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# What is the impact of perineural invasion on the prognosis of cervical cancer: a systematic review and meta-analysis

Guangyao Cai[1,2†], Siru Zhang[1,2†], Shangbin Gao[1,2], Ting Deng[1,2], He Huang[1,2], Yanling Feng[1,2] and Ting Wan[1,2*]

## Abstract

**Background** Perineural Invasion (PNI) is a marker of a highly invasive tumor with poor prognosis, but the real influence on the prognosis of cervical cancer is still debated. We aimed to systematically investigate the prognostic impact of PNI in cervical cancer.

**Methods** We searched PubMed, Embase, Cochrane databases, and ClinicalTrials.gov from inception to 20 April 2024. Cohort, case–control, and randomized controlled studies reporting the PNI status and survival outcomes of women with cervical cancer were included. Two reviewers extracted data independently and appraised study quality following the PRISMA guideline. The quality of the studies was assessed with Newcastle–Ottawa Scale. Random effect model was used if the heterogeneity was significant ($P \le 0.1$, $I^2 \ge 50\%$).

**Results** We included seven retrospective cohort studies (1561 women) in the analysis. PNI was remarkably associated with a worse survival (risk ratio [95% CI]: 2.79 [1.67- 4.66], $I^2 = 78\%$ for 5-year overall survival (OS); 2.16 [1.30–3.59], $I^2 = 84\%$ for 5-year disease-free survival (DFS)). After multivariate cox regression adjustment, the hazard ratio [95% CI] of PNI was 3.25 [1.09, 9.74] ($I^2 = 85\%$) for OS, and 2.50 [0.66, 9.46] ($I^2 = 89\%$) for DFS. PNI showed positive correlation with higher stage, larger tumor size, lymph node metastasis, deep stromal invasion, lymphovascular invasion, resection margin involvement, and parametrial invasion ($P < 0.05$). Besides, PNI was associated with higher possibility of adjuvant therapy (risk difference [95% CI]: 0.28 [0.04–0.52], $I^2 = 92\%$), especially for chemoradiation (0.25 [-0.02–0.53], $I^2 = 76\%$). Subgroup analysis showed patients with PNI had poorer prognosis than those without PNI in patients with LNM or large tumor size ($P < 0.05$).

**Conclusions** PNI demonstrated a significant association with reduced overall survival in cervical cancer patients and emerged as a potential independent prognostic indicator, which provided a foundation for future investigations to evaluate the clinical utility of PNI status in guiding therapeutic strategies.

**Trail registration** The protocol for this study was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) under identifying number CRD42022315970.

**Keywords** Cervical cancer, Perineural invasion, Prognosis, Overall survival, Disease-free survival, Nerve-sparing radical hysterectomy, Surgery, Adjuvant therapy, Metastasis

†Guangyao Cai and Siru Zhang contributed equally to this work.

*Correspondence:
Ting Wan
wanting@sysucc.org.cn
Full list of author information is available at the end of the article

## Background

Cervical cancer is the fourth most common cause of cancer incidence and mortality in women, with approximately 570,000 new cases and 311,000 deaths per year worldwide [1]. Clinical stage and pathologic variables are the main determinants of prognosis and served as the basis of treatment strategy for cervical cancer. The clinical practice guidelines of the National Comprehensive Cancer Network (NCCN) of cervical cancer suggested that lymph node metastasis (LNM), parametrial involvement, and positive margins of resection are high-risk factors of recurrence and indications of adjuvant chemoradiotherapy; tumor size, deep stromal invasion, and lymphovascular invasion (LVSI) are intermediate-risk factors and guide the adjuvant radiotherapy according to Sedlis criteria [2]. Because of a relatively better prognosis, patients without those risk factors don't routinely receive adjuvant therapy. With the development of pathology, more pathological factors have been explored for a more accurate prognosis risk evaluation and treatment decision. Perineural invasion (PNI) is one of them.

PNI is a pathological process where the tumor invades nerves and spread among nerve sheaths in the primary site [3]. PNI is common in cervical cancer, with a reported incidence of 7–35% in patients who underwent radical hysterectomy [4–10]. It has been increasingly confirmed that PNI is a marker of a highly invasive tumor with poor prognosis in cancers such as head and neck cancer, prostate cancer, and colorectal cancer [11–15]. It could be the potential fourth route of cancer spread [16, 17]. However, the real influence of PNI on the prognosis of cervical cancer is still debated. Some studies reported that no significant correlation between PNI and clinical outcomes [4, 5, 18, 19], some confirmed PNI was a risk factor of disease-free survival (DFS) or overall survival (OS) in univariate analysis but not in multivariate analysis [8, 9, 20–23], whereas others found that PNI was significantly an independent prognostic factor in multivariate survival analysis [6, 24]. Besides, PNI correlates with the high-risk and intermediate-risk prognostic factors of the prognosis of cervical cancer [4–10]. Because of the controversy on the prognostic impact of PNI, it has not been included in the risk factors of the prognosis of cervical cancer, and didn't determine the postoperative treatment of patients with cervical cancer.

Moreover, while nerve-sparing radical hysterectomy (NRSH) remains the standard surgical approach, emerging evidence suggests that the presence of PNI in the primary tumor might correlate with the pelvic nerve spreading which would be reserved in the NRSH [25, 26]. T. Kato et al. reported that the paravaginal recurrence of cervical cancer was associated with PNI and occurred impressively more common on the nerve-sparing side of the NSRH surgery, which suggested potential risk of NSRH in cervical cancer patients with positive PNI [27]. In summary, it is important to explore the effect of PNI on the prognosis of cervical cancer, especially considering the extensive use of pelvic nerve-sparing surgical approaches nowadays.

We aimed to systematically investigate whether PNI was an independent prognostic factor in cervical cancer. In addition, the association between PNI and clinicopathological risk factors or adjuvant therapy were explored.

## Methods

The protocol for this study was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) under identifying number CRD42022315970 and reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA), Meta-analysis Of Observational Studies in Epidemiology (MOOSE) recommendations, and Assessing the Methodologist Quality of Systematic Reviews 2 (AMSTAR 2) checklist [28–30].

### Eligibility criteria

Randomized control trials, cohort studies, or case–control studies were included according to the following criteria: 1) cervical cancers with histological subtypes of squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma; 2) reported on PNI in pathological findings; 3) had definitely available overall survival (OS) or disease-free survival (DFS); 4) had available baseline characteristics; 5) human studies.

We excluded studies if they met one of the following criteria: 1) reviews, conference abstracts, case reports, letters, editorials, and expert consensus which could not offer available data or didn't get peer review; 2) insufficient primary outcomes (5-year OS and DFS) of patients with PNI.

### Data sources and search strategy

We searched PubMed, Embase, the Cochrane Database, and Clinicaltrials.gov from inception to 20 April 2024. The key words included "perineural invasion", "prognosis" AND "cervical cancer" (search strategies in Supplementary eMethods). When available, both controlled vocabulary terms and text words were used. The electronic search was supplemented by manually evaluating the reference lists of the included studies, similar available systematic reviews [31, 32].

