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The prognostic value of excision repair cross-complementation group one enzyme expression in locally advanced cervical carcinoma patients treated with cisplatin–based treatment: a meta–analysis

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HIGHLIGHTS

- Cisplatin + radiotherapy is the standard regimen for treatment of locally advanced cervical carcinoma.
- No optimal biomarkers could be used to predict prognosis before treatment.
- Excision repair cross-complementation group one enzyme could serve as the promising biomarker for locally advanced cervical carcinoma patients.

ABSTRACT

Background Recently, several studies observed that locally advanced cervical carcinoma with negative excision repair crross-complementation group one enzyme expression has better outcomes in cisplatin-based chemotherapy or chemoradiotherapy than carcinoma with positive excission repair cross-complementation group one enzyme expression. In this meta-analysis, we quantitatively evaluated the prognostic value of excission repair cross-complementation group one enzyme expression in locally advanced cervical carcinoma patients receiving platinum-based chemotherapy or chemoradiotherapy.

Materials A systematic search for relevant studies was conducted in the PubMed, Cochrane Library, EMBASE and Medline databases. Fixed- or random-effects models were used for pooled analysis. The endpoints were overall survival and disease-free survival () reported as ORs and 95% CIs. The effects of excission repair cross-complementation group one enzyme expression on the clinicopathological parameters were measured by the pooled ORs and their 95% CIs.

Results Eight studies (612 patients in total) satisfied the inclusion criteria. Negative/low excission repair cross-complementation group one enzyme expression was significantly associated with better overall survival (OR, 1.92; 95% CI, 1.22 to 3.05; P = 0.005) and disease-free survival (OR, 5.77; 95% CI, 1.90 to 17.54; P = 0.002). Additionally, there were significant associations between excission repair cross-complementation group one enzyme expression and lymph node metastasis (OR, 2.57; 95% CI, 1.28 to 5.16; P = 0.008).

Conclusions This meta-analysis suggested that pretreatment excission repair cross-complementation group one enzyme expression might be a useful biomarker to predict prognoses for locally advanced cervical carcinoma patients receiving platinum-based chemotherapy or chemoradiotherapy.

INTRODUCTION

Cervical cancer is the fourth most commonly diagnosed cancer and the fourth leading cause of cancer deaths among women worldwide. The current standard treatment of locally advanced cervical cancer is cisplatin-based concurrent chemoradiotherapy followed by brachytherapy.[1] Despite the improvements in cancer therapies, the worldwide survival and prognosis of this malignancy are still very poor. Additionally, quite different efficacy exists among individual patients. It is critical to determine promising biomarkers to predict prognosis before treatment.

Excission repair cross-complementation group one enzyme, a protein that plays a role in several DNA repair pathways, was confirmed to have association with resistance to cisplatin-based chemotherapy or chemoradiotherapy, both in in vitro studies and in clinical studies, in various types of cancer, including lung cancer, gastric cancer, oesophageal cancer, bladder cancer, and epithelial ovarian cancer.[2–9] In in vitro studies, Britten et al showed that pretreatment excission repair cross-complementation group one enzyme mRNA levels had a significant relationship with cisplatin resistance in cervical cancer cell lines.[10] The clinical study of Ryu et al demonstrated that pretreatment excission repair cross-complementation group one enzyme expression status appears to have a prognostic impact on locally advanced cervical carcinoma and could be used to predict the tumour response and survival of patients receiving platinum-based chemotherapy.[11] In addition, Doll et al drew a similar conclusion.[12] Furthermore, Doll also recommended excission repair cross-complementation group one enzyme

FL297 as the appropriate reagent for excision repair cross-complementation group one enzyme detection.[12] However, Muallem et al did not observe a correlation between high levels of excision repair cross-complementation group one enzyme expression and favorable outcomes in patients with locally advanced cervical carcinoma treated with cisplatin-based chemoradiotherapy.[13] No definitive conclusions were drawn from these studies. Therefore, seven retrospective studies and one randomized trial were included in our meta-analysis to explore the relationships between excision repair cross-complementation group one enzyme expression status and patients with locally advanced cervical carcinoma treated with cisplatin-based treatment.

