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ORIGINAL RESEARCH

The benefit of taxane-based therapies over fluoropyrimidine plus platinum (FP) in the treatment of esophageal cancer: a meta-analysis of clinical studies

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Purpose: Fluoropyrimidine plus platinum (FP) is currently the standard treatment for esophageal cancer (EC). In recent years, taxane-based chemotherapy has also been used and has shown good efficacy in EC. This study aims to investigate the advantages of taxane-based over FP chemotherapy, as well as discuss its drawbacks, in the treatment of EC.

Patients and methods: A literature search was done for studies comparing clinical outcomes between taxane-based and FP chemotherapy in EC. Pooled analyses were performed to compare the efficacy and grade 3/4 adverse events in patients who received neoadjuvant chemotherapy (NACT), neoadjuvant chemoradiotherapy (NACRT), or definitive chemoradiotherapy (dCRT). Subgroup analyses were also conducted in esophageal squamous cell carcinoma (ESCC).

Results: Thirty-one studies with a total of 3,912 patients were included in the analysis. Better long-term survival was found in patients who received taxane-based NACT (progression-free survival (PFS): pooled HR=0.58, P=0.0008; and overall survival (OS): pooled HR=0.50, P<0.00001) and dCRT (PFS: pooled HR=0.75, P<0.0001). In NACRT, taxane-based treatment and FP showed similar efficacy. In ESCC patients, taxane-based treatment showed better OS (NACT: pooled HR=0.57, P=0.02; NACRT: pooled HR=0.51, P=0.03; and dCRT: pooled HR=0.73, P<0.0001) than FP chemotherapy. Furthermore, taxane-based therapy also showed a better short-term response (complete response (CR), objective response rate (ORR), disease control rate (DCR), or pathologic complete response (pCR). However, taxane-based therapy was significantly correlated with a higher incidence of grade 3/4 leukopenia, neutropenia, and diarrhea.

Conclusion: Compared to FP, taxane-based therapy produced better clinical response and outcomes in EC patients receiving NACT or dCRT, and in all types of therapy in patients with ESCC. Taxane-based treatment is associated with more frequent toxicity.

Keywords: digestive cancer, chemotherapy, survival, clinical cancer research

Introduction

Esophageal cancer (EC) is one of the most common malignancies worldwide, especially in developing countries.[1] From 2012 to 2015, it was estimated that the worldwide incidence and mortality of EC increased from 455,800–483,000 and from 400,200–439,000 respectively.[1,2] In China, EC is estimated as the third most common cancer and the fourth leading cause of cancer death among all the cancer types in 2015.[3] EC is usually diagnosed at an advanced stage as it is clinically inconspicuous and is characterized by high rates of locoregional recurrence and distant metastasis after primary surgical treatment.[4]

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The treatment options for EC include surgery with or without neoadjuvant treatment (chemotherapy or chemoradiotherapy)[5] and definitive chemoradiotherapy (dCRT).[6] Therefore, the choice of treatment plays a very important role in the prognosis of EC. Preoperative chemotherapy or chemoradiotherapy has become a treatment of choice for most locally advanced resectable cases,[5,7] and the definitive concurrent chemoradiotherapy (CCRT) has been established as a standard treatment for unresectable, locally advanced cases since results from the RTOG 85–01 trial were reported.[6] During the last decades, the overall prognosis of EC has slowly improved, partly because of the increasing practice of multidisciplinary management. Despite this, the 5-year survival rate remains low, with only about 19% based on the US National Cancer Institute's report in 2018.[8]

In the clinic, the most commonly used regimens are those consisting of platinum (carboplatin/cisplatin) combined with either fluorouracil (5-FU) or taxanes (paclitaxel/docetaxel) and their modifications. Fluoropyrimidine plus platinum (FP), especially cisplatin plus 5-FU (CF), was mostly used as a first-line treatment for several years, and became a standard regimen and category one recommendation for EC in many countries.[9,10] At the same time, taxane-based chemotherapy or chemoradiotherapy as a first-line therapy had also been shown to be effective in EC.[4,11,12] As a result, more and more studies attempted to find clinical benefits of taxane-based therapy over the FP regimen. Some studies indicated that taxane-based regimens were more effective than FP,[11,13–20] while other studies showed lower efficacy[21–23] or higher toxicity.[24–26] In view of these controversial results, we made this meta-analysis to investigate the benefits and disadvantages of taxane-based first-line therapy compared with FP therapy in the treatment of EC.

Materials and methods

Search strategy and study selection

Medline and Embase were searched for publications up to September 2017. The following search terms in the title were used without any language restriction: (esophageal OR esophagus OR oesophageal OR esophagus) AND (tumor OR cancer OR carcinoma OR neoplasm OR neoplasms) and (docetaxel OR paclitaxel OR taxane). In addition, references in all relative researches were reviewed for any further eligible studies. All studies included in the meta-analysis should meet the following criteria: 1) be a randomized controlled trial (RCT) or cohort study and 2) investigate curative effects or adverse events between taxane-based regimens and FP in EC. If more than one publication reported results from the same study, the latest updated data was extracted. Studies that included recurrent or metastatic EC and any prior interventions except for diagnostic biopsy were excluded from the analysis.

Endpoints of interest

Based on the chemotherapy regimens used, patients were classified into two main groups, namely the taxane group and the FP group. Patients were further divided into two subgroups, namely the neoadjuvant therapy (NAT) group and the dCRT group, according to the subsequent surgical intervention. The primary outcome measures were complete response (CR), objective response rate (ORR), disease control rate (DCR); hazard ratios (HRs) with their 95% CIs for progression-free survival (PFS) and overall survival (OS) after treatment; and grade 3/4 adverse events (anemia, neutropenia, leukopenia, thrombocytopenia, anorexia, nausea, vomiting, diarrhea, esophagitis, and pneumonia). Pathologic complete response (pCR) and R0 resection in the NAT group were also noted.

Data extraction

All studies searched were reviewed by two authors (T Wang and M Liu) independently to exclude irrelevant or duplicate publications. Data were extracted from all included studies. In the event of a discrepancy, a third reviewer (Y Chen) reviewed the study in question to reach a consensus. Details extracted from the included studies were the name of the first author, year of publication, study period, geographic area, sample size, median age, median follow-up, chemotherapy regimen, median radiation dose, treatment strategy, pathological type, clinical stage, and research type (Table 1). Odds ratio (OR) and its 95% CI were used to express the frequencies of CR, ORR, DCR, pCR, R0 resection, and different kinds of adverse events. HRs and their 95% CI for PFS and OS were also extracted from different studies. If the data for HR and its 95% CI cannot be acquired, the methods outlined by Tierney et al[27] were applied to get an estimated value. From Kaplan–Meier curves, Engauge Digitizer version 4.1 (available from http://digitizer.sourceforge.net/) was used to extract data which were then put in the calculation spreadsheet appended to Tierney et al's paper. Besides, data for disease-free survival (DFS) and recurrence-free survival (RFS) were all defined as PFS. Furthermore, patients who received sequential CRT were also included.

