Original Article

Relationship between positive margin and residual/recurrence after excision of cervical intraepithelial neoplasia: a systematic review and meta-analysis

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Background: The relationship between endocervical and ectocervical margin status and residual or recurrence after cervical intraepithelial neoplasia (CIN) resection has been controversial. We investigated the relationship between the excision margins and residual/recurrence to assess indicators for the scope of resection and the risk of treatment failure by using meta-analysis.

Methods: Literature searches were performed in PubMed, Medline, Embase, Central, Wangfang and CNKI databases. Patients after CIN resection were grouped according to whether there was residual or recurrence, and the differences in exposure factors between the two groups were compared. Or they were grouped by exposure factor, and compare the differences in residual and recurrence rates under different grouping conditions. The observed outcome was postoperative residual or recurrence. The risk of bias in the literature was assessed using the Newcastle-Ottawa Scale (NOS). The chi-square test were used for heterogeneity. Subgroup explored the sources of heterogeneity. Publication bias was assessed using funnel plots and Egger’s test.

Results: A total of 11 studies were included in this study, 8 studies were at low risk of bias and 3 studies were at high risk of bias. The 11 studies included 3065 patients, 774 patients with positive margins and 2,291 patients with negative margins. The rate of residual/recurrence after excision of CIN in patients with positive margins was significantly higher than in patients with negative margins [odds ratio (OR) =3.99, P<0.00001]. There was no heterogeneity among the studies (P=0.16), with publication bias (P<0.05). The residual/recurrence rate was significantly higher in patients with positive endocervical margins than in patients with negative endocervical margins (OR =2.59, P<0.00001). There was no heterogeneity among studies (P=0.78) and no publication bias (P<0.05). There was no significant difference in residual/recurrence rate between positive and negative ectocervical margins (OR =1.14, P=0.36). There was no heterogeneity among studies (P=0.32) and no publication bias (P<0.05).

Conclusions: Positive endocervical margins, but not external cervical margins, are risk factors for residual/recurrence of CIN after resection. Close attention to the status of the endocervical margins is recommended. More aggressive treatment and frequent follow-up are needed for patients with positive endocervical margins.

Keywords: Cervical intraepithelial neoplasia (CIN); ectocervical margins; endocervical margins; positive excision margins
Introduction

Cervical cancer is the most common malignant tumor of the female reproductive system, with new incidence accounting for 5% of all new cancer cases globally every year, most of which are in developing countries (1-3), and the mortality rate has increased in recent years (4). Cervical intraepithelial neoplasia (CIN) is a cervical precancerous lesion that is closely related to cervical cancer and its incidence has been increasing in recent years (5,6). According to the depth of the lesion, it is classified as CINI, CINII, and CINIII, and the risk of developing invasive cervical cancer increases with each level (7). The WHO basic practice guide for comprehensive prevention and treatment of cervical cancer emphasizes treatment of CINIII to inhibit the occurrence and development of cervical cancer (8). Cervical cancer can be avoided by screening cervical lesions and treating CIN.

Excision biopsy is a standard method of CIN treatment, but there is a risk of treatment failure. A study showed that 4–18% of patients had residue or recurrence detected within 2 years after the initial resection (9). The extent of resection has to be balanced with the side effects of the treatment. The extent of prior cervical resection has been associated with preterm birth and other adverse pregnancy events (10,11). The relationship between the status of endocervical and ectocervical cervical margins and residual/recurrence after CIN resection is controversial. Park et al. pointed out that a positive incisional margin will increase the residual or recurrence rate after CIN resection (12). Alder et al. (13) pointed out that the margin status cannot accurately predict postoperative residual or recurrence. A positive external cervical margin does not increase the associated risk. Differences in results between these studies may be related to subject bias, choice of surgical approach, and quality of follow-up. Most of the studies were independent retrospective analyses with small sizes and have not provided convincing evidence. Therefore, we conducted a meta-analysis to explore the relationship between the margin status, including the endocervical and ectocervical margin, and the residual or recurrence after CIN resection. We present the following article in accordance with the MOOSE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1466/rc).

Methods

Literature retrieval

A literature search was conducted in the PubMed, Medline, Embase, Central, Wangfang and CNKI databases, using the search terms (“CIN” OR “cervical intraepithelial neoplasia” OR “cervical dysplasia” OR “Cervical precancerous lesion”) AND (“margin” OR “recurrence”). Document language was not limited. The search deadline is April 18, 2022.

Literature screening

Inclusion criteria: (I) CIN patients undergoing resection; (II) subjects divided into groups according to whether there was residual or recurrence, and the differences in exposure factors between groups were compared, or the differences in residual and recurrence rates under different grouping conditions were compared according to exposure factors; (III) exposure factors include margin status; (IV) clear diagnosis of postoperative residual or recurrence after CIN in patients; (V) case-control study or cohort study.

Exclusion criteria: (I) duplicate report; (II) unclear diagnosis of CIN or unclear status of the margin; (III) lost to follow-up rate >20%; (IV) incomplete study data and unable to be provided by correspondence author.