METHODS

Search strategy

The databases of PubMed, Cochrane Library, EMBASE, and Medline were searched by using the following key words: (Cisplatin or Platinum or cis-Platinum or Platinol or Platidiam or CDDP), (Uterine Cervical Neoplasms or Cervical Neoplasms or Cervix Neoplasms or Uterine Cervix Cancers or Cervix Cancers or Cervical Cancers), (Excision Repair Cross-Complementation group one or excision repair cross-complementation group one enzyme), and (chemoradiotherapy or chemoradiation or radiochemotherapy or chemotherapy or radiotherapy or radiation or electromagnetic radiation). Only those studies published from 1990 to 31 May 2018 in English were considered. The references of the included studies and related citations were also checked manually for potentially relevant studies. Two independent investigators evaluated each study. A consensus was reached by discussion, or else a third investigator resolved the disagreements between the two reviewers.

Inclusion and exclusion criteria

Studies were included in the analysis if: they were randomized controlled trials or retrospective studies that compared the prognosis of negative/low expression of excision repair cross-complementation group one enzyme vs positive/high excision repair cross-complementation group one enzyme in the treatment of locally advanced cervical carcinoma; there was no evidence of distant metastasis in pretreatment imaging (stage I to IVA); or the long-term overall survival and disease-free survival were assessed as outcomes to measure the effect of the treatment. If studies were duplicates, the study with the most up-to-date results was included. Studies were excluded if patients had previous histories of chemotherapy or radiotherapy or other factors seriously affecting the survival and treatment processes.

We used the revised Jadad scale to evaluate the quality of the randomized controlled trials included in the primary outcome analysis. High-quality articles scored 4–7 points. The Newcastle-Ottawa Quality Assessment Scale was used to assess observational studies. On the basis of the Newcastle-Ottawa Quality Assessment Scale criteria, the studies were scored between 0 and 9 stars. Studies with six stars or greater were considered of sufficiently high quality.[14]

Statistical analysis

Overall survival and disease-free survival were the primary endpoints, and the effects of excision repair cross-complementation group one enzyme expression on the clinicopathological parameters were secondary endpoints. RevMan 5.1 software (Cochrane Collaboration's Information Management System) was used to conduct this meta-analysis. Variables among studies with minimal heterogeneity were assessed by the fixed effect model/Mantel-Haenszel method. Otherwise, the random-effects model/DerSimonian-Laird method was used when calculating the ORs and CIs of the specific events. Funnel plots and Harbord tests were used to examine potential publication bias in the meta-analysis.

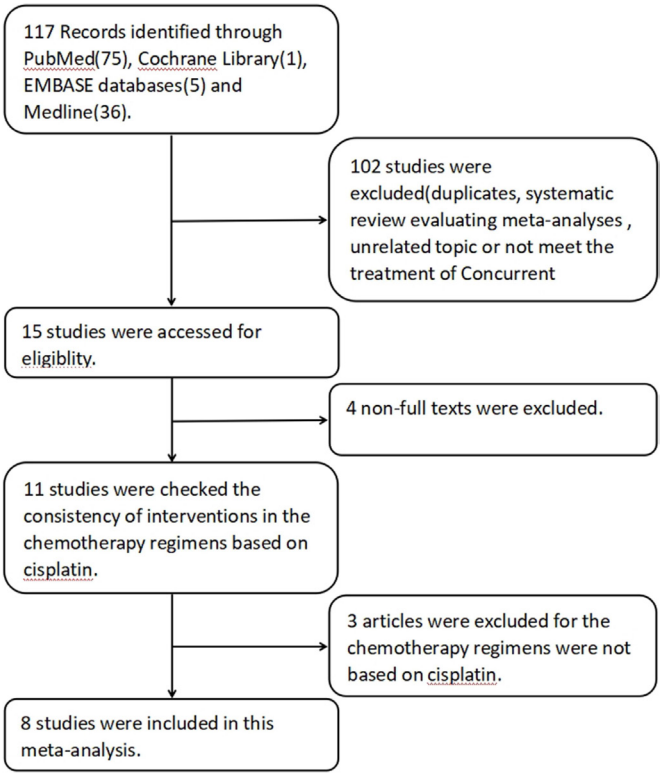

Figure 1 Flow chart depicting the selection of eligible studies.

RESULTS

Study selection and characteristics

The search initially yielded a total of 117 citations. A total of eight trials[11–13 15–19] were included in this review after exclusion of studies that did not meet the inclusion criteria or were duplicate publications, review articles, or meta-analyses. The study selection criteria for this meta-analysis are illustrated in Figure 1.