Quality assessment and statistical analysis

The quality of cohort studies was assessed using the nine-star Newcastle-Ottawa Quality Assessment Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp), while the Cochrane risk of bias tool was used for RCTs. In the nine-star Newcastle-Ottawa Quality Assessment Scale, scores of 1–3, 4–6, and 7–9 means low quality, medium quality, and high quality, respectively.

Studies with a median follow-up period <2 years were excluded when survival was analyzed. Pooled HRs for OS and PFS and pooled ORs for pCR, R0 resection, CR, ORR, DCR, and adverse events were obtained using the RevMan 5.3 analysis software. At the same time, a Z-test was used to examine the statistical significance of pooled estimates and the statistical heterogeneity was assessed by I^2 tests. Whenever there was significant heterogeneity ($P<0.05$ or $I^2>50\%$), the random effect model was applied to analyze the estimated values. Otherwise, the fixed effect model was used.[28] Tests for funnel plot asymmetry were used to examine bias in the results of meta-analyses. Begg's and Egger's tests, which were performed using the software of STATA (version 14.0; StataCorp, College Station, TX, USA), were used to estimate the publication bias of analysis involving at least 10 studies, and $P<0.05$ was considered to be of statistical significance.

Results

Search results and description of studies

A total of 516 potentially relevant articles were identified from the Medline and Embase databases. There were 462 articles excluded through examining the titles, abstracts, and full texts. In the remaining 54 articles, 24 were further excluded because they were duplicates (seven articles), had patients with prior intervention (five studies), did not have data that could be extracted (seven studies), or the non-taxane-based regimen was not FP (five studies). Through reviewing the references of the remaining 30 articles, two additional relevant studies were found and added. Finally, 32 articles with 3,912 patients were included in the final meta-analysis. A total of 26 articles[11–20,24–26,29–41] were published in full text, while six articles[21–23,42–44] were only in abstract form. Two of the 32 articles[14,37] described one study. Hence, there were 31 studies altogether (seven RCTs and 24 cohort studies). The detailed steps of study selection were summarized in Figure 1.

There were 18 studies from Asian countries (12 from China, six from Japan) and 13 studies from Western countries (six from America, three from the Netherlands, two from Canada, one from Germany, and one from the Czech Republic). Among all the included studies, 17 analyzed the benefits of neoadjuvant taxane-based therapy (neoadjuvant chemotherapy, NACT: seven studies; neoadjuvant chemo-radiotherapy, NACRT: 10 studies), 11 studies analyzed the clinical benefits of taxane-based dCRT, and three studies analyzed the benefits of both dCRT and NACRT in EC. Taxane-based regimens included taxane-based monotherapy (paclitaxel/docetaxel), two-drugs, or three-drugs therapy. The radiation doses for dCRT and NACRT ranged from 36–70 Gy and 36–69 Gy, respectively. HRs for OS and PFS could be directly or indirectly acquired on the basis of Kaplan–Meier curves from 20 studies and 13 studies, respectively. Most of the studies reported relevant adverse reactions and complications, and the common adverse events were anemia, leukopenia, neutropenia, thrombocytopenia, anorexia, nausea, vomiting, diarrhea, esophagitis, and pneumonia. The characteristics of all included studies published from 2000–2017 are shown in Table 1.

For patients with resectable or potentially resectable EC, NAT tends to be a good option,[5,7] while dCRT is usually administrated in unresectable cases. In this light, we conducted subgroup analyses of NACT, NACRT, and dCRT.

Quality assessment and publication bias

The quality scores of included cohort studies are summarized in Table S1 and Figure S1A, which ranged from 6–9, with a median score of 7. All these included studies had medium-to-high quality. No high risk of bias was found in any RCTs (Figures S1B and C). Funnel plots, Begg's, and Egger's tests were used to assess publication bias, and no publication biases were found. Plots of Begg's and Egger's tests are shown in Figure S2.

Taxane-based therapy confers better disease control and long-term survival but causes severe toxicity more frequently in patients compared with FP in patients who received NACT

Eight studies reported taxane-based NACT in EC, and seven were comparisons of TPF (taxane+platinum+fluoropyrimidine) and FP, while one was a comparison of paclitaxel+carboplatin and FP. From these clinical studies, we found that short-term clinical responses except CR were significantly better in patients who received taxane-based therapy than in those who received FP therapy

Table 1 The characteristics of all included studies

Author	Year	Study period	Geographic area	Sample size (taxane/non-taxane)	Median age (taxane/non-taxane, years)	Median follow-up (taxane/non-taxane, months)
Adelstein et al	2000	1991.08–1997.07	America	112 (40/72)	60	33
Roof et al	2006	1994–2002	America	164 (83/81)	61/64	54
Bader et al	2008	1993–2000	German	67 (35/32)	51.6/56.4	78.3/109.3
Hsu et al	2008	1999–2004	China	127 (57/70)	57/62.3	35
Zemanova et al	2010	2001.01–2005.08	Czech Republic	107 (44/63)	58/60	52
Courrech Staal et al	2011	1997–2007	Netherlands	81 (16/65)	70/60	15
Chen et al	2011	2005.01–2007.06	China	48 (24/24)	57	–
Wu et al	2012	2008.07–2009.12	China	154 (77/77)	61/60	–
Zhao et al	2012	2005.01.01–2008.05.31	China	90 (45/45)	–	14.2
Bai et al	2013	2009.08–2011.05	China	74 (36/38)	54/56	–
Blom et al	2014	2005.01–2010.07	Netherlands	165 (92/73)	62/64	–
Honing et al	2014	1996–2008	Netherlands	102 (55/47)	64.8/62.5	–
Katada et al	2014	2007.09–2010.12	Japan	79 (38/41)	64.4/64.2	27/42
Schellenberg et al	2014	2010.02–2013.02	Canada	112 (39/73)	–	–
Thomay et al	2014	2008.01–2013.06	America	71 (33/38)	–	9.1/18.2
Berman et al	2014	2008.07–2013.10	America	100 (49/51)	65	–
Kushida et al	2014	2001–2007	Japan	95 (55/40)	61.9/60.4	–
Yang et al	2015	2008.03–2010.01	China	68 (34/34)	59/56	9
Wang et al	2015	2012.06–2014.10	China	53 (25/28)	–	–
Nomura et al	2015	2003.01–2013.01	Japan	209 (60/149)	61/62	32.4
Ui et al	2015	2007.04–2011.09	Japan	76 (38/38)	62/66	22.8
Boggs et al	2015	1992–2012	America	159 (30/129)	–	–
Sun et al	2016	2009.03–2014.11	China	179 (83/96)	61/59	28
Hu et al	2016	2009.01–2013.12	China	202 (105/97)	61.3/61.1	44.6
Zhang et al	2016	2002–2013	China	317 (161/156)	58/56.4	21/24
Yamashita et al	2016	2007.09–2012.08	Japan	79 (38/41)	–	49

