Chemoradiotherapy alone or in combination with Endostar for patients with advanced non-small cell lung cancer: A systematic review and meta-analysis

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ABSTRACT

▶ Review article

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[#]Co-first authors: Zhenchao Tao, Jun Qiu and Yangyang Zhang Previous studies show inconsistent effect estimates for the efficacy of Endostar in patients with advanced non-small cell lung cancer (NSCLC) undergoing chemoradiotherapy. Therefore, this meta-analysis aimed to determine the effectiveness and safety on the basis of data obtained from available randomized controlled trials (RTCs). We find relevant articles reporting the use of Endostar combined with chemoradiotherapy regimens in the treatment of advanced NSCLC. The retrieval period was from June 2008 to June 2018. A total of 11 RTCs that recruited a total of 735 patients were included. Overall, the results indicated that patients who received Endostar plus chemoradiotherapy showed a significantly increased incidence of objective response rate (ORR) (relative risk [RR] = 1.48; 95% confidence interval [CI] = 1.31-1.67; P < 0.00001) and disease control rate (DCR) (RR = 1.17; 95% CI = 1.09-1.25; P < 0.00001) compared with those who received chemoradiotherapy alone. However, no significant difference was noted between groups for 1-year survival rate (RR = 1.06; 95% CI = 0.91-1.23; P = 0.48). Furthermore, combined Endostar with chemoradiotherapy did not yield a high incidence of stable and elevated Karnofsky performance score (RR = 1.06; 95% CI = 0.91-1.23; P = 0.48). Moreover, no significant difference was noted in the incidence of total toxicity between the two groups. The findings of our study indicated that treatment with Endostar plus chemoradiotherapy yielded a high incidence of ORR or DCR, but did not trigger excess adverse events in patients with NSCLC.

Keywords: Endostar, Lung cancer, Chemoradiotherapy, Meta-analysis, Efficacy; Safety.

INTRODUCTION

Lung cancer is the most frequently occurring malignant tumor and is a threat to human health $^{(1, 2)}$. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancers $^{(3, 4)}$. Since early diagnosis is still difficult, by the time a diagnosis is made, 70%–80% of the patients have missed the opportunity for radical resection $^{(5)}$. Despite the variety of treatments

present, the overall survival rate for advanced lung cancer is only 4–6 months, with a five-year survival rate of approximately 4.2% ⁽⁶⁾. Chemoradiotherapy is the primary method of treatment for advanced NSCLC ⁽⁷⁾, and was recommended in 2008 by the National Comprehensive Oncology Network of the United States as the standard regimen of unresectable NSCLC. However, this treatment is restricted by toxicity and side effects, and its therapeutic effect often plateaus (8).

An increased understanding of tumor molecular biology has led to biological targeting drugs that have enriched the treatment of lung cancer and have become an important weapon in the treatment of cancer.

In 1971, Folkman proposed the theory of antiangiogenesis. Tumor progression is divided into two stages, prevascular and vascular phases. During prevascularization, the diameter of the tumor is less than 3 mm, and no angiogenesis is noted. During this period, nutritional uptake and excretion of metabolites by tumor cells are accomplished by simple diffusion. During the vascular phase, neovascularization begins in the body of the tumor and establishes the microcirculation of the tumor itself. During this period, the tumor grows rapidly, and its malignant characteristics are revealed.

The transformation from prevascularization to vascular phase is known as the "angiogenesis switch" ⁽⁹⁾. Thus, the idea for treating tumor by antiangiogenesis targeting was proposed. of recombinant human vascular Injection endostatin (Endostar, YH-16) is a novel multitargeting antiangiogenic drug that was developed by a gene recombination technique. Its mechanism of action is inhibition of tumor neovascularization by selectively inhibiting the migration of vascular endothelial cells to block the nutrient supply to tumor cells, using antiproliferation and antimigration effects, and promoting apoptosis. Since its target action on vascular endothelial cells is less toxic to normal tissue cells, it is less likely to cause bone marrow suppression and gastrointestinal reaction. In addition, the genotype of tumor vascular endothelial cells is stable, and does not tent to lead to drug resistance. Therefore, Endostar has a broad spectrum, low toxicity, and no drug resistance.

The Chinese version of lung cancer diagnosis and treatment guidelines were recommended, combining with vinorelbine and cisplatin regimen for the treatment of stage III/IV NSCLC for initial or recurrent treatment ^(10, 11). Recent studies showed that Endostar combined with chemoradiotherapy can improve the efficacy and

quality of life (QoL) of patients with NSCLC. However, the sample size of each single study was small and the quality is different. Therefore, used а systematic evaluation we and meta-analysis to systematically and objectively evaluate the efficacy and safety of Endostar combined with chemoradiotherapy in the of NSCLC treatment to provide more evidence-based medical evidence for its future application in the treatment of advanced NSCLC.

MATERIALS AND METHODS

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement issued in 2009 (Checklist S1).

Identification of literature

We searched and identified relevant randomized controlled trials (RCTs) from PubMed, Google, Embase, China National Knowledge Internet, Wanfang, and Chinese Biology Medicine databases. The retrieval period was from June 2008 to June 2018. We adopted various medical subject headings terms and key words related to NSCLC and Endostar, including: "non-small cell lung cancer," "NSCLC," "lung cancer," "recombinant human endostatin," "rh-endostatin," "endostatin," "endostar," and "chemoradiotherapy." In addition, if we found information that was useful intimately associated with Endostar in the reference lists of the retrieved studies, these were also identified.

Inclusion and exclusion criteria

Inclusion criteria were: (1) RCTs, (2) patients diagnosed with NSCLC, (3) studies designed to compare Endostar plus chemoradiotherapy with chemoradiotherapy, and (4) reported outcome measures.

Exclusion criteria were: (1) animal studies (not human), (2) treatment of non-pulmonary lesions, but other metastatic lesions, (3) patients with other tumors, (4) lack of an effective control group, and (5) published literature selected for final publication.

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Collection of study variables

The data that we extracted included: (1) number of patients in each RCT, (2) publication date of literature, (3) clinical characteristics, (4) clinical intervention methods, (5) objective response rate (ORR), disease control rate (DCR), and one-year survival rate, and (6) QoL and adverse effects (AEs).

Outcome definition

Outcomes were defined for RCTs using Endostar combined with chemoradiotherapy versus chemoradiotherapy in the treatment of advanced NSCLC.

Quality assessment of included randomized controlled trials

Quality evaluation was conducted according to the Cochrane Handbook (version 5.0.1) as follows: (1) methods used to randomize groups of patients, (2) how to perform adequate setting blinding, (3) how to perform an adequate allocation and conceal the sequence, (4) withdrawal and its handling, with or without a description of the number and reasons for withdrawal: low risk of bias, unclear risk of bias, and high risk of bias ^(12, 13).

Statistical analysis

The meta-analysis used RevMan 5.3 and STATA15 Software. The relative risk (RR) was used to measure the treatment in the study. The effect quantity was expressed as 95% confidence interval (CI). Heterogeneity among the results of the study was tested using chi-square test. The fixed effect model combination analysis was applied if the similarity among the studies in the subgroup was sufficient ($I^2 < 50$, P > 0.1). Conversely, using the random-effects model, the sensitivity of ORR and DCR was analyzed by removing single study methods, and subgroup analysis was carried out according to average age, pathological type, and quality evaluation grade.

Visual inspections of funnel plots were conducted. Egger and Begg tests were also used to statistically assess the publication bias for investigated outcomes. All reported *P*-values were two-sided, and *P* < 0.05 was considered *Int. J. Radiat. Res., Vol. 19 No. 1, January 2021*

statistically significant for all included studies.

RESULTS

Selection of studies

After preliminary screening, 65 articles were retrieved: 31 articles were summary or nursing reports, or did not used radiotherapy, two were infratests, and one study was combined with other tumors. Furthermore, eight studies were descriptive and lacked controls, three were not randomized, five were without synchronous chemotherapy, three did not treating pulmonary lesions, and one was a repeat article, leaving a final total of 11 articles included in the analysis ⁽¹⁴⁻²⁴⁾ (figure 1). Manual searches of the references of the retrieved studies did not yield any further studies that met the inclusion criteria.



Figure 1. Flow chart of the literature search

Baseline characteristics

RCTs of Endostar combined with chemoradiotherapy versus chemoradiotherapy alone to treat NSCLC were selected in this study. The baseline characteristics of the studies and patients are summarized in table 1. Overall, 11 RCTs with a total of 735 NSCLC patients were included in the final analysis, which included 458 males and 277 females. The patients aged from 21 to 87 years. A total of 368 patients combined received Endostar with

chemoradiotherapy, and 367 patients received chemoradiotherapy alone. All the included studies were conducted in China. Pathological types included adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, and large cell carcinoma. Four studies included patients with stage III NSCLC, and the remaining seven studies included both stages III and IV NSCLC patients. The study quality of included studies is summarized in table 2. Overall, one study scored 4, one had a score of 3, and the remaining nine studies had scores of 2.

Study	Time	Sample (T/C)	Sex (M/F)	Age (T/C)	histopathology (N)	Stage (N)	End point	
Liu J 2009 ^{(14]}	2007-2008	31/31	54/17	29-68	A (24), S (38)	III (37), IV (25)	1,2,5	
Ma JB 2009 ^{(15]}	2007.1-2008.9	23/23	35/11	38-70/44-73	A (15), S (31)	III	1,2,3,4,5	
Ding Y 2011 (16)	2007.4-2010.3	14/14	23/5	45-63/46-66	A (20), S (6), L (2)	III	1,3,5	
Jiang ZG 2011 ^{(17]}	2009.2-2010.12	19/20	23/16	70-75/68-76	A (21), S (18)	III (24), IV (15)	1,2,4,5	
Yang Y 2012 ^{(18]}	2009.6-2012.6	20/20	24/16	45-87	A, S, AS	III and IV	1,2,4,5	
Chen XJ 2013 ^{(19]}	2009.4-2010.4	21/21	27/15	40-70/41-69	A (19), S (23)	III	1,2,3,5	
Liu HW 2013 ^{(20]}	2009.9-2011.8	78/80	82/76	45-71/43-72	A (72)/S (86)	III	1,2,5	
Zhang Y 2016 ⁽²¹⁾	2006.6-2009.9	36/36	37/35	21-60/17-65	NSCLC	III (39), IV (33)	1,2,5	
Zang V 2017 ⁽²²⁾	2012 2 2015 5	E7/E2	75/25	52.9±13.2/53.	A (34), S (57), AS	ען (20) אין (20) אין (20)	1245	
	2015.2-2015.5	57/55	/5/55	7±13.6	(19)	111 (56), 1V (72)	1,2,4,5	
Liu L 2017 ^{(23]}	2012 12 2015 1	20/20	16/11	<55:9 <i>,</i> ≥55:21/	A (20) S (22)	UU (24) IV (26)	172	
	2013.12-2013.1	50/50	40/14	<55:10, ≥55:20	A (30), 3 (22)	111 (24), IV (30)	1,2,3	
Xu H 2018 ^{(24]}	2013.1-2015.6	39/39	41/37	52-76/51-77	A	III (41), IV (37)	1,2,3,4,5	

Table 1. Basic information included in the clinical studies.

Table 2. Quality analysis of included studies.

Included study	Randomized method	Allocation hidden	Blind	Withdrawal research	Score of study
Liu J ⁽¹⁴⁾	Unclear	No use	No use	Sufficient	2
Ma JB ⁽¹⁵⁾	Unclear	No use	No use	Sufficient	2
Ding Y ⁽¹⁶⁾	Unclear	No use	Sufficient	Sufficient	4
Jiang ZG ⁽¹⁷⁾	Unclear	No use	No use	Sufficient	2
Yang Y ⁽¹⁸⁾	Unclear	No use	No use	Sufficient	2
Chen XJ ⁽¹⁹⁾	Unclear	No use	No use	Sufficient	2
Liu HW ⁽²⁰⁾	Unclear	No use	No use	Sufficient	2
Zhang Y ⁽²¹⁾	Unclear	No use	No use	Sufficient	2
Zang Y ⁽²²⁾	Unclear	No use	No use	Sufficient	2
Liu L ⁽²³⁾	Unclear	No use	No use	Sufficient	2
Xu H ⁽²⁴⁾	Sufficient	No use	No use	Sufficient	3

ORR

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There were 11 RCTs included in this study $(^{14-24)}$. A fixed effect model meta-analysis was chosen because $l^2 = 14\%$. The results showed that the ORR of the Endostar combined with chemoradiotherapy group was significantly higher than that of the chemoradiotherapy alone group (RR = 1.48, 95% CI = 1.31, 1.67, *P* < 0.00001; figure 2). Subgroup analysis showed *P* < 0.05 (Figure 3). Analysis of sensitivity by excluding the single item method did not have a significant effect on the overall result. The Egger

DCR There were 10 RCTs included in the present

P-value = 0.876; figure 4).

study ^(14, 15, 17-19, 21-24). A fixed effect model meta-analysis was chosen because $I^2 = 0\%$. The results showed that the DCR for the Endostar combined with chemoradiotherapy group was significantly higher than that of the chemoradiotherapy alone group (RR = 1.17, 95%)

and Begg calculation showed that there was no

publication bias (Egger P-value = 0.676, Begg

CI = 1.09-1.25, P < 0.00001; figure 5). Subgroup analysis showed P < 0.05 (figure 6). Analysis of sensitivity by excluding the single item method did not have a significant effect on the overall result. The Egger and Begg calculation of showed that there was no publication bias (Egger *P*-value = 0.845, Begg *P*-value = 0.754; figure 7).