### Data extraction

We obtained the following information: authors, publication year, country/ethnicity, study design, follow-up time,

study period, inclusion criteria, exclusion criteria, age, secondary review of pathological slides, surgery strategy, number of patients, clinical and pathological prognostic risk factors (clinical stage, histological type, tumor size, LNM, depth of stromal invasion, surgical margin, LVSI), and survival data. PNI was defined as cancer cells infiltrated any layer of nerve fibers (including the epineurium, perineurium, and endoneurium) or surrounded nerves. If results from both univariate and multivariate models were reported in one study, we extracted the results from the multivariate model.

All studies were independently screened by two specialized gynecological oncology doctors T Wan and G Cai during two stages (titles and abstracts review, and full-text review). Data was also extracted and checked by the two reviewers using a standardized collection form. Conflicts were resolved by fully discussion between the reviewers.

### Outcome assessment

The primary outcomes of interest in this review were risk ratios (RRs) of 5-year overall survival (OS) and 5-year disease-free survival (DFS) for patients with cervical cancer who had PNI compared with those who didn't have PNI. The reason we chose 5-year time interval was that it was eligible in all included studies and also matched the relatively slow progression nature of cervical cancer. The secondary outcomes included the hazard ratios (HRs) of total OS and DFS for patients with cervical cancer who had PNI compared with those who didn't have PNI, the risk difference (RD) of clinicopathological risk factors related to prognosis (clinical stage, histological type, tumor size, LNM, depth of stromal invasion, surgical margin, LVSI) for patients with PNI compared with those without PNI.

### Quality assessment

Since no randomized control trial was included, we used the Newcastle–Ottawa Quality Assessment Scale (NOS, http://www.ohri.ca/home.asp) to assess the included cohort or case–control studies. Only studies with a score $\geq 7$ were included in the final analysis.

### Statistical analysis

All statistical analysis and meta-analysis were conducted using the "meta" package (version 5.2–0) in R (version 4.0.1, R Foundation for Statistical Computing, Vienna, Austria) [33, 34]. Pooled estimates of relative risk (risk ratio (RR) and hazard ratio (HR)) with their respective 95% confidence intervals (CI) were assessed in survival analysis. Pooled estimates for risk factors related to prognosis were reported as risk difference (RD) with the 95% confidence interval (95% CI). Unexplained heterogeneity among studies was assessed using $I^2$ statistic. The random effect model was used if the heterogeneity was significant ($P \leq 0.1$, $I^2 \geq 50\%$). Otherwise, the fixed effect model should be adopted. The Egger regression tests were conducted to evaluate the publication bias. We conducted sensitivity analysis by deleting each study sequentially in order to examine how the removed data affected the overall RR or HR. Two-tailed $P < 0.05$ was considered statistically significant for all outcomes. Subgroup analyses was performed by those risk factors related to prognosis.

## Results

### Study selection

Following systematic search progress of PRISMA, a total of 65 studies were evaluated for eligibility among the 135 manuscripts that were retrieved. Nineteen records were removed for ineligible publication type, twenty-four for insufficient outcome data, six for repetitive data, and nine for NOS score $\leq 6$ (Table 1). Finally, seven studies were included in the meta-analysis (Fig. 1). The PRISMA checklist, MOOSE checklist, and AMSTAR-2 checklist were displayed in the supplementary files (Table S1-S3).

### Study characteristics

The characteristics of the included studies are presented in Table 2. The included studies contained seven retrospective cohort studies. 1561 cervical cancer patients with an International Federation of Gynecology and Obstetrics (FIGO) stage of IA2-IIB were included in the analysis. Six studies had a follow-up time longer than 60 months. The study period of all studies ended before 2018, which avoided the alteration in the FIGO staging system of cervical cancer. The mean age of patients in the seven studies differed from 44 to 50 years old. Five studies had reviewed the pathological slides to confirm the PNI status. All patients included received hysterectomy. The total number of patients ranges from 50 to 406, and the number of patients with PNI ranges from 7 to 162.

### Risk of bias of included studies

Based on Newcastle–Ottawa scale, Table 3 summarizes the quality assessments of the included studies. Most studies performed the multivariate regression analysis to control main confounding factors of prognosis (six studies adjusted stage, LNM, parametrial invasion, LVSI; five adjusted tumor size; four adjusted age, histological subtype, depth of cervical invasion, resection margin involvement; three adjusted adjuvant therapies), confirming the comparability of these studies.

### Synthesis of results

The pooled overall PNI incidence rate was 12.1% (95% CI 8.0%-18.4%, $I^2 = 96\%$) in patients with stage IA-IIB

**Table 1** Quality assessment according to the Newcastle–Ottawa Scale (NOS) for studies excluded at NOS score screening

| Author, publication year | Selection | | | | Comparability | Outcome | | | Total score |
|---|---|---|---|---|---|---|---|---|---|
| | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow up of cohorts | |
| Memarzadeh, 2003 [21] | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 5 |
| Skręt-Magierło, 2014 [18] | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 1 | 4 |
| Tian, 2016 | 1 | 1 | 1 | 0 | 2 | 0 | 0 | 1 | 6 |
| Vural, 2017 [23] | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 5 |
| Long, 2019 [20] | 1 | 1 | 1 | 0 | 2 | 0 | 0 | 0 | 5 |
| Kong, 2019 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 5 |
| Lee, 2022 [24] | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 3 |
| Wei, 2022 [22] | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 5 |
| Chen, 2024 | 1 | 1 | 1 | 0 | 2 | 0 | 0 | 0 | 5 |

cervical cancer (Figure S1). Patients with cervical cancer who had PNI had significantly higher risk of recurrence and death in five years comparing with those who didn't have PNI (RR [95% CI]: 2.79 [1.67- 4.66], $I^2=78\%$ for 5-year OS; 2.16 [1.30–3.59], $I^2=84\%$ for 5-year DFS) (Fig. 2). As we could see, the heterogeneity was strong ($I^2>50\%$) among included studies, therefore we used the random effect model in analysis. The HR [95% CI] of PNI for total OS after multivariate cox regression adjustment of clinicopathological factors and adjuvant treatments was 3.25 [1.09- 9.74], $I^2=85\%$ (Fig. 3A), indicating the remarkable and independent impact of PNI on the survival. The total DFS after adjustment was 2.50 [0.66, 9.46], $I^2=89\%$ (Fig. 3B). The Egger regression plots and the heterogeneity of the studies for the above four analyses were shown in Figure S2 and S3. Besides, we tried to further reduce the confounding effect of adjuvant treatments by conducting analysis solely based on the results from the three studies that included adjuvant treatments in their multivariate regression analyses (Figure S4). The results indicated that after adjusting adjuvant treatments, patients exhibiting PNI also showed a tendency towards worse survival outcomes in both DFS and OS, although these trends did not reach statistical significance.

Moreover, sensitivity analysis did not show any important changes in pooled RR for 5-year OS or RR for 5-year DFS no matter which study was left out; whereas HR for OS and HR for DFS could not keep significantly larger than one when omitting the studies from L Horn or T Wan, suggesting the HR for OS or for DFS lacked enough stability (Fig. 4).

