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META-ANALYSIS

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MTHFR C677T Polymorphism is Associated with Tumor Response to Preoperative Chemoradiotherapy: A Result Based on Previous Reports

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABE 1 Yue Zhao
CDF 1 Xingde Li
ACE 2 Xiangjun Kong

1 Department of Radiation Therapy, Cangzhou Central Hospital, Cangzhou, Hebei, P.R. China
2 Central Laboratory, Cangzhou Central Hospital, Cangzhou, Hebei, P.R. China

Corresponding Author: Xiangjun Kong, e-mail: drkongxj@163.com
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Background: Preoperative chemoradiotherapy (pRCT) followed by surgery has been widely practiced in locally advanced rectal cancer, esophageal cancer, gastric cancer and other cancers. However, the therapy also exerts some severe adverse effects and some of the patients show poor or no response. It is very important to develop biomarkers (e.g., gene polymorphisms) to identify patients who have a higher likelihood of responding to pRCT. Recently, a series of reports have investigated the association of the genetic polymorphisms in methylenetetrahydrofolate reductase (MTHFR) and epidermal growth factor receptor (EGFR) genes with the tumor response to pRCT; however, the results were inconsistent and inconclusive.

Material/Methods: A systematic review and meta-analysis was performed by searching relevant studies about the association of MTHFR and EGFR polymorphisms with the tumor regression grade (TRG) in response to pRCT in databases of PubMed, EMBAS, Web of science, Chinese National Knowledge Infrastructure, and Wanfang database up to March 30, 2015. The pooled odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs) were calculated to assess the strength of the association under 5 genetic models.

Results: A total of 11 eligible articles were included in the present meta-analysis, of which 8 studies were performed in rectal cancer and 3 studies were performed in esophageal cancer. We finally included 8 included studies containing 839 cases for MTHFR C677T, 5 studies involving 634 cases for MTHFR A1298C, 3 studies containing 340 cases for EGFR G497A, and 4 studies containing 396 cases for EGFR CA repeat. The pooled analysis results indicated that MTHFR C677T might be correlated with the tumor response to pRCT under the recessive model (CC *vs.* CTTT) in overall analysis (OR=1.426(1.074–1.894), P=0.014), rectal cancer (OR=1.483(1.102–1.996), P=0.009), and TRG 1–2 *vs.* 3–5 group (OR=1.423(1.046–1.936), P=0.025), while other polymorphism including MTHFR A1298C, EGFR G497A, and EGFR CA repeat polymorphisms exerted significant association under all genetic models in overall analysis or subgroup analysis.

Conclusions: MTHFR C677T might be correlated with the tumor response to pRCT. Further well-designed, larger-scale epidemiological studies are needed to validate our results.

MeSH Keywords: Chemoradiotherapy, Adjuvant • Meta-Analysis • Polymorphism, Single Nucleotide

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Background

Multimodality therapy clearly offers survival benefit over surgery alone, especially in high-stage cancers. In recent decades, preoperative chemoradiotherapy followed by surgery has been the standard therapy for locally advanced rectal cancer and its application is increasing in other cancers, such as esophageal cancer and gastric cancer [1]. However, the treatment also exerts some severe adverse effects and some patients are not sensitive to pRCT [2–4]. Thus, to identify patients who will benefit from the therapy strategy is very important. Therapy response is correlated not only with tumor types and tumor microenvironment, but also with patient genetics. Several biomarkers have been investigated to see if they are correlated with the response to pRCT, including the genetic polymorphisms in methylenetetrahydrofolate reductase (MTHFR) and epidermal growth factor receptor (EGFR) genes.

MTHFR can catalyze the conversion of 5,10-MTHF to 5-methylenetetrahydrofolate. There are 2 common polymorphisms in MTHFR – C677T (rs1801133) and A1298C (rs1801131) – that are widely investigated. Both of them can be used as predictors of the response to fluoropyrimidine-based chemotherapy [5]. EGFR is a member of the human epithelial receptor tyrosine kinase family and is also known as HER-1. Its kinase activity can regulate downstream gene expression, cellular proliferation, inhibition of apoptosis, and angiogenesis [6]. Its expression has been reported to be related to radiation resistance. A polymorphism in the EGFR gene has been reported to lead the substitution of an arginine (Arg) residue by a lysine (Lys) in codon 497 (G497A) [7]. Another polymorphism variant in EGFR is the CA repeats in intron 1 (rs11568315). EGFR transcription activity declines with an increasing number of CA repeats [8]. The alleles are carried as short (S) or long (L), according to the number of CA repeats. Although a series of studies have been performed to examine the association of MTHFR and EGFR polymorphisms with the tumor response to pRCT, the results were inconsistent and inconclusive. In the present study, we conducted a meta-analysis to evaluate the association of MTHFR and EGFR polymorphisms with the tumor response to pRCT.

Material and Methods

Publication search

We performed a systematic search for published articles in the database of PubMed, EMBASW, Web of Science, Chinese National Knowledge Infrastructure, and Wanfang on the association of MTHFR or EGFR polymorphisms and the response to preoperative chemoradiotherapy up to March 30, 2015. The following keywords and subject terms were used: "the methylenetetrahydrofolate reductase gene OR MTHFR", "Epidermal growth factor receptor OR EGFR", "polymorphism OR polymorphisms", and "Chemoradiation OR chemoradiotherapy OR chemo-radiotherapy OR radio-chemotherapy". The retrieved articles were screened by 2 authors independently, according to the inclusion and exclusion criteria and the review articles and reference lists of the primary studies were also screened.