Among the eight publications considered in this analysis, there were seven retrospective case series and one prospective randomized trial. The eight studies, with a combined sample size of 612 patients, were conducted in Japan, Korea, Argentina, Germany, Canada, and China and were published between 2011 and 2017. All the patients recruited in these studies were newly diagnosed with locally advanced cervical carcinoma and received primary radical treatment. Among the 612 patients, 298 patients expressed negative/low excision repair cross-complementation group one enzyme, while 314 patients expressed positive/high excision repair cross-complementation group one enzyme. For the retrospective studies, the Newcastle-Ottawa Quality Assessment Scale

grades were 6–7 stars (out of a maximum possible score of 9 stars). For all eight studies, the overall quality according to the Jadad scale was 3 out of 5. Table 1 shows the detailed analysis of the studies.

Primary endpoints: 3-year overall survival and 3-year disease-free survival

In the meta-analysis of 3-year overall survival (n=4 studies), no significant heterogeneity was observed among the trials. Therefore, the fixed-effects model was chosen for pooled analysis. The Harbord test showed a lack of significant heterogeneity among the trials (P>0.05). The analysis revealed that better OS was observed in the treatment of patients with negative/low excision repair cross-complementation group one enzyme expression (OR, 1.92; 95% CI, 1.22 to 3.05; P=0.005; Figure 2).

In the meta-analysis of 3 year disease-free survival (n=3 studies), no significant heterogeneity was observed among the trials. Therefore, the fixed-effects model was chosen for pooled analysis. The Harbord test showed a lack of significant heterogeneity among the trials (P>0.05). Patients with negative/low excision repair cross-complementation group one enzyme expression had better DFS (OR, 5.77; 95% CI, 1.90 to 17.54; P=0.002; Figure 3).

Secondary endpoints: clinicopathological parameters

In the meta-analysis of clinicopathological parameters, including age, tumour size, International Federation of Gynaecology and Obstetrics stage, histological grade, lymph node metastases, hemoglobin, and parametrial invasion, no significant heterogeneity was observed. Therefore, the fixed-effects model was chosen for pooled analysis. The Harbord test showed a lack of significant heterogeneity among the trials (P>0.05). Lymph node metastases have a statistical correlation with excision repair cross-complementation group one enzyme expression state (OR, 2.57; 95% CI, 1.28 to 5.16; P=0.008; Table 2). No statistical significance was observed for age (OR, 0.73; 95% CI, 0.40 to 1.33; P=0.31; Table 2), tumor size (OR, 1.76; 95% CI, 0.90 to 3.41; P=0.10; Table 2), International Federation of Gynaecology and Obstetrics stage (OR, 1.96; 95% CI, 0.85 to 4.53; P=0.11; Table 2), histological grade (OR, 1.95; 95% CI, 0.82 to 4.64; P=0.13; Table 2), hemoglobin (OR, 0.90; 95% CI, 0.43 to 1.91; P=0.79; Table 2), or parametrial invasion (OR, 1.46; 95% CI, 0.69 to 3.10; P=0.33; Table 2).

Risk of bias

The Harbord tests for all the indices did not show any evidence of publication bias (all P>0.05). (Details can be seen in the supplemental materials for the Harbord tests.)

DISCUSSION

Radiotherapy concurrent with cisplatin is the standard regimen used for treatment of locally advanced cervical carcinoma according to the National Comprehensive Cancer Network guidelines based on the results of five randomized trials.[20–24] However, not all locally advanced cervical carcinoma patients derive clinical benefit from such a treatment. It is critical to identify a novel predictive and prognostic marker to help guide clinical therapy for patients with locally advanced cervical carcinoma. In the past years, many molecular markers have been investigated. However, no biomarker has been routinely used in clinical practice because of their limited accuracy or the lack of an adequate validation method. Recently, several studies have suggested that excision repair cross-complementation group one is associated with resistance to platinum agent-based chemotherapy or chemoradiotherapy in locally advanced cervical carcinoma. Nevertheless, no consistent results have been reported. Therefore, we conducted a meta-analysis of the evidence obtained from all published studies in order to provide a quantitative reassessment of the association. This study involves a meta-analysis of published data regarding excision repair cross-complementation group one enzyme expression and its association with the progression and prognosis in locally advanced cervical carcinoma. We observed a positive relationship between excision repair cross-complementation group one enzyme overexpression and worse overall survival and disease-free survival. Furthermore, we also observed a significant association between high excision repair cross-complementation group one enzyme expression and lymph node metastasis.