We also calculated the association between PNI and the clinicopathological risk factors of prognosis (Fig. 5). PNI was significantly associated with higher stage, larger tumor size, LNM, deep stromal invasion, LVSI, resection margin involvement, and parametrial invasion, whereas no significant increase was observed in the occurrence of the adenocarcinoma component and positive vaginal margin. Besides, PNI was associated with higher possibility of adjuvant therapy (RD: 0.28 [0.04–0.52], $I^2=92\%$), especially for chemoradiation (RD: 0.25 [-0.02–0.53], $I^2=76\%$) (Fig. 6). These results suggested PNI might be an indicator of a more aggressive disease.

To better eliminate the potential interference of the known risk factors of cervical cancer, we explored the impact of PNI on total OS and DFS stratified by these risk factors (Fig. 7). In patients with LNM, PNI was a significant risk factor of poor prognosis (HR [95% CI]: 2.28 [1.16–4.48] for OS, 3.01 [1.01–8.96] for DFS) (Fig. 7A-B). Nevertheless, in patients without LNM, PNI only showed statistically difference on the HR of OS (HR [95% CI]: 5.65 [2.60–12.24] for OS, 3.75 [0.63–22.31] for DFS) (Fig. 7A-B). In patients with tumor size larger than 4 cm, patients with PNI had more unfavourable prognosis than those without PNI (HR [95% CI]: 7.37 [2.51–21.61] for OS, 4.44 [1.2–15.35] for DFS); in the rest of patients, only the HR of OS but not that of DFS reached the statistical difference between patients with PNI or not (HR [95% CI]: 4.51 [2.41–8.43] for OS, 3.50 [0.95–12.87] for DFS) (Fig. 7C-D). Owing to lacking available data, the pooled subgroup analysis could not be performed on FIGO stage, LVSI,

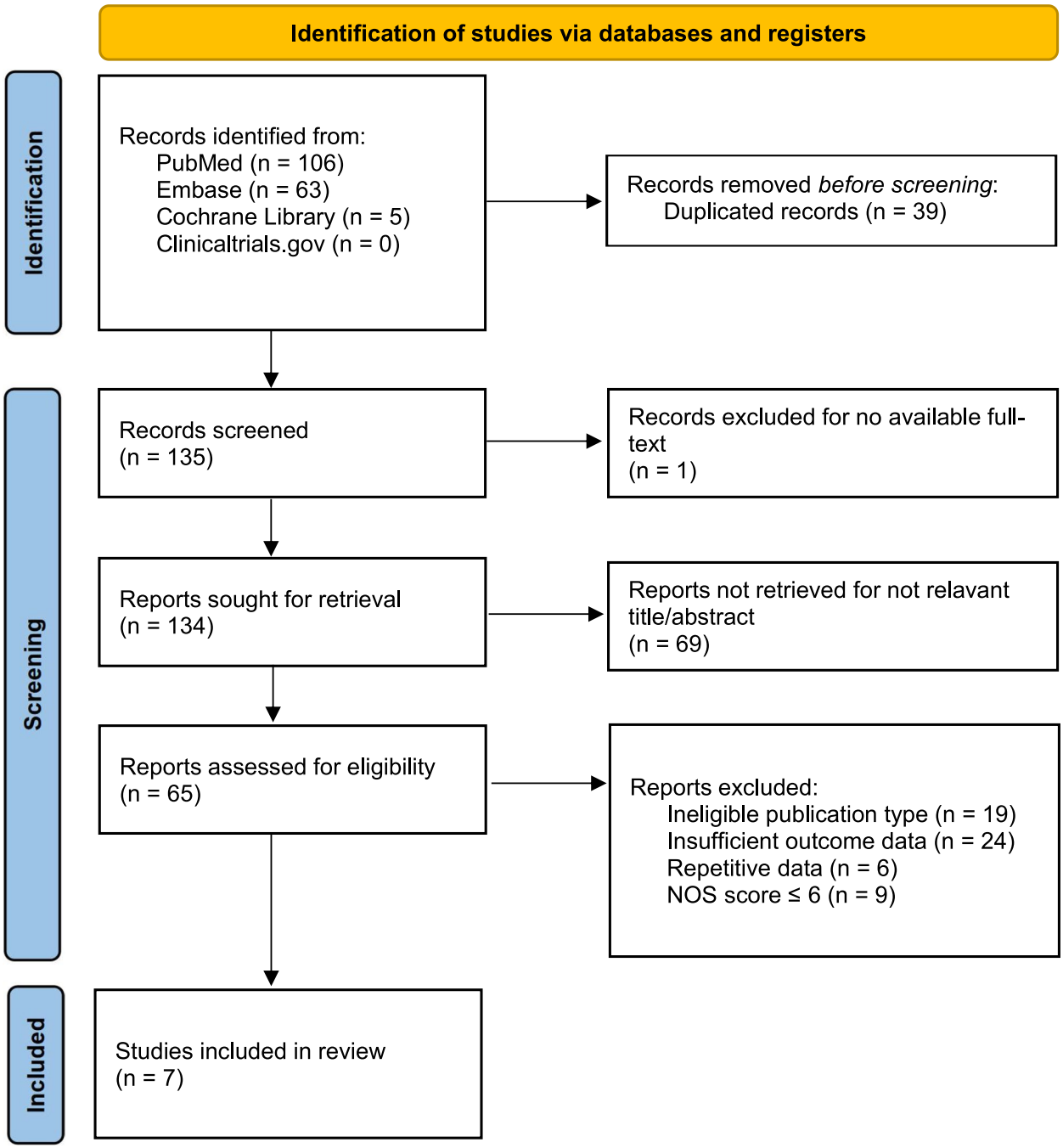


**Fig. 1** PRISMA flow diagram of the study

histological type, depth of stromal invasion, resection margin involvement, parametrial invasion, and adjuvant therapy. A re-analysis of the dataset from T Wan et al. [8] demonstrated that PNI retained prognostic impact for both total OS or DFS across all stratification subgroups (resection margin involvement, FIGO stage, histological type, LVSI, depth of stromal invasion), and the results of subgroup analyses in OS were more significant compared to DFS (Figure S5). However, the generalizability of these findings derived from a single study requires rigorous validation through multicenter cohorts or prospective investigations to establish clinical applicability. To conclude, PNI was significantly associated with poorer prognosis in patients with