Inclusion and exclusion criteria

Inclusion criteria: (1) evaluation of the association between MTHFR C677T, MTHFR A1298C, EGFR G497A, and EGFR CA repeat polymorphisms and response to preoperative chemoradiotherapy; (2) response to chemoradiotherapy was evaluated by tumor regression grade (TRG); (3) genotype frequency data could be obtained to estimate the odds ratio (OR) and

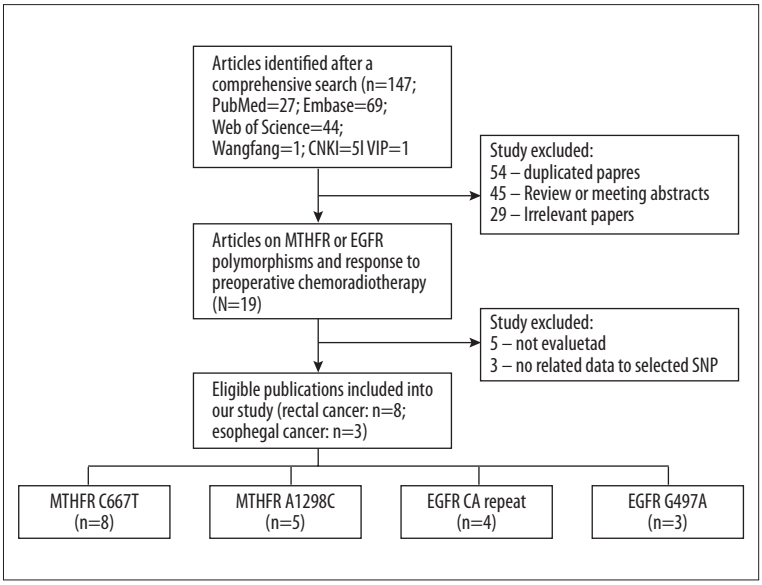

Figure 1. Flow chart of study selection.

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Table 1. Characteristics of the included studies.

Reference	Country	Ethnicity	Case	Age	M/F	Cancer type	Stage	Therapy strategy	Chemotherapy drugs	Radiation dose (Gy)	TRG Evaluation	Genotype method	Sample	Polymorphisms
Terrazzino et al., 2006	Italy	Caucasian	125	60 (31–79)	80/45	Rectal cancer	T2,3,4	RCT + surgery	5-FU	45.0	1–2 *vs.* 3–5	PCR	Blood	MTHFR C677T; A1298C
Sarbia et al., 2006	Germany	Caucasian	68	57 (37–70)	60/8	Esophageal cancer	T3/T4	RCT + surgery	5-FU folinic acid etoposide cisplatin	40.0	1 *vs.* 2–5	PCR-RFLP	Tumor	MTHFR C677T
Warnecke-Eberz et al., 2009	Germany	Caucasian	52	59 (38–73)	NA	Esophageal cancer	T2–4	RCT + surgery	Cisplatin/5-FU	36	1–2 *vs.* 3–5	TaqMan	Tumor	MTHFR C677T
Balboa et al., 2010	Spain	Caucasian	65	64 (37–85)	50/15	Rectal cancer	II/III	RCT + surgery	5-FU/capecitabine	50.5	1–2 *vs.* 3–5	SNaPshot	Blood	MTHFR C677T; A1298C, EGFR CA repeat
Garcia-Aguilar et al., 2011	Spain	Mixed	132	Responder: 56 (32–80); Nonresponder: 57 (26–87)	77/55	Rectal cancer	II/III	RCT + surgery	5-FU	50.4	1 *vs.* 2–5	Sanger sequencing	Tumor	MTHFR C677T
Cecchin et al., 2011	Italy	Caucasian	238	61 (20–79)	159/79	Rectal cancer	T2,3,4	RCT + surgery	5-FU	45.0-50.4	1–2 *vs.* 3–5	TaqMan	Blood	MTHFR C677T; A1298C
Hu-Lieskovan et al., 2011	Belgium; Slovenia; Germany	Caucasian	130	61 (33–83)	74/56	Rectal cancer	II/III/IV	RCT + surgery	Capecitabine/ cetuximab/5-FU	45/50.4	1–2 *vs.* 3–5	PCR-RFLP	Tumor	MTHFR C677T; A1298C, EGFR G497A; CA repeat
Hu-Lieskovan et al., 2011	Belgium; Slovenia; Germany	Caucasian	130	61 (33–83)	74/56	Rectal cancer	II/III/IV	RCT + surgery	Capecitabine/ cetuximab/5-FU	45/50.4	1 *vs.* 2–5	PCR-RFLP	Tumor	MTHFR C677T; A1298C, EGFR G497A; CA repeat
Paez et al., 2011	Spain	Caucasian	128	65 (32–83)	97/31	Rectal cancer	II/III	RCT + surgery	5-FU/capecitabine	45.0	1–2 *vs.* 3–5	Dynamic array	Blood	EGFR G497A
Lee et al., 2011	Taiwan	Aisan	132	<60, n=80; ≥60, n=68	NA	Esophageal cancer	IIa or less, n=55; IIb or more, n=93	RCT + surgery	Cisplatin/5-FU	40.0	1–2 *vs.* 3–5	PCR	Blood	EGFR CA repeat
Lamas et al., 2012	Spain	Caucasian	93	67 (39–86)	68/25	Rectal cancer	II/III	RCT + surgery	5-FU	50.4	1–2 *vs.* 3–5	SNaPshot	Blood	MTHFR C677T; A1298C, EGFR CA repeat
Sebio et al., 2015	Spain	Caucasian	84	67.6 (42–80)	55/29	Rectal cancer	II/III	RCT + surgery	Capecitabine	45.0	1 *vs.* 2–5	Dynamic array	Blood	EGFR G497A

95% confidence interval (CI). Articles were excluded based on the following criteria: (1) the data of TRG were not specific to polymorphism; (2) studies with insufficient or duplicate data; (3) meeting abstracts, letters, or review articles.

