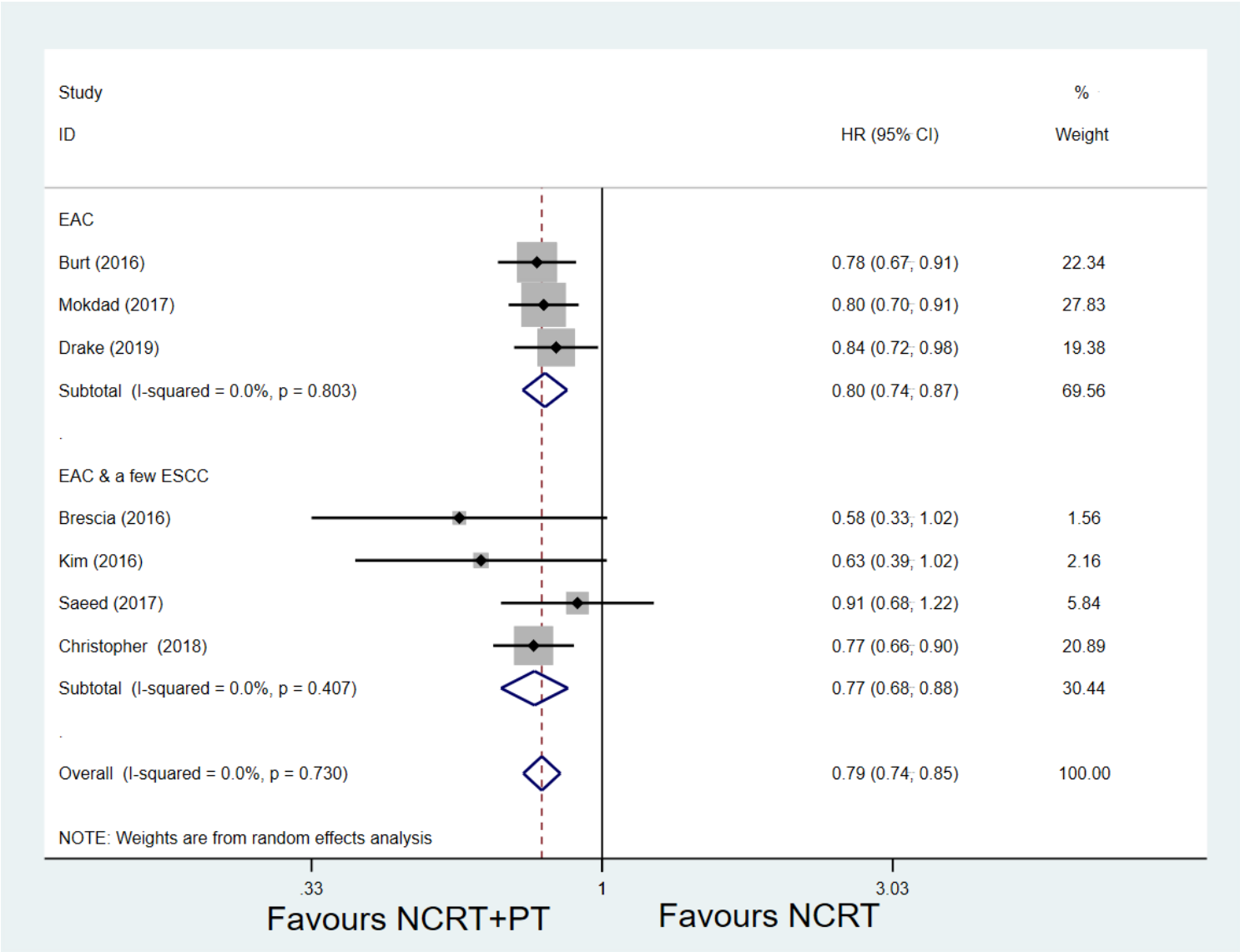