Excision repair cross-complementation group one enzyme protein has a close relationship with cisplatin resistance. Deoxyribonucleic acid repair plays a critical role in the development of cisplatin resistance.[25] Platinum salts inhibit deoxyribonucleic acid replication by creating platinum-deoxyribonucleic acid adducts that covalently cross-link deoxyribonucleic acid strands.[26] Nucleotide excision repair plays a central role in adduct removal. Therefore, excision repair cross-complementation group one enzyme, the rate-limiting enzyme in the nucleotide excision repair pathway, serves as a key mediator of cisplatin resistance.[27–29] Britten et al[10] found that the excision repair cross-complementation group one enzyme-encoding mRNA level predicted cisplatin resistance in human cervical cancer cell lines. Hasegawa et al[15] first analyzed the relationship between excision repair cross-complementation group one enzyme expression and prognosis in patients with uterine cervical adenocarcinoma treated with cisplatin-based chemotherapy or chemoradiotherapy with cisplatin, and they found that high excision repair cross-complementation group one enzyme protein expression was associated with poorer prognosis.

In addition, a number of clinical studies have been carried out to investigate the correlation between excision repair cross-complementation group one enzyme expression and the prognosis of locally advanced cervical carcinoma patients. However, the results of these numerous studies do not agree. Liang et al[16] assessed excision repair cross-complementation group one enzyme expression in 50 patients with cervical squamous cell carcinomas who received cisplatin-based concurrent chemoradiotherapy by an immunohistochemistry method. They found that excision repair cross-complementation group one enzyme-negative patients had a significantly higher complete response rate and better overall survival rates than excision repair cross-complementation group one enzyme-positive patients. The multicenter study conducted by Doll et al[12] showed similar results. However, in their previous study in 2010, where all patients with locally advanced cervical carcinoma received radiation alone, they arrived at the opposite conclusion: that patients whose tumors had low excision repair cross-complementation group one enzyme protein expression suffered from poorer prognosis.[30] These two contradictory conclusions might suggest that excision repair cross-complementation group one enzyme expression was not directly related to the repair of the radiation-induced deoxyribonucleic acid damage by the excision

Table 1 Characteristics of the included trials

Author/ Year	Type of study (years)	Country	Jadad or NOS score	NO. pts	Histological type	Median age (years)	Stage (FIGO)	ECCR1 assay	Cut-off for high expression	Positive(high) /negative(low) (NO.)	Treatment (predominant)	Median follow-up (months)	Out comes
Hasegawa/2011[15]	Retro (2000–2007)	Japan	*******	25	AC:25	46 (30–67)	Ib–IIb	IHC	nuclear staining scores 4–6 【6.1-5】	5/20	S±CCT/CCT&RT	NR	DFS, CP
Liang/2011[16]	Retro (NR)	Korea	*******	50	SCC:50	54 (40–73)	II–III	IHC	H-score>1.5 (IRS)	16/34	CCCRT	56.3 (8.1-103.5)	DSS, OS, CP, treatment response
Park/2011[17]	Retro (1999–2006)	Korea	******	43	SCC:36 Others:7	50 (36–78)	IIb	IHC	H-score>1.0 (IRS)	34/9	NACCT+S	45.0 (6.0–139.0)	DFS, CP, treatment response
Bai/2012[18]	Retro (2009–2010)	China	******	60	SCC:60	53 (36–80)	II-III	RT-PCR	0.0347 excission repair cross-complementation group one enzyme	29/31	CCCRT	NR	CP, treatment response
Doll/2013[12]	Retro/pro(1999–2004)	Canada	*******	264	NR	49 (NR)	I–IV	IHC	excission repair cross-complementation group one enzyme n/c ratio 1.43	132/132	CCCRT	54.0(3.8–110.4)	PFS, OS, CP
Muallem/2014[13]	Retro (2006–2012)	Germany	*******	112	SCC:100 AC:12	44 (26–82)	Ib–IVa	IHC	H-score>1.5 (IRS)	72/40	CCCRT±S	NR	PFS, OS
Zwenger/2015[19]	Pro (1993–2007)	Argentina	5	26	SCC:26	43.5 (24–74)	IIb–IVa	IHC	H-score>0.5 (IRS)	13/13	CCCRT	24.0 (1.2–220.8)	DFS, OS, CP, treatment response
Ryu/2017[11]	Retro (2004–2011)	Korea	*******	32	SCC:24AC:3 Others:5	51(34–67)	NR	IHC	H-score>1.5 (IRS)	13/19	CCT	NR	PFS, OS, CP, treatment response

AC, adenocarcinoma; CCCRT, cisplatin based concurrent chemoradiotherapy; CCT, cisplatin based chemotherapy; CP, clinicopathological parameters; DFS, disease free survival; IHC, immunohistochemistry; IRS, immunoreactive score; NACCT, neoadjuvant cisplatin based chemotherapy; NOS, Nottingham Ottawa Scale; NR, no report; OS, overall survival; PFS, progress free survival; RCT, randomised controlled trial; RT, radiotherapy; Retro, retrospective comparative study; S, surgery; SCC, squamous cell carcinoma; pts, patients.