Data extraction

Based on the inclusion and exclusion criteria, 2 investigators extracted the following information from all eligible studies: name of first author, year of publication, country of origin, ethnicity, age, sex ratio, cancer type, disease stage, chemotherapy drugs, radiation dose, and genotype frequency in responders and non-responders of MTHFR C677T, MTHFR A1298C, EGFR G497A, and EGFR CA repeat polymorphisms.

Quality score assessment

Two independent investigators assessed the methodological quality of every eligible article according to the Newcastle-Ottawa Scale (NOS) basing on 3 aspects: selection, comparability, and exposure, with scores ranging from 0 to 9 [9]. NOS score ≥7 was considered as high quality.

Statistical analysis

In the study, TRG grades were defined as grade 1: the absence of residual cancer; grade 2: the presence of rare residual cancer cells; grade 3: an increase in the number of residual cancer cells but with fibrosis predominating; grade 4: residual cancer

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Table 2. Summary of the meta-analysis results.

Polymorphism	Genetic model	Cancer type	N	OR (95%CI)	P_{OR}	Effect model	I^2 (%)	P_{Heter}	P_{Begg}	P_{Egger}
MTHFR C677T	C *vs.* T	All	7	1.178 (0.855–1.624)	0.317	R	53.6	0.044	0.230	0.562
		Rectal cancer	6	1.223 (0.860–1.738)	0.263	R	58.7	0.033		
		Esophageal cancer	1							
		TRG 1–2 *vs.* 3–5	6	1.097 (0.779–1.544)	0.596	R	53.9	0.055		
		TRG 1 *vs.* 2–5	2	1.590 (0.967–2.614)	**0.068**	R	45.9	0.074		
	CC *vs.* TT	All	7	1.185 (0.603–2.328)	0.623	R	51.2	0.056	0.548	0.835
		Rectal cancer	6	1.274 (0.576–2.817)	0.550	R	57.8	0.037		
		Esophageal cancer	1							
		TRG 1–2 *vs.* 3–5	6	1.063 (0.558–2.027)	0.852	R	48.2	0.086		
		TRG 1 *vs.* 2–5	2	2.221 (0.084–58.420)	0.632	R	76.0	0.041		
	CT *vs.* TT	All	6	0.727 (0.378–1.401)	0.341	R	44.2	0.096	0.548	0.746
		Rectal cancer	5	0.776 (0.369–1.633)	0.504	R	52.0	0.064		
		Esophageal cancer	1							
		TRG 1–2 *vs.* 3–5	6	0.689 (0.443–1.074)	0.100	F	31.9	0.197		
		TRG 1 *vs.* 2–5	2	1.233 (0.015–98.183)	0.925	R	85.5	0.009		
	CC *vs.* CTTT	All	7	1.426 (1.074–1.894)	**0.014**	F	18.6	0.283	0.386	0.363
		Rectal cancer	6	1.483 (1.102–1.996)	**0.009**	F	35.6	0.170		
		Esophageal cancer	2	0.953 (0.365–2.492)	0.922	F	0.0	0.770		
		TRG 1–2 *vs.* 3–5	6	1.423 (1.046–1.936)	**0.025**	F	37.8	0.154		
		TRG 1 *vs.* 2–5	3	1.619 (0.899–2.915)	0.108	F	0.0	0.664		
		Rectal cancer	2	1.766 (0.947–3.291)	**0.074**	F	0.0	0.750		
	CCCT *vs.* TT	All	7	0.913 (0.501–1.664)	0.767	R	46.8	0.080	0.764	0.742
		Rectal cancer	6	0.968 (0.476–1.970)	0.929	R	54.4	0.052		
		Esophageal cancer	1							
		TRG 1–2 *vs.* 3–5	6	0.863 (0.580–1.283)	0.466	F	39.1	0.145		
		TRG 1 *vs.* 2–5	2	1.773 (0.041–76.720)	0.766	R	82.2	0.018		
MTHFR A1298C	A *vs.* C	Rectal cancer	5	0.978 (0.771–1.241)	0.857	F	21.0	0.281	0.806	0.976
	AA *vs.* CC	Rectal cancer	5	1.169 (0.683–2.002)	0.569	F	37.7	0.170	0.462	0.550
	AC *vs.* CC	Rectal cancer	5	1.418 (0.824–2.439)	0.207	F	34.2	0.194	0.221	0.504
	AA *vs.* ACCC	Rectal cancer	5	0.875 (0.639–1.199)	0.406	F	0.0	0.458	0.806	0.912
	AAAC *vs.* CC	Rectal cancer	5	1.285 (0.768–2.148)	0.340	F	36.4	0.179	0.462	0.492

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Table 2 continued. Summary of the meta-analysis results.

