



Systematic Review Comparison of Efficacy and Safety of Taxanes Plus Platinum and Fluorouracil Plus Platinum in the First-Line Treatment of Esophageal Cancer: A Systematic Review and Meta-Analysis

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Abstract: Fluoropyrimidine plus platinum (FP) and taxanes plus platinum (TP) are standard treatments for esophageal cancer (EC). This systematic review and meta-analysis aim to explore the difference in the therapeutic effect and toxicity of FP and TP regimens in EC patients. PubMed, Embase, and Cochrane were fully searched and analyzed to find relevant articles on EC patients treated with FP and TP regimens up to 22 March 2022. Thirty-one studies, with a total of 3432 participants, were included in this review. The primary outcomes showed that the prognosis and therapeutic efficacy of TP groups were better than those of FP groups for the EC patients treated with definitive chemoradiotherapy treatment (3-year OS: RR: 1.25, 95% CI: 1.08–1.44, *p* = 0.003; 3-year PFS: RR: 1.43, 95% CI: 1.17–1.75, *p* = 0.0006; ORR: RR: 1.17, 95% CI: 1.06–1.29, *p* = 0.001). However, TP therapy was significantly correlated with a higher incidence of leukopenia and thrombocytopenia (*p* < 0.05). In the preoperative neoadjuvant chemoradiotherapy group, these two groups had a similar survival time (*p* > 0.05). The FP regimen corresponded to a higher incidence of thrombocytopenia, while the TP regimen was associated with an increased incidence of febrile leukopenia (*p* < 0.05). Therefore, TP regimens could generate both superior clinical response and survival benefits when compared with FP regimens in EC patients undergoing definitive chemoradiotherapy.

Keywords: chemoradiotherapy; esophageal cancer; fluorouracil; prognosis; taxanes; therapeutic effect

1. Introduction

Esophageal cancer (EC) is one of the most common malignant tumors worldwide [1,2]. GLOBOCAN 2020 reported that EC was listed globally as seventh for incidence and sixth for mortality [2]. Eastern Asia exhibits the highest regional incidence rates, partially because of the large burden in China [3]. The main pathological types of EC are esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) [3]. Although the diagnosis and treatment methods have improved significantly in the past decade, the prognosis of EC patients is still lower than expected [1]. At present, surgery still plays a primary role in the treatment of EC; additionally, the therapeutic effect of surgical monotherapy on some locally advanced EC patients is not satisfactory to clinicians [4,5]. Alternatively, neoadjuvant and radical therapies, such as chemotherapy, radiotherapy, or chemoradiotherapy (CRT), have been widely employed to improve the survival rate of EC patients [4,6,7].

Taxanes, platinum, and fluorouracil have long been recognized as important chemotherapeutic drugs in the treatment of EC [8,9]. Taxanes are mitotic inhibitors, which can restrain cell mitosis by promoting tubulin polymerization and inhibiting depolymerization so as to inhibit tumor growth. So far, there has been a wide range of cytotoxic effects on a variety



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Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). of solid tumors [10]. Tissue culture studies have shown the ability of taxanes to block and/or prolong cells in the G2 or M phase of the cell cycle [11]. It can also induce sensitive cell apoptosis and reduce the consumption of oxygen in solid tumors and, subsequently, increase the local oxygen supply [12]. Fluorouracil antitumor drugs inhibit DNA synthesis by mediating thymine nucleotide synthase activity, which has a beneficial effect on solid tumors, such as gastrointestinal tumors [13]. Fluorouracil can also play a radiosensitizing role by altering the distribution of the cell cycle [14]. At present, CRT is more effective than chemotherapy or radiotherapy alone; it can improve the local control rate, long-term survival rate, and quality of life of EC patients [7,15]. The classical concurrent chemoradiotherapy regimens are those consisting of platinum combined with either fluorouracil or taxanes (paclitaxel or docetaxel) [8,16]. A previous study also indicated that different neoadjuvant chemoradiotherapy (nCRT) or definitive chemoradiotherapy (dCRT) regimens might have dissimilar therapeutic benefits on EC patients [16]. This systematic review and meta-analysis evaluate the difference in the efficacy and toxicity of fluoropyrimidine plus platinum (FP) and taxanes plus platinum (TP) regimens in EC patients undergoing nCRT or dCRT.

2. Materials and Methods

2.1. Data Sources

This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [17]. Screening and data extraction processes were conducted by two independent reviewers, and the differences were resolved by a third reviewer. Multiple electronic databases, including Pubmed, Embase, and Cochrane, were systematically searched to find all the available articles published before 22 March 2022. The keywords or MeSH headings referenced were "Esophageal Neoplasms", "Esophageal Squamous Cell Carcinoma", "Adenocarcinoma of Esophagus", "Taxoids", "Paclitaxel", "Docetaxel", "Fluorouracil", "Capecitabine", "S1", and "Chemoradiotherapies". It should be noted that only human studies in the English language were considered for inclusion.

2.2. Inclusion Criteria

(1) Study design type: randomized controlled trial (RCT), cohort study, or case-control study; (2) Study object: patients diagnosed with EC (ESCC or EAC), as confirmed by pathological evidence; (3) Intervention measures: dCRT or nCRT. The first-line chemotherapy regimens were taxanes (paclitaxel or docetaxel) plus platinum and fluorouracil (5-FU or capecitabine or S1) plus platinum; (4) Study outcome: 3-year survival data, objective response rate (ORR), pathologic complete response (pCR), R0 resection rate, and grade 3 or above toxicity, which could be obtained from the article or survival curve.

2.3. Exclusion Criteria

(1) Articles that were published repeatedly; (2) Articles lacking full texts and responses from the corresponding authors; (3) Articles that were reviews, meeting summaries, singlecase reports, abstracts, expert consensuses, or editorials; (4) Studies with incomplete raw data; (5) Studies including patients with recurrence or metastasis after surgery and chemoradiotherapy; (6) Studies with too small a sample size (sample size < 30).

2.4. Data Extraction and Evidence Evaluation

According to the chemotherapy regimens used, EC patients were divided into two groups: TP and FP. They were further divided into two subgroups, namely, nCRT and dCRT groups, according to the subsequent surgical intervention. The outcomes measured were 3-year overall survival (OS) and 3-year progression-free survival (PFS). The ORR of the dCRT groups and the pCR and R0 resection of the nCRT groups were also included. The following data were extracted from the included articles: the first author, publication year, geographical region, pathological type, chemotherapy regimen, median radiotherapy

dose, number of patients, treatment strategy, clinical stage, follow-up time, 3-year OS and PFS, ORR, pCR, R0 resection rate and grade 3 or above toxicity. When the 3-year OS and PFS were not directly provided in the article, they were extracted from the survival curve using Eagauge Digitizer software. The extracted data were sorted using standard tables. The quality of the RCTs was evaluated using the Cochrane risk bias evaluation tool. The evaluation results were divided into high bias risk, low bias risk, and unknown bias risk. Cohort studies or case-control studies were assessed with the Newcastle Ottawa scale. There were 9 stars in the article quality evaluation, and articles with 6 stars or more were retained.

2.5. Statistical Methods

RevMan 5.3 analysis software was used to statistically analyze the relevant outcome indicators. The summary measure was the risk ratio (RR) with a 95% confidence interval (95% CI) for 3-year OS and 3-year PFS, and p < 0.05 was considered statistically significant. Q tests and I^2 tests were introduced to evaluate the heterogeneity of the results. According to relevant standards in the Cochrane Intervention System Evaluation Manual, the fixed-effect method was used if the heterogeneity was acceptable ($I^2 < 50\%$, p > 0.10). Once the heterogeneity was established ($I^2 \ge 50\%$ and $p \le 0.10$), a random effect model was performed. The sources of heterogeneity, such as methodological heterogeneity, statistical heterogeneity, and clinical heterogeneity, should be analyzed, and sensitivity analysis could be used to exclude a single study. The sensitivity analysis was carried out by Stata software version 14.0, and the risk of publication bias was determined using *Begg's* tests and *Egger's* tests. When p > 0.05, there was considered to be no publication bias. If the number of included articles was less than 10, no further bias test was required.

3. Results

3.1. Selection of Studies

The two evaluators developed retrieval strategies, respectively. Through preliminary inspection, a total of 1300 relevant studies were obtained, including 1298 which met the inclusion criteria and 2 similar reading articles. After further screening, 34 articles were obtained for further evaluation [18–51]. Among these studies, the chemotherapy regimen of one and the study objects of two did not meet the inclusion criteria. Finally, a total of 31 articles involving 3432 participants were included [18–48]. The detailed retrieval process of this review is shown in Figure 1.



Figure 1. Flow diagram of the selection process for included studies in the systematic review.

Among these articles, 14 were from China, 4 were from the United States, 3 were from Germany, 2 were from Canada, 2 were from the Netherlands, 1 was from Italy, 1 was from Australia, 1 was from India, 1 was from Thailand, and 2 were multicenter studies. A total of 12 articles included the treatment strategy of dCRT or concurrent chemoradiotherapy (CCRT), 14 involved nCRT, and 5 included dCRT/CCRT and nCRT. Among the 3432 patients included, 2477 had ESCC, 945 had EAC, and 10 had other pathological types. The characteristics of these selected studies are shown in Tables 1 and S1.

Geographical Research **Pathological Type** Treatment Chemotherapy No. of Patients Authors Year (TP/FP) Area Type (No.) Strategy Regimen

Table 1. Characteristics of 31 selected studies included in the systematic review and meta-analysis.

Hsu et al. [18]	2008	Taiwan, China	RCS	ESCC (127)	dCRT/nCRT	PTX + DDP vs. 5-FU + DDP	57/70
Bai et al. [19]	2013	China	RCT	ESCC (71)	CCRT	DTX + DDP vs. 5-FU + DDP	35/36
Huang et al. [20]	2020	China	RCS	ESCC (46)	CCRT	PTX/DTX + DDP/CBP vs. 5-FU + DDP	22/24
Hu et al. [21]	2016	China	RCS	ESCC (202)	dCRT	PTX + DDP vs. 5-FU + DDP	105/97
Münch et al. [22]	2018	Germany	RCS	ESCC (41)	dCRT	PTX + CBP vs. 5-FU + DDP	18/23
Qu et al. [23]	2017	Canada	RCS	ESCC/EAC (26/47)	dCRT	PTX + CBP vs. 5-FU + DDP/CBP PTX/DTX +	26/47
Sun et al. [24]	2016	China	RCS	ESCC (179)	dCRT	DDP/CBP vs. 5- FU/Tegafur/FT207 + DDP/NDP	83/96
Honing et al. [25]	2013	Multicenter	RCS	ESCC/EAC (51/51)	dCRT	PTX + CBP vs. 5-FU + DDP	55/47
Fang et al. [26]	2017	China	RCS	ESCC (82)	CCRT	PTX + DDP vs. S-1 + DDP	41/41
Yang et al. [27]	2015	China	RCT	ESCC (68)	CCRT	PTX + LBP vs. 5-FU + DDP	34/34
Zhao et al. [28]	2012	China	RCT	ESCC (90)	CCRT	DTX + DDP vs. 5-FU + DDP	45/45
Zhu et al. [29]	2017	China	RCT	ESCC (86)	CCRT	DTX + DDP vs. 5-FU + DDP	45/41
Zhang et al. [30]	2016	China	RCS	ESCC (204)	dCRT	DTX + DDP vs. 5-FU + DDP	102/102
Su et al. [31]	2021	Taiwan, China	PCS	ESCC/ÉAC (133/3)	CCRT/nCRT	PTX + CBP vs. 5-FU + DDP	87/49
Jiang et al. [32]	2020	Canada	RCS	ESCC/EAC (34/59)	dCRT/nCRT	PTX + CBP vs. 5-FU + DDP	40/53
Hsieh et al. [33]	2021	Taiwan, China	RCS	ESCC (229)	CCRT/nCRT	PTX + CBP vs. 5-FU + DDP	83/146
Dröge et al. [34]	2021	Germany	RCS	ESCC (90)	nCRT	PTX + CBP vs. 5-FU + DDP	27/63
Wong et al. [35]	2020	Hong Kong, China	RCS	ESCC (200)	nCRT	PTX + CBP vs. 5-FU + DDP	100/100
Bajwa et al. [36]	2018	India	RCS	ESCC/EAC (38/12)	nCRT	PTX + CBP vs. 5-FU/Cape + DDP	30/20
Xi et al. [37]	2017	China	RCS	ESCC (94)	nCRT	DTX + DDP vs. 5-FU + DDP	32/62
Sanford et al. [38]	2017	America	RCS	ESCC/EAC (18/94)	nCRT	PTX + CBP vs. 5-FU + DDP	77/35
Jipping et al. [39]	2017	Netherlands	RCS	ESCC/EAC (22/104)	nCRT	PTX + CBP vs. 5-FU + DDP	63/63
Haisley et al. [40]	2017	Australia	RCS	ESCC/EAC (20/122)	nCRT	PTX + CBP vs. 5-FU + DDP	87/55
Duff et al. [41]	2017	America	RCS	ESCC/EAC (3/35)	nCRT	PTX + CBP vs. 5-FU + DDP	14/24
Boggs et al. [42]	2014	America	RCS	ESCC/EAC (44/115)	nCRT	PTX + DDP/CBP vs. 5-FU + DDP	30/129
Blom et al. [43]	2013	Netherlands	RCS	ESCC/EAC/other (39/124/2)	nCRT	PTX + CBP vs. 5-FU + DDP	92/73

Authors	Year	Geographical Area	Research Type	Pathological Type (No.)	Treatment Strategy	Chemotherapy Regimen	No. of Patients (TP/FP)
Orditura et al. [44]	2011	Italy	RCS	ESCC/EAC (54/18)	nCRT	PTX + DDP vs. 5-FU + DDP	33/39
Adelstein et al. [45]	2000	America	RCS	ESCC/EAC/other (29/70/3)	nCRT	PTX + DDP vs. 5-FU + DDP	40/62
Münch et al. [46]	2017	Germany	RCS	ESCC (44)	nCRT	PTX + CBP vs. 5-FU + DDP	18/26
Tamtai et al. [47]	2017	Thailand	RCS	ESCC/EAC/other (113/6/5)	CCRT/nCRT	PTX + CBP vs. 5-FU + Platinum	60/64
Mukherjee et al. [48]	2017	Multicenter	RCT	EAC (85)	nCRT	PTX + CBP vs. Cape + OXA	43/42

Table 1. Cont.