**Table 2** Characteristics of included studies

| Author, publication year | Country/ Ethnicity | Design, follow-up time | Study period | Inclusion criteria | Exclusion criteria | Age (years) | Review pathological slides | Surgery | Total No. of patients | No. of PNI (+) | Adjusted parameters |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Horn, 2010 [10] | Germany | Retrospective cohort study, 61.6 months | Before 2010 | FIGO stage IB to IIB, SCC or adeno/ adenos-quamous carcinoma | Other histo-logic types, received neoadjuvant therapy, incomplete local tumor resection | 44 (range 23–80) | Yes | Piver type III abdomi-nal radical hysterectomy and pelvic lymphad-enectomy without para-aortal lymph node resec-tion | 194 | 68 | Stage, pathological grade, LNM, peritumoral desmoplastic change |
| ElSahwi, 2011 [5] | United States | Retrospective cohort study, 72 months | 1994—2007 | FIGO stage IA to IIA, SCC or adeno/ adenos-quamous carcinoma | Other histo-logic types | 46.79 ± 12.5 | Yes | Hysterectomy (1 patient of class I, 32 of class II, 159 of class III and retrop-eritoneal LN dissection) | 192 | 24 | Age, stage, his-tologic subtype, pathological grade, tumor size, adjuvant therapy, LNM, uterine exten-sion, parame-trial extension, LVSI |
| Cho, 2013 [4] | Korea | Retrospective cohort study, 70.5 months | Jan 2003 to May 2011 | FIGO stages IA2–IIA2, SCC or adeno/ adenos-quamous carcinoma | Other histo-logic types | 49.83 ± 12.36 | No | Radical hysterectomy and lymphad-enectomy | 185 | 13 | Age, stage, histologic subtype, tumor size, adjuvant treatment, LNM, resec-tion margin involvement, parametrial invasion, depth of stromal inva-sion, LVSI |
| Kwon, 2016 [10] | Korea | Retrospective cohort study, 80 months | Jan 2004 to Jun 2012 | Cervical can-cer who had been referred for postopera-tive RT | Not under-went radical hysterectomy and pelvic LN dissection; no high-risk factors | 50.44 ± 11.37 | No | Radical hysterectomy and pelvic LN dissec-tion, ± para-aortic LN sampling or dissection | 50 | 7 | NA |

**Table 2** (continued)

| Author, publication year | Country/ Ethnicity | Design, follow-up time | Study period | Inclusion criteria | Exclusion criteria | Age (years) | Review pathological slides | Surgery | Total No. of patients | No. of PNI (+) | Adjusted parameters |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Zhu, 2018 [9] | China | Retrospective cohort study, > 60 months | Jan 2007 to Dec 2012 | FIGO stage IA2 to IIA2, SCC or adeno/adenosquamous carcinoma, patients with preoperative tumors > 4 cm underwent NACT | Other histological subtypes, incomplete local tumor resection | 44.26 ± 7.95 | Yes | Radical hysterectomy and pelvic lymphadenectomy | 210 | 18 | Stage, tumor size, LNM, positive vaginal margin, depth of invasion, parametrial invasion, LVSI |
| Tang, 2019 [7] | China | Retrospective cohort study, > 60 months | Jan 2007 to Dec 2014 | FIGO stage IA2 to IIA2, availability of the clinical and pathological data | | 48.46 ± 9.57 | Yes | Radical hysterectomy and pelvic lymphadenectomy | 406 | 43 | Age, hypertension, diabetes, stage, histologic subtype, tumor size, LNM, depth of cervical invasion, surgical margin, LVSI |
| Wan, 2021 [8] | China | Retrospective cohort study, 55 months | Jan 2012 to Jun 2017 | FIGO stage IA2 to IIB, SCC or adeno/adenosquamous carcinoma | Other histological subtypes, had a cone biopsy or definite radiation before radical surgery | 50.06 ± 9.14 | Yes | Radical hysterectomy and pelvic lymphadenectomy | 324[a] | 162 | Age, stage, histologic subtype, pathological grade, tumor size, adjuvant treatment, LNM, resection margin involvement, parametrial invasion, depth of stromal invasion, LVSI |

*PNI* Perineural invasion, *SCC* Squamous-cell carcinoma, *NACT* New adjuvant chemotherapy treatment, *LN* Lymph node, *LNM* Lymph node metastasis, *LVSI* Lymphovascular invasion

[a] This study investigated 1836 patients with cervical cancer in which 162 had PNI, but conducted the prognosis analysis only in the 324 patients after propensity score matching (matching ratio 1:1)

**Table 3** Quality assessments of included studies based on Newcastle–Ottawa scale

| Author, publication year | Selection | | | | Comparability | Outcome | | | Total score |
|---|---|---|---|---|---|---|---|---|---|
| | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow up of cohorts | |
| Tang, 2019 [7] | 1 | 1 | 1 | 0 | 2 | 0 | 1 | 1 | 7 |
| Zhu, 2018 [9] | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 7 |
| Horn, 2010 [10] | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 7 |
| Cho, 2013 [4] | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 1 | 8 |
| ElSahwi, 2011 [5] | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 1 | 8 |
| Kwon, 2016 [10] | 0 | 1 | 1 | 0 | 2 | 1 | 1 | 1 | 7 |
| Wan, 2021 [8] | 1 | 1 | 1 | 0 | 2 | 1 | 0 | 1 | 7 |