Figure 2. Forest plot for the incidence of ORR between Endostar combined with chemoradiotherapy versus chemoradiotherapy







	Experim	ental	Control			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
Ma JB 2009	21	23	20	23	7.5%	1.05 [0.86, 1.29]	2009	+
Liu J 2009	23	31	20	31	7.5%	1.15 [0.82, 1.61]	2009	+-
Jiang ZG 2011	18	19	14	20	5.1%	1.35 [1.00, 1.84]	2011	<u>+</u>
Yang Y 2012	16	20	13	20	4.9%	1.23 [0.83, 1.82]	2012	
Chen XJ 2013	19	21	17	21	6.4%	1.12 [0.87, 1.43]	2013	+
Liu HW 2013	74	78	70	80	25.9%	1.08 [0.98, 1.20]	2013	•
Zhang Y 2016	36	36	30	36	11.4%	1.20 [1.03, 1.40]	2016	+
Liu L 2017	26	30	25	30	9.4%	1.04 [0.84, 1.29]	2017	+
Zang Y 2017	49	57	38	53	14.8%	1.20 [0.98, 1.46]	2017	-
Xu H 2018	30	39	19	39	7.1%	1.58 [1.10, 2.27]	2018	
Total (95% CI)		354		353	100.0%	1.17 [1.09, 1.25]		•
Total events	312		266					
Heterogeneity: Chi ² =	8.45, df =	9 (P = 0	.49); I ^z = I	0%				
Test for overall effect	Z = 4.46 (° < 0.00	001)					Eavoure (experimental) Eavoure (control)

Figure 5. Forest plot for the incidence of DCR between Endostar combined with chemoradiotherapy versus chemoradiotherapy alone.