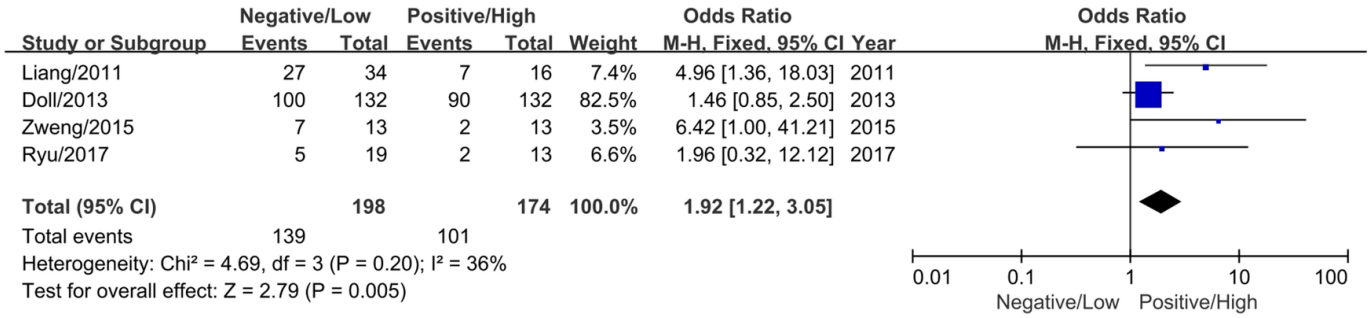

Figure 2 Forest plot of the association between high excision repair cross-complementation group one enzyme expression and 3-year overall survival.

repair cross-complementation group one enzyme-dependent deoxyribonucleic acid repair pathway but rather might reflect the deoxyribonucleic acid repair capacity in aggressive tumors. In 2014, Muallen et al[13] analyzed excision repair cross-complementation group one enzyme expression in 112 patients with locally advanced cervical carcinoma with an immunohistochemistry method. Among the 112 patients who received cisplatin-based chemoradiotherapy, those with high excision repair cross-complementation group one enzyme expression experienced significantly better 2-year overall survival and progression-free survival than those with low excision repair cross-complementation group one enzyme expression. Therefore, we conducted this meta-analysis to obtain a more refined evaluation after pooling the available evidence. Our results were consistent with the conclusion that negative/low excision repair cross-complementation group one enzyme expression was significantly associated with better prognosis. These results suggest that excision repair cross-complementation group one enzyme expression level may assist in selecting the patients most likely to benefit from platinum agent-based chemotherapy or chemoradiotherapy.

Additionally, the relationship between excision repair cross-complementation group one enzyme expression and clinicopathological parameters was analyzed. We found that only lymph node metastases have a statistical correlation with excision repair cross-complementation group one enzyme expression state. We assumed that excision repair cross-complementation group one enzyme status could represent the cell's intrinsic deoxyribonucleic acid repair ability and might reflect the extent of accumulated intratumoral deoxyribonucleic acid damage that may contribute to tumor progress or metastasis.[31] The pooled data also suggested a clear trend toward higher excision repair cross-complementation group one enzyme expression with poor differentiation and high International Federation of Gynaecology and Obstetrics stage, although the results of the statistical analyzes did not reach the significant level. Taken together, the pooled results in our meta-analysis support the hypothesis that excision repair cross-complementation group one enzyme overexpression might promote locally advanced cervical carcinoma metastasis and thus lead to a poor locally advanced cervical carcinoma prognosis.