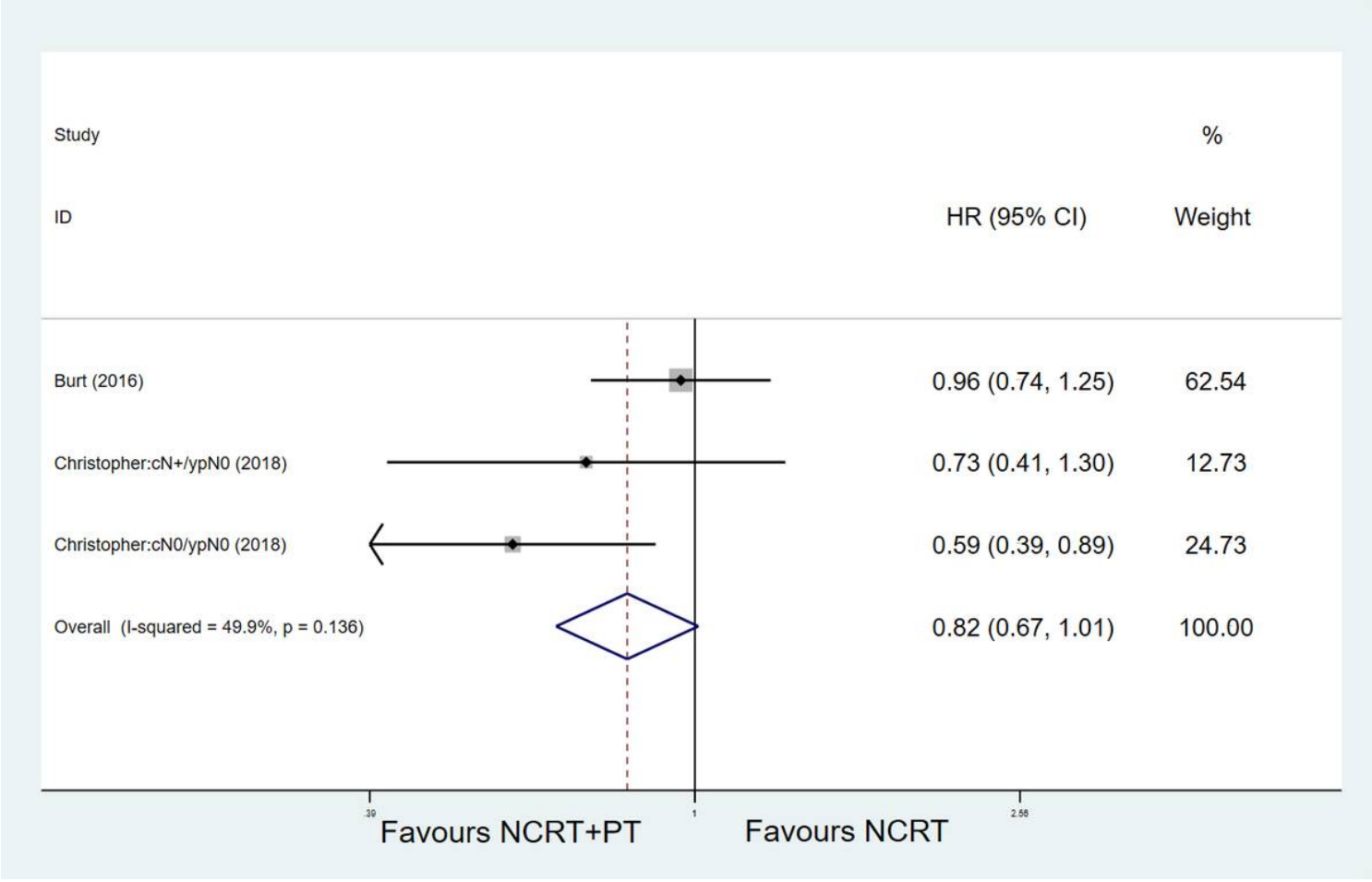