Polymorphism	Genetic model	Cancer type	N	OR (95%CI)	P_{OR}	Effect model	I^2 (%)	P_{Heter}	P_{Begg}	P_{Egger}
EGFR G497A	G *vs.* A	All	2	0.812 (0.561–1.176)	0.271	F	25.1	0.248		
	GG *vs.* AA	All	2	1.244 (0.519–2.982)	0.624	F	5.9	0.303		
	GA *vs.* AA	All	2	0.994 (0.398–2.486)	0.990	F	0.0	0.610		
	GG *vs.* GAAA	All	3	0.930 (0.431–2.007)	0.853	R	60.9	0.078	1.000	0.423
		TRG 1–2 *vs.* 3–5	2	1.267 (0.762–2.106)	0.362	F	15.6	0.276		
		TRG 1 *vs.* 2–5	2	0.913 (0.472–1.765)	0.362	R	76.3	0.040		
	GGGA *vs.* AA	All	2	1.139 (0.488–2.662)	0.763	F	0.0	0.384		
EGFR CA repeat	S *vs.* L	All	4	0.639 (0.397–1.030)	**0.066**	F	38.3	0.182	1.000	0.938
		Rectal Cancer	3	0.708 (0.299–1.677)	0.433	R	54.8	0.109		

outgrowing fibrosis; and grade 5: the absence of regressive changes [10,11]. Patients were subdivided into responders and non-responders (TRG 1–2 *vs.* 3–5 or 1 *vs.* 2–5). The pooled odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs) were calculated to assess the strength of the association between MTHFR C677T, MTHFR A1298C, EGFR G497A, and EGFR CA repeat polymorphisms and the response to preoperative chemoradiotherapy. A *p*-value <0.05 was used to indicate statistically significant association. Pooled ORs were performed under 5 genetic models: allelic model, homozygote model, heterozygote model, dominant model, and recessive model. If the response was evaluated by both TRG 1–2 *vs.* 3–5 and 1 *vs.* 2–5, only the TRG 1–2 *vs.* 3–5 data was included for the overall analysis and subgroup analysis stratified by cancer type. However, both were included when the subgroup analyses were performed according to the responder definition. The heterogeneity among the studies was assessed by the chi-square test based on Q statistic test and I^2 statistic tests. When P<0.1 or I^2 >50%, the heterogeneity was considered to be significant and then the pooled OR and 95%CIs were evaluated by the random-effects model (DerSimonian-Laird method); otherwise, the fixed-effects model (Mantel-Haenszel method) was used [12]. Potential publication bias was checked by Begg's funnel plots and Egger's test [13,14]. Sensitivity analysis was also conducted to evaluate the stability of the final results by deleting each study in turn. Subgroup analyses according cancer type and responder definition were also performed. Stata 12.0 software (StataCorp, College Station, TX, USA) was used to perform all analyses.

Results

Study characteristics

The literature selection process is shown in Figure 1. After initial identification, a total of 147 items were obtained. Of them, 54 were duplicated papers, 45 were review or meeting abstracts, and 29 were irrelevant papers. Then, 19 articles were left for further screening according to the inclusion and exclusion criteria by reading the full text. Subsequently, 8 articles were excluded; the treatment response to pRCT in 5 of them was not evaluated by tumor regression grade (TRG) and 3 articles did not report data related to the selected SNP. Finally, 11 eligible articles were included in the present meta-analysis [15–25]. Eight studies were performed in rectal cancer [15,18–22,24,25] and 3 studies were performed in esophageal cancer [16,17,23]. The methodological quality of each eligible article was assessed by NOS scale and all studies received a high NOS score (≥7, data not shown). Table 1 shows the characteristics of each study. The articles were published from 2006 to 2015. In the present study we finally analyzed 8 included studies containing 839 cases for MTHFR C677T [15–21,24], 5 studies involving 634 cases for MTHFR A1298C [15,18,20,21,24], 3 studies containing 340 cases for EGFR G497A [21,22,25], and 4 studies containing 396 cases for EGFR CA repeat [18,21,23,24].

Meta-analysis results

We firstly analyzed the association of MTHFR C677T with the response to pRCT under 5 genetic models. Overall, the C677T polymorphism was correlated with the response to pRCT in recessive model (CC *vs.* CTTT, OR=1.426(1.074–1.894), *P*=0.014, Table 2), but not in allele model, homozygote model, heterozygote model, or dominant model. In subgroup analysis according

