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 cross-complementation group one enzyme expression has better outcomes in cisplatin-based chemotherapy or chemoradiotherapy than carcinoma with positive excision repair cross-complementation group one enzyme expression. In this meta-analysis, we quantitatively evaluated the prognostic value of excision 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 excision 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 excision 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 excision 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 excision 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. 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.

Excision 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. In in vitro studies, Britten et al showed that pretreatment excision repair cross-complementation group one enzyme mRNA levels had a significant relationship with cisplatin resistance in cervical cancer cell lines. The clinical study of Ryu et al demonstrated that pretreatment excision 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. In addition, Doll et al drew a similar conclusion. Furthermore, Doll also recommended excision repair cross-complementation group one enzyme
FL297 as the appropriate reagent for excision repair cross-complementation group one enzyme detection. 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. 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.

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.

RESULTS

Study selection and characteristics
The search initially yielded a total of 117 citations. A total of eight trials 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, tumor size, International Federation of Gynaecology and Obstetrics stage, histological grade, lymph node metastases, hemo-globin, 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 al19 found that the excision repair cross-complementation group one enzyme-encoding mRNA level predicted cisplatin resistance in human cervical cancer cell lines. Hasegawa et al16 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 al16 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 al12 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 expression suffered from poorer prognosis.20 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
| Author/Year | Type of study (years) | Country | Jadad or NOS score | NO. pts | Histological type | Stage (FIGO) | ECCR1 assay | Cut-off for high expression | Positive(high)/negative(low) (NO.) | Treatment (predominant) | Median follow-up (months) | Out comes |
|-------------|-----------------------|---------|-------------------|---------|-------------------|--------------|-------------|--------------------------------|-------------------------------|------------------------|-------------------------|-----------|
| Hasegawa/2011 | Retro (2000–2007)    | Japan   | *****             | 25      | AC:25             | 46 (30–67)   | II–III      | IHC nuclear staining scores 4–6 [6.1-5] | 5/20                        | S±CCT/CCT&RT                      | NR                     | DFS, CP   |
| Liang/2011   | Retro (NR)            | Korea   | *****             | 50      | SCC:50            | 54 (40–73)   | II–III      | H-score>1.5 (IRS) | 16/34                       | CCCRT                  | 56.3 (8.1–103.5)             | DSS, OS, CP, treatment response |
| Park/2011    | 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)             | DSS, CP, treatment response |
| Bai/2012     | Retro (2009–2010)     | China   | *****             | 60      | SCC:60            | 53 (36–80)   | II–III      | RT-PCR 0.0347 excision repair cross-complementation group one enzyme | 29/31                       | CCCRT                  | NR                     | CP, treatment response |
| Doll/2013    | Retro/pro(1999–2004)  | Canada  | *****             | 264     | NR                | 49 (NR)      | I–IV        | IHC excision 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 | Retro (2006–2012)     | Germany | *****             | 112     | SCC:100 AC:12     | 44 (26–82)   | II–III      | IHC H-score>1.5 (IRS) | 72/40                       | CCCRT±S                | NR                     | PFS, OS   |
| Zwenger/2015 | Pro (1993–2007)       | Argentina | 5     | 26      | SCC:26            | 43.5 (24–74) | IIb–Na      | IHC H-score>0.5 (IRS) | 13/13                       | CCCRT                  | 24.0 (12.2–220.8)            | DSS, OS, CP, treatment response |
| Ryu/2017     | 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.
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{18},

### Table 1: Forest plot of the association between high excision repair cross-complementation group one enzyme expression and 3-year overall survival.

| Study or Subgroup | Negative/Low | Positive/High | Odds Ratio | M-H, Fixed, 95% CI | Year |
|-------------------|--------------|---------------|------------|-------------------|------|
| Liang\textsuperscript{2011} | 27 | 34 | 7 | 16 | 7.4% | 4.96 [1.36, 18.03] | 2011 |
| Doll\textsuperscript{2013} | 100 | 132 | 90 | 132 | 82.5% | 1.46 [0.85, 2.50] | 2013 |
| Zweng\textsuperscript{2015} | 7 | 13 | 2 | 13 | 3.5% | 6.42 [1.00, 41.21] | 2015 |
| Ryu\textsuperscript{2017} | 5 | 19 | 2 | 13 | 6.6% | 1.96 [0.32, 12.12] | 2017 |
| Total (95% CI) | 198 | 174 | 101 | 101 | 100.0% | 1.92 [1.22, 3.05] |

### Table 2: Forest plot of the association between high excision repair cross-complementation group one enzyme expression and 3-year disease free survival.

| Study or Subgroup | Negative/Low | Positive/High | Odds Ratio | M-H, Fixed, 95% CI | Year |
|-------------------|--------------|---------------|------------|-------------------|------|
| Hasegawa\textsuperscript{2011} | 17 | 20 | 1 | 5 | 8.3% | 22.67 [1.84, 279.37] | 2011 |
| Zweng\textsuperscript{2015} | 7 | 13 | 4 | 13 | 64.2% | 2.63 [0.53, 13.07] | 2015 |
| Ryu\textsuperscript{2017} | 8 | 9 | 17 | 34 | 27.5% | 8.00 [0.90, 71.11] | 2017 |
| Total (95% CI) | 42 | 52 | 22 | 22 | 100.0% | 5.77 [1.90, 17.54] |

### Notes:
- The forest plots and tables are used to illustrate the association between high excision repair cross-complementation group one enzyme expression and outcomes like overall survival and disease-free survival.
- The odds ratios and confidence intervals are provided to assess the magnitude and significance of the association.