Figure 1


Study
ID
HR (95% CI)
%
Weight
Burt (2016)
0.96 (0.74, 1.25)
62.54
Christopher:cN+/ypN0 (2018)
0.73 (0.41, 1.30)
12.73
Christopher:cN0/ypN0 (2018)
0.59 (0.39, 0.89)
24.73
Overall (I-squared = 49.9%, p = 0.136)
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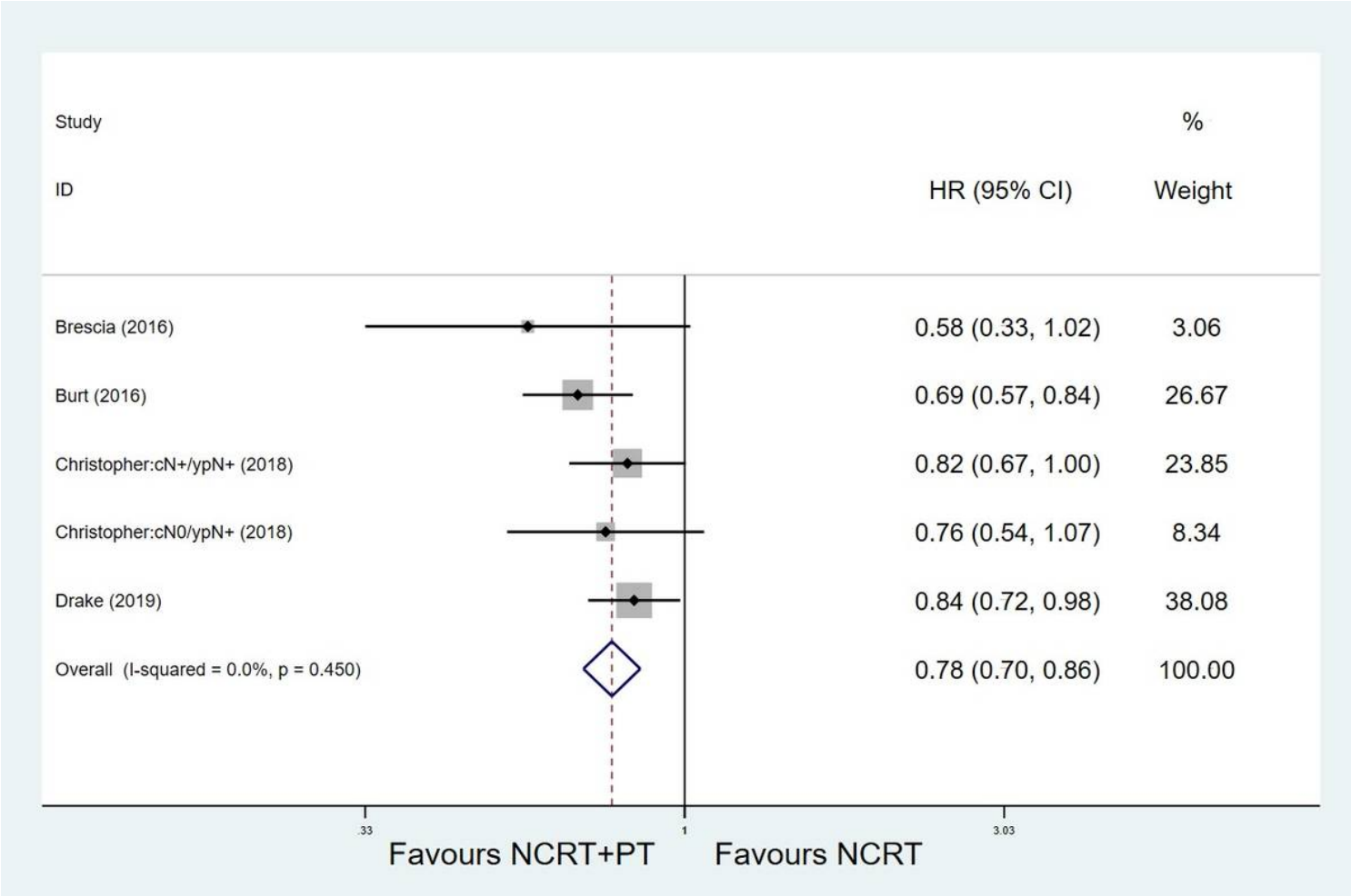
100.00
.39
1
2.58
Favours NCRT+PT
Favours NCRT