Chemotherapy regimens	Median radiation dose (taxane/non-taxane, Gy)	Treatment strategy	Pathological types	Clinical stage	Research type	Quality	Reference
PTX+DDP vs 5-FU+DDP	69	NACRT	AC/SCC/other	II–IV/unknown	CS	7	26
PTX+5-FU+DDP vs 5-FU+DDP	58.5	NACRT	AC/SCC	II, III, IV	CS	7	31
PTX+5-FU+LV+DDP vs 5-FU+LV+DDP	–	NACT	AC	T3/4	CS	7	33
PTX+DDP vs 5-FU+DDP	36/60	dCRT/NACRT	SCC	II, III	CS	7	32
PTX+5-FU+CBP/DDP vs 5-FU+CBP/DDP	45.1	NACRT	AC/SCC/other	II–IVa	CS	7	25
PTX+CBP vs 5-FU+DDP	50.4/36–50	CCRT/NACRT	AC/SCC/AC-SCC	II–IVa	CS	7	30
DTX+DDP vs 5-FU+DDP	60	CCRT	SCC	III, IVa	RCT	–	34
DTX+DDP vs 5-FU+DDP	40	NACRT	SCC	T3N0–1M0	RCT	–	40
DTX+DDP vs 5-FU+DDP	50.4	CCRT	SCC	II–IVa	RCT	–	20
DTX+DDP vs 5-FU+DDP	60	CCRT	SCC	IIB–IIIB	RCT	–	35
PTX+CBP vs 5-FU+DDP	41.4/50.4	NACRT	AC/SCC/other	T1-3N0–1M0	CS	7	29
PTX+CBP vs 5-FU+DDP	50.4	CCRT	AC/SCC	I–IV	CS	7	11
DTX+5-FU+DDP vs 5-FU+DDP	–	NACT	SCC	II, III	CS	7	37
PTX+CBP vs 5-FU+DDP	50	NACRT	–	–	CS	7	42
PTX+CBP vs 5-FU+DDP	50.4	NACRT	–	–	CS	9	23
PTX+CBP vs 5-FU+platinum	50.4	NACRT	AC/SCC	II, III, IV	CS	6	43
DTX vs 5-FU+DDP	40	NACRT	SCC	T2-4N1–3M0	CS	7	36
PTX+LBP vs 5-FU+DDP	60–70	CCRT	SCC	III, IVa	RCT	–	17
PTX+DDP vs 5-FU+DDP	56–60	CCRT	AC/SCC	–	RCT	–	38
DTX+5-FU+DDP vs 5-FU+DDP	–	NACT	SCC	II, III	CS	7	18
DTX+5-FU+DDP vs 5-FU+DDP	–	NACT	AC/SCC	II–IV	CS	7	19
PTX+CBP/DDP vs 5-FU+DDP	50.4	NACRT	AC/SCC	II, III, IV	CS	6	39
PTX/DTX+CBP/DDP/NDP vs fluoropyrimidine+DDP/NDP	56	dCRT	SCC	II–IV	CS	7	12
PTX+DDP vs 5-FU+DDP	54–60	CCRT	SCC	IIB, III	CS	7	13
DTX+DDP vs 5-FU+DDP	50–70	CCRT	SCC	II–IVa	CS	9	16
DTX+5-FU+DDP vs 5-FU+DDP	–	NACT	SCC	II, III	CS	7	14

(*Continued*)

Table 1 (*Continued*)

Author	Year	Study period	Geographic area	Sample size (taxane/non-taxane)	Median age (taxane/non-taxane, years)	Median follow-up (taxane/non-taxane, months)
Ojima et al	2016	2008.01–2012.12	Japan	77 (48/29)	65/68	37/48
Haisley et al	2016	2000.01–2015.07	America	142 (87/55)	–	–
Fang et al	2017	2009.01–2013.12	China	82 (41/41)	–	28.4
Akiyama et al	2017	2007.03–2016.12	Japan	63 (29/34)	64/64.3	–
Chen et al	2017	2012.04–2015.07	China	436 (218/218)	–	–
Sim et al	2017	2011–2015	Canada	101 (40/61)	62	43

Abbreviations: 5-FU, fluorouracil; AC, adenocarcinoma; ADM, adriamycin; CBP, carboplatin; CCRT, concurrent chemoradiotherapy; CPT-11, irinotecan; CS, cohort study; dCRT, definitive chemoradiotherapy; DDP, cisplatin; DTX, docetaxel; LBP, lobaplatin; NACRT, neoadjuvant chemoradiotherapy; NACT, neoadjuvant chemotherapy; NAT, neoadjuvant therapy; NDP, nedaplatin; PTX, paclitaxel; RCT, randomized controlled trail; SCC, squamous cell carcinoma.

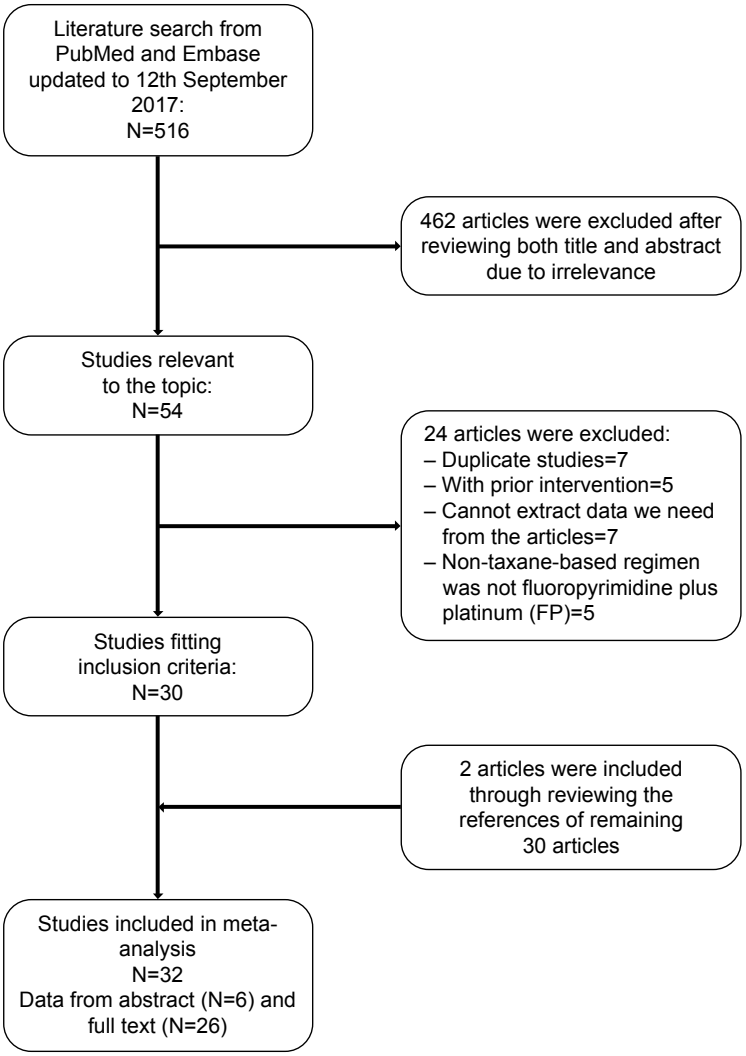


Figure 1 The flow chart of study selection.