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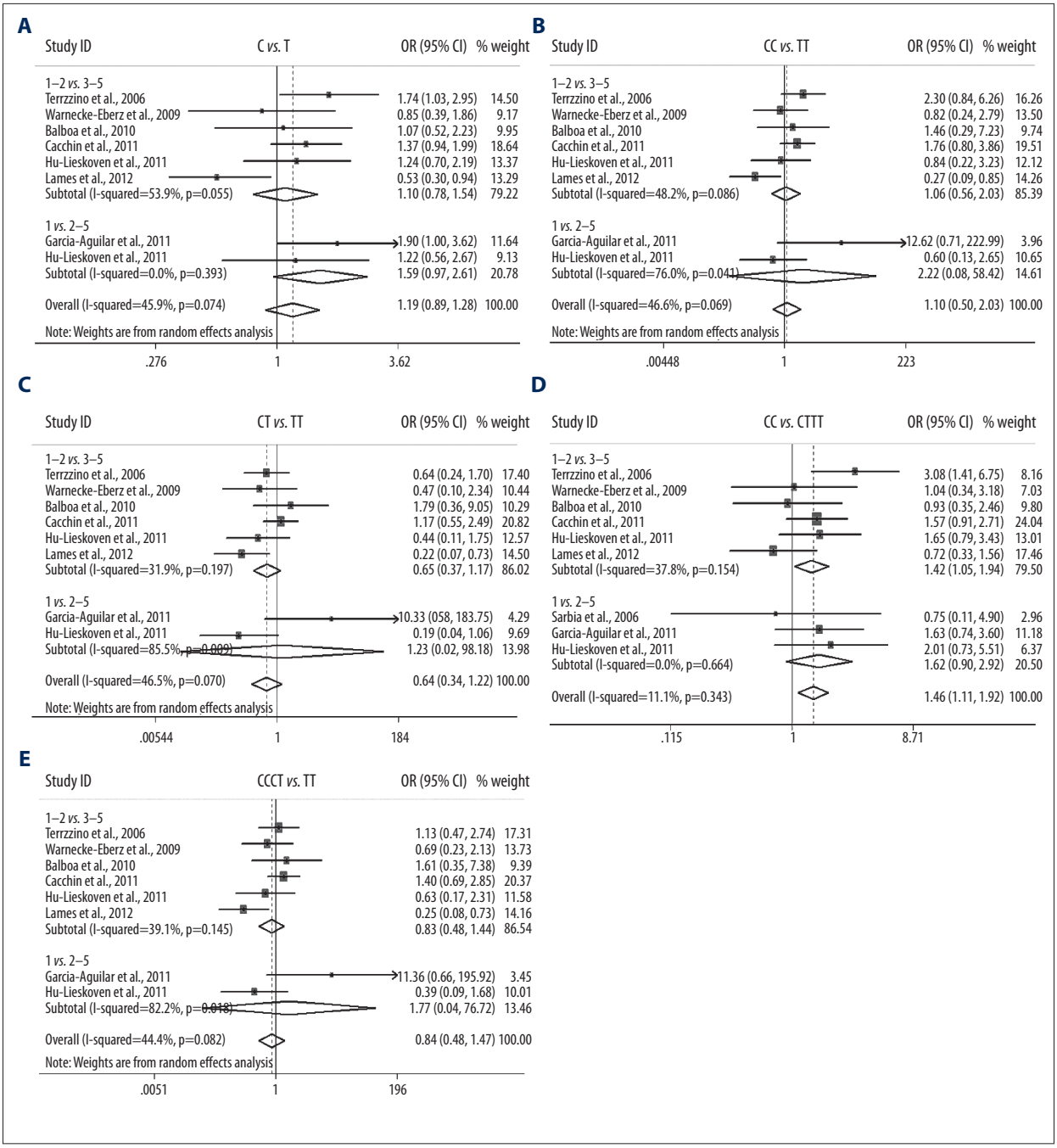

Figure 2. Forest plot for the association of MTHFR C677T polymorphism and the tumor response to pRCT stratified by the responder definition.

to cancer type, a significant association was also found in recessive model in rectal cancer (CC *vs.* CTTT, OR=1.483(1.102–1.996), *P*=0.009, Table 2), but no significant association existed in other genetic models. When the subgroup analysis was performed according to responder definition, a significant association was only found in recessive model in TRG 1–2 *vs.* 3–5 group (CC *vs.* CTTT, OR=1.423(1.046–1.936), *P*=0.025, Table 2, Figure 2). The results suggest that patients (especially those with rectal cancer) carrying CC genotype might benefit from pRCT compared with CT or TT carriers. The association between MTHFR A1298C, EGFR G497A, and EGFR CA repeat polymorphisms and the response to pRCT was also examined; however, no significant association was identified in overall or subgroup analyses, only a trend that EGFR short (S) CA repeat might harbor a unfavorable role in response to pRCT in overall analysis (S *vs.* L, OR=0.639(0.397–1.030), *P*=0.066, Table 2, Figure 4).