Data extraction

Two researchers (Feng and Huang) jointly extracted the author, title, publication time, sample size, margin status, number of residual or recurrent cases and other information in the study. Any missing data was obtained by contacting the author. If there was disagreement about the data, consensus was achieved through discussion.

Evaluation of the risk of bias in the literature

Two researchers used the Newcastle-Ottawa scale (NOS) to evaluate the risk of bias of the literature included in the study, including the selection of subjects (4 points), comparability between groups (2 points) and exposure
factor measurement (3 points), for a total of 9 points. A score ≥5 points was considered low risk of bias, otherwise high risk of bias (14). The two researchers jointly completed the literature risk of bias evaluation and disagreements were resolved by consensus.

Heterogeneity and publication bias tests

Statistical analysis

We used Cochrane software RevMan5.3 for statistical analysis of the data. The odds ratio (OR) value and 95% confidence interval (CI) of cohort studies and case-control studies were calculated for pooled analysis. OR values were not adjusted for other factors. The Chi-square test was used as the heterogeneity test. When I² corrected by degrees of freedom was >50% or P<0.1, it was considered that there was heterogeneity among the studies, and a random-effects model was used. Subgroup was used to explore the causes of heterogeneity. When I² corrected by degrees of freedom was ≤50% and P≥0.1, it was considered that there was no heterogeneity, and a fixed-effects model was used. Funnel plots and Egger test were used for the publication bias test. Two-way P<0.05 indicated statistical significance.

Results

Study data

A total of 1,961 studies were retrieved, 1,950 were excluded, and a final 11 (12,13,15-23) were included in the meta-analysis. Eight studies were at low risk of bias, and 3 studies were at high risk of bias. The 11 studies included 3,065 patients, 774 patients with positive margins and 2,291 patients with negative margins. Figure 1 is a flow chart of literature screening and Table 1 shows the baseline study information and NOS score.

Margin status and residual/recurrence

The 11 studies reported the correlation between the resection margin status and the residual or recurrence rate after CIN resection. There was no heterogeneity among the 11 studies (Chi²=14.27, P=0.16, I²=30%), and the fixed-effects model was selected for combined analysis as shown in Figure 2. The residual or recurrence rate of patients with a positive margin was significantly higher than for patients with a negative margin. The funnel plot and Egger test in Figure 3 showed the points biased to the left, indicating publication bias (P<0.05).
Status of the endocervical margin and residual or recurrence

A total of 7 studies reported the correlation between the status of the endocervical margin and the residual or recurrence rate after CIN resection. There was no heterogeneity among the studies (Chi² = 3.26, P = 0.18, I² = 0%), so the fixed-effects model was selected for combined analysis as shown in Figure 4. The residual or recurrence rate of patients with positive endocervical margins was significantly higher than for patients with negative margins. The funnel plot and Egger test in Figure 5 showed the roughly symmetrical distribution of the points within the confidence interval, indicating no publication bias (P > 0.05).

Status of the ectocervical margin and residual or recurrence

A total of 5 studies reported the correlation between the status of the ectocervical margin and the residual...
or recurrence rate after CIN resection. There was no heterogeneity among the studies ($\chi^2=4.71$, $P=0.32$, $I^2=15\%$), so the fixed-effects model was selected for combined analysis as shown in Figure 6. There was no significant difference in the residual or recurrence rate between positive and negative margins after resection. The funnel plot and Egger test showed in Figure 7 shows the roughly symmetrical distribution of the points within the
Discussion

We analyzed 11 studies including 3,065 patients after CIN resection that reported the correlation between resection margin status and the residual or recurrence rate. There were 774 patients with a positive margin, accounting for 25.25% of the total patients and similar to the 23.1% of patients with positive margins after resection reported previously (24). In our analysis, the postoperative residual or recurrence rate of patients with a positive margin was \( \approx 27.65\% \), and that of patients with a negative margin was \( \approx 7.99\% \), similar to the results of the previous meta-analysis (24). Our results showed that patients with positive margins had a 3.99 (95% CI: 3.18, 5.02) increased risk of postoperative residue or recurrence compared with patients with negative margins. A positive margin is a risk factor for residual or recurrence after resection, which is consistent with all the results of our analysis. However, one study has pointed out that the status of the margin could not accurately predict postoperative residual or recurrence (13). Some comorbidities, including human papillomavirus (HPV) persistent infection, HIV infection, viral hepatitis, malignant tumor and diabetes mellitus, are also risk factors for residual or recurrence after resection. Arbyn et al. believe that a positive margin increases the risk of postoperative residue or recurrence (11). Nevertheless, the accuracy of high-risk HPV test results in predicting cervical resection failure was higher than for the margin status. Alder et al. showed that when positivity for high-risk HPV and margins exists simultaneously, the increase in the risk of residual or recurrence was more significant, and much higher than for patients with positive high-risk HPV and negative margins (13). The combination of margin status and HPV test results could improve the accuracy of predicting residual or recurrence after resection. Cejtin et al. suggested that the predictive efficacy of endocervical curettage for residual or recurrence after CIN resection was better than margin status (16).