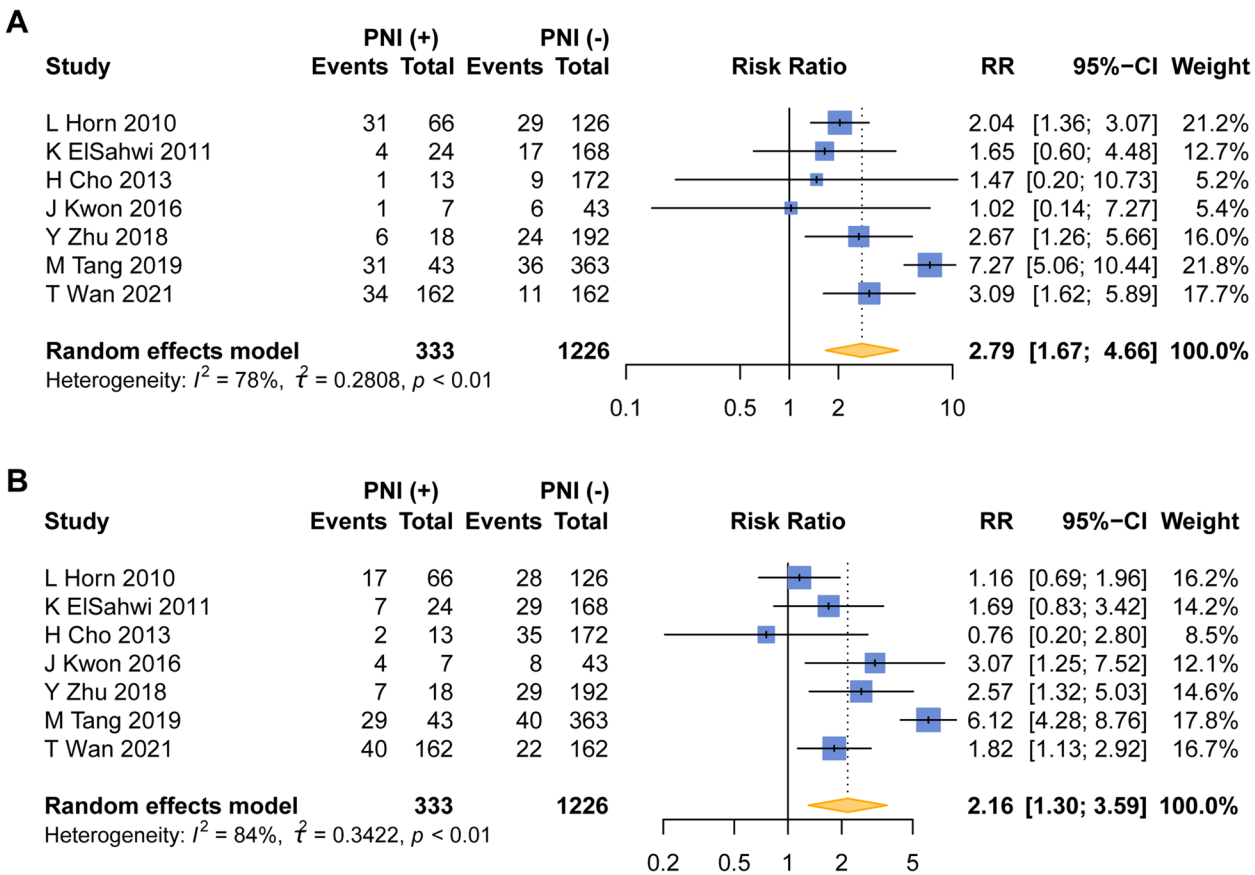


**Fig. 2** Meta-analysis of risk ratios (RRs) of 5-year overall survival and 5-year disease-free survival. Meta-analysis of risk ratios (RRs) of 5-year overall survival (**A**) and 5-year disease-free survival (**B**) for cervical cancer patients with PNI compared with those without PNI. PNI, perineural invasion. 95% CI, 95% confidence interval

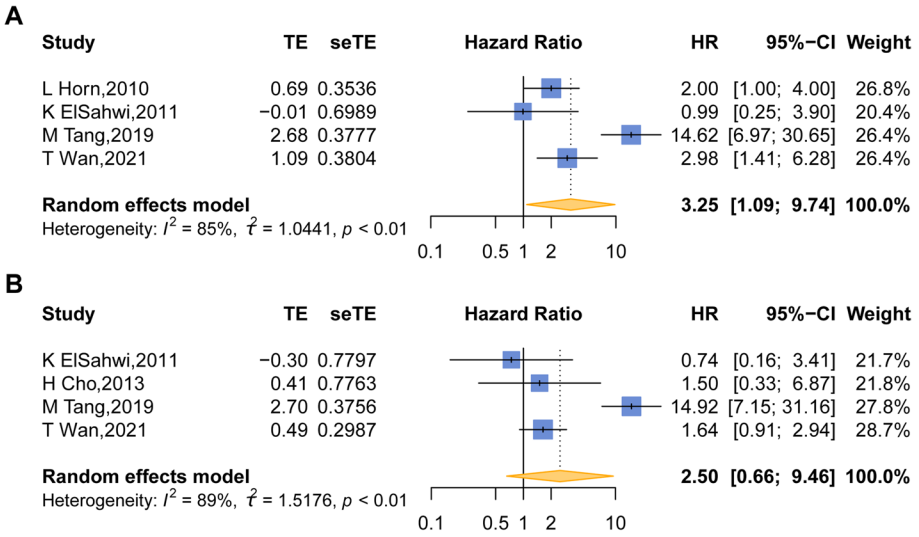


**Fig. 3** Meta-analysis of hazard ratios of overall survival and disease-free survival. Meta-analysis of hazard ratios (HRs) of overall survival (**A**) and disease-free survival (**B**) for cervical cancer patients with PNI compared with those without PNI. PNI, perineural invasion. 95% CI, 95% confidence interval. TE, Estimate of treatment effect. seTE, standard error of treatment estimate

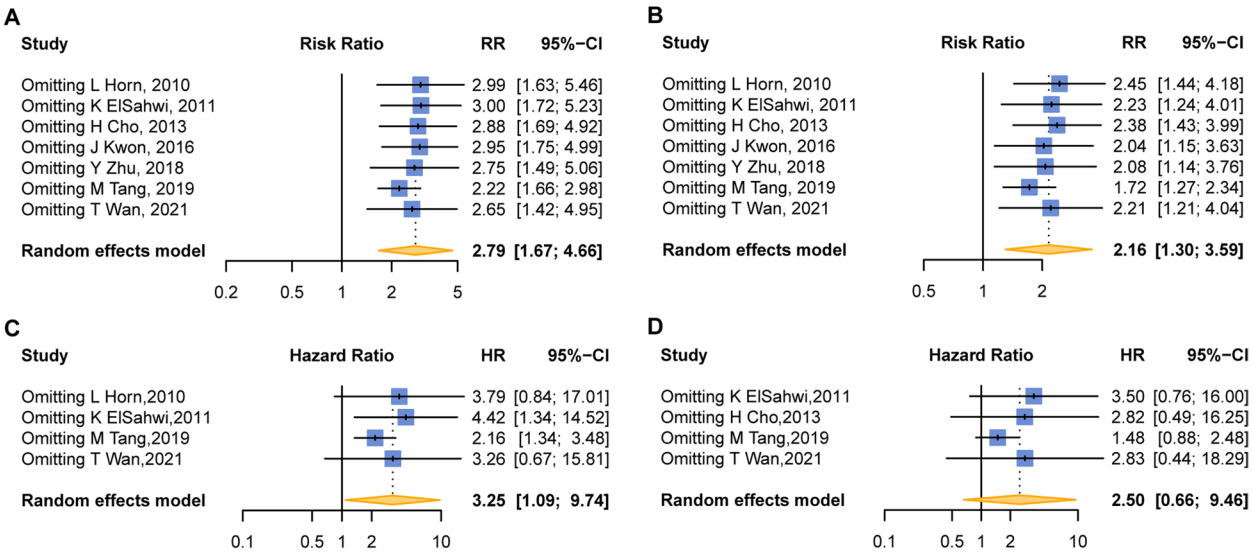


**Fig. 4** Sensitivity analysis of risk ratio of 5-year overall survival and of 5-year disease-free survival. Sensitivity analysis of risk ratio (RR) of 5-year overall survival (**A**) and RR of 5-year disease-free survival (**B**). Hazard ratio (HR) of overall survival (**C**) and HR of disease-free survival (**D**) for patients with cervical cancer who had PNI compared with those who didn't have PNI. PNI, perineural invasion. 95% CI, 95% confidence interval

LNM or large tumor size; while for patients without LNM or tumor size smaller than 4 cm, PNI correlated with remarkable shorter OS but not DFS. Whether PNI exhibits a similar correlation with unfavorable prognosis in pooled stratified analyses of other risk factors requires further exploration.