1.4.1 1.5 2.3 1.5 2.3 2.0% 1.52 ($0.52, 712, 12009$ J.J.J 2006 11 31 5 31 2.5% 2.88 ($0.86, 5.69, 2009$ J.J.J 2005 11 31 5 31 2.5% 2.88 ($0.86, 5.69, 2009$ July 2001 0 7.1 2.93 2.1% 5.01 ($0.4, 7.53, 2016$ 2.013 July 2001 0 5.7 1.2 35 5.1% 3.00 ($0.86, 6.69, 2017$ Out events 160 117 117 116 117 117 116 Interfor overall effect $Z = 5.21$ ($\theta < 0.00001$) 1.3% 5.33 ($1.7, 24.21$) 2011 0.00001 1.4.2 mean age->60 110 2.0 1.3% 5.33 ($1.7, 24.21$) 2011 0.00001 1.4.2 mean age->60 110 2.0 1.3% 5.33 ($1.17, 24.21$) 2011 0.00001 1.4.4 2018 2.1 1.2 2.7% 2.27 ($1.02, 0.012$ $0.010000000000000000000000000000000000$	Study or Subaroup	Experim Events	ental Total	Contr Events	ol Total	Weight	Odds Ratio M-H. Fixed, 95% Cl	Year	Odds Ratio M-H. Fixed. 95% Cl
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$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Liu J 2009	11	31	5	31	2.8%	2,86 (0,86, 9,56)	2009	
$ \begin{array}{c} u_1 \psi_2 (2) & 3 & 8 & 78 & 54 & 80 & 50^{48} & 327 [1.45, 2.36] & 2013 \\ hong Y 2017 & 30 & 57 & 12 & 53 & 5.14 & 530 [1.65, 6.68] & 2017 \\ hong Y 2017 & 30 & 57 & 12 & 53 & 5.14 & 530 [1.65, 6.68] & 2017 \\ hong Y 2017 & 30 & 57 & 12 & 53 & 5.14 & 530 [1.65, 6.68] & 2017 \\ hong Y 2017 & 10 & 57 & 12 & 50 & 10^{12} & 50 \\ hong Y 2017 & 7 & 20 & 000001 \\ \hline \begin{tabular}{lllllllllllllllllllllllllllllllllll$	Ding Y 2011	10	14	g	14	2.2%	1.39 [0.28, 6.84]	2011	
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$ \begin{array}{c} \mbox{and} (2017) & 30 & 57 & 12 & 53 & 51% & 30 (116, 6, 56) & 2017 \\ \mbox{birder} (955, 01) & 23 & 237 & 22106 & 315[2.04, 4.84] \\ \mbox{birder} (955, 02) & 250 & 117 & 48 (9 [0.6], 27.22] & 2011 \\ \mbox{and} (20, 2011) & 16 & 19 & 10 & 20 \\ \mbox{and} (20, 2011) & 16 & 19 & 10 & 20 \\ \mbox{and} (20, 2011) & 16 & 19 & 10 & 20 \\ \mbox{and} (20, 2011) & 16 & 19 & 10 & 20 \\ \mbox{and} (20, 2011) & 16 & 19 & 10 & 20 \\ \mbox{and} (20, 2011) & 16 & 19 & 100 & 9.15 \\ \mbox{and} (20, 2012) & 17 & 20 & 2.2 & 20 & 1.3% & 5.32 [1, 17, 24, 21] & 2011 \\ \mbox{and} (20, 2011) & 16 & 19 & 100 & 9.15 \\ \mbox{and} (20, 55, 01) & 99 & 100 & 9.15 & 3.64 [1, 54, 6, 65] \\ \mbox{and} (165, 02) & 28 & 39 & 16 & 39 \\ \mbox{and} (20, 65, 02) & 28 & 16 & 39 \\ \mbox{and} (20, 65, 02) & 28 & 16 & 39 \\ \mbox{and} (20, 65, 02) & 21 & 12 & 12 & 22\% & 1.32 [0, 52, 7, 12] & 2009 \\ \mbox{and} (16, 10, 10 & 14 & 9 & 14 & 22\% & 1.39 [0, 26, 5.66] & 2009 \\ \mbox{and} (20, 11) & 16 & 19 & 10 & 22 & 13\% & 5.33 [1, 17, 24, 21] & 2011 \\ \mbox{and} (20, 11) & 16 & 19 & 10 & 22 & 22\% & 5.30 [1, 46, 17, 53] & 2016 \\ \mbox{and} (20, 11) & 16 & 19 & 10 & 20 & 13\% & 5.33 [1, 17, 24, 21] & 2011 \\ \mbox{and} (20, 2011) & 10 & 14 & 9 & 14 & 22\% & 1.39 [0, 26, 5.66] & 2009 \\ \mbox{and} (20, 12) & 7 & 20 & 2 & 20 & 1.1\% & 489 [0, 66, 2722] & 2017 \\ \mbox{and} (20, 12) & 7 & 20 & 2 & 20 & 1.1\% & 489 [0, 66, 2722] & 2017 \\ \mbox{and} (20, 12) & 7 & 20 & 2 & 20 & 1.1\% & 489 [0, 66, 2722] & 2017 \\ \mbox{and} (20, 12) & 7 & 20 & 2 & 20 & 1.1\% & 489 [0, 66, 2722] & 2017 \\ \mbox{and} (20, 12) & 7 & 20 & 2 & 20 & 1.1\% & 489 [0, 66, 2722] & 2017 \\ \mbox{and} (20, 12) & 7 & 2 & 20 & 1.1\% & 489 [0, 66, 260] & 2009 \\ \mbox{and} (20, 12) & 7 & 2 & 20 & 1.1\% & 489 [0, 66, 260] & 2017 \\ \mbox{and} (20, 12) & 7 & 2 & 20 & 1.3\% & 480 [0, 66, 260] & 2017 \\ \mbox{and} (20, 12) & 7 & 2 & 20 & 1.1\% & 480 [0, 66, 260] & 2017 \\ \mbox{and} (20, 12) & 7 & 2 & 2 & 20 & 1.3\% & 330 [1, 66, 66] & 2017 \\ \mbox{and} (20, 12) & 7 & 2 & 2 & 20 & 1.3\% & 330 [1, 66, 66] & 2017 \\ $	Zhang Y 2016	32	36	22	36	2 1 %	5 09 11 48 17 53	2016	
$ \begin{array}{c} \text{ subtrain (15% sc)} & (17) & 237 & 237 & 21.08 & 3.15 (2.04, 4.84) & (17) \\ \text{ detergorish}, Ch2 = 2.73 & cf = 6 p = 0.80; p = 0.85 \\ \text{ feat for ownall effect 2 = 2.52 (p < 0.0001) & (1.3% & 6.53 (1.17, 24.21) 2011 \\ \text{ subtrain (16% cC)} & (20, 2001) & (1.3% & 6.53 (1.17, 24.21) 2011 \\ \text{ subtrain (250, CC)} & (20, 2001) & (1.3% & 6.53 (1.17, 24.21) 2011 \\ \text{ subtrain (250, CC)} & (20, 20, 20, 20, 20, 20, 20, 20, 20, 20, $	Zana V 2017	30	57	12	53	5 1 96	199 9 39 11 09 5	2010	
Total events 123 117 123 133	Subtotal (95% CI)	50	230	12	237	21.0%	3 15 [2 04 4 84]	2017	
$ \begin{array}{c} \text{unit reality} \\ def for overall effect 2 = 5.217, df = 5 (P = 0.80), P = 0.6, \\ \text{def for overall effect 2 = 5.517, df = 5 (P = 0.0001) \\ \text{def versil effect 2 = 5.517, df = 5 (P = 0.0001) \\ \text{def versil effect 2 = 5.517, df = 5 (P = 0.0001) \\ \text{def versil effect 2 = 1.529, effect 0 = 0.0001 \\ \text{def versil effect 2 = 1.529, effect 0 = 0.0001 \\ \text{def versil effect 2 = 1.529, effect 0 = 0.0001 \\ \text{def versil effect 2 = 1.529, effect 0 = 0.0001 \\ \text{def versil effect 2 = 2.547, effect 0 = 0.0001 \\ \text{def versil effect 2 = 2.547, effect 0 = 0.0001 \\ \text{def versil effect 2 = 2.547, effect 0 = 0.0001 \\ \text{def versil effect 2 = 2.547, effect 0 = 0.0001 \\ \text{def versil effect 2 = 2.547, effect 0 = 0.0001 \\ \text{def versil effect 2 = 2.547, effect 0 = 0.0001 \\ \text{def versil effect 2 = 2.547, effect 0 = 0.0001 \\ \text{def versil effect 2 = 2.547, effect 0 = 0.0001 \\ \text{def versil effect 2 = 2.547, effect 0 = 0.0001 \\ \text{def versil effect 2 = 2.557, effect 0 = 0.0001 \\ \text{def versil effect 2 = 2.557, effect 0 = 0.0001 \\ \text{def versil effect 2 = 2.557, effect 0 = 0.0001 \\ \text{def versil effect 2 = 2.557, effect 0 = 0.0001 \\ \text{def versil effect 2 = 2.557, effect 0 = 0.0001 \\ \text{def versil effect 2 = 2.557, effect 0 = 0.0001 \\ \text{def versil effect 2 = 2.557, effect 0 = 0.0001 \\ \text{def versil effect 2 = 2.557, effect 0 = 0.0001 \\ \text{def versil effect 2 = 2.557, effect 0 = 0.0001 \\ \text{def versil 2 = 2.557, effect 0 = 0.0001 \\ \text{def versil 2 = 2.557, effect 0 = 0.0001 \\ \text{def versil 2 = 2.557, effect 0 = 0.0001 \\ \text{def versil 2 = 2.557, effect 0 = 0.0001 \\ \text{def versil 2 = 2.557, effect 0 = 0.0001 \\ \text{def versil 2 = 0.0001 \\ \text{def $	Total overte	160	233	117	257	21.0%	5.15 [2.04, 4.04]		•
$\begin{aligned} \text{Harding length}, \text{ Ch}^{-1} = 2, f, g = 0 = 0.001 \\ \text{Harding and gas products} \\ \text{Harding for consultations} \\ Ha$	Hotorogeneity Ohiz-	2.27 46-4	c /D _ 0	000:12-0	- or				
$ \begin{array}{c} \mathbf{i.4.2 man age >=60 \\ larg 20 2011 & 16 & 19 & 10 & 20 \\ larg 20 2011 & 16 & 19 & 10 & 20 \\ may 1013 & 15 & 21 & 11 & 12 & 27\% & 227 & 222 & 2012 \\ may 1010 & 12 & 3 & 39 & 16 & 33 & 39\% & 366 [1.42, 9.42] & 2018 \\ may 1010 & 12 & 39 & 16 & 39 & 39\% & 366 [1.42, 9.42] & 2018 \\ may 1010 & 120 & 80 & 79 & 100 & 9.1\% & 3.64 [1.94, 6.81] \\ the corponenty () = 60 & 30 & 16 & 39 & 3.9\% & 3.66 [1.42, 9.42] & 2018 \\ mathetial (95\% (C) & 39 & 39 & 16 & 39 & 3.9\% & 3.66 [1.42, 9.42] & 2018 \\ mathetial (95\% (C) & 39 & 39 & 3.5\% & 3.66 [1.42, 9.42] & 2018 \\ may 2009 & 11 & 31 & 5 & 31 & 2.8\% & 2.86 [0.86, 9.56] & 2009 \\ may 2011 & 10 & 14 & 9 & 14 & 2.2\% & 1.39 [0.28, 6.84] & 2011 \\ may 2020 & 11 & 6 & 19 & 10 & 20 & 11\% & 5.31 \\ may 2020 & 11 & 6 & 19 & 10 & 20 & 11\% & 5.31 \\ may 2020 & 11 & 6 & 19 & 10 & 20 & 11\% & 5.31 \\ may 2011 & 10 & 14 & 9 & 14 & 2.2\% & 1.39 [0.28, 6.84] & 2011 \\ may 2011 & 10 & 14 & 9 & 14 & 2.2\% & 1.39 [0.28, 6.84] & 2011 \\ may 2011 & 10 & 14 & 9 & 14 & 2.2\% & 1.53 [0.54, 4.39] & 2017 \\ may 2012 & 7 & 20 & 2 & 20 & 1.1\% & 4.85 [0.66, 2.7.2] & 2009 \\ may 2013 & 52 & 21 & 51 & 21\% & 2.27 [1.63, 8.15] & 2013 \\ may 2013 & 15 & 21 & 11 & 21 & 2.7\% & 2.27 [0.26, 4.25] \\ thereogeneity ()^{2} = 5.02 & ()^{2} = 0.5\% & 32.7 11.53 & 2.8\% & 1.92 [0.52, 7.12] & 2009 \\ may 2013 & 15 & 21 & 11 & 21 & 2.7\% & 2.27 [0.26, 4.25] \\ thereogeneity ()^{2} = 5.02 & ()^{2} = 0.5\% & 32.7 11.53 & 2.8\% & 1.92 [0.52, 7.12] & 2009 \\ may 2010 & 32 & 35 & 15 & 2.8\% & 1.92 [0.52, 7.12] & 2009 \\ may 2010 & 32 & 36 & 15 & 32 & 2.8\% & 1.92 [0.52, 7.12] & 2009 \\ may 2010 & 32 & 35 & 15 & 2.8\% & 1.92 [0.52, 7.12] & 2009 \\ may 2010 & 10 & 315 & 31 & 2.8\% & 2.6\% (0.86, 6.66] & 2009 \\ may 2010 & 10 & 315 & 31 & 2.8\% & 2.6\% (0.86, 6.68] & 2001 \\ mathetial (65\% (C) & 315 & 3.14\% & 2.8\% & 3.06 [1.42, 9.42] & 2011 \\ may 2011 & 6 & 73 & 5 & 33 & 5.5\% & 3.06 [1.42, 9.42] & 2011 \\ may 2011 & 10 & 14 & 9 & 14 & 2.7\% & 5.5\% & 3.16 [1.42, 9.42] & 2011 \\ may 1010 & 10 & 14 & 9 & 14 & 2.7\% & 5.5\% & 3.16 [1.42, 9.42] & 2010 \\ $	Test for overall effect:	Z = 5.21 (F	9 < 0.00	001)	J 70				
$ \lim_{\text{samg 2}} 202011 16 19 10 20 1.3\% 6.33 [1.7, 24.21 \ 2011 \\ \text{samg Y 2012 } 7 20 2 20 1.1\% 4.85 [0.86, 27.22 \ 2012 \\ \text{shortsol 165\% (C) } 99 100 9.1\% 3.64 [1.42, 9.42 \ 2016 \\ \text{shortsol 165\% (C) } 99 100 9.1\% 3.64 [1.42, 9.42 \ 2016 \\ \text{shortsol 165\% (C) } 99 100 9.1\% 3.64 [1.42, 9.42 \ 2016 \\ \text{shortsol 165\% (C) } 39 39 39 39 3.9\% 3.66 [1.42, 9.42 \ 2016 \\ shortsol 27 Correct 16 for Correct$	1.14.2 mean age >=6	60							
fang Y 2012 7 20 2 20 1.1% 4.85 [0.86, 27.22] 2012 30 (H 2016) 28 3.65 [2013 364 [H 22, 8.42] 2018 364 [H 23, 8.45] 39 39% 3.66 [H 42, 8.42] 2018 364 [H 23, 8.45] 39 39% 3.66 [H 42, 8.42] 2018 364 [H 2016] 28 39 16 39 39% 3.66 [H 42, 8.42] 2018 364 [H 2016] 28 39 16 39 39% 3.66 [H 42, 8.42] 2018 364 [H 2016] 28 39 16 39 39 3.9% 3.66 [H 42, 8.42] 2018 364 [H 2016] 28 39 16 39 39 3.9% 3.66 [H 42, 8.42] 2018 364 [H 2016] 28 39 16 39 39 3.9% 3.66 [H 42, 8.42] 2018 364 [H 2016] 28 39 16 39 39 3.9% 3.66 [H 42, 8.42] 2018 364 [H 2016] 28 39 16 39 39 3.9% 3.66 [H 42, 8.42] 2018 364 [H 2016] 28 39 16 39 39 3.9% 3.66 [H 42, 8.42] 2018 364 [H 2016] 28 30 2011 16 19 10 20 12% 23 6 22 2% 132 [D 62, 7.12] 2009 364 30 2011 16 19 10 20 12% 32 6 32 2 36 21 3% 3.27 [H 45, 7.88] 2013 366 [H 2017] 30 57 12 2 33 5.1% 3.201 [B 64, 8.68] 2017 367 2017 30 57 12 53 5.1% 3.301 [B 64, 8.68] 2017 366 32 277 157 448 [H 2016] 277 30 57 12 53 5.1% 3.301 [B 64, 8.68] 2017 366 32 277 157 448 [H 2016] 277 30 57 12 53 5.1% 3.301 [B 64, 8.68] 2017 366 32 277 157 448 [H 2016] 277 12 003 17 30 49% 1.53 [D 64, 3.58] 2013 366 [H 20, 7.22] 2012 366 22 27 157 448 [H 2016] 28 31.1% 2.27 [L 23, 7.12] 2010 310 12 316 2.27 157 448 [H 2016] 28 31.1% 2.28 [L 27, 6.34] 2017 36 37 12 2 33 5.1% 3.301 [B 64, 8.68] 2017 366 78 54 80 59% 3.27 [H 45, 7.38] 2013 366 [H 20, 7.22] 2012 36 22 36 2.2 36	Jiang ZG 2011	16	19	10	20	1.3%	5.33 [1.17, 24.21]	2011	
$\begin{aligned} \begin{array}{cccccccccccccccccccccccccccccccccccc$	Yang Y 2012	7	20	2	20	1.1%	4.85 [0.86, 27.22]	2012	+
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Chen XJ 2013	15	21	11	21	2.7%	2.27 [0.63, 8.15]	2013	