Chemotherapy regimens	Median radiation dose (taxane/non-taxane, Gy)	Treatment strategy	Pathological types	Clinical stage	Research type	Quality	Reference
DTX+5-FU+DDP vs 5-FU+DDP	–	NACT	SCC	II–IV	CS	7	15
PTX+CBP vs 5-FU+DDP	–	NACT	–	–	CS	6	22
PTX+DDP vs S-1+DDP	60	CCRT	SCC	II–IVa	CS	7	24
DTX+5-FU+DDP vs 5-FU+DDP	–	NACT	SCC	II–IV	CS	6	41
PTX+5-FU vs 5-FU+DDP	61.2	CCRT	SCC	–	RCT	–	44
PTX+CBP vs 5-FU+DDP	–	CCRT/NACRT	AC/SCC	–	CS	7	21

(CR: pooled OR=0.52, 95% CI=0.21–1.28, P=0.15; ORR: pooled OR=0.26, 95% CI=0.14–0.49, $P<0.0001$; DCR: pooled OR=0.37, 95% CI=0.16–0.84, P=0.02; Figure 2A–C). Based on these results, we investigated whether the better clinical response in taxane-based NACT translated into higher R0 resection and pCR rates, and long-term survival. Our analysis showed that no difference was found in R0 resection (pooled OR=1.31, 95% CI=0.50–3.42, P=0.58) between taxane-based NACT and FP NACT (Figure 2D). However, taxane-based NACT had higher pCR rates (pooled HR=0.45, 95% CI=0.21–0.94, P=0.03; Figure 2E) and better outcomes in PFS (pooled HR=0.58, 95% CI=0.43–0.80, P=0.0008; Figure 2F) and OS (pooled HR=0.50, 95% CI=0.37–0.68, $P<0.0001$; Figure 2G) when compared to FP NACT. Based on these seven studies, we could find that taxane-based NACT caused more grade 3/4 neutropenia (pooled OR=13.28, 95% CI=1.37–129.01, P=0.03) and diarrhea (pooled OR=5.50, 95% CI=1.88–16.05, P=0.002) when compared with FP NACT (Figure S3). The prevalence of grade 3/4 anemia, leukopenia, thrombocytopenia, anorexia, nausea, and vomiting was similar (Table S3).

Taxane-based NACRT therapy and FP NACRT therapy showed similar efficacy and toxicity in EC patients

Including three studies that enrolled patients who received either taxane-based NACRT or taxane-based dCRT, a total of 13 studies were analyzed, among which 10 were comparisons of taxane plus platinum (TP) and FP, two compared TPF and FP, and one was a comparison of docetaxel and FP. There were no significant differences in ORR (pooled OR=1.06, 95% CI=0.63–1.77, P=0.83), DCR (pooled OR=1.04, 95% CI=0.46–2.33, P=0.93), R0 resection (pooled OR=0.76, 95% CI=0.30–1.96, P=0.58), pCR (pooled OR=1.15, 95% CI=0.90–1.49, P=0.27), PFS (pooled HR=1.25, 95% CI=0.42–3.72, P=0.69) and OS (pooled HR=0.91, 95% CI=0.69–1.20, P=0.52) between the taxane-based NACRT group and FP NACRT group (Table S2).

Between taxane-based NACRT and FP NACRT, there were no significant differences in grade 3/4 anemia (pooled OR=0.95, 95% CI=0.33–2.71, P=0.92), leukopenia (pooled OR=1.67, 95% CI=0.34–8.18 P=0.53), neutropenia (pooled OR=2.18, 95% CI=0.42–11.29, P=0.35), thrombocytopenia (pooled OR=0.21, 95% CI=0.01–2.88, P=0.24), nausea (pooled OR=0.61, 95% CI=0.18–2.13, P=0.44), vomiting (pooled OR=0.49, 95% CI=0.23–1.05, P=0.07), diarrhea (pooled OR=0.26, 95% CI=0.01–6.51, P=0.41), esophagitis (pooled OR=1.43, 95% CI=0.81–2.51, P=0.21) or pneumonia (pooled OR=0.38, 95% CI=0.08–1.93, P=0.24) (Table S3).

Taxane-based dCRT results in better disease control and long-term survival and also causes severe toxicity more frequently compared with FP dCRT

There were 14 studies (TP vs FP: 13 studies; paclitaxel+5-FU vs FP: one study) altogether comparing taxane-based regimens with FP regimen in patients who received dCRT. Additionally, the study by Katada et al[37] related to NACT

also reported some data on clinical responses in some patients who just received dCRT. Data for short-term clinical responses (CR, ORR, and DCR) were extracted and it showed that taxane-based regimens were better than the FP regimen (CR: pooled OR=0.61, 95% CI=0.42–0.88, *P*=0.009; ORR: pooled OR=0.60, 95% CI=0.44–0.81, *P*=0.001; and DCR: pooled OR=0.49, 95% CI=0.29–0.82, *P*=0.007; Figure 3A–C). Moreover, patients who received taxane-based dCRT had significantly better PFS (pooled HR=0.76, 95% CI=0.67–0.88, *P*=0.0001, Figure 3D). However, we failed to