Figure 2


Study
ID
HR (95% CI)
%
Weight
Brescia (2016)
0.58 (0.33, 1.02)
3.06
Burt (2016)
0.69 (0.57, 0.84)
26.67
Christopher:cN+/ypN+ (2018)
0.82 (0.67, 1.00)
23.85
Christopher:cN0/ypN+ (2018)
0.76 (0.54, 1.07)
8.34
Drake (2019)
0.84 (0.72, 0.98)
38.08
Overall (I-squared = 0.0%, p = 0.450)
0.78 (0.70, 0.86)
100.00
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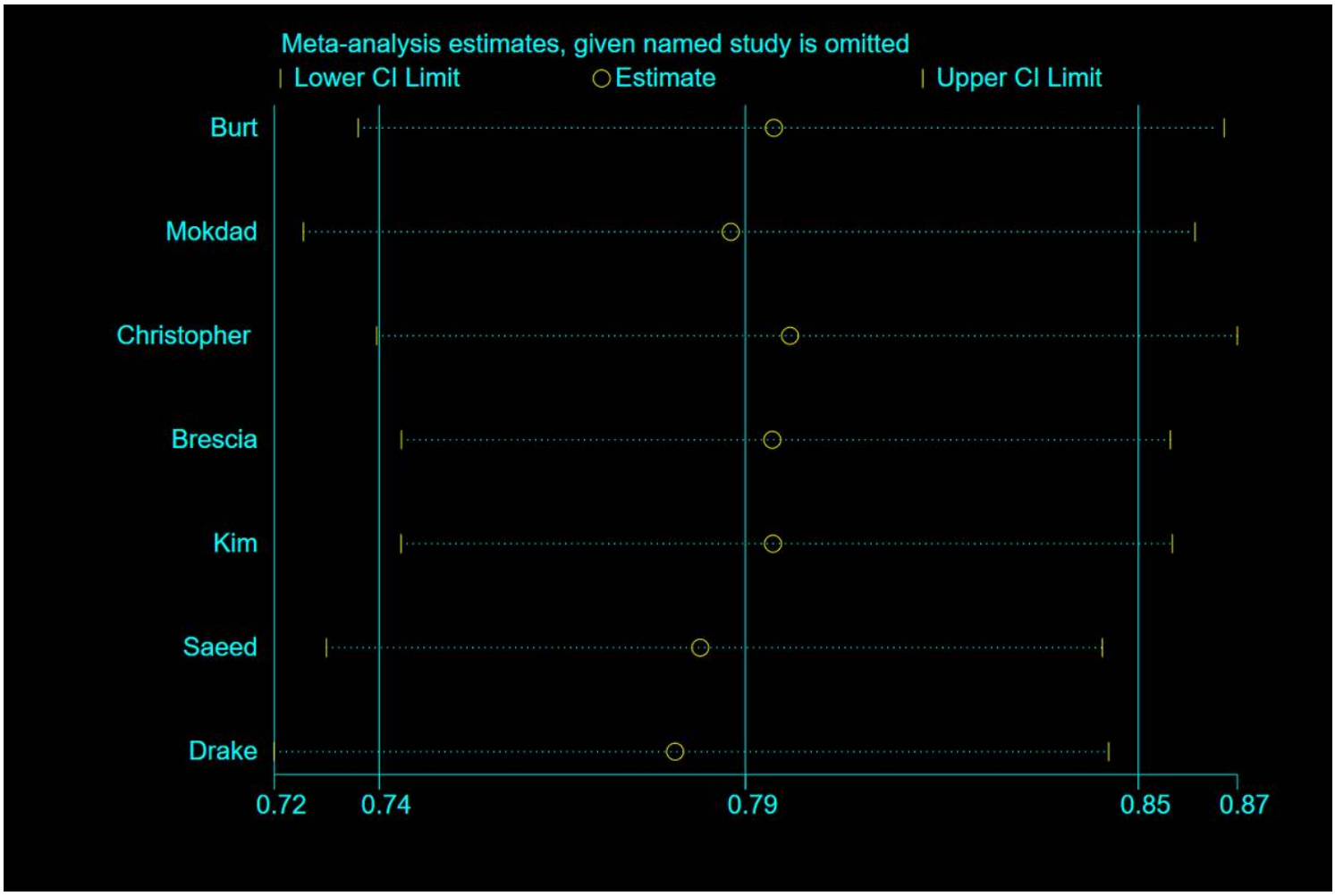
Favours NCRT+PT
Favours NCRT