Abbreviations: 5-FU, fluorouracil; Cape, capecitabine; CBP, carboplatin; CCRT, concurrent chemoradiotherapy; dCRT, definitive chemoradiotherapy; DDP, cisplatin; DTX, docetaxel; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; LBP, lobaplatin; nCRT, neoadjuvant chemoradiotherapy; NDP, nedaplatin; OXA, oxaliplatin; PTX, paclitaxel; PCS, prospective cohort study; RCS, retrospective cohort study; RCT, randomized controlled trial.

3.2. Quality Evaluation

Five RCTs with a low risk of bias evaluated using the Cochrane risk bias were included in this study (Figure 2). The 26 cohort studies had a medium-to-high quality, as assessed by the Newcastle Ottawa scale.



Figure 2. The Cochrane risk bias of five randomized controlled trials. (**a**) risk of bias graph; (**b**) risk of bias summary.

3.3. Survival Outcome

3.3.1. TP Results in Better Disease Control and Long-Term Survival Compared with FP in the dCRT Group

A total of 12 studies reported 3-year OS in EC patients treated with dCRT. In these studies (ESCC vs. EAC: 1118 vs. 98), the pathological types included two mixed ESCC and EAC cases [23,25], and the rest only included ESCC. The summary results illustrated that the 3-year OS of the TP group was better than that of the FP group (RR: 1.25, 95% CI: 1.08–1.44, p = 0.003), and there was no heterogeneity in these results ($I^2 = 24\%$, p = 0.21, Figure 3a).