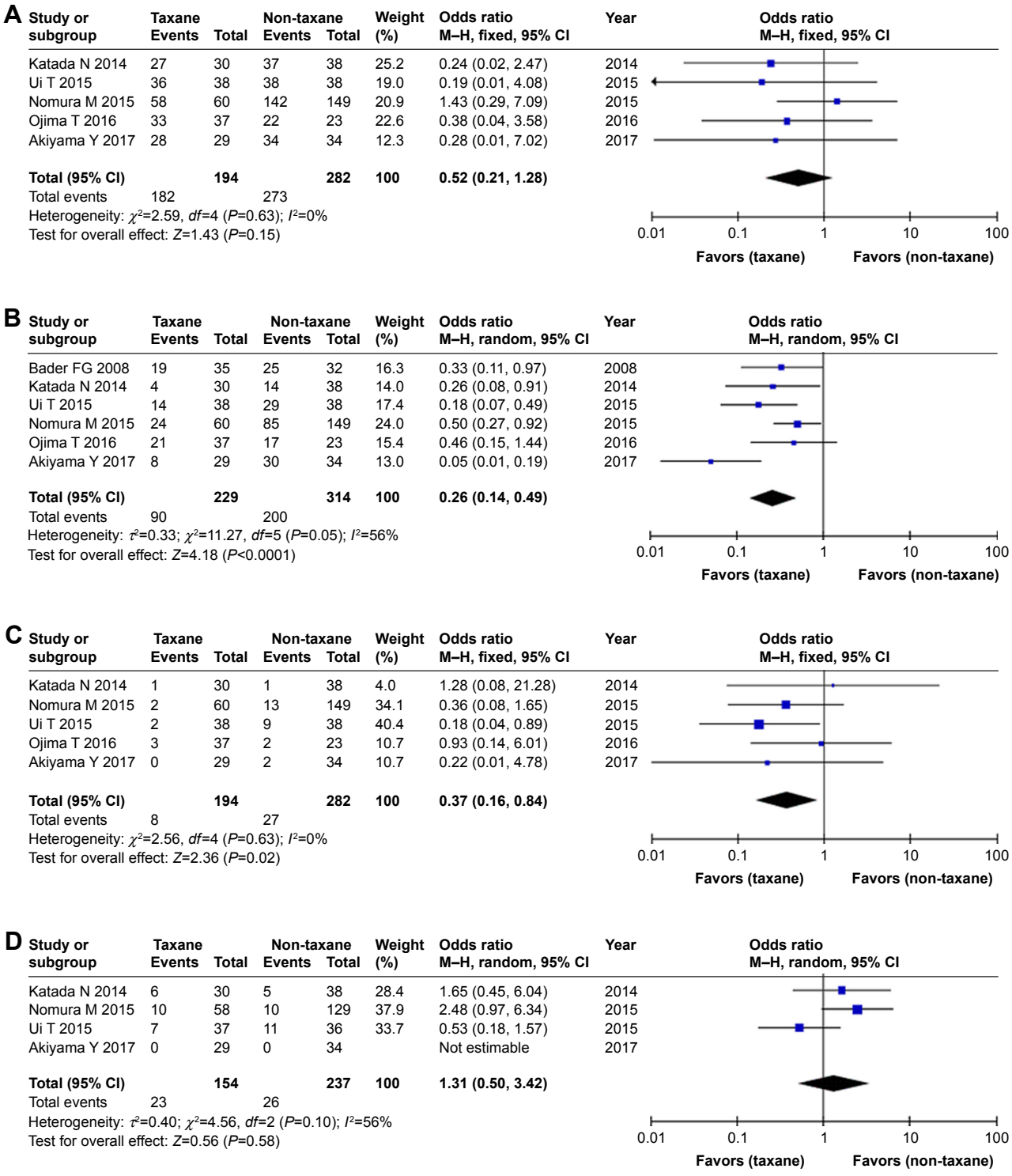


Figure 2 (*Continued*)

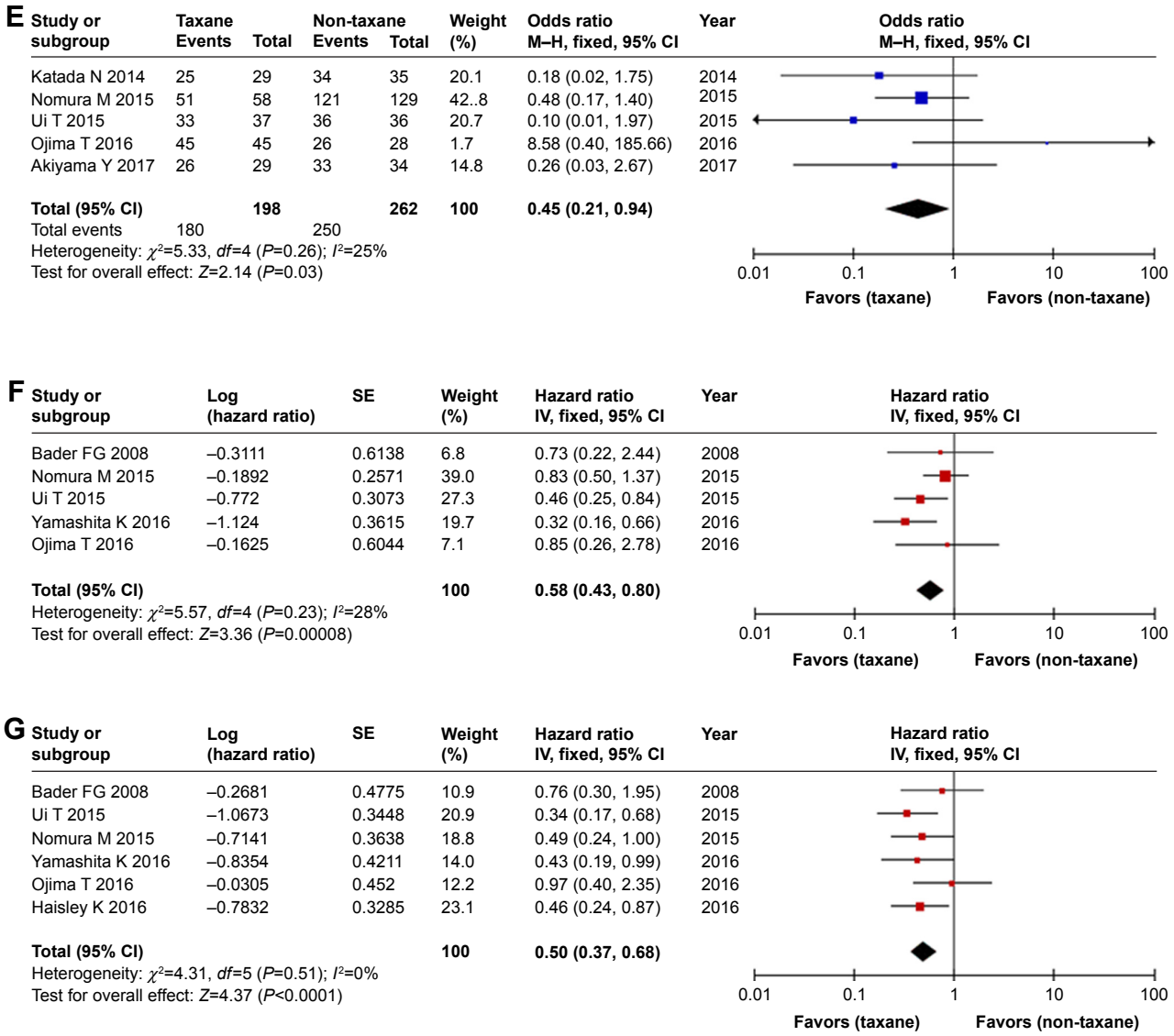


Figure 2 Analyses of curative effects between taxane-based NACT and FP based NACT in EC. (**A**) CR; (**B**) ORR; (**C**) DCR; (**D**) R0 resection; (**E**) pCR; (**F**) PFS; and (**G**) OS.
Abbreviations: CR, complete response; DCR, disease control rate; EC, esophageal cancer; NACT, neoadjuvant chemotherapy; ORR, objective response rate; OS, overall survival; pCR, pathological complete response; PFS, progression free survival; FP, fluoropyrimidine plus platinum.

find any benefit on OS (pooled HR=0.91, 95% CI=0.70–1.17, *P*=0.44, Figure 3E) in taxane-based dCRT.