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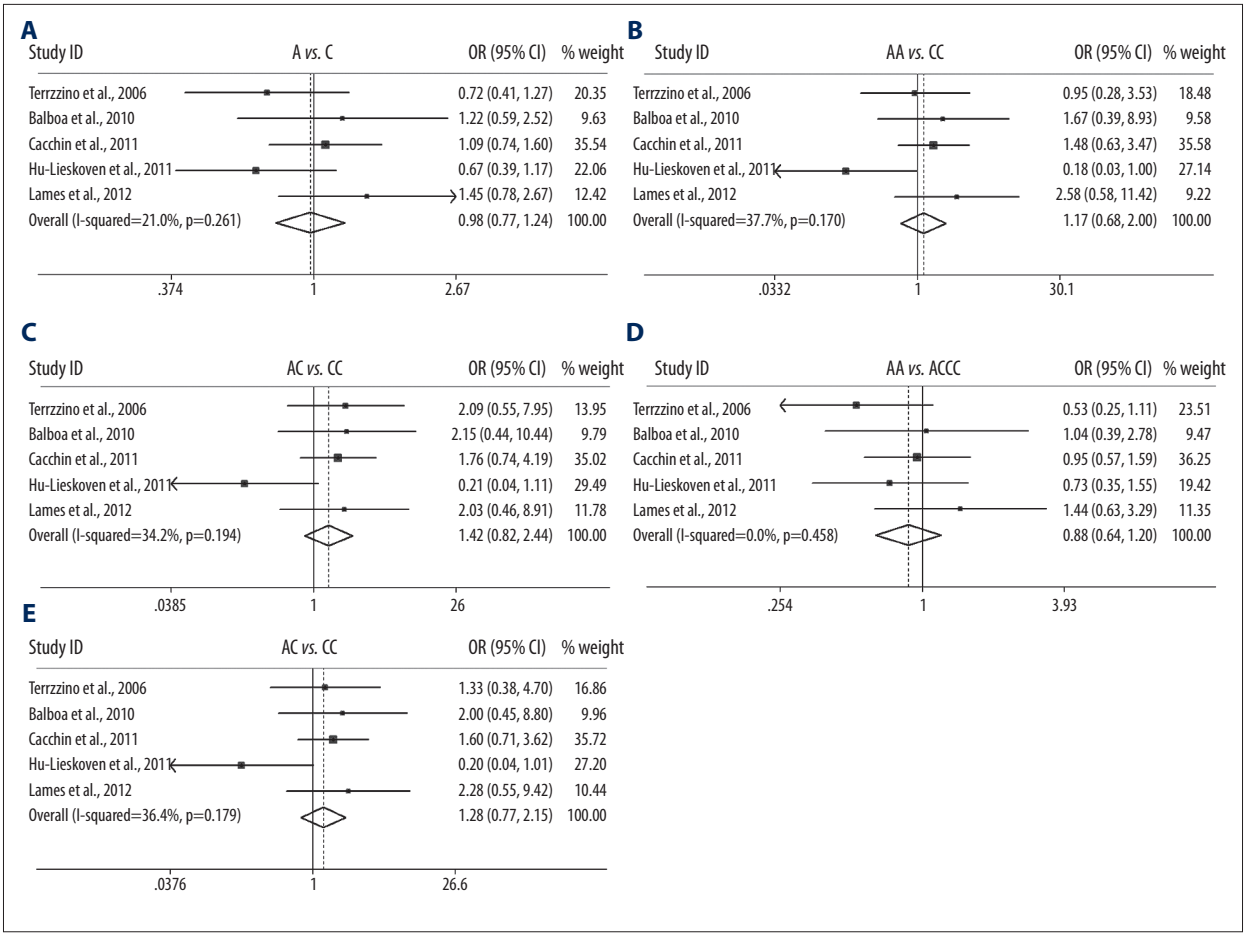

Figure 3. Forest plot for the association of MTHFR A1298C polymorphism and the tumor response to pRCT.

Sensitivity analysis and publication bias

Sensitivity analysis was performed to examine the influence of each single study on the estimated effects in all genetic models. For MTHFR C677T polymorphism, we arrived at almost the same results in all genetic models. For MTHFR A1298C, when the report by Hu et al. was deleted, a significant association was identified between the polymorphism and the response to pRCT under heterozygote model (AC *vs.* CC). For EGFR CA repeat, a significant association was also found between the polymorphism and the response when the report by Hu et al. was deleted. To evaluate the publication bias among the selected studies, Begg's funnel plot was used for polymorphisms of MTHFR C677T, MTHFR A1298C, and EGFR CA repeat, and symmetrical funnel plots were obtained in all genetic models (and data not shown), indicating lack of publication bias. In addition, Egger's test was also performed and the results indicated that no publication bias existed among all the studies for all the polymorphisms under 5 genetic models (Table 2).

Discussion

In the present study, we performed a meta-analysis by pooling 20 studies to investigate the association of MTHFR and EGFR polymorphisms with the tumor response to pRCT in cancers. The results suggested that MTHFR C677T might be correlated with the tumor response, while the polymorphisms of A1298C in MTHFR and G497A and CA repeat in EGFR were not associated with the response.

Preoperative chemoradiotherapy, also known as neo-adjuvant chemoradiotherapy, followed by surgery has provide an alternative choice for cancer therapy and offered survival benefit for several cancers, especially locally advanced rectal cancer, in which the treatment strategy has became a standard therapy. In high-stage esophageal cancer and gastric cancer, a series of studies proved that the patients undergoing pRCT combined with surgery had higher overall survival rate and disease-free survival rates compared with surgery alone or surgery combined with adjuvant therapy [26–28]. Nevertheless, pRCT also causes severe adverse effects and many patients show poor response to pRCT. Tumor response to treatment was correlated