(a)	TP	FP			Risk Ratio	Risk Ratio									
Study or Subgroup	Events Tota	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	(b)	TP		FP			Risk Ratio	Risk Ratio	
Bai et al. 2013	17 3	5 15	36	7.4%	1.17 [0.70, 1.95]		Study or Subgroup	Events	Total	Events	Total \	Neight	M-H, Random, 95% C	M-H, Random, 95%	CI
Fang et al. 2017	13 4	13	41	6.5%	1.00 [0.53, 1.89]	_ _	Fang et al. 2017	10	41	8	41	7.4%	1.25 [0.55, 2.85]	- -	
Honing et al. 2013	16 5	5 10	47	5.4%	1.37 [0.69, 2.72]	+	Honing et al. 2013	13	55	9	47	8.1%	1.23 [0.58, 2.63]	- -	
Hsu et al. 2008	10 1	3 8	26	3.3%	1.81 [0.89, 3.67]		Hsu et al. 2008	12	18	5	26	7.0%	3.47 [1.48, 8.13]		-
Hu et al. 2016	50 10	5 31	97	16.0%	1.49 [1.05, 2.12]		Hu et al. 2016	14	105	8	97	7.3%	1.62 [0.71, 3.68]	+	
Huang et al. 2020	10 2	2 10	24	4.8%	1.09 [0.56, 2.11]		Huang et al. 2020	7	22	5	24	5.8%	1.53 [0.57, 4.12]		
Münch et al. 2018	10 1	3 9	23	3.9%	1 42 [0 74 2 74]		Münch et al. 2018	10	18	7	23	8.3%	1.83 [0.87, 3.84]		
Quetal 2017	4 2	5 19	47	6.7%	0.38 [0.14, 1.00]		Qu et al. 2017	5	26	13	47	6.4%	0.70 [0.28, 1.73]		
Sun et al. 2016	32 8	33	96	15.2%	1 12 [0 76 1 65]	+	Sun et al. 2016	24	83	39	96	13.5%	0.71 [0.47, 1.08]		
Zhang et al. 2016	40 10	25	102	12.4%	1 60 [1 05 2 43]		Zhang et al. 2016	41	102	25	102	13.5%	1.64 [1.08, 2.48]		
Zhang et al. 2012	20 4	5 11	45	5.5%	1 82 [0 99 3 34]		Zhao et al. 2012	17	45	9	45	8.9%	1.89 [0.94, 3.78]		
Zhuotel 2012 Zhuetel 2017	26 4	2 25	30	13.0%	0.94 [0.67, 1.32]	+	Zhu et al. 2017	22	43	22	39	13.7%	0.91 [0.61, 1.36]	1	
210 60 01. 2017	20 4	, 20	00	10.070	0.04[0.07, 1.02]		Total (95% CI)		558		587	100.0%	1.31 [0.99, 1.74]	•	
Total (95% CI)	593		623	100.0%	1.25 [1.08, 1.44]	•	Total events	175		150					
Total events	248	209					Heterogeneity: Tau ² =	0.11; Chi ² :	= 21.13	, df = 10 (P = 0.02	2); l ² = 53	3%		+
Heterogeneity: Chi ² =	14.49. df = 11 (e = 0.21); I	² = 24%		H		Test for overall effect:	Z = 1.86 (P	= 0.06)				0.01 0.1 1	10 100
Test for overall effect:	Z = 2.95 (P = 0)	003)			0.01	0.1 1 10 100								Favours [FF] Favours	[[P]
		,				Favours [FP] Favours [TP]									
(c)	тр	FP			Risk Ratio	Rick Ratio									
(c) Study or Subgroup	TP Events Tota	FP	Total	Weight	Risk Ratio M-H Fixed 95% Cl	Risk Ratio M-H Fixed 95% Cl	(d)						Diel Datie		
(c) Study or Subgroup	TP Events Tota	FP I Events	Total	Weight	Risk Ratio M-H, Fixed, 95% Cl	Risk Ratio M-H, Fixed, 95% Cl	(d)	TP		FP			Risk Ratio	Risk Ratio	
(c) <u>Study or Subgroup</u> Fang et al. 2017 Honing et al. 2013	TP Events Tota 10 4	FP I Events	<u>Total</u> 41	<u>Weight</u> 7.5%	Risk Ratio <u>M-H, Fixed, 95% Cl</u> 1.25 [0.55, 2.85] 1.23 [0.58, 2.63]	Risk Ratio M-H, Fixed, 95% Cl	(d) Study or Subgroup	TP Events	Total	FP Events	Total	Weight	Risk Ratio M-H. Fixed, 95% Cl	Risk Ratio M-H. Fixed. 95% C	
(c) <u>Study or Subgroup</u> Fang et al. 2017 Honing et al. 2013 House tal. 2008	TP Events Tota 10 4 13 52	FP <u>I Events</u> 8 9 5 9	Total 41 47	Weight 7.5% 9.0%	Risk Ratio <u>M-H, Fixed, 95% Cl</u> 1.25 [0.55, 2.85] 1.23 [0.58, 2.63] 2.47 (1.48, 8.13]	Risk Ratio <u>M-H, Fixed, 95% Cl</u>	(d) <u>Study or Subgroup</u> Bai et al. 2013	TP Events 26	Total 35	FP Events 25	Total 36	<u>Weight</u> 10.0%	Risk Ratio <u>M-H. Fixed, 95% CI</u> 1.07 [0.80, 1.43]	Risk Ratio M-H. Fixed, 95% C	
(c) <u>Study or Subgroup</u> Fang et al. 2017 Honing et al. 2013 Hsu et al. 2008 Hu et al. 2016	TP Events Tota 10 4 13 5 12 1 14 10	FP <u>I Events</u> 5 9 3 5 5	Total 41 47 26	Weight 7.5% 9.0% 3.8%	Risk Ratio <u>M-H, Fixed, 95% Cl</u> 1.25 [0.55, 2.85] 1.23 [0.58, 2.63] 3.47 [1.48, 8.13] 1.62 (0.74, 2.68]	Risk Ratio M-H, Fixed, 95% Cl	(d) <u>Study or Subgroup</u> Bai et al. 2013 Fang et al. 2017	TP Events 26 34	<u>Total</u> 35 41	FP Events 25 34	<u>Total</u> 36 41	<u>Weight</u> 10.0% 13.8%	Risk Ratio <u>M-H. Fixed, 95% CI</u> 1.07 [0.80, 1.43] 1.00 [0.82, 1.22]	Risk Ratio M-H. Fixed, 95% C	
(c) <u>Study or Subgroup</u> Fang et al. 2017 Honing et al. 2013 Hsu et al. 2008 Hu et al. 2016 Hugge et al. 2020	TP Events Tota 10 4 13 53 12 13 14 103 7 22	FP <u>I Events</u> 9 3 5 8 5 5 8 5 8 5 8 5 8 5 8 5 8 5 8 5 8 5 8 5 8 5 8 5 8 5 8 5 8 5 8 5 8 5 8 5 5 8 5 8 5 8 5 8 8 8 8 8 8 8 8 8 8 8 8 8	Total 41 47 26 97 24	Weight 7.5% 9.0% 3.8% 7.7%	Risk Ratio <u>M-H, Fixed, 95% Cl</u> 1.25 [0.55, 2.85] 1.23 [0.58, 2.63] 3.47 [1.48, 8.13] 1.62 [0.71, 3.68] 1.53 (0.57, 4.13]	Risk Ratio M-H, Fixed, 95% Cl	(d) <u>Study or Subgroup</u> Bai et al. 2013 Fang et al. 2017 Hu et al. 2016	TP Events 26 34 55	Total 35 41 105	FP <u>Events</u> 25 34 37	Total 36 41 97	<u>Weight</u> 10.0% 13.8% 15.6%	Risk Ratio <u>M-H. Fixed. 95% Cl</u> 1.07 [0.80, 1.43] 1.00 [0.82, 1.22] 1.37 [1.00, 1.88]	Risk Ratio M-H. Fixed. 95% C	
(c) <u>Study or Subgroup</u> Fang et al. 2017 Honing et al. 2013 Hsu et al. 2008 Hu et al. 2016 Huang et al. 2020 Minche et al. 2019	TP <u>Events</u> Tota 10 4 13 55 12 11 14 10 7 22 10 11	FP <u>I Events</u> 8 5 9 3 5 5 8 2 5 7	Total 41 47 26 97 24 22	Weight 7.5% 9.0% 3.8% 7.7% 4.5%	Risk Ratio <u>M-H, Fixed, 95% Cl</u> 1.25 [0.55, 2.85] 1.23 [0.58, 2.63] 3.47 [1.48, 8.13] 1.62 [0.71, 3.68] 1.53 [0.57, 4.12] 1.83 [0.57, 4.12]	Risk Ratio M-H, Fixed, 95% Cl	(d) <u>Study or Subgroup</u> Bai et al. 2013 Fang et al. 2017 Hu et al. 2016 Huang et al. 2020	TP Events 26 34 55 18	Total 35 41 105 22	FP <u>Events</u> 25 34 37 16	Total 36 41 97 24	Weight 10.0% 13.8% 15.6% 6.2%	Risk Ratio <u>M-H. Fixed, 95% Cl</u> 1.07 [0.80, 1.43] 1.00 [0.82, 1.22] 1.37 [1.00, 1.88] 1.23 [0.87, 1.73]	Risk Ratio M-H. Fixed, 95% C	
(c) <u>Study or Subgroup</u> Fang et al. 2017 Honing et al. 2013 Hsu et al. 2008 Hu et al. 2016 Huang et al. 2020 Münch et al. 2018 Outstel 2017	TP <u>Events</u> Tota 10 4 13 55 12 11 14 10 7 22 10 11 5 22	FP <u>I Events</u> 8 9 8 5 8 5 8 5 8 2 5 8 7 7 12 12 12 12 12 12 12 12 12 12	Total 41 47 26 97 24 23	Weight 7.5% 9.0% 3.8% 7.7% 4.5% 5.7%	Risk Ratio <u>M-H, Fixed, 95% Cl</u> 1.25 [0.55, 2.85] 1.23 [0.58, 2.63] 3.47 [1.48, 8.13] 1.62 [0.71, 3.68] 1.53 [0.57, 4.12] 1.83 [0.87, 3.84] 0.70 [0.94, 4.73]	Risk Ratio M-H, Fixed, 95% Cl	(d) <u>Study or Subgroup</u> Bai et al. 2013 Fang et al. 2017 Hu et al. 2016 Huang et al. 2020 Sun et al. 2016	TP Events 26 34 55 18 58	Total 35 41 105 22 81	FP 25 34 37 16 61	Total 36 41 97 24 96	Weight 10.0% 13.8% 15.6% 6.2% 22.6%	Risk Ratio <u>M-H. Fixed, 95% CI</u> 1.07 [0.80, 1.43] 1.00 [0.82, 1.22] 1.37 [1.00, 1.88] 1.23 [0.87, 1.73] 1.13 [0.92, 1.38]	Risk Ratio M-H. Fixed, 95% C	
(c) Fang et al. 2017 Honing et al. 2017 Hsu et al. 2018 Hu et al. 2008 Hu et al. 2016 Huang et al. 2020 Münch et al. 2018 Qu et al. 2020	TP <u>Events</u> Tota 10 4 13 5 12 1 14 10 7 2 10 1 1 5 2 2 4	FP <u>I Events</u> 8 9 3 5 8 5 8 2 5 8 7 6 13 8 2 2 5 8 7 1 1 1 1 1 1 1 1 1 1 1 1 1	Total 41 47 26 97 24 23 47	Weight 7.5% 9.0% 3.8% 7.7% 4.5% 5.7% 8.6%	Risk Ratio <u>M-H, Fixed, 95% Cl</u> 1.25 [0.55, 2.85] 1.23 [0.58, 2.63] 3.47 [1.48, 8.13] 1.62 [0.71, 3.68] 1.53 [0.57, 4.12] 1.83 [0.87, 3.84] 0.70 [0.28, 1.73] 0.74 [4.64]	Risk Ratio M-H, Fixed, 95% Cl	(d) <u>Study or Subgroup</u> Bai et al. 2013 Fang et al. 2017 Hu et al. 2016 Huang et al. 2020 Sun et al. 2016 Yang et al. 2015	TP 26 34 55 18 58 25	Total 35 41 105 22 81 34	FP Events 25 34 37 16 61 17	Total 36 41 97 24 96 34	Weight 10.0% 13.8% 15.6% 6.2% 22.6% 6.9%	Risk Ratio <u>M-H. Fixed, 95% CI</u> 1.07 [0.80, 1.43] 1.00 [0.82, 1.22] 1.37 [1.00, 1.88] 1.23 [0.87, 1.73] 1.13 [0.92, 1.38] 1.47 [0.99, 2.18]	Risk Ratio M-H. Fixed, 95% C	
(c) <u>Study or Subgroup</u> Fang et al. 2017 Honing et al. 2013 Hsu et al. 2008 Hu et al. 2008 Hu et al. 2016 Huang et al. 2020 Münch et al. 2018 Qu et al. 2017 Sun et al. 2016	TP Events Tota 10 4 13 5 12 11 14 10 7 22 10 11 5 22 24 8 14 10	FP Events 8 5 9 5 8 5 8 2 5 8 7 5 13 3 3 9 2 5 1 2 5 1 1 1 1 1 1 1 1 1 1 1 1 1	Total 41 47 26 97 24 23 47 96	Weight 7.5% 9.0% 3.8% 7.7% 4.5% 5.7% 8.6% 0.0%	Risk Ratio <u>M-H, Fixed, 95% Cl</u> 1.25 [0.55, 2.85] 1.23 [0.58, 2.63] 3.47 [1.48, 8.13] 1.62 [0.71, 3.68] 1.53 [0.57, 4.12] 1.83 [0.87, 3.84] 0.70 [0.28, 1.73] 0.71 [0.47, 1.08] 4.64 [0.0, 2.41]	Risk Ratio M-H, Fixed, 95% Cl	(d) <u>Study or Subgroup</u> Bai et al. 2013 Fang et al. 2017 Hu et al. 2016 Huang et al. 2020 Sun et al. 2016 Yang et al. 2015 Zhao et al. 2012	TP Events 26 34 55 18 58 25 33	Total 35 41 105 22 81 34 45	FP <u>Events</u> 25 34 37 16 61 17 24	Total 36 41 97 24 96 34 45	Weight 10.0% 13.8% 15.6% 6.2% 22.6% 6.9% 9.7%	Risk Ratio <u>M-H. Fixed, 95% Cl</u> 1.07 [0.80, 1.43] 1.00 [0.82, 1.22] 1.37 [1.00, 1.88] 1.23 [0.87, 1.73] 1.13 [0.92, 1.38] 1.47 [0.99, 2.18] 1.38 [0.99, 1.90]	Risk Ratio M-H. Fixed. 95% C	
(c) <u>Study or Subgroup</u> Fang et al. 2017 Honing et al. 2013 Hsu et al. 2008 Hu et al. 2016 Huang et al. 2016 Münch et al. 2016 Qu et al. 2016 Zhang et al. 2016	TP Events Tota 10 4 13 5 12 14 14 10 7 2 10 14 5 20 24 8 41 10 7 2 2 10 14 5 20 2 14 14 10 14 10 15 10 14 10 15 10 14 10 15 10	FP Events 8 5 9 3 5 8 2 5 8 7 5 13 3 3 9 2 2 5 5 7 5 12 13 13 13 13 13 13 13 13 13 13	Total 41 47 26 97 24 23 47 96 102	Weight 7.5% 9.0% 3.8% 7.7% 4.5% 5.7% 8.6% 0.0% 23.3%	Risk Ratio M-H, Fixed, 95% Cl 1.25 [0.55, 2.85] 1.23 [0.58, 2.63] 3.47 [1.48, 8.13] 1.62 [0.71, 3.68] 1.53 [0.57, 4.12] 1.83 [0.87, 3.84] 0.70 [0.28, 1.73] 0.71 [0.47, 1.08] 1.64 [1.08, 2.48]	Risk Ratio M-H, Fixed, 95% Cl	(d) <u>Study or Subgroup</u> Bai et al. 2013 Fang et al. 2017 Hu et al. 2016 Huang et al. 2020 Sun et al. 2016 Yang et al. 2015 Zhao et al. 2012 Zhu et al. 2017	TP Events 26 34 55 18 58 25 33 33 38	Total 35 41 105 22 81 34 45 45	FP <u>Events</u> 25 34 37 16 61 17 24 36	Total 36 41 97 24 96 34 45 41	Weight 10.0% 13.8% 15.6% 6.2% 22.6% 6.9% 9.7% 15.3%	Risk Ratio <u>M-H. Fixed, 95% Cl</u> 1.07 [0.80, 1.43] 1.00 [0.82, 1.22] 1.37 [1.00, 1.88] 1.23 [0.87, 1.73] 1.13 [0.92, 1.38] 1.47 [0.99, 2.18] 1.38 [0.99, 1.90] 0.96 [0.81, 1.14]	Risk Ratio M-H. Fixed. 95% C	
(c) <u>Study or Subgroup</u> Fang et al. 2017 Honing et al. 2013 Hsu et al. 2008 Hu et al. 2016 Huang et al. 2016 Qu et al. 2017 Sun et al. 2016 Zhang et al. 2016 Zhang et al. 2012	TP Events Tota 10 4 13 5% 12 1% 14 10 7 2 10 1% 5 2 24 8% 41 10 17 4	FP Events 5 9 5 8 2 5 3 7 5 13 3 39 2 25 5 9 5 9	Total 41 47 26 97 24 23 47 96 102 45	Weight 7.5% 9.0% 3.8% 7.7% 4.5% 5.7% 8.6% 0.0% 23.3% 8.4%	Risk Ratio <u>M-H, Fixed, 95% Cl</u> 1.25 [0.55, 2.85] 1.23 [0.58, 2.63] 3.47 [1.48, 8.13] 1.62 [0.71, 3.68] 1.53 [0.57, 4.12] 1.83 [0.87, 3.84] 0.70 [0.28, 1.73] 0.71 [0.47, 1.08] 1.64 [1.08, 2.48] 1.89 [0.94, 3.78]	Risk Ratio M-H, Fixed, 95% Cl	(d) <u>Study or Subgroup</u> Bai et al. 2013 Fang et al. 2017 Hu et al. 2016 Huang et al. 2020 Sun et al. 2016 Yang et al. 2015 Zhao et al. 2012 Zhu et al. 2017	TP 26 34 55 18 58 25 33 38	Total 35 41 105 22 81 34 45 45	FP <u>Events</u> 25 34 37 61 17 24 36	Total 36 41 97 24 96 34 45 41	Weight 10.0% 13.8% 15.6% 6.2% 22.6% 6.9% 9.7% 15.3%	Risk Ratio <u>M-H. Fixed, 95% Cl</u> 1.07 [0.80, 1.43] 1.00 [0.82, 1.22] 1.37 [1.00, 1.88] 1.23 [0.87, 1.73] 1.13 [0.92, 1.38] 1.47 [0.99, 2.18] 1.38 [0.99, 1.90] 0.96 [0.81, 1.14]	Risk Ratio M-H. Fixed. 95% C	
(c) <u>Study or Subgroup</u> Fang et al. 2017 Honing et al. 2013 Hsu et al. 2008 Hu et al. 2016 Huang et al. 2016 Münch et al. 2017 Sun et al. 2016 Zhang et al. 2016 Zhao et al. 2012 Zhu et al. 2017	TP Events Tota 10 4 13 52 14 10 7 2 10 11 5 2 24 8 41 10 17 4 22 4	FP L Events 5 9 3 5 5 8 2 5 3 7 5 13 3 39 2 25 5 9 3 22	Total 41 47 26 97 24 23 47 96 102 45 39	Weight 7.5% 9.0% 3.8% 7.7% 4.5% 5.7% 8.6% 0.0% 23.3% 8.4% 21.5%	Risk Ratio M-H, Fixed, 95% Cl 1.25 [0.55, 2.85] 1.23 [0.58, 2.63] 3.47 [1.48, 8.13] 1.62 [0.71, 3.68] 1.53 [0.57, 4.12] 1.83 [0.57, 4.12] 1.83 [0.57, 3.84] 0.70 [0.28, 1.73] 0.71 [0.47, 1.08] 1.64 [1.08, 2.48] 1.89 [0.94, 3.78] 0.91 [0.61, 1.36]	Risk Ratio M-H, Fixed, 95% Cl	(d) <u>Study or Subgroup</u> Bai et al. 2013 Fang et al. 2017 Hu et al. 2016 Huang et al. 2020 Sun et al. 2016 Yang et al. 2015 Zhao et al. 2012 Zhu et al. 2017 Total (95% CI)	TP 26 34 55 18 58 25 33 38	Total 35 41 105 22 81 34 45 45 45 40 8	FP Events 25 34 37 16 61 17 24 36	Total 36 41 97 24 96 34 45 41 414	Weight 10.0% 13.8% 15.6% 6.2% 22.6% 6.9% 9.7% 15.3% 100.0%	Risk Ratio <u>M-H. Fixed, 95% Cl</u> 1.07 [0.80, 1.43] 1.00 [0.82, 1.22] 1.37 [1.00, 1.88] 1.23 [0.87, 1.73] 1.13 [0.92, 1.38] 1.47 [0.99, 2.18] 1.38 [0.99, 1.90] 0.96 [0.81, 1.14] 1.17 [1.06, 1.29]	Risk Ratio M-H. Fixed. 95% C	
(c) <u>Study or Subgroup</u> Fang et al. 2017 Honing et al. 2013 Hsu et al. 2008 Hu et al. 2016 Huang et al. 2020 Münch et al. 2018 Qu et al. 2017 Sun et al. 2016 Zhang et al. 2016 Zhao et al. 2012 Zhu et al. 2017 Total (95% CI)	TP Events Tota 10 4 13 52 12 14 14 10 7 2 10 14 5 2 24 8 41 10 17 4 22 4	FP Events 5 9 5 8 5 8 2 5 5 8 7 5 13 3 39 2 25 5 9 3 22 5 9 3 22 5	Total 41 47 26 97 24 23 47 96 102 45 39 491	Weight 7.5% 9.0% 3.8% 7.7% 4.5% 5.7% 8.6% 0.0% 23.3% 8.4% 21.5% 100.0%	Risk Ratio M-H, Fixed, 95% Cl 1.25 [0.55, 2.85] 1.23 [0.58, 2.63] 3.47 [1.48, 8.13] 1.62 [0.71, 3.68] 1.53 [0.57, 4.12] 1.83 [0.57, 4.12] 1.83 [0.7, 3.84] 0.70 [0.28, 1.73] 0.71 [0.47, 1.08] 1.64 [1.08, 2.48] 1.89 [0.94, 3.78] 0.91 [0.61, 1.36] 1.43 [1.17, 1.75]	Risk Ratio M-H, Fixed, 95% Cl	(d) <u>Study or Subgroup</u> Bai et al. 2013 Fang et al. 2017 Hu et al. 2016 Huang et al. 2020 Sun et al. 2016 Yang et al. 2015 Zhao et al. 2012 Zhu et al. 2017 Total (95% CI) Total events	TP <u>Events</u> 26 34 55 18 58 25 33 38 287	Total 35 41 105 22 81 34 45 45 45 40 8	FP <u>Events</u> 25 34 37 16 61 17 24 36 250	Total 36 41 97 24 96 34 45 41 41 414	Weight 10.0% 13.8% 15.6% 6.2% 22.6% 6.9% 9.7% 15.3% 100.0%	Risk Ratio <u>M-H. Fixed, 95% Cl</u> 1.07 [0.80, 1.43] 1.00 [0.82, 1.22] 1.37 [1.00, 1.88] 1.23 [0.87, 1.73] 1.13 [0.92, 1.38] 1.47 [0.99, 2.18] 1.38 [0.99, 1.90] 0.96 [0.81, 1.14] 1.17 [1.06, 1.29]	Risk Ratio M-H. Fixed. 95% C	
(c) <u>Study or Subgroup</u> Fang et al. 2017 Honing et al. 2013 Hsu et al. 2008 Hu et al. 2016 Huang et al. 2010 Münch et al. 2017 Sun et al. 2016 Zhang et al. 2016 Zhao et al. 2017 Total (95% CI) Total events	TP Events Tota 10 4 13 5% 12 1% 14 100 7 2 10 1% 5 2 24 8% 41 100 17 4% 22 4% 151 151	FP Events 5 9 5 8 2 5 3 7 5 13 3 39 2 25 5 9 3 22 5 9 3 22 5 9 3 22 5 9 3 22	Total 41 47 26 97 24 23 47 96 102 45 39 491	Weight 7.5% 9.0% 3.8% 4.5% 5.7% 8.6% 0.0% 23.3% 8.4% 21.5% 100.0%	Risk Ratio <u>M-H, Fixed, 95% Cl</u> 1.25 [0.55, 2.85] 1.23 [0.58, 2.63] 3.47 [1.48, 8.13] 1.62 [0.71, 3.68] 1.53 [0.57, 4.12] 1.83 [0.87, 3.84] 0.70 [0.28, 1.73] 0.71 [0.47, 1.08] 1.64 [1.08, 2.48] 1.89 [0.94, 3.78] 0.91 [0.61, 1.36] 1.43 [1.17, 1.75]	Risk Ratio M-H, Fixed, 95% Cl	(d) <u>Study or Subgroup</u> Bai et al. 2013 Fang et al. 2017 Hu et al. 2016 Huang et al. 2020 Sun et al. 2016 Yang et al. 2015 Zhao et al. 2012 Zhu et al. 2017 Total (95% CI) Total events Heterogeneity: Chi ² =	TP <u>Events</u> 26 34 55 18 58 25 33 38 287 11.47, df =	Total 35 41 105 22 81 34 45 45 408 : 7 (P =	FP <u>Events</u> 25 34 37 16 61 17 24 36 250 0.12); I ² =	Total 36 41 97 24 96 34 45 41 414 = 39%	Weight 10.0% 13.8% 15.6% 6.2% 22.6% 6.9% 9.7% 15.3% 100.0%	Risk Ratio <u>M-H, Fixed, 95% Cl</u> 1.07 [0.80, 1.43] 1.00 [0.82, 1.22] 1.37 [1.00, 1.88] 1.23 [0.87, 1.73] 1.13 [0.92, 1.38] 1.47 [0.99, 2.18] 1.38 [0.99, 1.90] 0.96 [0.81, 1.14] 1.17 [1.06, 1.29]	Risk Ratio M-H. Fixed. 95% C	
(c) <u>Study or Subgroup</u> Fang et al. 2017 Honing et al. 2013 Hsu et al. 2008 Hu et al. 2016 Huang et al. 2020 Münch et al. 2010 Qu et al. 2017 Sun et al. 2016 Zhao et al. 2012 Zhu et al. 2017 Total (95% CI) Total events Hataronanity, Chi2 =	TP Events Tota 10 4 13 5 12 1 14 10 7 2 10 1 5 2 24 8 41 10 17 4 22 4 15 13 27 df = 0.0	FP Events 8 9 3 5 8 2 5 8 2 5 8 2 5 9 3 2 2 5 9 3 2 2 5 9 3 2 2 5 9 3 2 2 5 9 3 3 3 3 9 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 9 9 3 2 2 5 9 9 3 2 2 5 9 9 3 2 2 5 9 9 3 2 2 5 9 9 3 2 2 5 9 3 2 2 5 9 3 2 2 5 9 3 2 2 5 9 3 2 2 5 9 3 2 2 5 5 9 3 2 2 5 5 9 3 2 2 5 5 9 3 2 2 5 5 9 3 2 2 5 5 9 3 2 2 5 5 9 7 7 7 7 7 9 3 2 2 5 5 9 7 7 7 7 7 7 7 8 7 7 7 9 7 7 7 7 7 7 7 7 7 7 7 7 7	Total 41 47 26 97 24 23 47 96 102 45 39 491	Weight 7.5% 9.0% 3.8% 7.7% 4.5% 5.7% 8.6% 0.0% 23.3% 8.4% 21.5% 100.0%	Risk Ratio M-H, Fixed, 95% Cl 1.25 [0.55, 2.85] 1.23 [0.58, 2.63] 3.47 [1.48, 8.13] 1.62 [0.71, 3.68] 1.53 [0.87, 3.84] 0.70 [0.28, 1.73] 0.71 [0.47, 1.08] 1.64 [1.08, 2.48] 1.89 [0.94, 3.78] 0.91 [0.61, 1.36] 1.43 [1.17, 1.75]	Risk Ratio M-H, Fixed, 95% Cl	(d) <u>Study or Subgroup</u> Bai et al. 2013 Fang et al. 2017 Hu et al. 2016 Huang et al. 2020 Sun et al. 2016 Yang et al. 2015 Zhao et al. 2012 Zhu et al. 2017 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	TP <u>Events</u> 26 34 55 18 58 25 33 38 287 11.47, df = Z = 3.20 (l	Total 35 41 105 22 81 34 45 45 408 : 7 (P = P = 0.00	FP <u>Events</u> 25 34 37 16 61 17 24 36 250 0.12); ² =	Total 36 41 97 24 96 34 45 41 414 = 39%	Weight 10.0% 13.8% 15.6% 6.2% 22.6% 6.9% 9.7% 15.3% 100.0%	Risk Ratio <u>M-H, Fixed, 95% Cl</u> 1.07 [0.80, 1.43] 1.00 [0.82, 1.22] 1.37 [1.00, 1.88] 1.23 [0.87, 1.73] 1.13 [0.92, 1.38] 1.47 [0.99, 2.18] 1.38 [0.99, 1.90] 0.96 [0.81, 1.14] 1.17 [1.06, 1.29]	Risk Ratio M-H. Fixed, 95% C	+
(c) <u>Study or Subgroup</u> Fang et al. 2017 Honing et al. 2013 Hsu et al. 2008 Hu et al. 2016 Huang et al. 2020 Münch et al. 2018 Qu et al. 2017 Sun et al. 2016 Zhang et al. 2016 Zhao et al. 2012 Zhu et al. 2017 Total (95% CI) Total events Heterogeneity: Chi ² = Tact for overall affect	TP Events Tota 10 4 13 55 12 11 14 10 7 0 11 5 22 24 88 41 10 17 44 22 4 474 151 13.27, df = 9 (P 7 - 3 43 (P - 0	FP Events 8 9 3 5 8 2 5 8 2 5 8 2 5 9 3 2 2 5 9 3 2 2 5 9 3 2 2 5 9 3 2 2 5 9 3 2 2 5 9 1 3 3 1 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 8 2 5 5 9 3 2 2 5 5 9 3 2 2 5 5 9 8 2 2 5 5 9 3 2 2 5 5 9 3 2 2 5 5 9 3 2 2 5 5 9 3 2 2 5 5 9 3 2 2 5 5 9 3 2 2 5 5 9 9 3 2 2 5 5 9 9 3 2 2 5 5 9 9 3 2 2 5 5 9 9 3 2 2 5 5 5 9 9 9 3 2 2 5 5 111 1 111 1 1 1 1 1 1 1 1 1	Total 41 47 26 97 24 23 47 96 102 45 39 491 = 32%	Weight 7.5% 9.0% 3.8% 7.7% 4.5% 5.7% 8.6% 0.0% 23.3% 8.4% 21.5% 100.0%	Risk Ratio M-H, Fixed, 95% Cl 1.25 [0.55, 2.85] 1.23 [0.58, 2.63] 3.47 [1.48, 8.13] 1.62 [0.71, 3.68] 1.53 [0.57, 4.12] 1.83 [0.87, 3.84] 0.70 [0.28, 1.73] 0.71 [0.47, 1.08] 1.64 [1.08, 2.48] 1.89 [0.94, 3.78] 0.91 [0.61, 1.36] 1.43 [1.17, 1.75]	Risk Ratio M-H, Fixed, 95% Cl 	(d) <u>Study or Subgroup</u> Bai et al. 2013 Fang et al. 2017 Hu et al. 2016 Huang et al. 2020 Sun et al. 2016 Yang et al. 2015 Zhao et al. 2012 Zhu et al. 2017 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	TP <u>Events</u> 26 34 55 18 58 25 33 38 287 11.47, df = Z = 3.20 (f	Total 35 41 105 22 81 34 45 45 408 7 (P = 0.00	FP <u>Events</u> 25 34 37 16 61 17 24 36 250 0.12); ² = 01)	Total 36 41 97 24 96 34 45 41 414 414 = 39%	Weight 10.0% 13.8% 15.6% 6.2% 22.6% 6.9% 9.7% 15.3% 100.0%	Risk Ratio <u>M-H. Fixed, 95% Cl</u> 1.07 [0.80, 1.43] 1.00 [0.82, 1.22] 1.37 [1.00, 1.88] 1.23 [0.87, 1.73] 1.13 [0.92, 1.38] 1.47 [0.99, 2.18] 1.38 [0.99, 1.90] 0.96 [0.81, 1.14] 1.17 [1.06, 1.29]	Risk Ratio M-H. Fixed, 95% C	