Patients receiving taxane-based dCRT tend to have higher incidence rates of grade 3/4 leukopenia (pooled OR=1.85, 95% CI=1.34–2.55, *P*=0.0002) and pneumonia (pooled OR=2.32, 95% CI=1.23–4.38, *P*=0.009) when compared to FP dCRT. There was less grade 3/4 nausea (OR=0.03, 95% CI=0.00–0.21, *P*=0.0005) and vomiting (OR=0.04, 95% CI=0.01–0.19, *P*<0.0001) in taxane-based therapy. However, it must be noted that this was based on only one study that compared paclitaxel plus 5-FU with CF,[44] and that cisplatin frequently causes gastrointestinal toxicity (Figure S4).

Clinical benefits of taxane-based therapy in Esophageal squamous cell carcinoma (ESCC) patients

ESCC is the most common type of EC in Asia and Eastern Europe.[1] In ESCC, taxanes were shown to be highly effective in several clinical trials.[45–48] Thus, we performed a separate analysis on the clinical benefits of taxane-based regimens in ESCC.

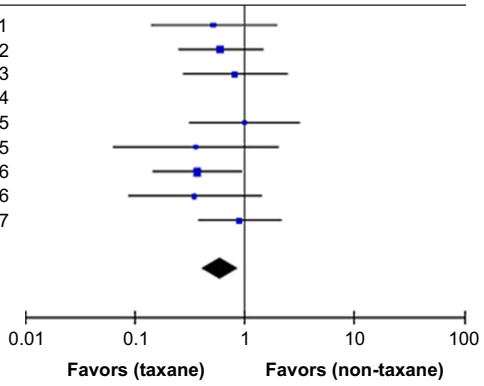
In ESCC patients who received taxane-based therapy NACT, there were four studies (TPF vs FP) comparing curative effects of two different regimens. We found that taxane-based NACT produced better ORR (pooled OR=0.26, 95% CI=0.10–0.67, *P*=0.005) and OS (pooled HR=0.57,

A

Study or subgroup	Taxane Events	Total	Non-taxane Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI	Year
Chen SZ 2011	16	24	19	24	9.0	0.53 (0.14, 1.93)	2011
Zhao T 2012	27	45	32	45	18.1	0.61 (0.25, 1.47)	2012
Bai MH 2013	26	35	28	36	10.0	0.83 (0.28, 2.46)	2013
Katada N 2014	8	8	3	3		Not estimable	2014
Wang J 2015	17	25	19	28	8.1	1.01 (0.32, 3.20)	2015
Yang JS 2015	29	34	32	34	6.7	0.36 (0.07, 2.01)	2015
Hu GF 2016	87	105	90	97	22.7	0.38 (0.15, 0.94)	2016
Sun XJ 2016	76	83	93	96	10.3	0.35 (0.09, 1.40)	2016
Fang M 2017	20	41	21	41	15.2	0.91 (0.38, 2.16)	2017
Total (95% CI)		**400**		**404**	**100**	**0.61 (0.42, 0.88)**	
Total events	306		337				

Heterogeneity: χ^2=3.91, *df*=7 (*P*=0.79); I^2=0%

Test for overall effect: *Z*=2.62 (*P*=0.009)

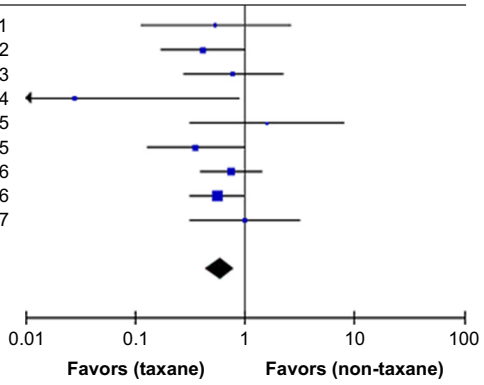


B

Study or subgroup	Taxane Events	Total	Non-taxane Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI	Year
Chen SZ 2011	3	24	5	24	4.1	0.54 (0.11, 2.58)	2011
Zhao T 2012	12	45	21	45	14.3	0.42 (0.17, 1.00)	2012
Bai MH 2013	9	35	11	36	7.5	0.79 (0.28, 2.22)	2013
Katada N 2014	1	8	3	3	3.7	0.03 (0.00, 0.89)	2014
Wang J 2015	4	25	3	28	2.2	1.59 (0.32, 7.90)	2015
Yang JS 2015	9	34	17	34	11.6	0.36 (0.13, 0.99)	2015
Sun XJ 2016	25	83	35	96	21.0	0.75 (0.40, 1.41)	2016
Hu GF 2016	50	105	60	97	30.3	0.56 (0.32, 0.98)	2016
Fang M 2017	7	41	7	41	5.4	1.00 (0.32, 3.16)	2017
Total (95% CI)		**400**		**404**	**100**	**0.60 (0.44, 0.81)**	
Total events	120		162				

Heterogeneity: χ^2=7.64, *df*=8 (*P*=0.47); I^2=0%

Test for overall effect: *Z*=3.30 (*P*=0.0010)

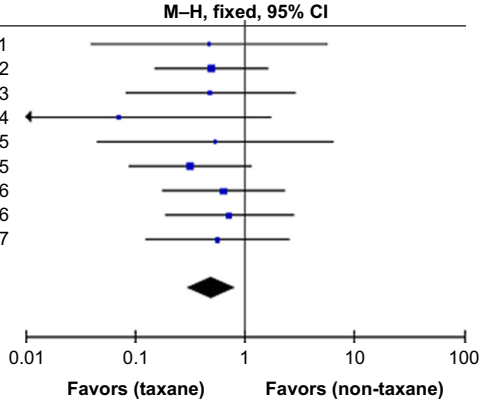


C

Study or subgroup	Taxane Events	Total	Non-taxane Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI	Year
Chen SZ 2011	1	24	2	24	4.5	0.48 (0.04, 5.66)	2011
Zhao T 2012	5	45	9	45	18.8	0.50 (0.15, 1.63)	2012
Bai MH 2013	2	35	4	36	8.7	0.48 (0.08, 2.83)	2013
Katada N 2014	1	8	2	3	6.0	0.07 (0.00, 1.73)	2014
Wang J 2015	1	25	2	28	4.2	0.54 (0.05, 6.36)	2015
Yang JS 2015	4	34	10	34	20.7	0.32 (0.09, 1.15)	2015
Sun XJ 2016	4	83	7	96	14.5	0.64 (0.18, 2.28)	2016
Hu GF 2016	4	105	5	97	11.7	0.73 (0.19, 2.80)	2016
Fang M 2017	3	41	5	41	10.9	0.57 (0.13, 2.55)	2017
Total (95% CI)		**400**		**404**	**100**	**0.49 (0.29, 0.82)**	
Total events	25		46				

Heterogeneity: χ^2=2.39, *df*=8 (*P*=0.97); I^2=0%

Test for overall effect: *Z*=2.70 (*P*=0.007)