biblicital (95% C) 99 100 9.1% 3.64 [1.94, 6.81] 1614 events 66 39 148 corporative ($\Lambda f^2 = 0.83$, $f^2 = 0.8$ (Fa to overall effect $Z = 4.03 (P < 0.001)$ 14.4 and value carcinoma 40 H 2018 28 39 3.9% 3.66 [1.42, 9.42] 2018 300 3.9% 3.66 [1.42, 9.42] 2018 3016 events 22 1616 events 22 1.5 23 2.9% 1.82 (0.62, 9.71) 2.009 45.08 2009 19 22 15 23 2.9% 1.82 (0.62, 9.71) 2.009 45.08 2009 19 22 15 23 2.9% 1.82 (0.62, 9.71) 2.009 45.08 2009 19 22 20 1.1% 4.81 (0.62, 9.22) 2.011 301 2.000 19 22 2.0 1.1% 4.81 (0.62, 9.22) 2.012 301 2.001 16 19 10 2.0 1.3% 5.33 (1.17, 24.21) 2.011 301 2.020 15 2.1 11 2.1 2.7% 2.27 (0.63, 8.15) 2.013 301 2.017 2.0 3.0 17 30 4.9% 1.53 (0.64, 4.36) 2.017 301 2.017 2.0 3.0 17 30 4.9% 1.53 (0.64, 4.36) 2.017 301 2.017 2.0 3.0 17 30 4.9% 1.53 (0.64, 4.36) 2.017 301 2.017 3.0 5.7 12 5.5 1.5 1.8. 3.01 (1.64, 8.66) 2.017 301 2.017 3.0 5.7 12 5.5 1.5 1.8. 3.01 (1.64, 7.53) 2.016 301 2.017 3.0 5.7 12 5.5 1.5 1.8. 3.01 (1.64, 7.53) 2.016 301 2.017 3.0 5.7 12 5.3 5.1% 3.30 (1.66, 8.66) 2.017 301 2.000 18 2.3 15 2.2 2.9% 1.92 (0.52, 7.12) 2.009 301 events 2.77 157 157 168 corponetly Ch ² = 1.02 (f = 0.02) (f = 0.02) (f = 0.0001) 3.45 5.35 (1.44, 2.47) 1.57 3.00 (1.44, 17.53) 2.016 3.00 (1.64, 8.66) 2.017 3.01 2.017 3.0 5.7 12 5.3 5.1% 3.30 (1.66, 8.68) 2.017 3.01 2.017 3.0 5.7 12 5.3 5.1% 3.30 (1.66, 8.68) 2.017 3.01 2.017 3.0 5.7 12 5.3 5.1% 3.30 (1.66, 8.68) 2.017 3.01 2.017 3.0 5.7 12 5.3 5.1% 3.30 (1.66, 8.68) 2.017 3.01 2.017 3.0 5.7 12 5.3 5.1% 3.30 (1.64, 4.75) 2.016 3.01 2.017 3.0 5.7 12 5.3 5.1% 3.30 (1.64, 4.75) 2.016 3.01 2.017 3.0 5.7 12 5.3 5.1% 3.30 (1.64, 8.68) 2.017 3.01 2.017 3.0 5.7 12 5.3 5.1% 3.30 (1.64, 8.68) 2.017 3.01 2.017 3.0 5.7 12 5.3 5.1% 3.30 (1.66, 8.68) 2.017 3.01 2.017 3.0 5.7 12 5.3 5.1% 3.30 (1.66, 8.68) 2.017 3.01 2.017 3.0 5.7 12 5.3 5.1% 3.30 (1.66, 8.68) 2.017 3.01 2.017 3.0 5.7 12 5.3 5.1% 3.30 (1.66, 8.68) 2.017 3.01 2.017 3.0 5.7 12 5.3 5.1% 3.00 (1.66, 8.68) 2.017 3.01 2.017 3.0 5.7 12 5.3 5.1% 3.00 (1.66, 8.68) 2.	Xu H 2018	28	39	16	39	3.9%	3.66 [1.42, 9.42]	2018	
Total events 68 39 Hereogeneity: Chef = 037, 67 = 0637, F = 0% Festfor overall effect $Z = 4.03 (P < 0.0001)$ L14.3 only adencacricinoma (uH 2016 28 39 39 39 39 39 3.66 [1.42, 9.42] 2018 Subtoral (95% C) 29 10 16 Herorgeneity: Not applicable Festfor overall effect $Z = 2.06 (P = 0.007)$ L14.4 not only adencacricinoma Jul 2009 11 21 5 21 2.8% 1.82 [0.52, 7.12] 2009 fiamg 202011 16 19 10 20 1.3% 5.33 [1.72, 2.42] 2011 Jul 2009 18 2.3 15 22 1.1% 4.86 [0.66, 2.56] 2019 fiamg 202011 16 19 10 20 1.3% 5.33 [1.72, 2.42] 2012 Jul 2009 18 2.2 36 2.2 36 2.1% 5.09 [1.45, 1.75, 3] 2013 Jul 2017 20 3 0.17 30 57 11 2 7% 2.27 [10.38, 1.55] 2013 Jul 2017 30 57 12 53 5.1% 3.80 [1.46, 8.68] 2017 Jul 2017 30 57 12 53 5.1% 3.80 [1.46, 8.68] 2017 Jul 2017 30 57 12 53 5.1% 3.80 [1.46, 8.68] 2017 Jul 2017 30 57 12 53 5.1% 3.80 [1.46, 8.68] 2017 Jul 2017 30 57 12 53 5.1% 3.80 [1.46, 8.68] 2017 Jul 2017 30 57 12 53 5.1% 3.80 [1.46, 8.68] 2017 Jul 2017 30 57 12 53 5.1% 3.80 [1.46, 8.68] 2017 Jul 2017 30 57 12 53 5.1% 3.80 [1.46, 1.753] 2016 Jul 2018 18 22 36 22 36 2.2% 5.08 [1.42, 7.12] 2009 Jul 2009 18 23 15 2.3 2.8% 1.92 [0.52, 7.12] 2009 Jul 2017 30 57 12 53 5.1% 3.80 [1.66, 8.68] 2017 Jul 2017 30 57 12 53 5.1% 3.80 [1.66, 8.68] 2017 Jul 2017 30 57 12 53 5.1% 3.80 [1.66, 8.68] 2017 Jul 2017 16 12 20 0.13% 5.33 1.17, 24.21] 2011 48 98 20.201 16 16 10 2.0 13% 5.33 1.17, 24.21] 2011 Jul 2017 10 17 20 30 17 30 49% 1.52 [0.54, 4.32] 2017 Jul 2017 10 10 14 9 14 2.2% 1.39 [0.28, 8.84] 2017 Jul 2017 20 3 50 27 145 7.38] 2015 Jul 2017 10 14 49 14 2.2% 1.39 [0.28, 8.84] 2017 Jul 2017 20 35 5.2 53 5.1% 3.80 [1.61, 8.68] 2017 Jul 2017 10 14 9 14 2.2% 1.39 [0.28, 8.84] 2017 Jul 2017 20 35 5.2 53 5.5 6.1% 2.84 [1.27, 5.3] Festfor overall effect Z= 1.30 (P < 0.0001) 4.4.5 score of study >-3 Jul 2016 23 38 22 45 Herorgeneity: Chf = 1.30, 0f = 31 (P = 1.00) (P = 0% Herorgeneity: Chf = 1.30, 0f = 31 (P = 1.00) (P = 0% Herorgeneity: Chf = 1.30, 0f = 31 (P = 1.00) (P = 0% Herorgeneity: Chf = 1.30, 0f = 31 (P	Subtotal (95% CI)		99		100	9.1%	3.64 [1.94, 6.81]		
1 + 1 + 2 + 0 + 0	Total events	66		39			• • • •		
The set for overall effect $Z = 4.03$ ($P < 0.0001$) 1.14.3 only addencearcinoma (a) H 2015 28 39 16 39 3.9% 3.86 [1.42, 9.42] 2018 1.14.4 not only addencearcinoma (a) J 2009 11 31 5 31 2.8% 2.86 [0.86, 9.56] 2009 1.14.4 not only addencearcinoma (a) J 2009 11 3 15 23 2.8% 1.92 [0.52, 7.12] 2009 1.14.4 not only addencearcinoma (a) J 2009 11 3 15 31 2.8% 2.86 [0.86, 9.56] 2019 1.14.4 not only addencearcinoma (a) J 2009 11 3 15 31 2.8% 2.86 [0.86, 9.56] 2019 1.15 2011 16 19 10 20 1.3% 5.33 [1.17, 2.4.1] 2011 1.16 ang 2011 16 19 10 20 1.3% 5.33 [1.17, 2.4.1] 2011 1.17 20 3 20 1.15 4 485 [0.86, 2.72] 2012 (a) HW 2013 68 78 54 80 5.9% 3.27 [1.45, 7.38] 2013 1.18 2017 20 0 17 3 0 57 12 53 5.1% 3.80 [1.86, 8.68] 2017 1.18 2017 30 57 12 53 5.1% 3.80 [1.86, 8.68] 2017 1.19 2016 32 36 22.2 36 2.1% 5.09 [1.48, 17.53] 2016 1.19 2017 30 57 12 53 5.1% 3.80 [1.86, 8.68] 2017 1.19 2016 32 36 12 20 1.1% 4.85 [0.86, 2.722] 2012 1.19 40 201 3.9% 5.33 [1.17, 2.41] 2011 1.19 2017 30 57 12 53 5.1% 3.80 [1.86, 8.68] 2017 1.19 2012 7 20 2 20 1.1% 4.85 [0.86, 2.722] 2012 1.19 4.9% 1.92 [0.52, 7.12] 2009 1.19 2012 7 20 3 20 31 [1.19] 4.11 201 1.3% 1.19 2016 32 36 22 36 2.1% 5.09 [1.41, 1.53] 2016 1.19 2012 7 1 20 3 17 30 57 12 53 5.1% 3.80 [1.86, 8.68] 2017 1.19 4.9% 1.53 [1.14, 4.47] 1.19 1.10 14 9 1.14 2.2% 5.09 [1.41, 1.53] 2016 1.19 2016 32 36 22 36 2.1% 5.09 [1.41, 4.47] 1.19 2016 32 36 22 36 2.1% 5.09 [1.41, 4.47] 1.19 2016 32 36 2.1% 5.09 [1.41, 4.47] 1.19 2016 32 38 2.1% 5.09 [1.42, 9.42] 2016 1.19 2017 30 57 12 53 5.1% 3.80 [1.68, 8.68] 2017 1.19 2017 30 57 12 53 5.1% 3.80 [1.68, 8.68] 2017 1.19 2018 32 36 2.2% 50 [1.42, 9.42] 2016 1.19 2018 24.12 (2.7, 6.34] 1.19 2018 28 39 16 39 3.9% 3.66 [1.42, 9.42] 2016 1.19 2018 28 39 16 39 3.9% 3.66 [1.42, 9.42] 2016 1.19 2014 2017 1.10 14 9 14 2.2% 1.39 [0.28, 6.84] 2011 1.19 2016 28 39 16 39 3.9% 3.66 [1.42, 9.42] 2016 1.19 2016 2017 1.10 174 100.1% 1.28 4.1% (2.7, 5.3	Heterogeneit/: Chi ² =	0.87 df=	3 (P = 0	83) 12 = 1	196				
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Test for overall effect:	Z = 4.03 (F	P < 0.00	01)					
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Total events 28 16 Total events 28 28 16 Test for overall effect $Z = 2.69$ (P = 0.007) 1.4.4 not only adenocar cinoma Jul 2009 11 31 5 31 2.8% 2.66 [0.66, 9.56] 2009 Jing Y 2011 10 14 9 14 2.2% 1.39 [0.28, 6.84] 2011 Tang Y 2012 7 20 2 20 1.1% 4.65 [0.68, 27.21] 2019 Jing Y 2012 7 20 2 20 1.1% 4.65 [0.68, 27.22] 2012 Jul HW 2013 68 78 54 80 5.9% 3.271 [4.5, 7.38] 2013 Jing Y 2016 32 36 22 36 2.1% 5.09 [1.48, 17.53] 2016 Jul 2107 20 30 17 30 4.9% 1.53 [0.54, 4.68] 2017 Jing Y 2017 30 57 12 53 5.1% 3.801 [1.68, 8.68] 2017 Jing Y 2017 30 57 12 53 5.1% 3.801 [1.68, 8.68] 2017 Jing Y 2017 30 57 12 6.3 3.1% 2.97 [2.08, 4.25] Total events 227 157 Telefrogeneity: Ch ² = 5.05 (P = 0.83); P = 0% Test for overall effect Z = 5.95 (P = 0.00001) 1.45. Score of study~3 telerogeneity: Ch ² = 4.12 (J = 8 (P = 0.85); P = 0% Test for overall effect Z = 6.00 (P = 0.85); P = 0% Test for overall effect Z = 6.00 (P = 0.05); P = 0% Test for overall effect Z = 6.00 (P = 0.0001) 1.45. Score of study~3 telerogeneity: Ch ² = 4.12 (J = 8 (P = 0.85); P = 0% Test for overall effect Z = 0.00 (P < 0.00001) 1.46. Score of study~3 Jing Y 2017 30 57 12 53 51% 3.801 [6.8, 8.61] 2017 Jul W 2013 165 22 11 12 2.7% 3.271 [0.3, 8.15] 2013 Jing Y 2017 30 57 12 53 51% 3.801 [6.8, 8.61] 2017 Jul W 2013 15 21 11 2.27% 3.271 [0.3, 8.15] 2013 Jing Y 2017 30 57 12 53 51% 3.801 [6.8, 8.61] 2017 Jul W 2013 15 21 11 2.27% 3.801 [6.8, 8.61] 2017 Jul W 2013 15 23 11 2.28% 3.09 [2.14, 4.47] Total events 217 148 Heterogeneity: Ch ² = 4.12, df = 8 (P = 0.85); P = 0% Test for overall effect Z = 2.54 (P = 0.05); P = 0% Test for overall effect Z = 2.54 (P = 0.01); P = 5% Test for overall effect Z = 2.54 (P = 0.01); P = 5% Test for overall effect Z = 2.54 (P = 0.01); P = 5% Test for overall effect Z = 1.30, df = 31 (P = 1.00); P = 0% Test for overall effect Z = 1.30, df = 31 (P = 1.00); P = 0% Test for overall effect Z = 1.30, df = 31 (P = 1.00); P = 0% Test for overall effect Z = 1.30, df = 31 (P = 1.00); P = 0%	Subtotal (95% CI)		39		39	3.9%	3.66 [1.42, 9.42]		
Heterogeneity. Not applicable Fest for overall effect $Z = 2.69$ ($P = 0.007$) L14.4 not only adenocarcinoma Lu 2009 11 31 5 31 2.8% 2.86 [0.86, 9.56] 2009 fa UE 2009 18 23 15 23 2.8% 1.92 [0.52, 7.12] 2009 fa UE 2009 18 23 15 23 2.8% 1.92 [0.52, 7.12] 2019 Jun 4V 2011 16 19 10 20 1.3% 5.33 [1.17, 24.21] 2011 Jun 4V 2013 68 78 54 80 5.9% 3.27 [1.45, 7.38] 2013 Jhang Y 2016 32 36 22 36 2.1% 5.09 [1.46, 17.53] 2016 Jun 2017 20 30 17 30 4.9% 1.53 [0.64, 84] 2017 Jabotal 205% C1) 329 328 31.1% 2.97 [2.08, 4.25] Vial 2009 18 23 15 23 2.8% 1.92 [0.52, 7.12] 2009 Jun 4V 2013 68 78 54 80 5.9% 3.27 [1.45, 7.38] 2017 Jabotal 205% C1) 329 328 31.1% 2.97 [2.08, 4.25] Vial 2009 18 23 15 23 2.8% 1.92 [0.52, 7.12] 2009 Jun 2009 18 23 15 23 2.8% 1.92 [0.52, 7.12] 2009 Jun 2009 18 23 15 23 2.8% 1.92 [0.52, 7.12] 2009 Jun 2009 18 23 15 23 2.8% 1.92 [0.52, 7.12] 2009 Jun 2009 18 23 15 2.28 2.1% 5.09 [1.45, 7.38] 2017 Jabotal 2011 16 19 10 20 1.3% 5.33 [1.17, 24.21] 2011 Jang Y 2012 7 20 2 2 11 [% 4.56] 2013 Jhang Y 2013 55 21 11 2.27% 2.27 [10.38, 152] 2013 Jhang Y 2016 32 38 22 36 2.1% 5.09 [1.45, 7.38] 2013 Jhang Y 2016 32 38 22 36 2.1% 5.09 [1.45, 7.38] 2013 Jhang Y 2016 32 38 22 36 2.1% 5.09 [1.45, 7.38] 2013 Jhang Y 2016 32 38 22 36 2.1% 5.09 [1.45, 7.53] 2016 Jun 2017 30 57 12 53 51% 5.09 [1.45, 7.53] 2016 Jun 2017 30 57 12 53 51% 5.09 [1.45, 7.53] 2016 Jun 2017 30 57 12 53 51% 5.09 [1.45, 7.53] 2016 Jun 2017 30 57 12 53 51% 5.09 [1.45, 7.53] 2016 Jun 2017 30 57 12 53 51% 5.09 [1.44, 4.47] Vial 2018 28 39 16 6 39 3.99% 3.86 [1.42, 2.42] 2018 Jun 2019 2011 10 14 9 14 2.2% 1.39 [0.28, 6.84] 2011 Jun 2019 203 35 53 6.1% 2.84 [1.27, 6.34] Vial 2018 2015 2.54 (P = 0.05)) Vial 2016 (P = 1.50,	Total events	28		16			_		