Figure 3. Analyses of curative effects in TP and FP groups in EC patients treated with dCRT. (a) 3-year OS; (b) 3-year PFS; (c) 3-year PFS after correction; (d) ORR.

The difference in the 3-year PFS of TP and FP regimens in EC patients receiving dCRT was compared across eleven studies. Among these studies (ESCC vs. EAC: 1047 vs. 98), two included ESCC and EAC [23,25], and the remaining studies included ESCC. Due to the heterogeneity of the results ($I^2 = 53\%$, p = 0.02, Figure 3b), a sensitivity analysis was conducted on the 11 studies. The study by Sun et al. [24] had a great impact on the heterogeneity, which might have been related to the inclusion of multiple chemotherapy regimens in this study (Figure S1a). After removing this study, there was low heterogeneity in the remaining studies ($I^2 = 32\%$, p = 0.15). Compared with the FP group, the TP group had better 3-year PFS results (RR: 1.43, 95% CI: 1.17–1.75, p = 0.0006, Figure 3c).

A total of 8 studies reported the ORR in 822 ESCC patients treated with dCRT. We found that the TP group had better ORR results than the FP group (RR: 1.17, 95% CI: 1.06–1.29, p = 0.001), which had low heterogeneity ($I^2 = 39\%$, p = 0.12, Figure 3d).

3.3.2. TP and FP Regimens Had Similar Survival Efficacy in EC Patients Treated with nCRT

For patients that underwent nCRT, the 3-year OS of TP and FP regimens was compared across 13 studies. Among these studies (ESCC vs. EAC: 740 vs. 616), 7 included ESCC and EAC, and the remaining only included ESCC. Due to the high heterogeneity ($I^2 = 52\%$, p = 0.02, Figure 4a), a sensitivity analysis was performed (Figure S1b). After excluding the study by Haisley et al. [40], which seriously affected the heterogeneity, the heterogeneity result was acceptable ($I^2 = 24\%$, p = 0.21, Figure 4b). Furthermore, no significant difference in the 3-year OS of TP and FP groups (RR: 0.93, 95% CI: 0.82–1.05, p = 0.26, Figure 4b) could be found.

This review included 10 studies on the 3-year PFS in EC patients receiving nCRT, among which 4 included ESCC plus EAC, and 6 included ESCC (ESCC vs. EAC: 580 vs. 432). There was high heterogeneity in the summary results ($I^2 = 45\%$, p = 0.06, Figure 4c). Through sensitivity analysis, it was found that the study by Duff et al. [41] might have a great impact on the heterogeneity because of its small research data (Figure S1c). The remaining studies were not heterogeneous after removing this study ($I^2 = 30\%$, p = 0.17). The results showed that no difference was found in the 3-year PFS of TP and FP groups (RR: 0.99, 95% CI: 0.86–1.13, p = 0.84, Figure 4d).

A total of 16 studies reported the pCR in EC patients treated with nCRT. Among these studies (ESCC vs. EAC: 822 vs. 639), 10 included ESCC and EAC cases, 5 reported ESCC cases, and 1 included EAC. The summary result showed that the pCR in the FP group was better than that of the TP group (RR: 0.81, 95% CI: 0.68–0.96, p = 0.02). These results had low heterogeneity ($I^2 = 24\%$, p = 0.18, Figure 4e).