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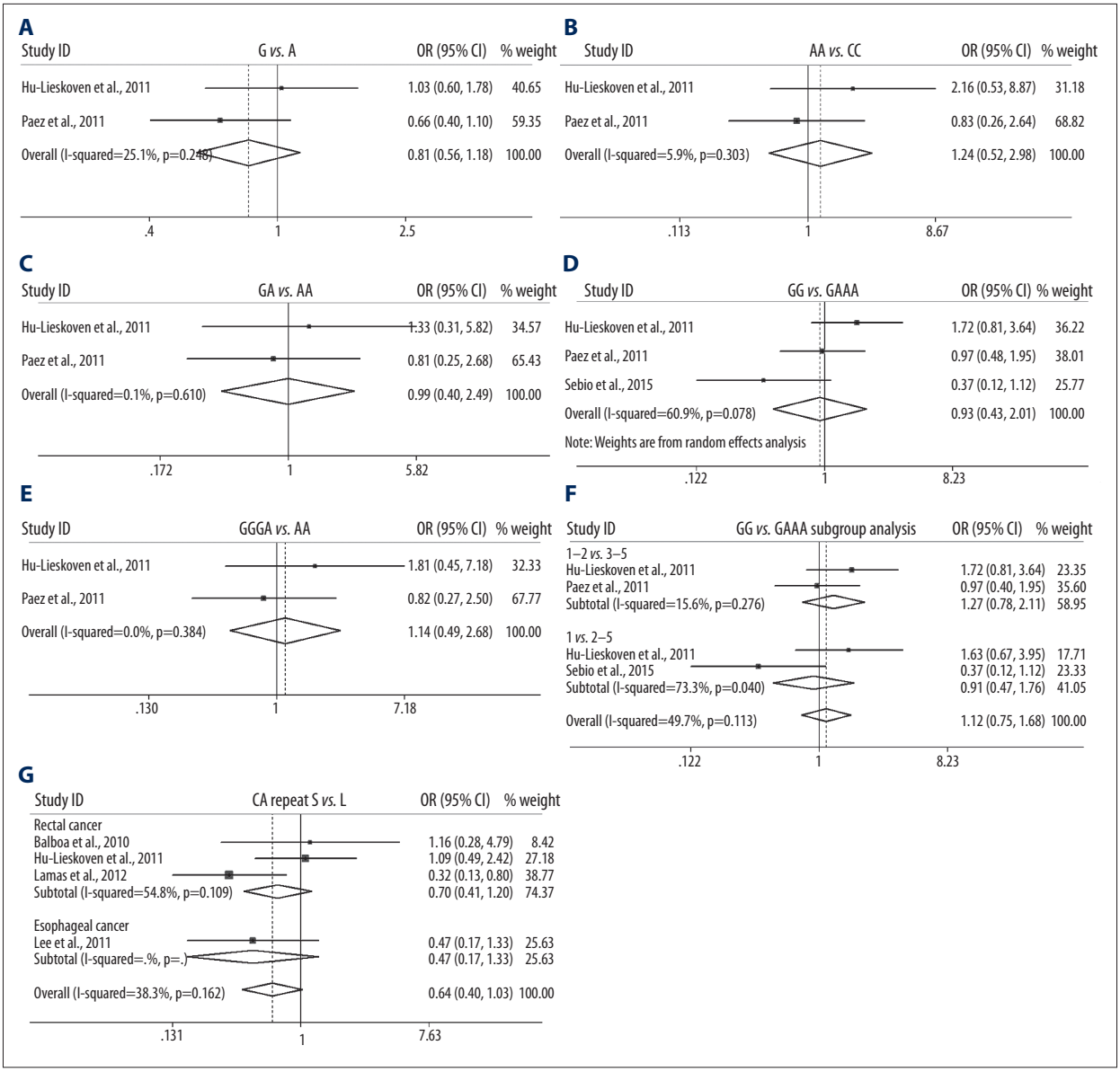

Figure 4. Forest plot for the association of EGFR G497A and CA repeat polymorphisms and the tumor response to pRCT.

with tumor type and tumor microenvironment, as well as patient genetics, so it is important to discover the biomarkers to identify patients who will benefit from pRCT and advance the development of individual therapy.

In the past decade many researchers have focused on the investigation of the biomarkers in predicting the tumor response to pRCT; however, the results are not consistent and valuable biomarkers are still lacking. Because many studies have determined the association of MTHFR polymorphisms with the tumor response to pRCT, we performed a systematic search in literature databases for related studies and conducted a meta-analysis to investigate the association between MTHFR polymorphisms and the response to pRCT, also including the EGFR polymorphisms. The results suggested that MTHFR C677T might be correlated with the tumor response to pRCT under the recessive model in overall analysis, rectal cancer, and TRG 1–2 *vs.* 3–5 group, while other polymorphism exert significant association under all genetic models in overall analysis or subgroup analyses. In addition, only a trend of association between EGFR CA repeat and the tumor response to pRCT was found. To the best of our knowledge, this is the first meta-analysis to address the association between MTHFR and EGFR polymorphisms and the response to pRCT, in which we tried to pool all the potential related studies regardless of cancer type. However, some limitations existed in the study. Firstly, the study number and the sample size were very small, especially for EGFR polymorphisms and esophageal cancer, which

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also led to the lack of stability of the results for MTHFR A1298C polymorphism. Another limitation was that all the original studies were performed in white populations except for 1 that was carried out in Asians. Thus, further well-designed studies with larger sample sizes focusing on more ethnicities should be conducted to confirm the results.

Conclusions

In summary, we obtained a comprehensive result from the current meta-analysis that MTHFR C677T polymorphism was correlated with the response to pRCT in overall and in rectal cancer, while MTHFR A1298C and EGFR G497A and CA repeat polymorphisms showed no significant association with the tumor response to pRCT.

Disclosure

The authors have not received any funding or benefits from industry in relation to this study.

Conflict of interest

None.