Test for overall effect $Z = 2.69$ ($P = 0.007$) 1.14.4 not only adenocarcinoma Jul 2009 11 31 5 31 2.8% 2.86 [0.86, 9.56] 2009 Jing Y 2011 10 14 9 14 2.2% 1.39 [0.28, 6.84] 2011 Jing Y 2011 10 14 9 14 2.2% 1.39 [0.28, 6.84] 2011 Jing Y 2012 7 20 2 20 1.1% 4.85 [0.86, 7.22] 2013 Jhen Y 2013 65 78 54 80 5.9% 3.27 [1.4, 7.53] 2016 Jul 2017 20 30 17 30 4.9% 1.53 [0.54, 4.36] 2017 Jang Y 2016 32 36 22.3 6 2.1% 5.09 [1.46, 1.753] 2016 Jul 2017 20 30 17 30 4.9% 1.53 [0.54, 4.36] 2017 Jang Y 2016 32 36 22 36 2.1% 5.09 [1.46, 1.753] 2016 Jul 2017 20 30 17 30 4.9% 1.53 [0.52, 7.12] 2009 Jul 2017 20 30 17 30 4.9% 1.53 [0.52, 7.12] 2009 Jul 2017 20 30 17 30 4.9% 1.53 [0.52, 7.12] 2009 Jul 2017 20 30 17 30 4.9% 1.53 [0.52, 7.12] 2009 Jul 2017 20 30 17 30 4.9% 1.53 [0.52, 7.12] 2009 Jul 2017 20 30 17 30 4.9% 1.53 [0.54, 4.36] 2017 Jang Y 2017 30 57 12 53 5.1% 3.80 [1.66, 8.68] 2017 Jul 4W 2013 68 78 54 80 5.9% 3.27 [1.45, 7.38] 2013 Jhen XJ 2013 15 21 11 21 2.7% 2.27 [0.63, 8.15] 2013 Jhang Y 2016 32 36 22 36 2.1% 5.09 [1.48, 17.53] 2016 Jul 2017 20 0 17 30 4.9% 1.53 [0.54, 4.36] 2017 Jul 4W 2013 68 78 54 80 5.9% 3.27 [1.45, 7.38] 2013 Jhang Y 2016 32 36 12 3 5.1% 3.80 [1.66, 8.68] 2017 Jul 4W 2013 15 21 11 21 2.7% 3.27 [0.43, 4.36] 2017 Jul 4W 2018 32 36 12 3 5.1% 3.80 [1.66, 8.68] 2017 Jul 4W 2018 28 39 16 9 3.98 3.66 [2.017 Jul 4W 2016 32 36 12 3 5.1% 3.80 [1.42, 9.42] 2018 Jul 2017 10 14 9 14 2.2% 1.39 [0.28, 6.84] 2011 Jul 4W 2018 28 39 16 19 3.39 3.65 [1.42, 9.42] 2018 Jul 4W 2018 28 39 16 19 3.39 3.65 [1.42, 9.42] 2018 Jul 4W 2018 28 39 16 19 3.38 0.16 5.68 80 2017 Jul 4W 2018 28 39 16 19 3.39 3.65 [1.42, 9.42] 2018 Jul 4W 2018 28 39 16 19 3.93 3.65 [1.42, 9.42] 2018 Jul 4W 2018 28 39 16 19 3.93 3.65 [1.42, 9.42] 2018 Jul 4W 2018 28 39 16 19 3.93 3.65 [1.42, 9.42] 2018 Jul 4W 2018 28 39 16 19 3.93 3.65 [1.42, 9.42] 2018 Jul 4W 2018 28 39 16 19 3.93 3.65 [1.42, 9.42] 2018 Jul 4W 2018 28 39 16 29 2.62 [1.60, 1] \bullet Jul 40 10 \bullet Jul 40 10 \bullet Jul 40 10 \bullet Jul 40 10 \bullet Jul 40 J	Heterogeneity: Not ap	plicable							
L14.4 not only adenocarcinoma Lu J 2009 11 31 5 31 2.8% 2.86 [0.86, 9.56] 2009 As JE 2009 18 23 15 23 2.8% 1.92 [0.52, 7.12] 2009 Jing Y 2011 10 14 9 14 2.2% 1.39 [0.28, 6.84] 2011 Trang Y 2012 7 20 2 20 11% 4 56 [0.86, 72.22] 2012 Lu HV 2013 68 78 54 80 5.9% 3.27 [1.45, 7.38] 2013 Jinhen XJ 2013 15 21 11 21 2.7% 2.27 [0.53, 8.15] 2013 Jinhen XJ 2013 15 21 11 21 2.7% 5.09 [1.48, 17.53] 2016 Jul 2017 20 30 17 30 4.9% 1.53 [0.54, 4.36] 2017 Jing Y 2016 32 36 22 36 2.1% 5.09 [1.48, 17.53] 2016 Jul 2017 30 57 12 53 5.1% 3.80 [1.66, 8.66] 2017 Jul 2017 30 57 12 53 5.1% 3.80 [1.66, 8.66] 2017 Jul 2017 30 57 12 53 5.1% 3.80 [1.66, 8.66] 2017 Jul 2017 30 57 12 53 5.1% 3.80 [1.66, 8.66] 2017 Jul 2017 30 57 12 53 5.1% 3.80 [1.67, 712] 2009 Jiang Z0 2011 18 19 10 20 1.3% 5.33 [1.17, 24.21] 2011 Jul 2009 18 23 15 22 01.1% 4.86 [0.86, 56] 2009 Jiang Z0 2011 18 19 10 20 1.3% 5.33 [1.17, 24.21] 2011 Jul 2017 20 30 17 30 4.9% 1.53 [0.54, 4.36] 2017 Jul 2013 15 21 11 21 2.7% 2.27 [0.13, 8.15] 2013 Jhen XJ 2013 15 21 11 2.1% 5.09 [1.48, 17.53] 2016 Jul 2017 20 30 17 30 4.9% 1.53 [0.54, 4.36] 2017 Jul 2017 20 30 17 30 4.9% 1.53 [0.54, 4.36] 2017 Jul 2017 30 57 12 53 5.1% 3.80 [1.68, 8.68] 2017 Jul 2017 10 30 17 30 4.9% 1.53 [0.54, 4.36] 2017 Jul 2017 20 30 17 30 4.9% 1.53 [0.54, 4.36] 2017 Jul 2017 20 30 17 30 4.9% 1.53 [0.54, 4.36] 2017 Jul 2017 20 30 17 30 4.9% 1.53 [0.54, 4.36] 2017 Jul 2017 20 30 17 30 4.9% 1.53 [0.54, 4.36] 2017 Jul 2017 30 57 12 53 5.1% 3.80 [1.68, 8.68] 2017 Jul 2018 28 9 16 39 3.9% 3.66 [1.42, 9.42] 2018 Jul 2018 28 9 16 39 3.9% 3.66 [1.42, 9.42] 2018 Jul 2018 28 9 16 39 3.9% 3.66 [1.42, 9.42] 2018 Jul 2018 28 9 16 39 3.9% 3.66 [1.42, 9.42] 2018 Jul 2018 28 9 16 39 3.9% 3.66 [1.42, 9.42] 2018 Jul 2018 28 9 16 39 3.9% 3.66 [1.42, 9.42] 2018 Jul 2018 28 9 16 39 3.9% 3.66 [1.42, 9.42] 2018 Jul 2018 28 9 16 39 3.9% 3.66 [1.42, 9.42] 2018 Jul 2018 28 9 16 39 3.9% 3.66 [1.42, 9.42] 2018 Jul 2018 28 9 16 39 3.9% 3.66 [1.42, 9.42] 2018 Jul 2018 28 9 16 39 3.9% 3.66 [1.42,	Test for overall effect:	Z = 2.69 (F	P = 0.00	7)					
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	1.14.4 not only adeno	carcinom	а	-					
	Liu J 2009	11	31	5	31	2.8%	2.86 [0.86, 9.56]	2009	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	Ma JB 2009	18	23	15	23	2.8%	1.92 [0.52, 7.12]	2009	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Ding Y 2011	10	14	9	14	2.2%	1.39 [0.28, 6.84]	2011	
$ \begin{array}{c} \operatorname{sing} Y 2012 & 7 & 20 & 2 & 20 & 1.1\% & 4.85 [0.86, 27.22] & 2012 \\ \operatorname{bern} XJ 2013 & 15 & 21 & 11 & 21 & 2.7\% & 2.27 [0.63, 8.15] & 2013 \\ \operatorname{bern} XJ 2013 & 15 & 21 & 11 & 21 & 2.7\% & 2.27 [0.63, 8.15] & 2013 \\ \operatorname{bern} XJ 2016 & 32 & 36 & 22 & 36 & 2.1\% & 5.09 [1.49, 17.53] & 2016 \\ \operatorname{bern} XJ 2017 & 30 & 57 & 12 & 53 & 5.1\% & 3.80 [1.66, 8.68] & 2017 \\ \operatorname{bern} XJ 2017 & 30 & 57 & 12 & 53 & 5.1\% & 3.80 [1.66, 8.68] & 2017 \\ \operatorname{bern} XJ 2017 & 30 & 57 & 12 & 53 & 5.1\% & 3.80 [1.66, 8.68] & 2017 \\ \operatorname{bern} XJ 2017 & 30 & 57 & 12 & 53 & 1.4\% & 2.97 [2.08, 4.25] \\ \operatorname{bern} XJ 2017 & 30 & 57 & 12 & 53 & 1.4\% & 2.97 [2.08, 4.25] \\ \operatorname{bern} XJ 2019 & 11 & 31 & 5 & 31 & 2.9\% & 2.86 [0.68, 9.56] & 2009 \\ \operatorname{bern} XJ 2019 & 11 & 31 & 5 & 31 & 2.9\% & 2.86 [0.68, 9.56] & 2009 \\ \operatorname{bern} XJ 2013 & 16 & 19 & 10 & 20 & 1.3\% & 5.33 [1.7, 42.21] & 2011 \\ \operatorname{'ang} Y 2012 & 7 & 20 & 2 & 20 & 1.1\% & 4.65 [0.86, 27.22] & 2013 \\ \operatorname{'hen} XJ 2013 & 16 & 21 & 11 & 21 & 2.7\% & 2.27 [0.63, 8.15] & 2013 \\ \operatorname{'hen} XJ 2013 & 16 & 21 & 11 & 21 & 2.7\% & 2.27 [0.63, 8.16] & 2017 \\ \operatorname{'ang} Y 2016 & 32 & 36 & 22 & 36 & 2.1\% & 5.09 [1.48, 17.53] & 2013 \\ \operatorname{'hen} XJ 2013 & 15 & 21 & 11 & 21 & 2.7\% & 2.27 [0.63, 8.16] & 2017 \\ \operatorname{'ang} Y 2017 & 30 & 57 & 12 & 53 & 5.1\% & 3.80 [1.66, 8.68] & 2017 \\ \operatorname{'ang} Y 2017 & 30 & 57 & 12 & 53 & 5.1\% & 3.80 [1.66, 8.68] & 2017 \\ \operatorname{'ang} Y 2017 & 30 & 57 & 12 & 53 & 5.1\% & 3.80 [1.66, 8.68] & 2017 \\ \operatorname{'ang} Y 2017 & 30 & 57 & 12 & 53 & 5.1\% & 3.80 [1.66, 8.68] & 2017 \\ \operatorname{'ang} Y 2017 & 10 & 14 & 9 & 14 & 2.2\% & 1.39 [0.28, 6.84] & 2011 \\ \operatorname{'atal events} & 39 & 16 & 39 & 3.9\% & 3.66 [1.42, 9.42] & 2018 \\ \operatorname{'atal events} & 39 & 16 & 39 & 3.9\% & 3.66 [1.42, 9.42] & 2018 \\ \operatorname{'atal events} & 745 & 502 \\ \operatorname{'est for overall effect} Z = 1.39 (p = 1.00); P = 0\% \\ \operatorname{'est for overall effect} Z = 1.32 (p < -0.0001) \\ \end{array}$	Jiang ZG 2011	16	19	10	20	1.3%	5.33 [1.17, 24.21]	2011	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Yang Y 2012	7	20	2	20	1.1%	4.85 [0.86, 27.22]	2012	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Liu HW 2013	68	78	54	80	5.9%	3.27 [1.45, 7.38]	2013	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Chen XJ 2013	15	21	11	21	2.7%	2.27 [0.63, 8.15]	2013	
Lul 2017 20 30 17 30 4.9% 1.53 [0.54, 4.36] 2017 Tang Y 2017 30 57 12 53 5.1% 3.80 [1.66, 8.68] 2017 Total events 227 157 Teleterogeneity. Chi ^P = 5.02, df = 9 ($P = 0.83$); $P = 0\%$ Test for overall effect Z = 5.95 ($P < 0.00001$) L14.5 score of study<3 tag Z0 2011 18 19 10 20 1.3% 5.33 [1.17, 24.21] 2011 'ang Y 2012 7 20 2 20 1.1% 4.85 [0.86, 9.56] 2019 Ju J 2009 11 31 5 21 2.7% 2.27 [1.03, 81] 2013 'hen XJ 2013 15 21 11 21 7% 2.27 [1.03, 81] 2013 'hang Y 2016 32 36 22 36 2.1% 5.09 [1.48, 17.53] 2016 Ju L 2017 20 30 17 30 4.9% 1.53 [0.54, 4.36] 2017 Total events 217 148 Teterogeneity. Chi ^P = 4.12, df = 8 ($P = 0.83$); $P = 0\%$ 'est for overall effect Z = 6.00 ($P < 0.00001$) L14.6 score of study>=3 Ning Y 2011 10 14 9 14 2.2% 1.39 [0.28, 6.84] 2011 (Ju H 2018 28 39 16 39 3.9% 3.66 [1.42, 9.42] 2018 Jubtotal (95% Cl) 53 53 6.1% 2.84 [1.27, 6.34] 'otal events 38 25 teterogeneity. Chi ^P = 1.3.0, df = 31 ($P = 1.00$); $P = 0\%$ 'est for overall effect Z = 2.54 ($P = 0.01$); $P = 0\%$ 'est for overall effect Z = 2.54 ($P = 0.01$); $P = 0\%$ 'est for overall effect Z = 1.300, df = 31 ($P = 1.00$); $P = 0\%$ 'est for overall effect Z = 1.300, df = 31 ($P = 1.00$); $P = 0\%$	Zhang Y 2016	32	36	22	36	2 1 %	5 09 (1 48 17 53)	2016	
Larg Y 2017 10 50 11 2 53 5.1% 3.80 [1.66, 8.68] 2017 Subtotal (95% Cl) 329 328 31.1% 2.97 [2.08, 4.25] Total events 227 157 Teletrogenetily. Chi ^P = 5.02, df = 9 ($P = 0.83$); $P = 0$ % Test for overall effect Z = 5.95 ($P < 0.00001$) L14.5 score of study <3 As JE 2009 18 23 15 23 2.8% 1.92 [0.52, 7.12] 2009 July 2009 18 19 10 20 1.3% 5.33 [1.17, 24.21] 2011 'ang Y 2012 7 20 2 20 1.1% 4.55 [0.86, 9.56] 2013 Shen XJ 2013 15 21 11 21 2.7% 2.27 [0.63, 8.15] 2013 Shen XJ 2013 15 21 11 21 2.7% 2.27 [0.63, 8.15] 2013 Shen XJ 2013 15 21 11 21 2.7% 2.27 [0.63, 8.15] 2013 Shen XJ 2013 15 21 11 21 2.7% 1.27 [1.57, 7.3] 2016 July 2016 32 36 22 36 2.1% 5.09 [1.48, 17.53] 2016 July 2017 20 30 17 30 4.9% 1.53 [0.54, 4.37] 'ang Y 2017 30 57 12 53 5.1% 3.80 [1.66, 8.68] 2017 'ang Y 2017 30 57 12 53 5.1% 3.80 [1.66, 8.68] 2017 'ang Y 2017 30 57 12 53 5.1% 3.80 [1.66, 8.68] 2017 'ang Y 2011 10 14 9 14 2.2% 1.39 [0.28, 6.84] 2011 (JH 2018 28 39 16 39 3.9% 3.66 [1.42, 9.42] 2018 Subtotal (95% Cl) 53 53 6.1% 2.84 [1.27, 6.34] 'otal events 38 25 'est for overall effect Z = 2.54 ($P = 0.31$); $P = 5\%$ 'est for overall effect Z = 2.54 ($P = 0.31$); $P = 5\%$ 'est for overall effect Z = 2.54 ($P = 0.01$) otal (95% Cl) 1074 1071 100.0% 3.12 [2.56, 3.80] 'otal events 745 502 'est for overall effect Z = 1.30, df = 31 ($P = 1.00$); $P = 0\%$ 'est for overall effect Z = 1.30, df = 31 ($P = 1.00$); $P = 0\%$	Liu 1 2017	20	30	17	30	4 9%	1 53 10 54 4 361	2017	_ _
Subtract (195% C1) 329 328 31.1% 2.97 [2.08, 4.25] Total events 227 157 Test events 227 157 Test events 227 157 Test events 227 157 Test for overall effect Z = 5.95 (P < 0.00001)	Zang Y 2017	30	57	12	53	51%	3 80 [1 66 8 68]	2017	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Subtotal (95% CI)	50	329	12	328	31 1%	2 97 [2 08 4 25]	2017	•
$\begin{array}{c} \text{Let roty entry: } Chi^{2} = 5.22 & \text{(I = 9)} (P = 0.83); P = 0\% \\ \text{Test for overall effect } Z = 5.95 (P < 0.00001) \\ \hline \text{L4.5 score of study $<:3$ \\ \text{da JB 2009 11 31 5 31 2.8\% 2.86 [0.86, 26.62] 2009 \\ \text{Ju J 2009 11 16 19 10 20 1.3\% 5.33 [1.7, 24.21] 2019 \\ \text{Jang ZG 2011 16 19 10 20 2.2 20 1.1\% 4.85 [0.86, 27.22] 2012 \\ \text{Ju HW 2013 68 78 54 80 5.9\% 3.27 [1.45, 7.38] 2013 \\ \text{Shen XJ 2013 15 21 11 21 2.7\% 2.27 [0.63, 8.15] 2013 \\ \text{Shen XJ 2013 15 21 12 2.7\% 2.36 [1.46, 7.38] 2017 \\ \text{Ju Le 2017 20 30 17 30 4.9\% 1.53 [0.54, 4.36] 2017 \\ \text{Ju L 2017 20 30 17 30 4.9\% 1.53 [0.54, 4.36] 2017 \\ \text{Ju L 2017 20 30 17 30 5.7 12 53 5.1\% 3.80 [1.66, 8.68] 2017 \\ \text{Ju L 2017 20 30 17 30 5.7 12 5.3 5.1\% 3.80 [1.66, 8.68] 2017 \\ \text{Ju L 2017 20 30 17 30 5.7 12 5.3 5.1\% 3.80 [1.66, 8.68] 2017 \\ \text{Ju L 2017 20 30 17 30 5.7 12 5.3 5.1\% 3.80 [1.66, 8.68] 2017 \\ \text{Ju L 2017 20 30 17 30 5.7 12 5.3 5.1\% 3.80 [1.66, 8.68] 2017 \\ \text{Ju L 2017 20 30 17 30 5.7 12 5.3 5.1\% 3.80 [1.66, 8.68] 2017 \\ \text{Ju L 2017 20 30 17 30 5.7 12 5.3 5.1\% 3.80 [1.66, 8.68] 2017 \\ \text{Ju L 2017 30 5.7 12 5.3 5.1\% 3.80 [1.66, 8.68] 2017 \\ \text{Ju L 2017 30 5.7 12 5.3 5.1\% 3.80 [1.66, 8.68] 2017 \\ \text{Ju L 2018 28 39 16 39 3.9\% 3.66 [1.42, 9.42] 2018 \\ \text{Ju L 2018 28 39 16 39 3.9\% 3.66 [1.42, 9.42] 2018 \\ \text{Ju L 2018 28 39 16 39 3.9\% 3.66 [1.42, 9.42] 2018 \\ \text{Ju L 2018 195\% CI) 53 53 53 6.1\% 2.84 [1.27, 6.34] \\ \text{Total events 38 25 \\ \text{is eft or overall effect } Z = 1.05, df = 1 (P = 0.31); P = 5\% \\ \text{is eft or overall effect } Z = 2.54 (P = 0.01) \\ \hline \text{Total events 745 502} \\ \text{is eft or overall effect } Z = 1.320, df = 31 (P = 1.00); P = 0\% \\ \text{is eff or overall effect } Z = 1.320, df = 31 (P = 1.00); P = 0\% \\ \text{is eff or overall effect } Z = 1.320, df = 31 (P = 1.00); P = 0\% \\ \text{is eff or overall effect } Z = 1.320, df = 31 (P = 1.00); P = 0\% \\ \text{is eff or overall effect } Z = 1.320, df = 31 (P = 1.00); P = 0\% \\ \text{is eff or overall effect } Z = 1.320, df = 31 (P = 1.00); P = 0\% \\ \text{is eff or overall effect } Z = 1.320, df = 31 (Q = 0.0001) \\ \hline \begin{array}{$	Total quanta	227	525	457	520	51.170	2.57 [2.00, 4.25]		•