There were 11 studies comparing the R0 resection rates of TP and FP regimens in EC patients undergoing nCRT. In these studies (ESCC vs. EAC: 719 vs. 263), the pathological types included six mixed ESCC and EAC types, four only included ESCC, and one included EAC. The summary results showed that the R0 resection rate of TP was better than that of the FP group (RR: 1.06, 95% CI: 1.01–1.11, p = 0.02), and there was no heterogeneity in this result ($I^2 = 38\%$, p = 0.10, Figure 4f).

(a)	TP	FP	Risk Ratio	Risk Ratio	(b)					
Study or Subgroup	Events Total E	vents Total Weight	M-H. Random. 95% CI	M-H. Random. 95% Cl	Study of Substant	TP F	FP to Total Waight	Risk Ratio	Risk Ratio	
Adelstein et al. 2000	12 40	22 62 5.9%	0.85 [0.47, 1.51]		Adelatein at al. 2000	Events Iotal Even	nts lotal weight	M-H, FIXed, 95% CI	M-H, Fixed, 95% CI	
Blom et al. 2013	49 86	38 63 11.7%	0.94 [0.72, 1.24]	+	Riom et al. 2000	12 40 2	22 02 0.3%	0.05[0.47, 1.51]	+	
Boggs et al. 2014	11 30	62 129 7.0%	0.76 [0.46, 1.26]	-+	Borns et al. 2013	11 30 6	62 129 8.5%	0.76 [0.46, 1.26]	-	
Dröge et al. 2021	18 27	35 63 10.0%	1.20 [0.85, 1.70]	+-	Dröge et al. 2021	18 27 3	35 63 7.7%	1 20 [0.85, 1 70]	+	
Duff et al. 2017	1 14	11 24 0.8%	0.16 [0.02, 1.08]		Duff et al. 2017	1 14 1	11 24 3.0%	0.16 [0.02, 1.08]		
Haisley et al. 2017	21 87	29 55 7.9%	0.46 [0.29, 0.72]		Haisley et al. 2017	21 87 2	29 55 0.0%	0.46 [0.29, 0.72]		
Hsu et al. 2008	18 39	18 44 7.2%	1.13 [0.69, 1.84]	+	Hsu et al. 2008	18 39 1	18 44 6.2%	1,13 [0.69, 1.84]		
Jiang et al. 2020	14 27	19 30 7.8%	0.82 [0.52, 1.29]		Jiang et al. 2020	14 27 1	19 30 6.6%	0.82 [0.52, 1.29]		
Jipping et al. 2017	34 63	31 63 10.1%	1.10 [0.78, 1.54]	+	Jipping et al. 2017	34 63 3	31 63 11.3%	1.10 [0.78, 1.54]	+	
Münch et al. 2017	9 18	15 26 6.1%	0.87 [0.49, 1.53]	-	Münch et al. 2017	9 18 1	15 26 4.5%	0.87 [0.49, 1.53]	-	
Orditura et al. 2011	12 33	16 39 5.8%	0.89 [0.49, 1.60]	_ _ _	Orditura et al. 2011	12 33 1	16 39 5.3%	0.89 [0.49, 1.60]		
Wong et al. 2020	36 100	48 100 10.3%	0.75 [0.54, 1.04]		Wong et al. 2020	36 100 4	48 100 17.5%	0.75 [0.54, 1.04]	-	
Xietal 2017	21 32	29 62 9.6%	1 40 [0.97, 2 02]		Xi et al. 2017	21 32 2	29 62 7.2%	1.40 [0.97, 2.02]	-	
Total (95% CI)	596	760 100.0%	0.90 [0.76, 1.07]	•	Total (95% CI)	509	705 100.0%	0.93 [0.82, 1.05]	•	
Total events	256	373			l otal events	235 34	44	L		
Heterogeneity: Tau ² =	0.05; Chi ² = 24.84, d	df = 12 (P = 0.02); I ² = 52	.%		Heterogeneity: Chr =	14.39, df = 11 (P = 0.21)); 1² = 24%	0.01	0.1 1 10	100
Test for overall effect:	Z = 1.16 (P = 0.25)		0.01	U.1 1 1U	100 Test for overall effect	Z = 1.13 (P = 0.26)			Favours [FP] Favours [TP]	
				Favous[FF] Favous[FF]						
(c)					(d)					
(0)	TP	FP	Risk Ratio	Risk Ratio	(4)	TP F	FP	Risk Ratio	Risk Ratio	
Study or Subgroup	Events Total E	vents Total Weight	M-H, Random, 95% Cl	M-H. Random, 95% Cl	Study or Subgroup	Events Total Even	ts Total Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	
Adelstein et al. 2000	14 40	25 62 8.7%	0.87 [0.52, 1.46]		Adelstein et al. 2000	14 40 2	25 62 9.5%	0.87 [0.52, 1.46]		
Boggs et al. 2014	10 30	50 129 8.1%	0.86 [0.50, 1.49]	1	Boggs et al. 2014	10 30 5	50 129 9.1%	0.86 [0.50, 1.49]	-	
Droge et al. 2021 Duff et el. 2017	1/ 2/	33 63 12.7% 12 24 0.5%	1.20 [0.83, 1.75]		Droge et al. 2021	1/ 2/ 3	53 53 9.5%	1.20 [0.83, 1.75]	-	
Duff et al. 2017	0 14	13 24 0.5%	0.00 [0.00, 0.90]	_	Duff et al. 2017	0 14 1	13 24 U.U%	0.06 [0.00, 0.96]	-	
Haustey et al. 2017 Heustal 2008	2/ 0/	24 55 10.9%	1 17 [0.46, 1.10]		Haustel 2008	2/ 0/ 2	24 00 14.270	1 17 [0.46, 1.10]		
liang et al. 2000	10 27	13 30 6.6%	0.85 [0.45, 1.62]	_	liang et al. 2000	10 27 1	13 30 6.0%	0.85 [0.45, 1.62]	_	
linning et al. 2017	35 63	35 63 14.9%	1 00 [0 73 1 37]	+	linning et al. 2017	35 63 3	35 63 16.9%	1 00 [0 73 1 37]	+	
Wong et al. 2020	28 59	35 62 13.6%	0.84 [0.59, 1.19]	-	Wong et al. 2020	28 59 3	35 62 16.5%	0.84 [0.59, 1.19]	-	
Xi et al. 2017	15 32	15 62 7.6%	1.94 [1.09, 3.44]		Xi et al. 2017	15 32 1	15 62 4.9%	1.94 [1.09, 3.44]		
Total (95% CI)	418	594 100.0%	0.99 [0.82, 1.20]	•	Total (95% CI)	404	570 100.0%	0.99 [0.86, 1.13]	•	
Total events	186	272			Total events	186 25	59			
Heterogeneity: Tau ² =	: 0.04; Chi ² = 16.25, d	df = 9 (P = 0.06); l ² = 45	6 0.01	0.1 1 10	100 Heterogeneity: Chi ² =	11.51, df = 8 (P = 0.17);	I ² = 30%	0.01	0.1 1 10	100
Test for overall effect:	Z = 0.10 (P = 0.92)		0.01	Favours [FP] Favours [TP]	Test for overall effect	Z = 0.20 (P = 0.84)		0.01	Favours [FP] Favours [TP]	100
(-)										
(e)	TP	FP	Risk Ratio	Risk Ratio						
Study or Subgroup	Events Total	Events Total Weigh	M-H, Fixed, 95% CI	M-H. Fixed, 95% CI						
Bajwa et al. 2018	14 30	5 20 2.8%	1.87 [0.80, 4.37]	+ -	(f)	TD	50	Dials Datia	Diel: Detie	
Blom et al. 2013	21 86	24 63 13.1%	0.64 [0.39, 1.04]		Study or Subgroup	Events Total Ever	nts Total Weight	M-H Fixed 95% CI	M-H Fixed 95% CI	
Boggs et al. 2014	9 30	58 129 10.4%	0.67 [0.37, 1.19]		Baiwa et al. 2018	30 30	20 20 6.6%	1 00 10 92 1 081	+	
Dröge et al. 2021	9 27	26 63 7.4%	0.81 [0.44, 1.49]		Blom et al. 2013	82 86	60 63 18.7%	1.00 [0.93, 1.08]	+	
Duff et al. 2017	3 14	11 24 3.8%	0.47 [0.16, 1.40]		Boggs et al. 2014	27 30 1	10 129 11.2%	1.06 [0.92, 1.21]	+	
Haisley et al. 2017	19 87	18 55 10.5%	0.67 [0.39, 1.16]		Dröge et al. 2021	27 27	63 63 10.4%	1.00 [0.95, 1.06]	+	
Hsien et al. 2021	3 30	6 54 2.0% 9 20 2.6%	0.90 [0.24, 3.34]		Mukherjee et al. 2017	33 41	26 36 7.5%	1.11 [0.87, 1.43]	+	
Jiang et al. 2020	4 27	17 63 810	0.30 [0.19, 1.04]		Münch et al. 2017	18 18	26 26 5.9%	1.00 [0.91, 1.09]	t	
Mukheriee et al. 2017	7 12 41	4 36 2.0%	2.63 [0.93, 7.45]	<u> </u>	Orditura et al. 2011	33 33	29 39 7.3%	1.34 [1.11, 1.61]	-	
Münch et al. 2017	5 18	10 26 3.9%	0.72 [0.30, 1.76]		Su et al. 2021	33 43	9 11 3.9%	0.94 [0.68, 1.30]	<u> </u>	
Orditura et al. 2011	10 33	9 39 3.9%	1.31 [0.61, 2.84]	- -	Tamtai et al. 2017	11 26	7 22 2.0%	1.33 [0.62, 2.84]	<u> </u>	
Sanford et al. 2017	13 77	13 35 8.5%	0.45 [0.24, 0.88]		Wong et al. 2020	59 69	62 76 15.9%	1.05 [0.91, 1.21]	1	
Tamtai et al. 2017	4 13	3 9 1.7%	0.92 [0.27, 3.17]		Xi et al. 2017	31 32	58 62 10.6%	1.04 [0.95, 1.13]	[
Wong et al. 2020	17 69	27 76 12.2%	0.69 [0.42, 1.16]		Total (95% CI)	435	547 100 0%	1.06 [1.01, 1.11]		
Xi et al. 2017	13 32	19 62 6.1%	1.33 [0.76, 2.33]	+	Total events	384 4	470	The fueld and	[
				1						
					Heterogeneity: Chi ² =	16.05, df = 10 (P = 0.10)	: ² = 38%			
Total (95% CI)	677	784 100.0%	0.81 [0.68, 0.96]	•	Heterogeneity: Chi ² = Test for overall effect:	16.05, df = 10 (P = 0.10); Z = 2.26 (P = 0.02)	; I² = 38%	0.01	0.1 1 10	100
Total (95% CI) Total events	677 170	784 100.0% 258 218) 12 - 24%	0.81 [0.68, 0.96]	•	Heterogeneity: Chi ² = Test for overall effect:	16.05, df = 10 (P = 0.10); Z = 2.26 (P = 0.02)	; l² = 38%	0.01	0.1 1 10 Favours [FP] Favours [TP]	100
Total (95% CI) Total events Heterogeneity: Chi ² =	677 170 19.81, df = 15 (P = (784 100.0% 258 0.18); I² = 24%	0.81 [0.68, 0.96]	0.1 1 10	Heterogeneity: Chi ² = Test for overall effect: 100	16.05, df = 10 (P = 0.10); Z = 2.26 (P = 0.02)	; I² = 38%	0.01	0.1 1 10 Favours [FP] Favours [TP]	100

Figure 4. Analysis of curative effects of TP and FP groups in EC patients treated with nCRT. (a) 3-year OS; (b) 3-year OS after correction; (c) 3-year PFS; (d) 3-year PFS after correction; (e) pCR; (f) R0 resection.



Figure 5. Funnel plots for publication bias. (a) 3-year OS in dCRT; (b) 3-year PFS in dCRT; (c) 3-year OS in nCRT; (d) 3-year PFS in nCRT; (e) pCR; (f) R0 resection.

3.3.3. Bias Test

The outcome indices for the 3-year OS, 3-year PFS, pCR, and R0 resection rate in dCRT and nCRT groups were analyzed (Figure 5). The *p* values of *Begg's* tests and *Egger's* tests were greater than 0.05, which suggested that there was no publication bias in this study (Table 2).

	3-Year OS of dCRT	3-Year PFS of dCRT	3-Year OS of nCRT	3-Year PFS of nCRT	pCR	R0 Resection
<i>Begg's</i> test	0.837	0.858	0.304	1.000	0.300	0.174
<i>Egger's</i> test	0.727	0.410	0.110	0.788	0.342	0.210

Table 2. Symmetry test of funnel plots.

Abbreviations: OS, overall survival; pCR, pathologic complete response; PFS, progression free survival.