## Discussion

In this comprehensive meta-analysis of seven studies which included 1561 patients with cervical cancer, we found (a) patients with PNI had significantly reduced rate of 5-year OS and DFS comparing to those without PNI; (b) PNI showed strongly positive correlation with

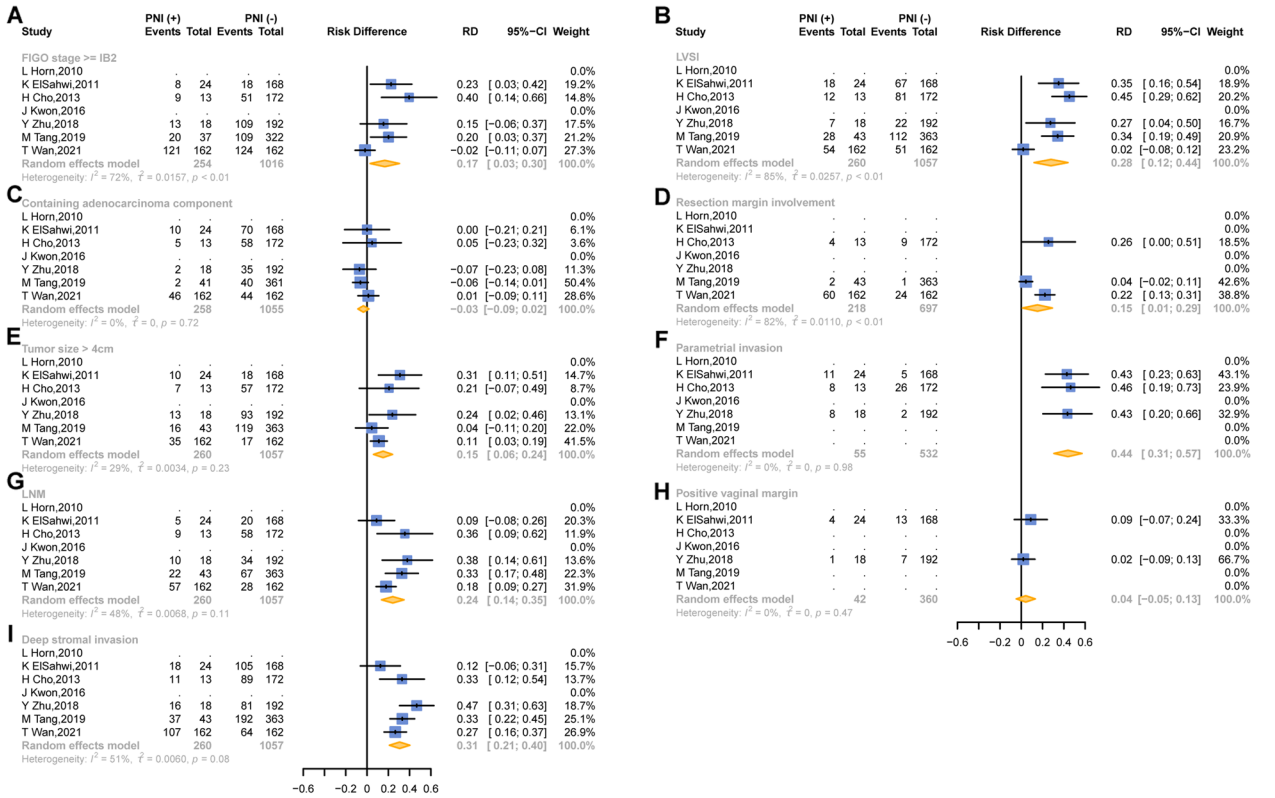


**Fig. 5** Meta-analysis of risk difference for risk factors. Meta-analysis of risk difference for risk factors of cervical cancer in patients with cervical cancer who had PNI compared with those who didn't have PNI. 95% CI, 95% confidence interval. RD, risk difference. LVSI, lymphovascular invasion. LNM, lymph node metastasis

multiple risk factors of prognosis (higher stage, larger tumor size, LNM, deep stromal invasion, LVSI, resection margin involvement, and parametrial invasion), and was significantly associated with adjuvant therapy; (c) PNI was an independent risk factor for OS after adjustments for confounders through multivariate regression or subgroup analysis, but the robustness of the results warranted more high-quality data to support.

In total, PNI was not only associated with remarkably a worse survival (RR [95% CI]: 2.79 [1.67–4.66], $I^2$ = 78% for 5-year OS; 2.16 [1.30–3.59], $I^2$ = 84% for 5-year DFS), but also an independent risk factor of the total OS (HR [95% CI]: 3.25 [1.09–9.74], $I^2$ = 85%) after multivariate cox regression adjustment for cervical cancer (Figs. 2 and 3). The total DFS analysis also suggested that patients with PNI had 2.5 times risk compared with those without PNI, although the difference didn't reach statistical significance. The sensitivity analysis confirmed the results of the primary analysis in RR for 5-year OS and DFS (Fig. 4). While the subgroup analyses were consistent with results to the PNI's impact on HR of total OS (Fig. 7), PNI's impact on HR of total OS was found not stable enough, as indicated by the sensitivity analysis and the pooled multivariate analysis of studies adjusting adjuvant therapy (Fig. 4, S4). The heterogeneity of the included studies explained these discrepancies between the HR results of OS and DFS. Besides, previous literature suggested PNI might have a relatively larger effect in OS than DFS was probably due to PNI-related treatment resistance after disease progressed, resulting in increased mortality [35]. In summary, our analysis suggested PNI was an important marker of poor outcome of cervical cancer.

Our study revealed that there was a considerable proportion of cervical cancers to invade nerves in the primary tumor, with the pooled PNI rate of 12.1% (95% CI 8.0%-18.4%, $I^2$ = 96%). As the previous literature indicated, PNI in the primary tumor might be associated with the pelvic nerve spreading that might be reserved in NSRH, and increase the risk of local recurrence. [25–27]. It was also observed that tumor could spread along nerves to seed metastatic growth at distant sites in a previous research. Capek et al. reviewed a series of 17 cases of perilumbosacral plexus spreading malignancies at Mayo Clinic, including cervical, colorectal, and bladder cancer, and the results showed that