The traderogenetity: $Chi^{\mu} = 3.02$, $di = 3$ ($\mu = 0.83$), $\mu = 0.85$ Test for overall effect: $Z = 5.95$ ($P < 0.00001$) 1.14.5 score of study <3 4.3 J8 2009 18 23 15 23 2.8% 1.92 [0.52, 7.12] 2009 ju J 2009 11 31 5 31 2.8% 2.86 [0.86, 9.56] 2009 ju J 2009 11 31 5 31 2.8% 2.86 [0.86, 9.56] 2009 ju J 2009 11 31 5 31 2.8% 2.86 [0.86, 9.56] 2019 ju HW 2013 68 78 54 80 5.9% 3.27 [1.45, 7.38] 2013 then XJ 2013 15 21 11 21 2.7% 2.27 [0.63, 8.15] 2013 then XJ 2013 15 21 11 21 2.7% 2.27 [0.63, 8.15] 2013 then XJ 2013 15 21 31 28.8% 3.09 [2.14, 17.53] 2016 ju L 2017 20 30 17 30 4.9% 1.53 [0.54, 4.36] 2017 that y 2017 30 57 12 53 5.1% 3.80 [1.66, 8.68] 2017 ind y 2017 30 57 12 53 5.1% 3.80 [1.66, 8.68] 2017 ind y 2017 30 57 12 53 5.1% 3.80 [1.66, 8.68] 2017 ind events 217 148 teterogeneity: $Chi^{\mu} = 4.12$, $df = 8$ ($P = 0.85$); $P = 0\%$ is for overall effect: $Z = 6.00$ ($P < 0.00001$) 1.14.6 score of study >=3 Ding Y 2011 10 14 9 14 2.2% 1.39 [0.28, 6.84] 2011 ut H 2018 28 39 16 39 3.9% 3.66 [1.42, 9.42] 2018 is thrower all effect: $Z = 1.05$, $df = 1$ ($P = 0.31$); $P = 5\%$ is stor overall effect: $Z = 2.54$ ($P = 0.01$) is tal events 745 502 is ther overall effect: $Z = 1.3.90$, $df = 31$ ($P = 1.00$); $P = 0\%$ is stor overall effect: $Z = 1.3.90$, $df = 31$ ($P = 1.00$); $P = 0\%$ is stor overall effect: $Z = 1.3.90$, $df = 31$ ($P = 1.00$); $P = 0\%$ is stor overall effect: $Z = 1.3.90$, $df = 31$ ($P = 1.00$); $P = 0\%$ is stor overall effect: $Z = 1.3.90$, $df = 31$ ($P = 1.00$); $P = 0\%$ is stor overall effect: $Z = 1.3.90$, $df = 31$ ($P = 1.00$); $P = 0\%$ is stor overall effect: $Z = 1.3.90$, $df = 31$ ($P = 1.00$); $P = 0\%$ is stor overall effect: $Z = 1.3.90$, $df = 31$ ($P = 1.00$); $P = 0\%$ is stor overall effect: $Z = 1.3.90$, $df = 31$ ($P = 1.00$); $P = 0\%$ is stor overall effect: $Z = 1.3.90$, $df = 31$ ($P = 1.00$); $P = 0\%$ is stor overall effect: $Z = 1.3.90$, $df = 31$ ($P = 1.00$); $P = 0\%$	Total events	227 5 00 - 46 - 4	0 0 - 0	107	200				
1.14.5 score of study < 3 Aa JB 2009 18 23 15 23 2.8% 1.92 [0.52, 7.12] 2009 Ju J 2009 11 31 5 31 2.8% 2.86 [0.66, 9.56] 2009 Ju J 2009 11 31 5 31 2.8% 5.33 [1.17, 24.21] 2011 (ang Y 2012 7 20 2 0 1.1% 4.85 [0.86, 27.22] 2012 Ju HW 2013 68 78 54 80 5.9% 3.27 [1.45, 7.38] 2013 Chen XJ 2013 15 21 11 21 2.7% 2.27 [0.63, 8.15] 2013 Jang Y 2016 32 36 22 36 2.1% 5.09 [1.48, 17.53] 2016 Ju L 2017 20 30 17 30 4.9% 1.53 [0.54, 4.36] 2017 Stabtotal (95% CI) 315 314 28.8% 3.09 [2.14, 4.47] 7 7 Cital events 217 148 14 2.2% 1.39 [0.28, 6.84] 2011 1.0 1.0 Uhtotal (95% CI) 53	Test for overall effect:	5.02, ui = 5 Z = 5.95 (F	9 (P = 0. P < 0.00	001)	J 70				
Ala JB 2009 18 23 15 23 2.8% 1.92 [0.52, 7.12] 2009 Jul J 2009 11 31 5 31 2.8% 2.86 [0.86, 9.66] 2009 Jiang ZG 2011 16 19 10 20 1.3% 5.33 [1.7, 24.21] 2011 Jiang ZG 2011 16 19 10 20 1.1% 4.85 [0.86, 27.21] 2011 Jiu HW 2013 68 78 54 80 5.9% 3.27 [1.45, 7.38] 2013 Shang Y 2016 32 36 22 36 2.1% 5.09 [1.48, 17.53] 2016 Ju L 2017 20 31.5 314 28.3% 3.09 [2.14, 4.47] 2017 State Y 2017 30 57 12 53 5.1% 3.80 [1.66, 8.68] 2017 Jubtotal (95% CI) 315 314 28.3% 3.09 [2.14, 4.47] 2018 2018 Jubtotal (95% CI) 53 5.3 6.1% 2.84 [1.27, 6.34] 2011 4 Val 4 2018 28 39 16 39 3.9% 3.66 [1.42, 9.4	1.14.5 score of study	<3							
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Ma.IB 2009	19	22	15	22	2.8%	19210 52 7 1 21	2000	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Liu 1 2009	10	23	10	23	2.070	2 96 (0 96 0 66)	2009	+
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Liana 70 2005	40	31	0	31	4.0%	2.00 [0.00, 9.00]	2009	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Jiang 20 2011	10	19	10	20	1.5%	0.33 [1.17, 24.21]	2011	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Tang T 2012	~	20	2	20	1.1%	4.85 [0.86, 27.22]	2012	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	LIU HVV 2013	68	/8	54	80	5.9%	3.27 [1.45, 7.38]	2013	
Thang Y 2016 32 36 22 36 2.1% $5.09 [1.48, 17.53] 2016$ $Ju \downarrow 2017$ 20 30 17 30 4.9% $1.53 [0.54, 4.36] 2017$ 2 ang Y 2017 30 57 12 53 $5.1%$ $3.80 [1.66, 8.68] 20173 30 57$ 12 53 $5.1%$ $3.80 [1.66, 8.68] 20175 a 14 28.8%$ $3.09 [2.14, 4.47]Total events 217 148teterogeneity: ChiP = 4.12, df = 8 (P = 0.85); IP = 0%"est for overall effect: Z = 6.00 (P < 0.00001)1.14.6 score of study >= 3Ding Y 2011 10 14 9 14 2.2% 1.39 [0.28, 6.84] 2011(u \downarrow 2018 28 39 16 39 3.9\% 3.66 [1.42, 9.42] 2018u \downarrow 2018 28 39 16 39 3.9\% 3.66 [1.42, 9.42] 2018u \downarrow 2018 28 39 16 39 3.9\% 3.66 [1.42, 9.42] 2018u \downarrow 2018 28 39 16 39 3.9\% 3.66 [1.42, 9.42] 2018u \downarrow 2018 28 39 16 39 3.9\% 3.66 [1.42, 9.42] 2018u \downarrow 12018 28 39 16 39 3.9\% 3.66 [1.42, 9.42] 2018 28 1000000000000000000000000000000$	Chen XJ 2013	15	21	11	21	2.7%	2.27 [0.63, 8.15]	2013	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Zhang Y 2016	32	36	22	36	2.1%	5.09 [1.48, 17.53]	2016	
Zang Y 2017 30 57 12 53 5.1% 3.80 [1.66, 8.68] 2017 Subtotal (95% Cl) 315 314 28.8% 3.09 [2.14, 4.47] Total events 217 148 Heterogeneity: Chi ^a = 4.12, df = 8 (P = 0.85); $ ^{a} = 0\%$ a est for overall effect: Z = 6.00 (P < 0.00001) L14.6 score of study>=3 2 2 39 16 39 3.9% 3.66 [1.42, 9.42] 2018 Subtotal (95% Cl) 53 53 6.1% 2.84 [1.27, 6.34] 2 2 Total events 38 25 2 <t< td=""><td>Liu L 2017</td><td>20</td><td>30</td><td>17</td><td>30</td><td>4.9%</td><td>1.53 [0.54, 4.36]</td><td>2017</td><td>-</td></t<>	Liu L 2017	20	30	17	30	4.9%	1.53 [0.54, 4.36]	2017	-
Subtotal (95% CI) 315 314 28.8% $3.09 [2.14, 4.47]$ Total events 217 148 Heterogeneity: Chi ^P = 4.12, df = 8 (P = 0.85); I ^P = 0% Fest for overall effect: Z = 6.00 (P < 0.00001) 1.14.6 score of study >= 3 Ding Y 2011 10 14 9 14 2.2% 1.39 [0.28, 6.84] 2011 (U + 2018 28 39 16 39 3.9% 3.66 [1.42, 9.42] 2018 Subtotal (95% CI) 53 53 6.1% 2.84 [1.27, 6.34] Total events 38 25 Heterogeneity: Chi ^P = 1.05, df = 1 (P = 0.31); I ^P = 5% Test for overall effect: Z = 2.54 (P = 0.01) Total events 745 502 Heterogeneity: Chi ^P = 13.90, df = 31 (P = 1.00); I ^P = 0% Test for overall effect Z = 11.32 (P < 0.00001)	Zang Y 2017	30	57	12	53	5.1%	3.80 [1.66, 8.68]	2017	
Total events 217 148 Heterogeneity: Chi ² = 4.12, df = 8 (P = 0.85); $i^{2} = 0\%$ Test for overall effect: Z = 6.00 (P < 0.00001) 1.14.6 score of study >= 3 Ding Y 2011 10 14 9 14 2.2% 1.39 [0.28, 6.84] 2011 (u H 2018 28 39 16 39 3.9% 3.66 [1.42, 9.42] 2018 1.14.6 score of study >= 3 Ding Y 2011 10 14 9 14 2.2% 1.39 [0.28, 6.84] 2011 (u H 2018 28 39 16 39 3.9% 3.66 [1.42, 9.42] 2018 1.14.6 score of study >= 3 Ding Y 2011 10 14 9 14 2.2% 1.39 [0.28, 6.84] 2011 (u H 2018 28 39 16 39 3.9% 3.66 [1.42, 9.42] 2018 1.15 Studtotal (95% Cl) 53 53 6.1% 2.84 [1.27, 6.34] Total events 38 25 Heterogeneity: Chi ² = 1.05, df = 1 (P = 0.31); $i^{2} = 5\%$ Test for overall effect: Z = 2.54 (P = 0.01) 1.10 10 1.10	Subtotal (95% CI)		315		314	28.8%	3.09 [2.14, 4.47]		◆
Heterogeneity: $Chi^{2} = 4.12$, $df = 8$ (P = 0.85); $i^{2} = 0\%$ Fest for overall effect: $Z = 6.00$ (P < 0.00001) 1.14.6 score of study>=3 Ding Y 2011 10 14 9 14 2.2% 1.39 [0.28, 6.84] 2011 (u H 2018 28 39 16 39 3.9% 3.66 [1.42, 9.42] 2018 Subtotal (95% CI) 53 53 6.1% 2.84 [1.27, 6.34] Total events 38 25 Heterogeneity: $Chi^{2} = 1.05$, $df = 1$ (P = 0.31); $i^{2} = 5\%$ Test for overall effect: $Z = 2.54$ (P = 0.01) Total (95% CI) 1074 1071 100.0% 3.12 [2.56, 3.80] Total events 745 502 Heterogeneity: $Chi^{2} = 11.320$, $df = 31$ (P = 1.00); $i^{2} = 0\%$ Test for overall effect: $Z = 11.32$ (P < 0.00001)	Total events	217		148					
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Heterogeneity: Chi ² =	4.12, df = 3	8 (P = 0.	85); ² = (3%				
$\begin{array}{c c c c c c c c c c c c c c c c c c c $		() 00.00 (r	- 0.00	,					
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	1.14.6 SCOLE OF STUDY	>=3		-					
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Ding Y 2011	10	14	9	14	2.2%	1.39 [0.28, 6.84]	2011	
Subtotal (95% CI) 53 53 6.1% 2.84 [1.27, 6.34] Total events 38 25 teterogeneity: Chi ² = 1.05, df = 1 (P = 0.31); i ² = 5% 'est for overall effect: $Z = 2.54$ (P = 0.01) total (95% CI) 1074 1071 100.0% 3.12 [2.56, 3.80] total events 745 502 teterogeneity: Chi ² = 13.290, df = 31 (P = 1.00); i ² = 0% 'est for overall effect: $Z = 11.32$ (P < 0.00001)	Xu H 2018	28	39	16	39	3.9%	3.66 [1.42, 9.42]	2018	
Total events 38 25 Heterogeneity: Chi ² = 1.05, df = 1 (P = 0.31); l ² = 5% 'est for overall effect: Z = 2.54 (P = 0.01) 'otal (95% Cl) 1074 1071 100.0% 3.12 [2.56, 3.80] 'otal events 745 502 'eterogeneity: Chi ² = 13.90, df = 31 (P = 1.00); l ² = 0% 0.01 0.1 1 10 10 'est for overall effect: Z = 11.32 (P < 0.00001)	Subtotal (95% CI)		53		53	6.1%	2.84 [1.27, 6.34]		
Heterogeneity: Chi ^a = 1.05, df = 1 (P = 0.31); l ^a = 5% Fest for overall effect: Z = 2.54 (P = 0.01) Total (95% Cl) 1074 1071 100.0% 3.12 [2.56, 3.80] Total (95% Cl) 1074 1071 100.0% 3.12 [2.56, 3.80] Total events 745 502 Heterogeneity: Chi ^a = 13.90, df = 31 (P = 1.00); l ^a = 0% 0.01 0.01 10 Test for overall effect: Z = 11.32 (P < 0.00001)	Total events	38		25					
iotal (95% Cl) 1074 1071 100.0% 3.12 [2.56, 3.80] iotal events 745 502 eleterogeneity: Chi ² = 13.90, df = 31 (P = 1.00); I ² = 0% 0.01 0.1 1 10 10 'est for overall effect: Z = 11.32 (P < 0.00001)	Heterogeneity: Chi ² =	1.05, df = 1	1 (P = 0. P = 0.041	31); I² = 9	5%				
oraci (95% Cl) 1074 1071 100.0% 3.12 [2.56, 3.80] oraci (95% Cl) 502	Test of overall ellect.	z = 2.34 (f	0.01;	,		100			
Total events 745 502 Heterogeneity: Chi ² = 13.90, df = 31 (P = 1.00); l ² = 0% Set for overall effect: Z = 11.32 (P < 0.00001) Out 0.1 1 10 10	Total (95% CI)		1074		1071	100.0%	3.12 [2.56, 3.80]		▼
Heterogeneity: Chi² = 13.90, df = 31 (P = 1.00); l² = 0% 0.1 1 10 10 'est for overall effect: Z = 11.32 (P < 0.00001)	Total events	745		502					
Test for overall effect: Z = 11.32 (P < 0.00001)	Heterogeneity: Chi ² =	13.90, df=	: 31 (P =	: 1.00); I²	= 0%				
	Test for overall effect:	Z=11.32	(P < 0.0	0001)					U.UI U.I I IU IUL