3.4. Toxicity

Within this study, the related toxicity (grade \geq 3) of TP and FP regimens in EC patients treated with dCRT was summarized. Patients receiving TP regimens tended to have a higher incidence of leucopenia than those undergoing FP regimens (RR: 1.28, 95% CI: 1.05–1.58, p = 0.02, Figure 6a). There were no significant differences in the incidence of anemia (RR: 0.76, 95% CI: 0.44–1.33, *p* = 0.34, Figure 6b), pneumonia (RR: 0.71, 95% CI: 0.38–1.34, *p* = 0.30, Figure 6c), and mucositis (RR: 0.85, 95% CI: 0.50–1.44, *p* = 0.55, Figure 6d) between TP and FP groups. The above results had low heterogeneity ($l^2 < 50\%$, p > 0.10). A total of eight articles on thrombocytopenia caused by chemotherapy regimens were included. The results illustrated a certain heterogeneity ($I^2 = 52\%$, p = 0.04). Further sensitivity analysis also established that the study by Sun et al. [24] had a great impact on the heterogeneity due to its inclusion of multiple chemotherapy regimens (Figure S1d). After removing this study, there was no heterogeneity in the remaining studies ($I^2 = 29\%$, p = 0.21), and the TP group had a higher incidence of thrombocytopenia when compared with the FP group (RR: 1.65, 95% CI: 1.02–2.68, p = 0.04, Figure 6e). A total of seven articles on nausea/vomiting caused by these two chemotherapy regimens were included. After correcting the heterogeneity through sensitivity analysis (Figure S1e), the results showed that there was no significant difference in the incidence of nausea/vomiting between the two groups (RR: 1.02, 95% CI: 0.59-1.77, p = 0.94, Figure 6f).

For the relationship between the toxicity (grade \geq 3) and different chemotherapy regimens in EC patients undergoing nCRT, the summary results showed that incidences of thrombocytopenia in EC patients treated with FP regimens were higher than in those undergoing TP regimens (RR: 0.33, 95% CI: 0.14–0.79, *p* = 0.01, Figure 7a). We also found that the TP regimen caused more febrile neutropenia than FP regimen (RR: 1.78, 95% CI: 1.07–2.98, *p* = 0.03, Figure 7b). However, there were no significant differences in the incidence of anemia (RR: 0.64, 95% CI: 0.26–1.54, *p* = 0.32, Figure 7c), nausea/vomiting (RR: 0.88, 95% CI: 0.47–1.65, *p* = 0.70, Figure 7d), esophagitis (RR: 1.30, 95% CI: 0.67–2.52, *p* = 0.44, Figure 7e) and diarrhea (RR: 0.98, 95% CI: 0.19–5.00, *p* = 0.98, Figure 7f) between these two groups. All the above results had no heterogeneity (Figure 7).



Figure 6. The related toxicity of TP and FP in EC patients treated with dCRT. (**a**) leucopenia; (**b**) anemia; (**c**) pneumonia; (**d**) mucositis; (**e**) thrombocytopenia; (**f**) nausea/vomiting.

(a)	TP	FP			Risk Ratio	Risk Ratio		(b)									
Study or Subgroup	Events Total	Events	Total W	Veight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl		(0)	TP		FP			Risk Ratio		Risk Ratio	
Adelstein et al. 2000	0 40	7	72	26.9%	0.12 [0.01, 2.03]			Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	1	M-H. Fixed, 95% CI	
Blom et al. 2013	1 92	6	73 3	33.4%	0.13 [0.02, 1.07]			Adelstein et al. 2000	16	40	12	72	53.7%	2.40 [1.26, 4.56]		−■ −	
Dröge et al. 2021	1 27	' 1	63	3.0%	2.33 [0.15, 35.95]		_	Mukherjee et al. 2017	1	42	0	38	3.3%	2.72 [0.11, 64.85]			
Mukherjee et al. 2017	0 42	! 1	38	7.9%	0.30 [0.01, 7.21]			Sanford et al. 2017	4	77	4	35	34.5%	0.45 [0.12, 1.71]			
Münch et al. 2017	0 18	4	26	18.6%	0.16 [0.01, 2.76]			Xi et al. 2017	3	32	2	62	8.5%	2.91 [0.51, 16.52]			
Xi et al. 2017	2 32	3	62	10.2%	1.29 [0.23, 7.34]												
								Total (95% CI)		191		207	100.0%	1.78 [1.07, 2.98]		◆	
Total (95% CI)	251		334 1	00.0%	0.33 [0.14, 0.79]			Total events	24		18						
Total events	4	22						Heterogeneity: Chi ² = 5	.27, df = 3	(P = 0.1	5); l ² = 4	3%			<u> </u>		
Heterogeneity: Chi ² = 5	.82, df = 5 (P = 0	.32); l ² = 14	4%				400	Test for overall effect: Z	Z = 2.20 (F	e = 0.03)					0.01		100
Test for overall effect: Z	2 = 2.47 (P = 0.01	I)			0.01	0.1 1 10 Favours (TP) Favours (EP)	100		(,						Favours [1P] Favours [FP]	
						Favous[IF] Favous[FF]											
(-)								(1)									
(c)	TP	FP			Risk Ratio	Risk Ratio		(d)	ТР		FP			Risk Ratio		Risk Ratio	
Study or Subgroup	Events Total	Events	Total W	Veight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl		Study or Subgroup	Events	Total E	vents	Total	Weight	M-H, Fixed, 95% Cl	I	M-H, Fixed, 95% Cl	
Blom et al. 2013	0 92	3	73	33 4%	0 11 [0 01 2 17]			Adelstein et al. 2000	0	40	1	72	5.9%	0 59 [0 02, 14 24]	_		
Dröge et al. 2021	1 27	4	63	20.5%	0.58 [0.07, 4.98]			Blom et al. 2013	8	92	. 9	73	54.9%	0 71 [0 29, 1 74]		_ _	
Mukheriee et al. 2017	0 42	1	38	13.5%	0.30 [0.01, 7.21]			Dröge et al. 2021	1	27	0	63	1.7%	6 86 [0 29, 163 19]			→
Münch et al. 2017	1 18	3	26	21.0%	0.48 [0.05, 4.27]			Sanford et al. 2017	8	77	4	35	30.1%	0.91 [0.29, 2.82]			
Xi et al. 2017	3 32	2	62	11.7%	2.91 [0.51, 16.52]			Xi et al. 2017	1	32	2	62	7.4%	0.97 [0.09, 10.28]			
		-			[]						-						
Total (95% CI)	211		262 1	00.0%	0.64 [0.26, 1.54]			Total (95% CI)		268		305	100.0%	0.88 [0.47, 1.65]			
Total events	5	13				-		Total events	18		16						
Heterogeneity: Chi ² = 4	52 df = 4 (P = 0	(34): ² = 12	2%		⊢—			Heterogeneity: Chi ² = 1	91 df = 4	(P = 0.7)	(5): ² = ()%			—		
Test for overall effect: 7	r = 1.00 (P = 0.32)	2)	_ //		0.01	0.1 1 10	100	Test for overall effect: 7	7 = 0.39 (F	P = 0.70	0), 1				0.01	0.1 1 10	100
	- 1.00 (1 - 0.02	-/				Favours [TP] Favours [FP]			- 0.00 (i	0.10)						Favours [TP] Favours [FP]	
(e)	-				Disk Datis	Disk Datis		(f)									
Chudu an Outhmourn	IP Evente Tetel	FP Eto	Total M	Valuela	RISK Ratio	RISK RATIO		(1)	TP		FP			Risk Ratio		Risk Ratio	
Study or Subgroup	Events Total	Events		veight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl		Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H, Fixed, 95% Cl	
Blom et al. 2013	9 92	. 7	73	50.8%	1.02 [0.40, 2.61]			Blom et al. 2013	0	92	1	73	58.0%	0.27 [0.01, 6.42]			
Mukherjee et al. 2017	2 42	2	38	13.7%	0.90 [0.13, 6.11]	1		Mukherjee et al. 2017	1	42	0	38	18.2%	2.72 [0.11, 64.85]			
Sanford et al. 2017	14 77	2	35	17.9%	3.18 [0.76, 13.25]			Sanford et al. 2017	1	77	0	35	23.8%	1.38 [0.06, 33.17]			-
Xi et al. 2017	1 32	4	62	17.7%	0.48 [0.06, 4.16]												
Total (95% CI)	243		208 1	00.0%	1 30 10 67 2 521	•		Total (95% CI)		211		146	100.0%	0.98 [0.19, 5.00]			
Total evente	243	15	200 1	00.070	1.00 [0.01, 2.02]	-		Total events	2		1						
Heterogeneity: Chi2 - 2	20 71 df = 3 /P = 0	GI 0 = 21 -(NN	×		H			Heterogeneity: Chi ² = 1	.09. df = 2	(P = 0.5	8): ² = 0	1%			—		— I
Test for overall effect: 7	1.71, ul = 3(P = 0)	(.4+4), 1° = 0° 1)	/0		0.01	0.1 1 10	100	Test for overall effect: 7	7 = 0.03 (F	r = 0.98	-,,. •				0.01	0.1 1 10	100
rescior overall effect. 2	0.11 (F - 0.44	*)				Favours [TP] Favours [FP]		1350101 0701011 011000. 2	. 0.00 (1	0.00)						Favours [TP] Favours [FP]	

Figure 7. Related toxicity of TP and FP in EC patients treated with nCRT. (a) thrombocytopenia; (b) febrile neutropenia; (c) anemia; (d) nausea/vomiting; (e) esophagitis; (f) diarrhea.

4. Discussion

EC has always been one of the most common malignant tumors worldwide [2]. Numerous measures have aimed to improve the EC prognosis of multimodal treatment, including improved surgical procedures, precise radiotherapy technologies, and the combined application of antitumor drugs [1]. FP is a recognized first-line chemotherapy regimen for EC [5,52]. With the rapid development of its clinical practice and application, the TP regimen has also proved to be effective in the treatment of EC [53]. According to the National Comprehensive Cancer Network Guideline 2022, radical chemoradiotherapy is the first-line treatment for unresectable, locally advanced EC, and nCRT has sufficient medical evidence for the treatment of resectable, locally advanced EC; this is also recommended as a routine treatment [54]. The preferred regimens include fluorouracil plus oxaliplatin, fluorouracil plus cisplatin, and paclitaxel plus carboplatin [54]. Paclitaxel plus carboplatin and fluorouracil plus oxaliplatin are the most recommended preoperative chemotherapy regimens for localized thoracic esophageal or esophagogastric junction adenocarcinomas [54]. To date, there has been no consensus on the strengths and weaknesses of TP and FP chemotherapy regimens in chemoradiotherapy for EC. The present study examined the differences in the therapeutic efficacy and related toxicity of TP and FP in EC patients, and it found that the prognosis and therapeutic response of EC patients undergoing TP-dCRT treatment were superior to those of patients treated with FP-dCRT treatment. However, these two regimens had a similar survival time in EC patients undergoing nCRT. Furthermore, our review found that TP and FP regimens differed significantly in the aspect of myelosuppression.

By summarizing, we divided the included articles into dCRT groups and nCRT groups. We found that EC patients undergoing dCRT benefited more from the TP regimen than the FP regimen, and patients who received the TP regimen had significantly longer survival time and better ORRs. A meta-analysis of 31 studies illustrated that taxane-based treatment produced better clinical responses and outcomes than FP therapy in EC patients receiving dCRT [16]. Li et al. [55] investigated 59 EC patients receiving dCRT and found that cisplatin plus paclitaxel regimens had better ORR and longer survival than cisplatin plus 5-FU regimens. Zhao et al. [28] evaluated the efficacy and safety of two chemoradiotherapy regimens (5-FU plus cisplatin and docetaxel plus cisplatin) in patients with unresectable, locally advanced ESCC. They discovered that the ORR and OS of the TP regimen were better than those of the FP regimen. These conclusions are consistent with our study's deduction that taxane-based chemoradiotherapy seems to have better clinical benefits than a fluorouracil-based regimen in EC patients receiving dCRT. Paclitaxel produces cytotoxic activity against EC and can interfere with microtubule depolymerization and cell division, which are moderate radiosensitizers for some human tumor cells [10]. Previous studies have shown that taxanes could enhance the response to radiation by inducing mitotic arrest and apoptosis in mouse tumor cells [10,11]. The sensitization of radiotherapy might be the reason why taxanes are superior to fluorouracil in EC patients undergoing dCRT. However, it should be noted that most of the dCRT studies in this review are from Asia, and the proportion of ESCC participants is more than 90%. Whether the TP-dCRT regimen has a therapeutic advantage in EAC needs to be further studied.