Figure 3


Meta-analysis estimates, given named study is omitted
Lower CI Limit
Estimate
Upper CI Limit
Burt
Mokdad
Christopher
Brescia
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Drake
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0.74
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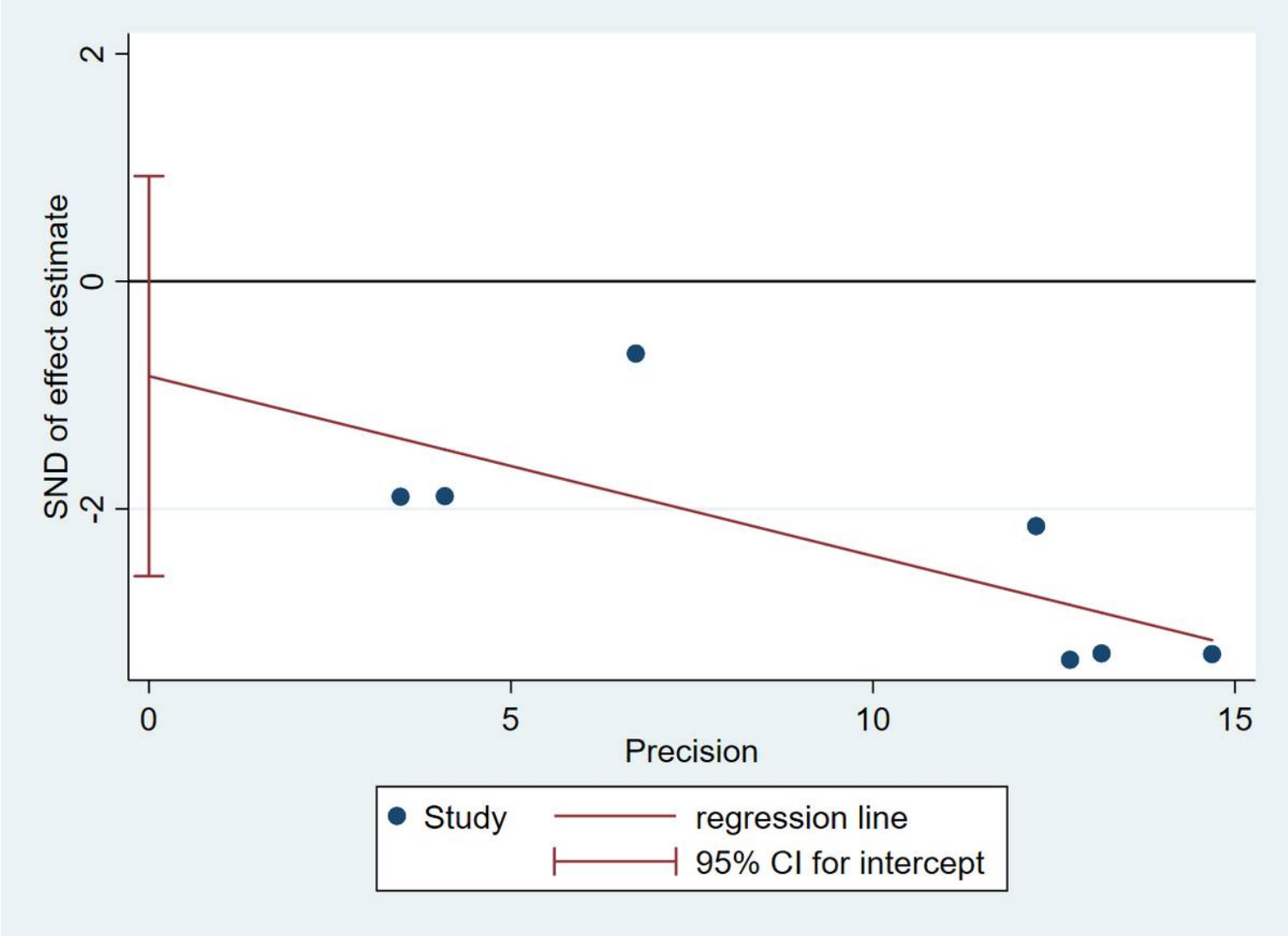
0.87

Figure 4


SND of effect estimate
2
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-2
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5
10
15
Precision
Study
regression line
95% CI for intercept

Figure 5