Figure 3. Subgroup analysis for ORR.

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	Experim	ental	Contr	ol		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
1.15.1 mean age < 60)							
Ma JB 2009	21	23	20	23	2.1%	1.57 [0.24, 10.44]	2009	
Liu J 2009	23	31	20	31	6.2%	1.58 [0.53, 4.70]	2009	
Liu HW 2013	74	78	70	80	4.2%	2.64 [0.79, 8.82]	2013	
Zhang Y 2016	36	36	30	36	0.5%	15.56 [0.84, 287.40]	2016	
Zang Y 2017	49	57	38	53	6.6%	2.42 (0.93, 6.30)	2017	↓ • • • •
Subtotal (95% CI)		225		223	19.6%	2.44 [1.39, 4.28]		
Total events	203		178					-
Heterogeneity: Chi ² = Test for overall effect:	2.38, df = - Z = 3.12 (F	4 (P = 0. P = 0.00	.67); I² = 1 2)	0%				
1.15.2 mean age>=60)							
Jiang ZG 2011	18	19	14	20	0.9%	7.71 [0.83, 71.69]	2011	
Yang Y 2012	16	20	13	20	3.1%	2.15 [0.52, 9.00]	2012	
Chen XJ 2013	19	21	17	21	1.9%	2.24 [0.36, 13.78]	2013	
Xu H 2018	30	39	19	39	5.2%	3.51 (1.32, 9.30)	2018	│ ─ • ─
Subtotal (95% CI)		99		100	11.1%	3.23 [1.62, 6.45]		
Total events	83		63					-
Hotorogonoitr Chil-	1 00 46-	2/0 - 0	70\-12-1	006				
Test for overall effect:	Z = 3.33 (F	9 = 0.00	09)	0.10				
1.15.3 only adenocar	cinoma	~ ~						
Xu H 2018	30	39	19	39	5.2%	3.51 [1.32, 9.30]	2018	
Subtotal (95% CI)		39		39	5.2%	3.51 [1.32, 9.30]		
Total events	30		19					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 2.53 (F	P = 0.01))					
1.15.4 not only adeno	carcinom	а						
Ma.IB 2009	21	23	20	23	21%	1 57 (0 24 10 44)	2009	
Ma 00 2003	21	23	20	20	6.200	1 50 (0 52 4 70)	2003	
Liu J 2009	23		20	31	0.2%	7.36 [0.33, 4.70]	2009	
Jiang 20 2011	10	19	14	20	0.9%	7.71 [0.83, 71.09]	2011	
Yang Y 2012	16	20	13	20	3.1%	2.15 [0.52, 9.00]	2012	
Chen XJ 2013	19	21	17	21	1.9%	2.24 [0.36, 13.78]	2013	
Liu HW 2013	74	78	70	80	4.2%	2.64 [0.79, 8.82]	2013	
Zhang Y 2016	36	36	30	36	0.5%	15.56 [0.84, 287.40]	2016	· · · · · · · · · · · · · · · · · · ·
Liu L 2017	26	30	25	30	4.0%	1.30 [0.31, 5.40]	2017	
Zang Y 2017	49	57	38	53	6.6%	2.42 [0.93, 6.30]	2017	
Subtotal (95% CI)		315		314	29.4%	2.40 [1.52, 3.79]		
Total events	282		247					
Heterogeneity: Chi ² = Test for overall effect:	4.15, df = 3 Z = 3.74 (F	8 (P = 0. P = 0.00	.84); I² = 1 02)	0%				
1.15.5 score of study	<3							
Ma JB 2009	21	23	20	23	2.1%	1.57 [0.24, 10.44]	2009	
Liu J 2009	23	31	20	31	6.2%	1.58 [0.53, 4.70]	2009	_ _ +•
Jiang ZG 2011	18	19	14	20	0.9%	7.71 [0.83.71.69]	2011	+
Yang Y 2012	16	20	13	20	31%	2.15 [0.52 9.00]	2012	
Liu HW/ 2013	74	79	70	80	4 296	2 64 10 70 9 921	2013	+
Chen X 2012	10	21	17	21	1 0 06	2.04 [0.13, 0.02]	2012	
7hong V 2013	13	21		21	0.69	16 66 [0 04 207 40]	2013	
Zonally i 2010 Zona V 2017	30	50	30	50	0.0%	2 42 (0.04, 207.40)	2010	
∠ang 12017 Liu L2047	49	57	38	33	0.0%	2.42 [0.93, 0.30]	2017	
Liu L 2017 Subtotal (05% CP	26	30	25	30	4.0%	1.30 [0.31, 5.40]	2017	
Subtotal (95% CI)		315		514	29.4%	2.40 [1.52, 3.79]		
Total events	282		247					
Heterogeneity: Chi ² = Test for overall effect:	4.15, df = 3 Z = 3.74 (F	8 (P = 0. P = 0.00	.84); I² = 1 02)	0%				
1.15.6 score of study	>=3							
Xu H 2018	30	39	19	39	5.2%	3.51 [1.32, 9.30]	2018	
Subtotal (95% CI)		39		39	5.2%	3.51 [1.32, 9.30]		
Total events	30		19			-		
Heterogeneity: Not ap	plicable	P = 0.04)					
. Sould' Overall Eliett.	2.00 (r	- 0.01,	, ,					
Total (95% CI)		1032		1029	100.0%	2.62 [2.05, 3.34]		◆
Total events	910		773					
Heterogeneity: Chi ² =	13.58, df =	= 28 (P =	0.99); l ^a	= 0%				
Test for overall effect:	Z = 7.75 (F	P < 0.00	001)					U.U. U.1 1 1U 100
Test for subaroup diff	erences: C	Chi² = 1.3	39. df = 5	(P = 0	.93), ² = 0	1%		Favours (experimental) Favours (control)