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

**Figure 3** Forest plot of the association between high excision repair cross-complementation group one enzyme expression and 3-year disease free survival.
while excision repair cross-complementation group one enzyme expression was analyzed by immunohistochemistry in the other seven trials. 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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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30.
2. Lord RV, Brabender J, Gandara D, et al. Low ERCC1 expression correlates with prolonged survival after cisplatin plus gemcitabine chemotherapy in non-small cell lung cancer. Clin Cancer Res 2002;8:2286–91.
3. Azuma K, Komohara Y, Sasada T, et al. Excision repair cross-complementation group 1 predicts progression-free and overall survival in non-small cell lung cancer patients treated with platinum-based chemotherapy. Cancer Sci 2007;98:1336–43.
4. Olaussen KA, Dunant A, Forget P, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med 2006;355:983–91.
5. Metzger R, Leichman CG, Danenberg KD, et al. ERCC1 mRNA levels complement thymidylate synthase mRNA levels in predicting response and survival for gastric cancer patients receiving combination cisplatin and fluorouracil chemotherapy. J Clin Oncol 1998;16:309–16.
6. Kim MK, Cho KJ, Kwon GY, et al. ERCC1 predicting chemoradiation resistance and poor outcome in oesophageal cancer. Eur J Surg Oncol 2008;44:54–60.
7. Bellmunt J, Paz-Ares L, Cuello M, et al. Gene expression of ERCC1 as a novel prognostic marker in advanced bladder cancer patients receiving cisplatin-based chemotherapy. Ann Oncol 2007;18:522–8.
8. Steffenensen KD, Waldstrøm M, Jakobsen A. The relationship of platinum resistance and ERCC1 protein expression in epithelial ovarian cancer. Int J Gynecol Cancer 2009;19:820–5.
9. Schell-Bertram S, Tylus-Schaaf P, du Bois A, et al. Excision repair cross-complementation group 1 protein overexpression as a predictor of poor survival for high-grade serous ovarian adenocarcinoma. Gynecol Oncol 2010;119:325–31.
10. Britten RA, Liu D, Tessier A, et al. ERCC1 expression as a molecular marker of cisplatin resistance in human cervical tumor cells. Int J Cancer 2000;89:453–7.
11. Ryu H, Song IC, Choi YS, et al. ERCC1 expression status predicts the response and survival of patients with metastatic or recurrent cervical cancer treated via platinum-based chemotherapy. Medicine 2017;96:e9402.
12. Dill CM, Aquino-Parsons C, Pintilie M, et al. The significance of tumoral ERCC1 status in patients with locally advanced cervical cancer treated with chemoradiation therapy: a multicenter clinicopathologic analysis. Int J Radiat Oncol Biol Phys 2013;85:721–7.
13. Muellem MZ, Maritz S, Richter R, et al. ERCC1 expression as a predictive marker of cervical cancer treated with cisplatin-based chemoradiation. Anticancer Res 2014;34:401–6.
14. Wells GA, Shea BJ, O’Connell D. The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis[J]. Appl Environ Agric 2014;18:727–34.
15. Hasegawa K, Kato R, Tori Y, et al. The relationship between ERCC1 expression and clinical outcome in patients with FIGO stage I to stage II uterine cervical adenocarcinoma. Int J Gynecol Cancer 2011;21:1479–85.
16. Liang ZL, Song EK, Ko YB, et al. Excision repair cross-complementation group 1 expression predicts response and survival in locally advanced cervical carcinoma patients treated with concurrent chemoradiotherapy. Histopathology 2011;59:564–7.
17. Park JS, Jeon EK, Chun SH, et al. ERCC1 (excision repair cross-complementation group 1) expression as a predictor for response of neoadjuvant chemotherapy for FIGO stage 2B uterine cervix cancer. *Gynecol Oncol* 2011;120:275–9.

18. Bai ZL, Wang YY, Zhe H, et al. ERCC1 mRNA levels can predict the response to cisplatin-based concurrent chemoradiotherapy of locally advanced cervical squamous cell carcinoma. *Radiat Oncol* 2012;7:221–221.

19. Zwenger AO, Grosman G, Iturbe J, et al. Expression of ERCC1 and TUBB3 in locally advanced cervical squamous cell cancer and its correlation with different therapeutic regimens. *Int J Biol Markers* 2015;30:301–14.

20. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med* 1999;340:1154–61.

21. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med* 1999;340:1137–43.

22. Peters WA, Liu PY, Barrett RJ, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol* 2000;18:1606–13.

23. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999;340:1144–53.

24. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a gynecologic oncology group and southwest oncology group study. *J Clin Oncol* 1999;17:1339–48.

25. Reed E. Platinum-DNA adduct, nucleotide excision repair and platinum based anti-cancer chemotherapy. *Cancer Treat Rev* 1998;24:331–44.

26. Kelland L. The resurgence of platinum-based cancer chemotherapy. *Nat Rev Cancer* 2007;7:573–84.

27. Zamble DB, Mu D, Reardon JT, et al. Repair of cisplatin--DNA adducts by the mammalian excision nuclease. *Biochemistry* 1996;35:10004–13.

28. Sancar A. Mechanisms of DNA excision repair. *Science* 1994;266:1954–6.

29. Mu D, Hsu DS, Sancar A. Reaction mechanism of human DNA repair excision nuclease. *J Biol Chem* 1996;271:8285–94.

30. Doll CM, Prystajecky M, Eliaziw M, et al. Low ERCC1 mRNA and protein expression are associated with worse survival in cervical cancer patients treated with radiation alone. *Radiother Oncol* 2010;97:352–9.

31. Simon GR, Ismail-Khan R, Bepler G. Nuclear excision repair-based personalized therapy for non-small cell lung cancer: from hypothesis to reality. *Int J Biochem Cell Biol* 2007;39–1318–28.