Our study does have some limitations. First, the studies included in the meta-analysis were mainly retrospective analyses. It is possible that other unknown confounders could bias the data. The association between excision repair cross-complementation group one enzyme expression and worse survival should be analyzed through larger multicenter prospective studies using standardized, unbiased laboratory methods and well-matched patients and controls. Second, the cut-off values for high or low excision repair cross-complementation group one enzyme expression were different in the studies. The different cut-off values between studies may affect the results and account for the inconsistencies. However, it was difficult to provide an exact definition for 'high' or 'low' expression in view of the different excision repair cross-complementation group one enzyme detection methods used. Therefore, future studies on this topic should use a consistent definition for 'high' or 'low' expression and use the same excision repair cross-complementation group one enzyme detection method. What is more, the technology used to distinguish the level of excision repair cross-complementation group one enzyme expression differed. Reverse transcription polymerase chain reaction assays were used to distinguish the level of excision repair cross-complementation group one enzyme expression in the study of Bai et al[18],

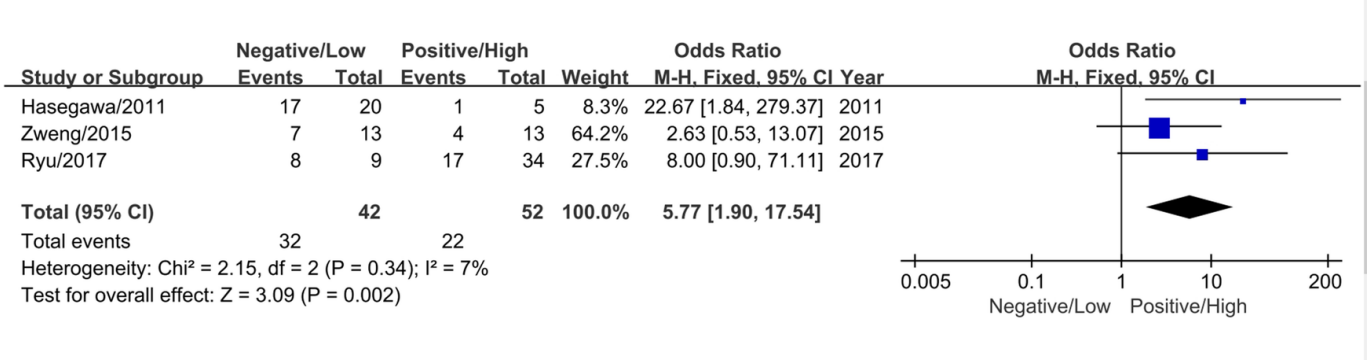

Figure 3 Forest plot of the association between high excision repair cross-complementation group one enzyme expression and 3-year disease free survival.

Table 2 Clinicopathological parameters meta-analysis results

Analysis	No. of studies	No. of patients	HR (95% CI)	P value	Model	Heterogeneity (I^2 %/P)	Harbord test (P)
Age (≤55Y vs. >55Y)	5	343	0.73(0.40 to 1.33)	0.31	F	0.0/0.97	0.39
Tumor size (≤4cm vs. >4cm)	4	290	1.76(0.90 to 3.41)	0.10	F	0.0/0.94	0.45
FIGO stage (I+II vs. III+IV)	3	240	1.96(0.85 to 4.53)	0.11	F	0.0/0.62	0.32
Histological grade (G1+G2 vs. G3)	3	208	1.95(0.82 to 4.64)	0.13	F	0.0/0.65	0.79
Lymph node metastases (N0 vs. N1+N2)	4	291	2.57(1.28 to 5.16)	0.00	F	0.0/0.84	0.39
Hemoglobin (≤11.5g/dL vs. >11.5g/dL)	3	226	0.90(0.43 to 1.91)	0.79	F	0.0/0.50	0.96
Parametrial invasion (yes vs. no)	3	226	1.46(0.69 to 3.10)	0.33	F	0.56/0.10	0.52

F:fixed-effect model; FIGO:International Federation of Gynaecology and Obstetrics; No:number.

while excision repair cross-complementation group one enzyme expression was analyzed by immunohistochemistry in the other seven trails. Finally, subgroup analyses could not be performed due to the diversity of methods used to assess treatment outcomes. Many favorable characteristics and endpoints could not be chosen for analysis. Given the limitations listed above, our results should be interpreted with caution.

To our knowledge, this is the first systematic review that evaluates the association between excision repair cross-complementation group one enzyme expression and locally advanced cervical carcinoma prognosis. We found that negative/low excision repair cross-complementation group one enzyme expression seems to significantly correlate with better prognosis. Pretreatment excision repair cross-complementation group one enzyme expression status might be used to predict prognoses for locally advanced cervical carcinoma patients receiving platinum-based chemotherapy or chemoradiotherapy.

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