Our findings demonstrate that TP and FP regimens produced similar prognoses in EC patients undergoing nCRT. Meanwhile, the pCR of the FP group was better than that of the TP group, and the R0 resection rate of the TP group was superior to that of the FP group. Similar to our results, Dröge et al. [34] found that there was no significant difference between the OS and PFS of the TP group and the FP group, and the pCR of the FP group was better than that of the TP group in patients receiving nCRT. In previous meta-analyses, taxane-based treatment and FP therapy showed similar OS, PFS, pCR, and R0 resection rates in EC patients receiving nCRT, which is not completely consistent with our results [16]. Compared with the chemotherapy regimens in the above article (including paclitaxel plus fluorouracil, paclitaxel plus fluorouracil plus platinum, and docetaxel single drug), our study refined the chemotherapy regimen into paclitaxel plus platinum or fluorouracil plus platinum, which

reduced the heterogeneity caused by the chemotherapy regimens. In addition, the number of articles included in the present study is also increased. More importantly, this study improved the robustness of the results to a certain extent through sensitivity analysis. At present, there are multiple studies exploring the modes of neoadjuvant therapy, including neoadjuvant chemotherapy combined with immunotherapy and nCRT combined with immunotherapy, and some have achieved excellent results. We look forward to updated research data, which will continue to improve the existing treatment modes [56,57].

Our results demonstrated that the incidence of myelosuppression (leucopenia and thrombocytopenia) in the TP regimen was higher than that of the FP regimen in EC patients undergoing dCRT, which was consistent with the data of Zhu et al. [29]. We further compared EC patients receiving nCRT with the conclusion that FP and TP groups correspond to higher incidences of thrombocytopenia and febrile leukopenia, respectively. Blom et al. [43] also reported similar results referring to the higher thrombocytopenia rate in FP-nCRT. Several other studies reported that incidences of febrile neutropenia in TP regimens were higher than in FP regimens in EC patients receiving nCRT [37,38,45]. All these studies also proved the rationality of our investigation. Interestingly, the incidence of thrombocytopenia in different chemotherapy regimens obtained entirely different results for dCRT and nCRT. The reason for this situation might be related to the differences in drug type and dose of the chemotherapy regimens. In the nCRT group, the TP regimen was mostly paclitaxel plus carboplatin, and the FP regimen was mostly 5-FU plus cisplatin. Cisplatin is generally greater in toxicity than carboplatin and is more likely to cause renal damage, which may influence the production of thrombopoietin and reduce platelet production [25,58]. Meanwhile, among the eight included nCRT studies, the FP group in five studies had a higher fluorouracil dose, and the FP group in two studies had a greater radiation dose. These factors might have caused higher incidences of thrombocytopenia in FP regimens than in TP regimens in the nCRT group. However, the TP regimen was more likely to give rise to myelosuppression in the dCRT group. Most of the dCRT participants were elderly patients who had an increased risk of myelosuppressive-associated complications from chemotherapy. Studies have shown a decrease in the function of the bone marrow with age. Meanwhile, Huang et al. [20] demonstrated increased hematologic toxicity with taxane-based regimens in elderly EC patients treated with dCRT. In addition, the radiotherapy dose in the dCRT group was slightly higher than in the nCRT group, and a larger radiotherapy dose could also aggravate the toxicity [59]. These might be the reasons for these different results; more in-depth studies are needed in the future.

There are also some limitations in this study. Firstly, since some articles did not provide the relevant survival data directly, Eagauge Digitizer software was used to extract the data from the survival curve and calculate the results indirectly. Secondly, most of our analyzed data came from retrospective cohort studies with inherent limitations and some inevitable selection bias. Thirdly, the review was not registered, but the meta-analysis was carried out in strict accordance with the PRISMA statement. Fourthly, because of the difficulties in screening participants, this review did not conduct a subgroup analysis according to pathological types. In addition, the influence of confounding factors from some small-size studies cannot be excluded. According to the above limitations, the multicenter, high quality, and large sample size studies need to be further discussed.

5. Conclusions

This study indicated that taxanes combined with platinum could produce superior clinical responses and survival benefits when compared with fluorouracil combined with platinum in EC patients treated with dCRT. Meanwhile, the two treatment regimens have equivalent survival benefits for EC patients undergoing nCRT. These findings might provide guidance for clinicians to choose appropriate treatment regimens for patients with esophageal cancer.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/curroncol29090519/s1, Figure S1. Sensitivity analysis. (a) 3-year PFS in dCRT; (b) 3-year OS in nCRT; (c) 3-year PFS in nCRT; (d) thrombocytopenia in dCRT; (e) nausea/vomiting in dCRT. Table S1. Survival rate of 31 selected studies included in the systematic review and meta-analysis.

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References

- D'Journo, X.B.; Thomas, P.A. Current management of esophageal cancer. J. Thorac. Dis. 2014, 6 (Suppl. 2), S253–S264. [CrossRef] [PubMed]
- Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 2021, 71, 209–249. [CrossRef] [PubMed]
- 3. Zhang, H.Z.; Jin, G.F.; Shen, H.B. Epidemiologic differences in esophageal cancer between Asian and western populations. *Chin. J. Cancer* **2012**, *31*, 281–286. [CrossRef] [PubMed]
- 4. Yamashita, H.; Seto, Y.; Takenaka, R.; Okuma, K.; Kiritooshi, T.; Mori, K.; Yamada, K.; Fukuda, T.; Kaminishi, M.; Abe, O.; et al. Survival comparison between radical surgery and definitive chemoradiation in 267 esophageal squamous cell carcinomas in a single institution: A propensity-matchedstudy. *PLoS ONE* **2017**, *12*, e0177133. [CrossRef] [PubMed]
- Stahl, M.; Budach, W.; Meyer, H.J.; Cervantes, A. Esophageal cancer: Clinical practice guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 2010, 21 (Suppl. 5), v46–v49. [CrossRef]
- 6. Allum, W.H.; Stenning, S.P.; Bancewicz, J.; Clark, P.I.; Langley, R.E. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J. Clin. Oncol.* **2009**, *27*, 5062–5067. [CrossRef]
- Swisher, S.G.; Hofstetter, W.; Komaki, R.; Correa, A.M.; Erasmus, J.; Lee, J.H.; Liao, Z.X.; Maru, D.; Mehran, R.; Patel, S.; et al. Improved long-term outcome with chemoradiotherapy strategies in esophageal cancer. *Ann. Thorac. Surg.* 2010, *90*, 892–898, discussion 898–899. [CrossRef]
- van Hagen, P.; Hulshof, M.C.C.M.; van Lanschot, J.J.B.; Steyerberg, E.W.; van Berge Henegouwen, M.I.; Wijnhoven, B.P.L.; Richel, D.J.; Nieuwenhuijzen, G.A.P.; Hospers, G.A.P.; Bonenkamp, J.J.; et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N. Engl. J. Med.* 2012, 366, 2074–2084. [CrossRef]
- Huang, T.C.; Hsu, C.H.; Lin, C.C.; Tu, Y.K. Systematic review and network meta-analysis: Neoadjuvant chemoradiotherapy for locoregional esophageal cancer. *Jpn. J. Clin. Oncol.* 2015, 45, 1023–1028. [CrossRef]
- 10. Choy, H. Combining taxanes with radiation for solid tumors. Int. J. Cancer 2000, 90, 113–127. [CrossRef]
- 11. Tishler, R.B.; Schiff, P.B.; Geard, C.R.; Hall, E.J. Taxol: A novel radiation sensitizer. *Int. J. Radiat. Oncol. Biol. Phys.* **1992**, 22, 613–617. [CrossRef]
- 12. Milross, C.G.; Mason, K.A.; Hunter, N.R.; Chung, W.K.; Peters, L.J.; Milas, L. Relationship of mitotic arrest and apoptosis to antitumor effect of paclitaxel. *J. Natl. Cancer Inst.* **1996**, *88*, 1308–1314. [CrossRef] [PubMed]
- 13. Zhang, M.; Zhang, M.; Li, R.; Zhang, R. Melatonin sensitizes esophageal cancer cells to 5fluorouracil via promotion of apoptosis by regulating EZH2 expression. *Oncol. Rep.* **2021**, *45*, 22. [CrossRef] [PubMed]
- 14. Zhang, N.; Yin, Y.; Xu, S.J.; Chen, W.S. 5-Fluorouracil: Mechanisms of resistance and reversal strategies. *Molecules* **2008**, *13*, 1551–1569. [CrossRef]
- 15. Lv, J.; Cao, X.F.; Zhu, B.; Ji, L.; Tao, L.; Wang, D.D. Long-term efficacy of perioperative chemoradiotherapy on esophageal squamous cell carcinoma. *World J. Gastroenterol.* **2010**, *16*, 1649–1654. [CrossRef]
- 16. Wang, T.; Yu, J.; Liu, M.; Chen, Y.; Zhu, C.; Lu, L.; Wang, M.; Liu, X.; Zhang, X.; Chen, Y.; et al. The benefit of taxane-based therapies over fluoropyrimidine plus platinum (FP) in the treatment of esophageal cancer: A meta-analysis of clinical studies. *Drug Des. Dev. Ther.* **2019**, *13*, 539–553. [CrossRef]
- Liberati, A.; Altman, D.G.; Tetzlaff, J.; Mulrow, C.; Gøtzsche, P.C.; Ioannidis, J.P.A.; Clarke, M.; Devereaux, P.J.; Kleijnen, J.; Moher, D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. *BMJ* 2009, 339, b2700. [CrossRef]

- Hsu, F.M.; Lin, C.C.; Lee, J.M.; Chang, Y.L.; Hsu, C.H.; Tsai, Y.C.; Lee, Y.C.; Cheng, J.C.H. Improved local control by surgery and paclitaxel-based chemoradiation for esophageal squamous cell carcinoma: Results of a retrospective non-randomized study. *J. Surg. Oncol.* 2008, *98*, 34–41. [CrossRef]
- 19. Bai, M.; Wang, B.; Wang, X.; Ma, H.; Wang, Y.; Wang, Z. Randomized trial of weekly docetaxel and cisplatin combined with concurrent 3DCRT in patients with locally advanced esophageal cancer. *Chin.-Ger. J. Clin. Oncol.* **2013**, *12*, 361–364. [CrossRef]
- 20. Huang, C.; Huang, D.; Zhu, Y.; Xie, G.; Wang, H.; Shi, J.; Jia, B.; Yuan, Y.; Zhang, W. Comparison of a concurrent fluorouracil-based regimen and a taxane-based regimen combined with radiotherapy in elderly patients with esophageal squamous cell carcinoma. *Transl. Oncol.* **2020**, *13*, 100736. [CrossRef]
- Hu, G.; Wang, Z.; Wang, Y.; Zhang, Q.; Tang, N.; Guo, J.; Liu, L.; Han, X. Comparison of cisplatinum/paclitaxel with cisplatinum/5fluorouracil as first-line therapy for nonsurgical locally advanced esophageal squamous cell carcinoma patients. *Drug Des. Dev. Ther.* 2016, 10, 2129–2136. [CrossRef] [PubMed]
- Münch, S.; Pigorsch, S.U.; Devečka, M.; Dapper, H.; Weichert, W.; Friess, H.; Braren, R.; Combs, S.E.; Habermehl, D. Comparison of definite chemoradiation therapy with carboplatin/paclitaxel or cisplatin/5-fluoruracil in patients with squamous cell carcinoma of the esophagus. *Radiat. Oncol.* 2018, 13, 139. [CrossRef] [PubMed]
- 23. Qu, X.M.; Biagi, J.J.; Hopman, W.M.; Mahmud, A. Shifting practice in definitive chemoradiation for localized esophageal cancer. *Curr. Oncol.* 2017, 24, e379–e387. [CrossRef]
- 24. Sun, X.; Han, S.; Gu, F.; Lin, G.; Wang, Z.; Wang, Y.; Xu, Y. A retrospective comparison of taxane and fluorouracil-based chemoradiotherapy in patients with Inoperable esophageal squamous cell carcinoma. *J. Cancer* **2016**, *7*, 1066–1073. [CrossRef] [PubMed]
- Honing, J.; Smit, J.K.; Muijs, K.T.; Burgerhof, H.G.; Plukker, J.T.; Beukema, J.C.; Hospers, G.A. A comparison of carboplatin with paclitaxel and cisplatinum with 5-fluorouracil in definitive chemoradiotherapy in esophageal cancer patients. *Ann. Oncol.* 2014, 25, 638–643. [CrossRef]
- Fang, M.; Song, T.; Liang, X.; Lv, S.; Li, J.; Xu, H.; Luo, L.; Jia, Y. Comparative study of cisplatin-based definitive concurrent chemoradiotherapy with S-1 versus paclitaxel for unresectable locally advanced esophageal squamous cell carcinoma. *Oncotarget* 2017, *8*, 37080–37090. [CrossRef]
- Yang, J.S.; Wang, T.; Qiu, M.Q.; Li, Q.L. Comparison of efficacy and toxicity profiles between paclitaxel/lobapoatin- and cisplatin/5-fluorouracil-based concurrent chemoradiotherapy of advanced inoperable oesophageal cancer. *Intern. Med. J.* 2015, 45, 757–761. [CrossRef]
- Zhao, T.; Chen, H.; Zhang, T. Docetaxel and cisplatin concurrent with radiotherapy versus 5-fluorouracil and cisplatin concurrent with radiotherapy in treatment for locally advanced oesophageal squamous cell carcinoma: A randomized clinical study. *Med. Oncol.* 2012, 29, 3017–3023. [CrossRef]
- Zhu, Y.; Zhang, W.; Li, Q.; Li, Q.; Qiu, B.; Liu, H.; Liu, M.; Hu, Y. A phase II randomized controlled trial: Definitive concurrent chemoradiotherapy with docetaxel plus cisplatin versus 5-fluorouracil plus cisplatin in patients with oesophageal squamous cell carcinoma. *J. Cancer* 2017, *8*, 3657–3666. [CrossRef]
- Zhang, P.; Xi, M.; Li, Q.Q.; Hu, Y.H.; Guo, X.; Zhao, L.; Liu, H.; Liu, S.L.; Luo, L.L.; Liu, Q.; et al. Concurrent cisplatin and 5-fluorouracil versus concurrent cisplatin and docetaxel with radiotherapy for esophageal squamous cell carcinoma: A propensity score-matched analysis. Oncotarget 2016, 7, 44686–44694. [CrossRef]
- Su, P.H.; Hsueh, S.W.; Tseng, C.K.; Ho, M.M.; Su, P.J.; Hung, C.Y.; Yeh, K.Y.; Chang, P.H.; Hung, Y.S.; Ho, Y.W.; et al. Paclitaxel and carboplatin versus cisplatin and 5-fluorouracil in concurrent chemoradiotherapy in patients with esophageal cancer. *In Vivo* 2021, 35, 3391–3399. [CrossRef] [PubMed]
- Jiang, D.M.; Sim, H.W.; Espin-Garcia, O.; Chan, B.A.; Natori, A.; Lim, C.H.; Moignard, S.; Chen, E.X.; Liu, G.; Darling, G.; et al. Chemoradiotherapy using carboplatin plus paclitaxel versus cisplatin plus fluorouracil for esophageal or gastroesophageal junction cancer. *Oncology* 2021, *99*, 49–56. [CrossRef] [PubMed]
- Hsieh, J.C.H.; Chiang, P.C.; Hung, T.M.; Chao, Y.K.; Kuo, Y.C.; Wen, C.T.; Su, P.J.; Peng, M.T.; Chen, H.W.; Liu, H.L.; et al. Definitive concurrent chemoradiotherapy with paclitaxel plus carboplatin is superior to cisplatin plus 5-fluorouracil in patients with inoperable esophageal squamous cell carcinoma using retrospective, real-world evidence. *Cancer Med.* 2021, *10*, 8300–8309. [CrossRef] [PubMed]
- Dröge, L.H.; Karras, P.J.; Guhlich, M.; Schirmer, M.A.; Ghadimi, M.; Rieken, S.; Conradi, L.C.; Leu, M. Preoperative radiochemotherapy in esophageal squamous cell cancer with 5-fluorouracil/cisplatin or carboplatin/paclitaxel: Treatment practice over a 20-year period and implications for the individual treatment modalities. *Cancers* 2021, *13*, 1813. [CrossRef]
- Wong, I.Y.H.; Lam, K.O.; Zhang, R.Q.; Chan, W.W.L.; Wong, C.L.Y.; Chan, F.S.Y.; Kwong, D.L.W.; Law, S.Y.K. Neoadjuvant chemoradiotherapy using cisplatin and 5-fluorouracil (PF) versus carboplatin and paclitaxel (cross regimen) for esophageal equamous cell carcinoma (ESCC): A propensity score-matched study. *Ann. Surg.* 2020, 272, 779–785. [CrossRef]
- 36. Bajwa, H.K.; Singareddy, R.; Reddy, M.M.; Raju, K.A.; Rao, S.T.; Rajappa, S.J. Preoperative chemoradiation in carcinoma esophagus: Experience from a tertiary cancer center in India. *Indian J. Med. Paediatr. Oncol.* **2018**, *39*, 272–275. [CrossRef]
- Xi, M.; Zhang, P.; Zhang, L.; Yang, Y.D.; Liu, S.L.; Li, Y.; Fu, J.H.; Liu, M.Z. Comparing docetaxel plus cisplatin versus fluorouracil plus cisplatin in esophageal squamous cell carcinoma treated with neoadjuvant chemoradiotherapy. *Jpn. J. Clin. Oncol.* 2017, 47, 683–689. [CrossRef]