References:

1. Spolverato G, Pucciarelli S, Bertorelle R et al: Predictive factors of the response of rectal cancer to neoadjuvant radiochemotherapy. Cancers (Basel), 2011; 3: 2176–94
2. Pucciarelli S, Del Bianco P, Efficace F et al: Patient-reported outcomes after neoadjuvant chemoradiotherapy for rectal cancer: a multicenter prospective observational study. Ann Surg, 2011; 253: 71–77
3. Minsky BD, Cohen AM, Kemeny N et al: Combined modality therapy of rectal cancer: decreased acute toxicity with the preoperative approach. J Clin Oncol, 1992; 10: 1218–24
4. Mohiuddin M, Hayne M, Regine WF et al: Prognostic significance of postchemoradiation stage following preoperative chemotherapy and radiation for advanced/recurrent rectal cancers. Int J Radiat Oncol Biol Phys, 2000; 48: 1075–80
5. Etienne MC, Formento JL, Chazal M et al: Methylenetetrahydrofolate reductase gene polymorphisms and response to fluorouracil-based treatment in advanced colorectal cancer patients. Pharmacogenetics, 2004; 14: 785–92
6. Laskin JJ, Sandler AB: Epidermal growth factor receptor: a promising target in solid tumours. Cancer Treat Rev, 2004; 30: 1–17
7. Moriai T, Kobrin MS, Hope C et al: A variant epidermal growth factor receptor exhibits altered type alpha transforming growth factor binding and transmembrane signaling. Proc Natl Acad Sci USA, 1994; 91: 10217–21
8. Amador ML, Oppenheimer D, Perea S et al: An epidermal growth factor receptor intron 1 polymorphism mediates response to epidermal growth factor receptor inhibitors. Cancer Res, 2004; 64: 9139–43
9. Wells G, Shea B, O'Connell D et al: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Journal 2014
10. Mandard AM, Dalibard F, Mandard JC et al: Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer, 1994; 73: 2680–86
11. Dworak O, Keilholz L, Hoffmann A: Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorectal Dis, 1997; 12: 19–23
12. DerSimonian R, Laird N: Meta-analysis in clinical trials. Control Clin Trials, 1986; 7: 177–88
13. Begg CB, Mazumdar M: Operating characteristics of a rank correlation test for publication bias. Biometrics, 1994; 50: 1088–101
14. Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. BMJ, 1997; 315: 629–34
15. Terrazzino S, Agostini M, Pucciarelli S et al: A haplotype of the methylenetetrahydrofolate reductase gene predicts poor tumor response in rectal cancer patients receiving preoperative chemoradiation. Pharmacogenet Genomics, 2006; 16: 817–24
16. Sarbia M, Stahl M, von Weyhern C et al: The prognostic significance of genetic polymorphisms (Methylenetetrahydrofolate Reductase C677T, Methionine Synthase A2756G, Thymidilate Synthase tandem repeat polymorphism) in multimodally treated oesophageal squamous cell carcinoma. Br J Cancer, 2006; 94: 203–7
17. Warnecke-Eberz U, Vallboehmer D, Alakus H et al: ERCC1 and XRCC1 gene polymorphisms predict response to neoadjuvant radiochemotherapy in esophageal cancer. J Gastrointest Surg, 2009; 13: 1411–21
18. Balboa E, Duran G, Lamas MJ et al: Pharmacogenetic analysis in neoadjuvant chemoradiation for rectal cancer: high incidence of somatic mutations and their relation with response. Pharmacogenomics, 2010; 11: 747–61
19. Garcia-Aguilar J, Chen Z, Smith DD et al: Identification of a biomarker profile associated with resistance to neoadjuvant chemoradiation therapy in rectal cancer. Ann Surg, 2011; 254: 486–92; discussion 492–93
20. Cecchin E, Agostini M, Pucciarelli S et al: Tumor response is predicted by patient genetic profile in rectal cancer patients treated with neo-adjuvant chemo-radiotherapy. Pharmacogenomics J, 2011; 11: 214–26
21. Hu-Lieskovan S, Vallbohmer D, Zhang W et al: EGF61 polymorphism predicts complete pathologic response to cetuximab-based chemoradiation independent of KRAS status in locally advanced rectal cancer patients. Clin Cancer Res, 2011; 17: 5161–69
22. Paez D, Salazar J, Pare L et al: Pharmacogenetic study in rectal cancer patients treated with preoperative chemoradiotherapy: polymorphisms in thymidylate synthase, epidermal growth factor receptor, GSTP1, and DNA repair genes. Int J Radiat Oncol Biol Phys, 2011; 81: 1319–27
23. Lee JM, Yang SY, Yang PW et al: Polymorphism in epidermal growth factor receptor intron 1 predicts prognosis of patients with esophageal cancer after chemoradiation and surgery. Ann Surg Oncol, 2011; 18: 2066–73
24. Lamas MJ, Duran G, Gomez A et al: X-ray cross-complementing group 1 and thymidylate synthase polymorphisms might predict response to chemoradiotherapy in rectal cancer patients. Int J Radiat Oncol Biol Phys, 2012; 82: 138–44
25. Sebio A, Salazar J, Paez D et al: EGFR ligands and DNA repair genes: genomic predictors of complete response after capecitabine-based chemoradiotherapy in locally advanced rectal cancer. Pharmacogenomics J, 2015; 15: 77–83
26. Jiang Y, Ajani JA: Multidisciplinary management of gastric cancer. Curr Opin Gastroenterol, 2010; 26: 640–46
27. Matsuda S, Takahashi T, Fukada J et al: Phase I study of neoadjuvant chemoradiotherapy with S-1 plus biweekly cisplatin for advanced gastric cancer patients with lymph node metastasis: -KOGC04. Radiat Oncol, 2014; 9: 9
28. Jang R, Darling G, Wong RK: Multimodality approaches for the curative treatment of esophageal cancer. J Natl Compr Canc Netw, 2015; 13: 229–38

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