Figure 6. Subgroup analysis for DCR.



One-year survival rate

There were five RCTs included in this study ^(15, 16, 19, 23, 24). A fixed effect model meta-analysis was chosen because $I^2 = 36\%$. The results showed that there was no significant difference in one-year survival rate between the two groups (RR = 1.06, 95% CI = 0.91, 1.23, *P* = 0.48). Analysis of sensitivity by removing a single item method did not have a significant effect on the overall result (figure 8).

QoL

There were four RCTs included in this study ^(1, 9, 11, 15). A random effect model meta-analysis was chosen because $I^2 = 69\%$. The results showed that there was no significant difference in QoL between the two groups (RR = 1.20, 95% CI 0.95 = 1.51, P > 4.56). The funnel plot graph was asymmetric, indicating a possible publication bias (figure 9).





	Experim	ental	l Control			Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl			
Ma JB 2009	20	23	19	23	26.1%	1.05 [0.82, 1.35]	2009	+			
Jiang ZG 2011	18	19	18	20	30.2%	1.05 [0.88, 1.26]	2011	+			
Yang Y 2012	17	20	14	20	20.4%	1.21 [0.86, 1.71]	2012				
Zang Y 2017	47	57	27	53	23.3%	1.62 [1.21, 2.16]	2017				
Total (95% CI)		119		116	100.0%	1.20 [0.95, 1.51]		•			
Total events	102		78								
Heterogeneity: Tau ² =	= 0.04; Chi ²	= 9.69,	df = 3 (P	= 0.02); I z = 69%	6					
Test for overall effect:	Z=1.54 (F	P = 0.12)					Favours (experimental) Favours (control)			

Figure 9. Forest plot for the incidence of QoL between Endostar combined with chemoradiotherapy versus chemoradiotherapy alone.

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AEs

The incidence of radiation pneumonia, radiation esophagitis, bone marrow depression, liver function, renal function, digestive tract reaction, and cardiac toxicity was analyzed. There was no significant difference in any side effects between the two groups ($l^2 < 50$ for all, fixed effect model analysis) (table 3).

AEs	Inclusion study	l ²	RR	95%CI	Р
Radiation pneumonitis	4 RCTs ^[15-17,20]	0% (fixed effect model)	1.09	[0.84,1.42]	0.50
Radiation esophagitis	5 RCTs ^[14-17,20]	0% (fixed effect model)	1.09	[0.88,1.35]	0.43
WBC	7 RCTs ^[14,15,17,18,20-22]	0% (fixed effect model)	1.03	[0.94,1.14]	0.50
PLT	7 RCTs ^[14-18,20,22]	0% (fixed effect model)	0.92	[0.80,1.06]	0.26
Hb	5 RCTs ^[14,15,17,18,22]	0% (fixed effect model)	1.02	[0.81,1.29]	0.84
Liver dysfunction	5 RCTs ^[15,17,18,20,22]	10% (fixed effect model)	1.22	[0.88,1.70]	0.23
Renal dysfunction	4 RCTs ^[15,17,20,22]	0% (fixed effect model)	1.03	[0.54,1.94]	0.93
Nausea and vomiting	8 RCTs ^[15-18,20-22,24]	0% (fixed effect model)	1.11	[0.94,1.30]	0.22
Electrocardiogram abnormality	7 RCTs ^[15-20,22]	0% (fixed effect model)	1.99	[1.00,3.96]	0.05

Table 3.	Com	parative	analysi	is of	side	effects	between	two	group	s.
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DISCUSSION

Many recent clinical studies have shown that with Endostar combined different chemotherapy regimens has a curative effect on NSCLC at different stages (25-32). However, there was no meta-analysis that investigated the effectiveness of Endostar combined with chemoradiotherapy, and thus cannot be used to guide clinical practice. This meta-analysis was conducted based on 735 patients from 11 RCTs. The results showed that ORR and DCR (71.26% and 88.62%, respectively) in the Endostar combined with chemoradiotherapy group was significantly better than that in the chemoradiotherapy group (47.14% and 75.35%, respectively) (RR_{ORR} = 1.48, 95% CI_{ORR} 1.31-1.67, PORR < 0.00001 and RRDCR = 1.17, 95% CIDCR $1.09-1.25, P_{DCR}$ < 0.00001, respectively). Subgroup analysis of age, pathological type, and of literature showed evaluation quality significant statistical differences between each subgroup of ORR and DCR (P < 0.05). Analysis of sensitivity by removing a single item did not have an obvious influence on the whole result.

This mechanism is mainly due to the presence of hypoxic cells in solid tumor tumors. The radiosensitivity of hypoxic cells is only one-third of that of oxygen-enriched cells. Vascular endothelial growth factor (VEGF) plays a key role in hypoxic cell generation and radiation resistance ^(33, 34). After radiotherapy,

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tumor cell proliferation was accelerated and the tumor blood vessels were damaged, making the existing blood vessels unable to supply oxygen effectively and aggravating the hypoxia of the tumor cells. Hypoxia can increase the activity of hypoxia-inducible factor. Furthermore, the hypoxia-inducible gene, VEGF, was activated ⁽³⁵⁾, leading to its overexpression ⁽³⁶⁾. High expression of VEGF in tumor tissues may cause tumor angiogenesis. Neoplastic vessels lack the characteristics of normal mature vascular tissues, and are distorted or disordered, and may form giant capillaries, known as sinusoid vessels. Abnormal arteriovenous anastomosis leads to increasingly poor circulation and exacerbates the anoxia of the tumor. This vicious circle eventually leads to tumor resistance to radiotherapy (37). Recombinant human vascular (Endostar) endothelin reduce can the expression of VEGF, temporarily normalize the vascular structure of the tumor, improve the function of tumor blood vessel, enhance the cooperative use of tumor oxygen, and enhance the sensitivity of tumor cells to radiotherapy (38). Endostar not only increases the sensitivity of radiotherapy, but also normalizes the tumor blood vessels and the microenvironment, and makes the vascular structure regular and the vascular basement membrane intact, increases perivascular Sertoli cells and the nutrition ability of the vascular supply, and enhances the antierosion ability, making it easier for drugs to

act on tumor cells and have synergistic effects with chemotherapy (39). Moreover, Endol itself the effect of influencing cell has cvcle distribution and inducing apoptosis (40). Our results also showed an improvement in stabilizer rate of QoL was significantly higher in Endostar combined with chemoradiotherapy (85.86%)compared with group the chemoradiotherapy group (66.67%). This is likely related to the higher ORR and DCR in the combined Endostar and chemoradiotherapy group.

In addition, we analyzed the one-year survival rate of the Endostar plus chemoradiotherapy group (73.23%) and found higher than it was that of the chemoradiotherapy group (69.29%), but this was not statistically significant (RR = 1.06, 95%) CI = 0.91, 1.23, P = 0.48). Moreover, analysis of the literature on OoL showed that the increased rate of Karnofsky performance score in the Endostar plus chemoradiotherapy group was significant that more than of the chemoradiotherapy group. The potential reason for this could be the high incidences of ORR and DCR in patients treated with Endostar plus chemoradiotherapy. However, the difference for QoL between groups was not statistically significant (RR = 1.20, 95% CI = 0.95-1.51, P = 0.12). These non-significant differences for one-year survival rate and QoL may be attributed to the smaller number of included studies that reported these findings; moreover, the power might not be enough to detect differences. Therefore, potential further large-scale RCTs should be conducted to verify these findings.

Previous studies reported that Endostar may reduce microvessel density, and induce cardiomyocytes, leading to cardiotoxicity (41,42). Moreover, this is the main adverse reaction in clinical use of Endostar and is an important factor that limits its use (25, 43). However, in this study, we did not find a significant increased risk of serious cardiac toxicity in patients treated with Endostar. However, the probability of abnormal electrocardiogram in Endostar combined with chemoradiotherapy group (9.48%) higher was than that in chemoradiotherapy alone group (4.76%), but the difference was not statistically significant (RR = 1.99, 95% CI = 1.00, 3.96, P = 0.05). These results may show a publication bias, and more clinical studies are needed to verify this finding. addition, the incidence of radiation In pneumonia, radiation esophagitis, bone marrow depression, nausea, and vomiting were not increased in the Endostar combined with chemoradiotherapy group, which was consistent with previous studies (44,45). The non-significant differences may be attributed to the low incidence of AEs, and the power was not enough to detect the potential differences. Therefore, we suggested that the combination of Endostar with chemoradiotherapy is safe and effective for use in the treatment of advanced NSCLC.

This study has several limitations. First, most the included studies lacked adequate of subgroup analysis of data such as progression free survival and one-year survival rate. Second, the quality of the 11 articles included in this study was not high and there may have been a bias that affected the accuracy and reliability of the results. Third, the sample size of some studies is too small, and most patients were from China (because Endostar was approved by the China State Food and Drug Administration and applied in treatment of lung cancer), which may lead to geographical and ethnic differences. Finally, there are a few reports on the long-term curative effects; therefore, the long-term effects of Endostar plus chemoradiotherapy remains unclear.

CONCLUSIONS

We can conclude that Endostar combined with chemoradiotherapy may improve the ORR and DCR of patients with advanced NSCLC, and improve the QoL of patients. Furthermore, it was not shown to increase side effects, and is, therefore, worth considering in clinical practice. More high-quality clinical trials are required to verify this conclusion.

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