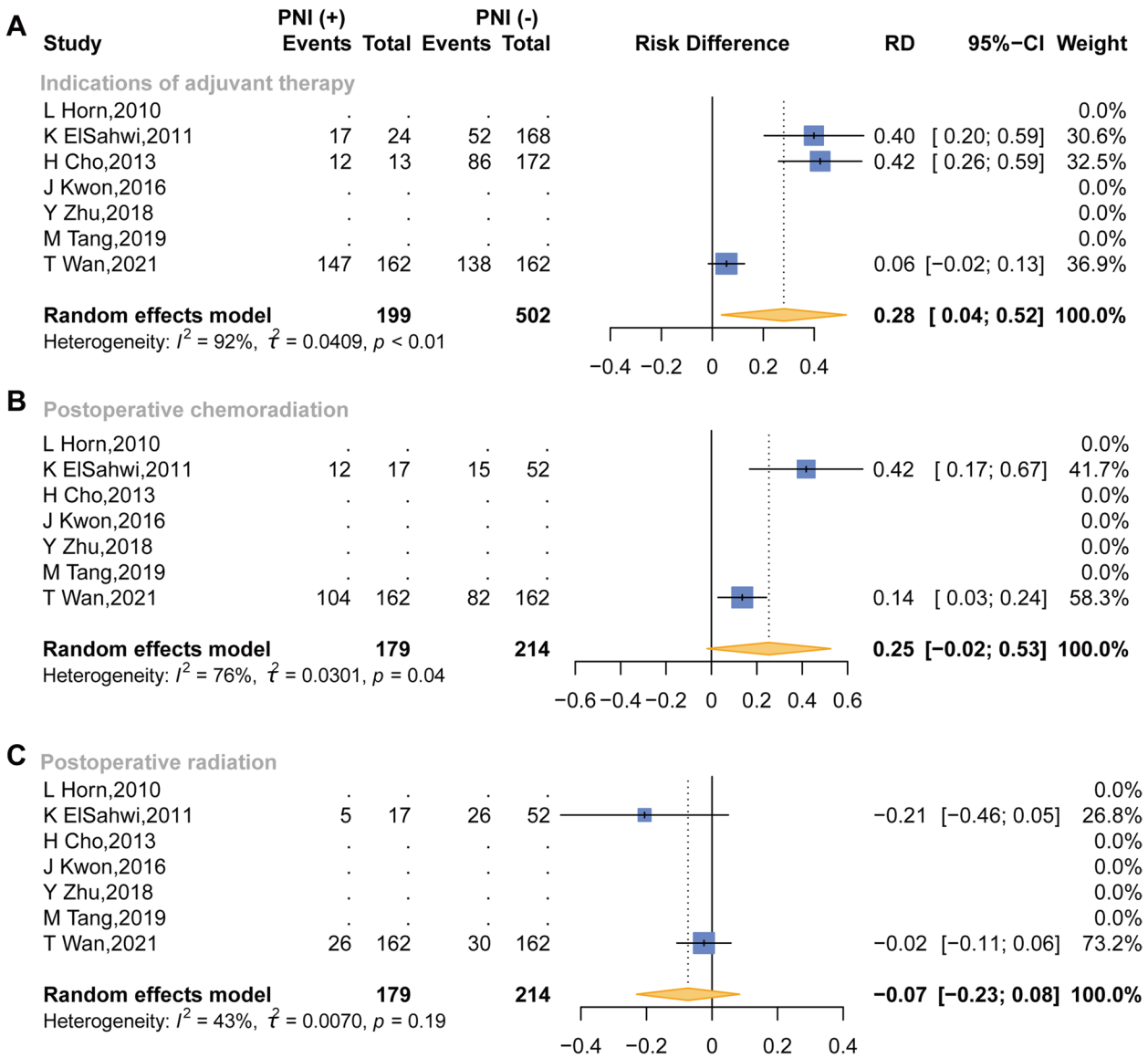


**Fig. 6** Meta-analysis of risk difference for postoperative therapy. Meta-analysis of risk difference for postoperative therapy in patients with cervical cancer who had PNI compared with those who didn't have PNI. 95% CI, 95% confidence interval. RD, risk difference

L5-S1 spinal nerves and sciatic nerves were most frequently involved [25]. In this research they proposed a theory regarded lumbosacral plexus metastasis as a consequence of tumor cells using the pelvic splanchnic nerves as conduits and invading from the end organ, and it was possible for tumors to spread along osseous and muscle nerve branches, resulting in metastases in muscles and bones [25]. Since pelvic splanchnic nerves were reserved in NRSH, it might potentially increase the risk of tumor recurrence and metastasis, leading to the poor prognosis in cervical cancer with positive PNI.

Nerve fiber takes part in the composition of the microenvironment at tumor periphery. Studying PNI could contribute to understanding cancer dissemination. According to multiple clinical and mechanism on neurotropic malignancies (i.e., pancreatic cancer), cancer cells trigger a cascade of inflammation and wound healing when damaging the perineurium [36–38]. Injured nerves secrete growth factors such as glial cell derived neurotrophic factor (GDNF), neurturin (NRTN) and artemin (ARTN) that further boost cancer cell proliferation [39]. Stellate cells and Schwann cells contribute in the neural

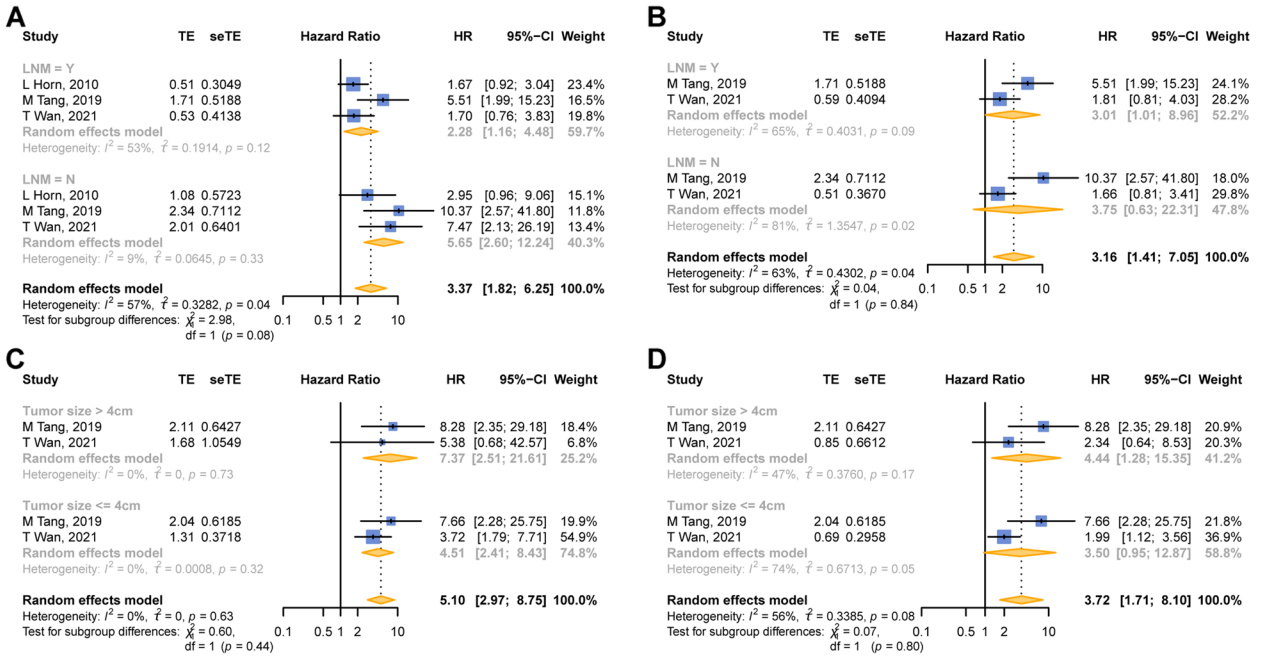


**Fig. 7** Subgroup analysis for lymph node metastasis and tumor size. Subgroup analysis for LNM in overall survival (**A**) and disease-free survival (**B**) and tumor size in overall survival (**C**) and disease-free survival (**D**). PNI, perineural invasion. 95% CI, 95% confidence interval. TE, Estimate of treatment effect. seTE, standard error of treatment estimate. LNM, lymph node metastasis. Large size, tumor size larger than 4 cm

dissemination of cancer even at an early stage by promoting perineural extracellular matrix (ECM) degradation and the movement of cancer cells through tissue barriers and neurogenesis around neoplastic cells [16, 40, 41]. This also explained why PNI-positive patients had a poorer prognosis. In addition, it has been identified that chemokine CCL-2 which is mainly secreted by Schwann cells and its receptor CCR2 are key elements in cancer-nerve crosstalk, which facilitates a PNI microenvironment [42]. The role of PNI in cervical cancer should be looked into further in the light of the previously mentioned neurotropic malignancies.