D

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, fixed, 95% CI	Year
Hsu FM 2008	–0.8254	0.4262	2.7	0.44 (0.19, 1.01)	2008
Honing J 2014	0.0697	0.228	9.5	1.07 (0.69, 1.68)	2014
Sun XJ 2016	–0.0101	0.2471	8.1	0.99 (0.61, 1.61)	2016
Zhang P 2016	–0.2754	0.0969	52.4	0.76 (0.63, 0.92)	2016
Hu GF 2016	–0.5062	0.1583	19.6	0.60 (0.44, 0.82)	2016
Fang M 2017	–0.1219	0.2532	7.7	0.89 (0.54, 1.45)	2017
Total (95% CI)			**100**	**0.76 (0.67, 0.88)**	

Heterogeneity: χ^2=7.60, *df*=5 (*P*=0.18); I^2=34%

Test for overall effect: *Z*=3.85 (*P*=0.0001)

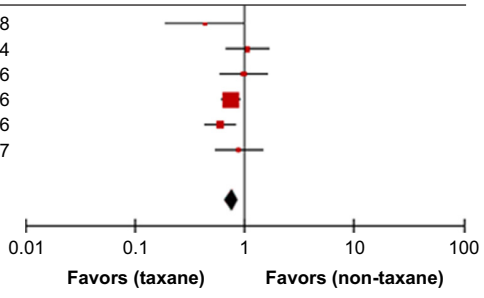


Figure 3 (*Continued*)

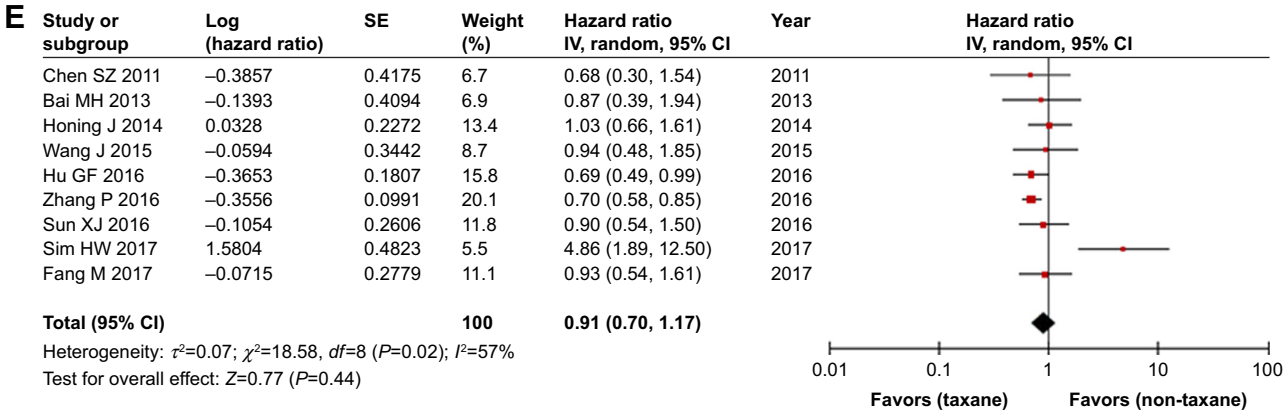


Figure 3 Analyses of curative effects between taxane-based dCRT and FP-based dCRT in EC. (**A**) CR; (**B**) ORR; (**C**) DCR; (**D**) PFS; and (**E**) OS.
Abbreviations: CR, complete response; DCR, disease control rate; dCRT, definitive chemoradiotherapy; EC, esophageal cancer; ORR, objective response rate; OS, overall survival; PFS, progression free survival.

95% CI=0.36–0.90, *P*=0.02). There was a higher frequency of grade 3/4 leukopenia (OR=35.00, 95% CI=2.01–610.34, *P*=0.01), neutropenia (pooled OR=33.71, 95% CI=9.58–118.7, *P*=0.002), and diarrhea (pooled OR=10.76, 95% CI=1.86–62.07, *P*=0.008) (Tables S2 and S3).

In ESCC patients who received taxane-based therapy NACRT, we found that taxane-based NACRT could bring about better pCR (pooled OR=0.50, 95% CI=0.28–0.89, *P*=0.02) and OS (HR=0.51, 95% CI=0.28–0.93, *P*=0.03). Grade 3/4 leukopenia (OR=4.79, 95% CI=1.52–15.08, *P*=0.007) was more frequent when compared with FP NACRT (Tables S2 and S3). No significant differences were found in CR, ORR, DCR, R0 resection, PFS, or other adverse events (Tables S2 and S3).

In ESCC patients who received taxane-based therapy dCRT, we analyzed nine studies comparing TP with FP and one study comparing paclitaxel+5-FU with FP. Taxane-based dCRT resulted in better short-term clinical response (CR: pooled OR=0.57, 95% CI=0.38–0.85, *P*=0.006; ORR: pooled OR=0.58, 95% CI=0.42–0.79, *P*=0.0005; and DCR: pooled OR=0.49, 95% CI=0.29–0.893, *P*=0.008) and survival (PFS: pooled HR=0.74, 95% CI=0.64–0.85, *P*<0.0001; and OS: pooled HR=0.73, 95% CI=0.63–0.85, *P*<0.0001) compared to FP dCRT (Table S2). However, taxane-based dCRT caused higher rates of grade 3/4 leukopenia (pooled OR=1.80, 95% CI=1.30–2.49, *P*=0.0004) and pneumonia (pooled OR=2.32, 95% CI=1.23–4.38, *P*=0.009; Table S3).

Discussion

Nowadays, meta-analysis has become a very popular and powerful tool in evaluating the benefit or disadvantage of an intervention. Through pooling data from quantities of individual studies, meta-analysis could overcome limitations of small sample sizes or rare outcomes and increase the generalizability of study results. In addition, meta-analysis uses a process of computing weighted averages, and more accurate results will be assigned more weight in the computation of average,[49] which, to some extent, eliminates the influence of different populations of patients and other biases which come with cohort studies. Therefore, it is more precise in estimating effects of interest when compared to an individual study.[49] In our present study, we use the meta-analysis to investigate the benefits of taxane-based first-line therapy in the treatment of EC.

Taxanes, including paclitaxel and docetaxel, have been approved by the US Food and Drug Administration (FDA) for the treatment of many malignancies, including ovarian cancer, esophageal cancer, breast cancer, non-small-cell lung cancer and other types of malignancies.[50] This class of drugs promotes the formation of stable microtubules, prolongs the G2 and M phases of the cell cycle, induces cell apoptosis, and inhibits the motility of cancer cells.[51] In the treatment of EC, the FP regimen has been considered standard and has been widely used for more than 30 years. Recently, taxanes combined with platinum also produced good responses and was another first-line chemotherapeutic regimen. To date, there is no consensus as to whether taxane-based chemotherapy is better than FP.

Our results show that patients who received NACT and dCRT benefit more from taxane-based therapy than from FP treatment. In patients who received NACRT therapy, taxane-based treatment and FP therapy showed similar efficacy and toxicities. With the SCC subtype, taxane-based therapy had a higher activity than FP therapy in NACT, dCRT, and NACRT. However, taxane-based regimens were associated with higher rates of severe leukopenia, neutropenia, diarrhea,

or pneumonia when compared with the FP regimen. The cumulative incidence rates of grade 3/4 leukopenia, neutropenia, diarrhea, and pneumonia were 28%, 50%, 5%, and 3%, respectively, in the taxane group by using R software (Figure S5). Fortunately, there was no significant difference in treatment-related deaths between the taxane group and FP group (pooled OR=0.73, 95% CI=0.38–1.40, *P*=0.34, Figure S6).