- Sanford, N.N.; Catalano, P.J.; Enzinger, P.C.; King, B.L.; Bueno, R.; Martin, N.E.; Hong, T.S.; Wo, J.Y.; Mamon, H.J. A retrospective comparison of neoadjuvant chemoradiotherapy regimens for locally advanced esophageal cancer. *Dis. Esophagus* 2017, 30, 1–8. [CrossRef]
- Jipping, K.M.; Hulshoff, J.B.; van Amerongen, E.A.; Bright, T.I.; Watson, D.I.; Plukker, J.T.M. Influence of tumor response and treatment schedule on the distribution of tumor recurrence in esophageal cancer patients treated with neoadjuvant chemoradiotherapy. J. Surg. Oncol. 2017, 116, 1096–1102. [CrossRef]
- Haisley, K.R.; Hart, K.D.; Nabavizadeh, N.; Bensch, K.G.; Vaccaro, G.M.; Thomas, C.R.; Schipper, P.H.; Hunter, J.G.; Dolan, J.P. Neoadjuvant chemoradiotherapy with concurrent cisplatin/5-fluorouracil is associated with increased pathologic complete response and improved survival compared to carboplatin/paclitaxel in patients with locally advanced esophageal cancer. *Dis. Esophagus* 2017, 30, 1–7. [CrossRef]
- 41. Duff, J.M.; Peters, H.C.; Zingarelli, W.; Ben-David, K.; Sarosi, G.; Thomas, R.M. Comparative effectiveness of preoperative treatment regimens in patients with potentially resectable esophageal cancer. *JAMA Surg.* 2017, 152, 103–105. [CrossRef] [PubMed]
- 42. Boggs, D.H.; Tarabolous, C.; Morris, C.G.; Hanna, A.; Burrows, W.; Horiba, N.; Suntharalingam, M. Analysis of pathological complete response rates with paclitaxel-based regimens in trimodality therapy for esophageal cancer. *Dis. Esophagus* 2015, *28*, 619–625. [CrossRef] [PubMed]
- Blom, R.L.G.M.; Sosef, M.N.; Nap, M.; Lammering, G.; van den Berkmortel, F.; Hulshof, M.C.C.M.; Meijer, S.L.; Wilmink, H.W.; van Berge Henegouwen, M.I. Comparison of two neoadjuvant chemoradiotherapy regimens in patients with potentially curable esophageal carcinoma. *Dis. Esophagus* 2014, 27, 380–387. [CrossRef] [PubMed]
- Orditura, M.; Galizia, G.; Morgillo, F.; Martinelli, E.; Lieto, E.; Vitiello, F.; Di Martino, N.; Pacelli, R.; Renda, A.; Ciardiello, F.; et al. Complete response to preoperative chemoradiation and survival in esophageal cancer: A pooled analysis of three single-institution phase II trials. *Dis. Esophagus* 2012, *25*, 130–136. [CrossRef] [PubMed]
- Adelstein, D.J.; Rice, T.W.; Rybicki, L.A.; Larto, M.A.; Ciezki, J.; Saxton, J.; DeCamp, M.; Vargo, J.J.; Dumot, J.A.; Zuccaro, G. Does paclitaxel improve the chemoradiotherapy of locoregionally advanced esophageal cancer? A nonrandomized comparison with fluorouracil-based therapy. J. Clin. Oncol. 2000, 18, 2032–2039. [CrossRef] [PubMed]
- Münch, S.; Pigorsch, S.U.; Feith, M.; Slotta-Huspenina, J.; Weichert, W.; Friess, H.; Combs, S.E.; Habermehl, D. Comparison of neoadjuvant chemoradiation with carboplatin/paclitaxel or cisplatin/5-fluoruracil in patients with squamous cell carcinoma of the esophagus. *Radiat. Oncol.* 2017, 12, 182. [CrossRef]
- Tamtai, A.; Jiarpinitnun, C.; Hiranyatheb, P.; Unwanatham, N.; Sirachainun, E.; Supsamutchai, C.; Pattaranutaporn, P.; Ngamphaiboon, N. Tolerability and efficacy of concurrent chemoradiotherapy comparing carboplatin/paclitaxel versus platinum/5-FU regimen for locally advanced esophageal and esophagogastric junction cancers. *Med. Oncol.* 2017, 34, 157. [CrossRef]
- Mukherjee, S.; Hurt, C.N.; Gwynne, S.; Sebag-Montefiore, D.; Radhakrishna, G.; Gollins, S.; Hawkins, M.; Grabsch, H.I.; Jones, G.; Falk, S.; et al. NEOSCOPE: A randomised phase II study of induction chemotherapy followed by oxaliplatin/capecitabine or carboplatin/paclitaxel based pre-operative chemoradiation for resectable oesophageal adenocarcinoma. *Eur. J. Cancer* 2017, 74, 38–46. [CrossRef]
- Li, C.Y.; Huang, P.M.; Chu, P.Y.; Chen, P.M.; Lin, M.W.; Kuo, S.W.; Lee, J.M. Predictors of survival in esophageal squamous cell carcinoma with pathologic major response after neoadjuvant chemoradiation therapy and surgery: The impact of chemotherapy protocols. *BioMed Res. Int.* 2016, 2016, 6423297. [CrossRef]
- 50. Bao, Y.; Liu, S.L.; Zhou, Q.C.; Cai, P.Q.; Anfossi, S.; Li, Q.Q.; Hu, Y.H.; Liu, M.Z.; Fu, J.H.; Rong, T.H.; et al. Three-dimensional conformal radiotherapy with concurrent chemotherapy for postoperative recurrence of esophageal squamous cell carcinoma: Clinical efficacy and failure pattern. *Radiat. Oncol.* **2013**, *8*, 241. [CrossRef]
- 51. Zhang, J.; Peng, F.; Li, N.; Liu, Y.; Xu, Y.; Zhou, L.; Wang, J.; Zhu, J.; Huang, M.; Gong, Y. Salvage concurrent radio-chemotherapy for post-operative local recurrence of squamous-cell esophageal cancer. *Radiat. Oncol.* **2012**, *7*, 93. [CrossRef] [PubMed]
- 52. Shapiro, J.; van Lanschot, J.J.B.; Hulshof, M.C.C.M.; van Hagen, P.; van Berge Henegouwen, M.I.; Wijnhoven, B.P.L.; van Laarhoven, H.W.M.; Nieuwenhuijzen, G.A.P.; Hospers, G.A.P.; Bonenkamp, J.J.; et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (cross): Long-term results of a randomised controlled trial. *Lancet Oncol.* **2015**, *16*, 1090–1098. [CrossRef]
- Noronha, V.; Prabhash, K.; Joshi, A.; Patil, V.M.; Talole, S.; Nakti, D.; Sahu, A.; Shah, S.; Ghosh-Laskar, S.; Patil, P.S.; et al. Clinical outcome in definitive concurrent chemoradiation with weekly paclitaxel and carboplatin for locally advanced esophageal and junctional cancer. Oncol. Res. 2016, 23, 183–195. [CrossRef]
- 54. NCCN. Practise Guidelines in Oncology-Esophageal and Esophagogastric Junction Cancers. Available online: https://www.nccn.org/professionals/physician_gls/PDF/esophageal.pdf (accessed on 22 March 2022).
- 55. Li, Q.Q.; Liu, M.Z.; Hu, Y.H.; Liu, H.; He, Z.Y.; Lin, H.X. Definitive concomitant chemoradiotherapy with docetaxel and cisplatin in squamous esopheageal carcinoma. *Dis. Esophagus* **2010**, *23*, 253–259. [CrossRef] [PubMed]
- Li, C.; Zhao, S.; Zheng, Y.; Han, Y.; Chen, X.; Cheng, Z.; Wu, Y.; Feng, X.; Qi, W.; Chen, K.; et al. Preoperative pembrolizumab combined with chemoradiotherapy for oesophageal squamous cell carcinoma (PALACE-1). *Eur. J. Cancer* 2021, 144, 232–241. [CrossRef] [PubMed]
- 57. Yu, R.; Wang, W.; Li, T.; Li, J.; Zhao, K.; Wang, W.; Liang, L.; Wu, H.; Ai, T.; Huang, W.; et al. RATIONALE 311, Tislelizumab plus concurrent chemoradiotherapy for localized esophageal squamous cell carcinoma. *Future Oncol.* **2021**, *17*, 4081–4089. [CrossRef]

- 58. Athauda, A.; Watkins, D.; Mohammed, K.; Chau, I.; Starling, N.; Rao, S.; Tait, D.; Aitken, K.; Cunningham, D. Cisplatin substitution with carboplatin during radical chemoradiotherapy for oesophagogastric carcinoma: Outcomes from a tertiary centre. *Anticancer Res.* **2018**, *38*, 5943–5949. [CrossRef]
- 59. Bruce, D.M.; Thomas, F.P.; Robert, J.G.; Thomas, M.P.; James, M.; Ritsuko, K.; Gordon, O.; Seth, A.R.; David, P.K. INT 0123 (radiation therapy oncology group 94-05) phase III trial of combined-modality therapy for esophageal cancer: High-dose versus standard-dose radiation therapy. *J. Clin. Oncol.* **2002**, *20*, 1167–1174. [CrossRef]