The clear association between PNI and metastases in several cancers strongly suggests a role for PNI in tumor dissemination, and PNI as a potential tumor spread method has been proved as an important prognostic factor and indication for postoperative therapy in many cancers [11–15]. Patients with head and neck squamous cell carcinoma whose postoperative pathological examination revealed PNI were suggested supplement radiotherapy [43]; supplementary chemotherapy is needed in gastric cancer with stages above T2 if PNI is positive [44]; the NCCN guidelines point out PNI in colorectal cancer or pancreatic cancer is an independent prognostic risk factor and an indication of postoperative adjuvant chemotherapy [45–47]. Considering the poor prognosis of patients with PNI positive cervical cancer, evaluating the status of PNI preoperatively could have crucial implications for risk stratification and treatment of cervical cancer. In patients with PNI, NSRH should be used at the surgeon's carefully discretion.

Furthermore, whether PNI should be listed as an indication for adjuvant therapy is controversial yet. Our finding that patients with PNI had a 15% increased risk of positive resection margin (Fig. 5D) indicated that PNI made complete tumor removal with safe margins more difficult. According to the NCCN guideline, patients with cervical cancer should receive adjuvant radiochemotherapy after the radical surgery to prevent local or regional recurrence if the pathological examination reported one of the following risk factors: LNM, parametrial involvement, and the presence of positive margins on surgical resection specimens. Large tumor size, deep stromal invasion, and lymphovascular space invasion are also emerging as prominent risk factors for disease recurrence in early-stage cervical cancer [2]. PNI was not only related to most of these risk factors, but also associated with a worse total OS of cervical cancer after adjustment of these risk factors. Besides, patients with cervical cancer who had PNI had significantly higher rate of adjuvant therapy, although the influence of other risk factors could not be ruled out (Fig. 6). In conclude, these results suggested that PNI was associated with a more aggressive disease, which might be a potential indicator for adjuvant therapy.

Cui L. et al. reported a meta-analysis about the prognostic impact on cervical cancer in 2015 which found PNI had a pooled HR from univariate cox regression as 2.207 (95% CI 1.356–3.592) [31]. However, this research didn't report the quality control on included studies or adjust the potential confounders such as LNM, tumor size, etc., which limited the reliability of the results [31]. To provide more accurate evidence on the impact of PNI for cervical cancer, more retrospective studies have been conducted these years. A comprehensive systematic literature review is needed to summarize the various reports to concretely clarify how much the PNI independently affect the prognosis of cervical cancer. Our study used rigorous methods to maximize the convincing of the results, including following PRISMA and MOOSE guidelines for reporting, applying Newcastle–Ottawa Scale for study quality evaluation, using effect values from multivariate cox regression to control the influence of confounders on the prognosis, and performing sensitivity analyses and subgroup analyses to confirm the adequacy of the main outcome. Besides, we analyzed the influence of PNI on postoperative therapy decision that had been neglected by most of studies and the previous meta-analysis, which was an important supplement to our conclusion.

This meta-analysis is notable for its large total population size of 1561 women with cervical cancer from different ethnic backgrounds, as well as its comprehensive data collection including both univariate and multivariate effect values, subgroup data, treatment data.

There were limitations, however. Firstly, all the included studies were retrospective, the heterogeneity was significant among included studies, which limited the quality of evidence. Notably, nine studies were excluded because their NOS scores didn't reach seven (Table 1), some of which demonstrated substantial sample sizes ($n \geq 100$), indicating it is important to improve the normativity of the report of retrospective studies to make every reported precious case meaningful. Secondly, in regard to the PNI diagnosis definition, some of included studies might underestimated the incidence of PNI because they didn't have experienced gynecological pathologists to review the pathological slides or didn't use anti-S-100 staining to assist pathological diagnosis [4, 6, 7, 9, 10]. Future report on PNI should pay attention on this issue. Furthermore, due to the unavailability of individual patient-level data from all studies included except the one from T Wan et al., we were unable to perform the pooled subgroup analyses based on various clinicopathological characteristics and adjuvant treatment factors, with the exception of LNM and tumor size. This limitation has constrained our ability to conduct a comprehensive, multi-faceted validation of the impact of PNI on patient outcomes. While evidence remained limited, stratified analyses from one previous literature employing those establishing risk factors tentatively suggested a relationship between PNI and unfavorable outcomes in cervical cancer. We eagerly anticipate future high-quality prospective studies that can further elucidate PNI's role in the prognosis of cervical cancer.

## Conclusion

Our study suggested PNI was associated with a poorer survival of cervical cancer and might act as an independent prognostic factor of outcomes of cervical cancer. Although this study does not address direct evidence on the impact of nerve-sparing surgical approaches on PNI-related outcomes, the established prognostic validity provides a foundation for future investigations to evaluate the clinical utility of PNI status in guiding therapeutic strategies.

### Abbreviations

| | |
|---|---|
| PNI | Perineural Invasion |
| NCCN | The National Comprehensive Cancer Network |
| LNM | Lymph node metastasis |
| LVSI | Lymphovascular invasion |
| OS | Overall survival |
| DFS | Disease-free survival |
| PRISMA | The Preferred Reporting Items for Systematic Review and Meta-Analysis |
| MOOSE | Meta-analysis Of Observational Studies in Epidemiology |
| AMSTAR 2 | Assessing the Methodologist Quality of Systematic Reviews 2 |
| RR | Risk ratio |
| HR | Hazard ratios |
| RD | Risk difference |
| CI | Confidence interval |
| NOS | Newcastle-Ottawa Scale |
| FIGO | International Federation of Gynecology and Obstetrics |
| TE | Estimate of treatment effect |
| seTE | Standard error of treatment estimate |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13838-1.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

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Not applicable.

### Authors' contributions

T wan, G Cai and S Zhang conceived of and designed the study; G Cai and S Zhang, collected the data; G Cai, S Zhang and S Gao performed statistical analyses; G Cai, S Gao, T Deng and H Huang interpreted the data; G Cai and S Zhang drafted the manuscript; T Wan, Y Feng, and G Cai critically reviewed the manuscript. All authors read and approved the final manuscript.

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**Data availability**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

**Author details**
[1]Department of Gynecologic Oncology, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, People's Republic of China. [2]Guangdong Provincial Clinical Research Center for Obstetrical and Gynecological Diseases, Guangzhou, People's Republic of China.

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