The primary treatment options for EC include preoperative chemoradiotherapy/chemotherapy, esophagectomy, and definitive CCRT. Among these options, neoadjuvant therapy, including chemotherapy and chemoradiotherapy followed by surgery, has been proven to improve OS in patients with resectable EC when compared to surgery alone.[5] In the Medical Research Council OEO2 trial, patients receiving NACT with CF had longer DFS and OS than those receiving surgery alone.[52] Presently, only CF is recommended for preoperative chemotherapy for EC, and it is only used for adenocarcinoma of the thoracic esophagus or esophagogastric junction cancers (EGJ) and not in SCC. However, in the OGSG1003 trial, patients with ESCC receiving taxane-based NACT had a 2-year RFS of 64.1% and a 2-year OS of 78.6%.[53] Our results showed that taxane-based NACT is associated with better short-term tumor response and long-term survival benefits compared with FP NACT. Similar results were also found in ESCC patients. In this case, taxane-based regimens could be useful for preoperative chemotherapy in EC. However, more RCTs are needed to provide enough evidence.

NACRT is another important option for EC patients. The preferred regimens classified as category one for preoperative chemoradiation in EC include paclitaxel plus carboplatin and fluorouracil plus oxaliplatin (NCCN Guidelines, Version 2, 2018). Data from individual studies showed that both the median PFS and OS in patients who received NACRT with paclitaxel and carboplatin from the CROSS trial were longer than those in patients who received NACRT with fluorouracil and cisplatin from the FFCD 9901 trial (PFS: 37.7 months vs 27.8 months; OS: 48.6 months vs 31.8 months).[4,54] However, clinical stage and tumor location of patients included in the CROSS trial are different from those of the FFCD9901. In the CROSS trial, there were 22% patients located in esophagogastric junction, 84% patients with cT3 and 65% patients with cN1. In contrast, there were 100% patients with esophageal cancer, 15.3% patients with cT3, and 29.6% patients with cN1 in FFCD9901. The median age (60 years in CROSS vs 58.1 years in FFCD9901), radiation dose (41.4 Gy in CROSS vs 45 Gy in FFCD9901), and WHO performance score were similar. It was more interesting that patients with more advanced stage in the CROSS study had longer PFS and OS than patients with a relatively earlier stage in the FFCD 9901 trial. Although this result was just based on the very simple comparison of reported data, we could find the difference of chemotherapeutic regimes between two studies. As a result, it is worthy of analyzing whether different chemotherapeutic regimes affect the survival. In our study, no significant differences were found between taxane-based regimens and FP regimen in the subgroup of NACRT. Between NACT and NACRT, the main difference was whether radiation intervention was used. Therefore, it seems that radiation is the main confounding factor and it is necessary to analyze whether additional intervention of radiation could cause severe adverse events which may hide the benefit of taxane-based chemotherapy. We found that no significant differences were found in grade 3/4 leukopenia and neutropenia, two common toxicities in our study (Figure S7). So, at least for now, we couldn't attribute the absence of taxane-based chemotherapeutic benefit to the advent of severe adverse events caused by NACRT. We hope the PROTECT-1402 study will give us some answers about this issue. Furthermore, whether the benefit of taxane-based chemotherapy can be hidden by radiation still needs further discussion.

While we did not find any benefits of taxane-based NACRT in all EC patients, we did see that taxane-based NACRT improved pCR and OS in SCC when compared with FP regimens. Similar to our results, Huang et al[55] found that the HRs (95% CI) of paclitaxel plus platinum regimen in the entire, SCC, and adenocarcinoma population were 0.80 (0.60–1.06), 0.61 (0.41–0.91), and 0.91 (0.61–1.36), respectively, when compared with FP NACRT. Furthermore, our results also support the rationale behind the ongoing randomized phase 2 PROTECT-1402 trial (NCT02359968), which tries to compare preoperative chemoradiation with either paclitaxel plus carboplatin or FOLFOX in esophageal and junctional cancer with either adenocarcinoma or squamous cell carcinoma.

For unresectable EC, definitive CCRT has become a standard treatment since the results of RTOG 85–01 were reported.[6] Several studies conducted thereafter confirmed the efficacy of dCRT in the treatment of EC. FP was used as a standard concurrent chemotherapeutic regimen in most studies and classified as category one level recommendation. In recent years, taxane plus carboplatin/cisplatin was also recommended based on a series of clinical trials,[56,57] but this combination is the only category 2A recommendation. Although both regimens are deemed effective, there is

currently no consensus as to whether taxane-based dCRT regimens are better than FP dCRT. The results of several studies are conflicting.[11,17,21,24] Schellenberg et al[42] reported that cisplatin+5 FU or carboplatin+paclitaxel concurrent with radiation showed no difference in PFS, while Hu et al[13] found that both median PFS and OS in the taxane group were significantly better than in the FP group (median PFS, 15.9 vs 13.0 months and median OS, 33.9 vs 23.1 months, respectively). In our study, we found that taxane-based therapy produced better clinical response and PFS, but failed to show an improvement in OS. As for adverse events, taxane-based dCRT showed a higher incidence of grade 3/4 leukopenia and pneumonia.

While the most common histologic type of EC in patients from the Western countries is adenocarcinoma, most Asian patients would have SCC.[58] In a multicenter Phase II trial of sequential preoperative induction chemotherapy and chemoradiation,[59] it was reported that patients with SCC had better response rates and survival compared to patients with adenocarcinoma. This, however, was not statistically significant. In patients with SCC, however, our results similarly showed that taxane-based dCRT resulted not only in better clinical responses, but also in longer PFS and OS. With these results, it might be worth considering the re-evaluation of the recommendations on the use of taxanes in dCRT.

It must be noted, however, that, while 32 articles were included in our meta-analysis, data could be extracted only from what was made available in the abstract and the published paper. Some data for OS and PFS were extracted from Kaplan–Meier curves and calculated indirectly to get HRs. Significant heterogeneities were found in many subgroups, and many subgroup analyses took into account <10 trials. Furthermore, among all the studies included, there were only a few RCTs, and some of the studies were only of medium quality. The incomplete data might have restricted our analysis on the benefits of taxane-based regimens in patients with adenocarcinoma.

Conclusion

Taxane-based regimens could produce better clinical response and outcomes, but are associated with increased toxicity (mainly leukopenia, neutropenia, and diarrhea) compared to FP regimens. EC patients who received NACT, dCRT, or those with an SCC benefit more from taxane-based therapy. In the future, more trials should be conducted, especially in SCC, to define the best niche for taxane-based regimens in the treatment of EC.

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Disclosure

The authors report no conflicts of interest in this work.

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