We analyzed the relationship between endocervical and ectocervical margin status and residual or recurrence after resection. A positive endocervical margin was a risk factor for postoperative residual or recurrence, but a positive ectocervical margin did not increase the risk of postoperative residue or recurrence. The results of Alder et al. (13), Demarquet et al. (19), and Leguevaque et al. (20) are consistent with our results. Those studies clearly pointed out that a positive cervical intimal margin was a risk factor for postoperative residue or recurrence, whereas a positive cervical outer margin did not increase the risk. Cejtin et al. believe that positive endocervical and ectocervical margins in HIV-positive patients will increase the risk of postoperative residue or recurrence (16). Chikazawa et al. suggested the risk of residue or recurrence increased when the ectocervical margin was positive or both the endocervical and ectocervical margins were positive (18). Our analysis suggested that the status of the endocervical margin might more accurately predict the postoperative residual or recurrence rate, but this needs to be confirmed by further research.

The status of the margin is affected by some factors, one being the surgical method (24). The proportion of positive margins after electrosurgical resection might be higher than after cold knife resection, but our analysis showed no clinical significance. Electrosurgery may lead to fragmentation of the resected specimens, so false-positive margins might be more common. Another study (25) pointed out that positive margins might be related to surgical experience; that is, operative skill was directly related to the proportion of positive margins. Lesion size and conical resection size correlated with margin status (24). Demarquet et al. pointed out that the size of the resection affected the occurrence of postoperative residue or recurrence, and the extent of pyramidal resection should be carefully controlled (19). At present, there is no consensus on further treatment of positive margins after resection of CIN.

In conclusion, a positive endocervical margin but not positive ectocervical margins increases the risk. Some studies included in the analysis were at significant risk of bias, which may have affected the results to some extent.
Prospective studies with large samples are still needed to confirm our results. For patients with a positive endocervical margin, more active treatment measures are recommended.

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Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1466/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1466/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Vu M, Yu J, Awolude OA, et al. Cervical cancer worldwide. Curr Probl Cancer 2018;42:457-65.
2. von Knebel Doeberitz M. Cervical cancer is preventable today. MMW Fortschr Med 2021;163:51-3.
3. Eun TJ, Perkins RB. Screening for Cervical Cancer. Med Clin North Am 2020;104:1063-78.
4. Li DJ, Shi J, Jin J, et al. Epidemiological trend of cervical cancer. Zhonghua Zhong Liu Za Zhi 2021;43:912-6.
5. Carrero YN, Callejas DE, Mosquera JA. In situ immunopathological events in human cervical intraepithelial neoplasia and cervical cancer: Review. Transl Oncol 2021;14:101058.
6. Ajmani G, Kelsberg G, Safranek S. Screening for Cervical Intraepithelial Neoplasia with Patient-Collected HPV Samples. Am Fam Physician 2021;103:181-2.
7. Kumari S, Bhor VM. Association of cervicovaginal dysbiosis mediated HPV infection with cervical intraepithelial neoplasia. Microb Pathog 2021;152:104780.
8. Jarmulowicz MR, Jenkins D, Barton SE, et al. Cytological status and lesion size: a further dimension in cervical intraepithelial neoplasia. Br J Obstet Gynaecol 1989;96:1061-6.
9. Arbyn M, Ronco G, Anttila A, et al. Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. Vaccine 2012;30 Suppl 5:F88-99.
10. Moss EL, Arbyn M, Dollery E, et al. European Federation of Colposcopy quality standards Delphi consultation. Eur J Obstet Gynecol Reprod Biol 2013;170:255-8.
11. Arbyn M, Kyrgiou M, Simonsen C, et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. BMJ 2008;337:a1284.
12. Park JY, Lee KH, Dong SM, et al. The association of pre-conization high-risk HPV load and the persistence of HPV infection and persistence/recurrence of cervical intraepithelial neoplasia after conization. Gynecol Oncol 2008;108:549-54.
13. Alder S, Megyessi D, Sundström K, et al. Incomplete excision of cervical intraepithelial neoplasia as a predictor of the risk of recurrent disease-a 16-year follow-up study. Am J Obstet Gynecol 2020;222:e1-172.e12.
14. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available online: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm
15. Alonso I, Torné A, Puig-Tintoré LM, et al. Pre- and post-conization high-risk HPV testing predicts residual/recurrent disease in patients treated for CIN 2-3. Gynecol Oncol 2006;103:631-6.
16. Cejtin HE, Zimmerman L, Mathews M, et al. Predictors of Persistent or Recurrent Disease After Loop Electrosurgical Excision Procedure. J Low Genit Tract Dis 2017;21:59-63.
17. Lu CH, Liu FS, Kuo CJ, et al. Prediction of persistence or recurrence after conization for cervical intraepithelial neoplasia III. Obstet Gynecol 2006;107:830-5.
18. Chikazawa K, Notsu S, Motomatsu S, et al. Predictors of recurrent/residual disease after loop electrosurgical excisional procedure. J Obstet Gynaecol Res 2016;42:457-63.
19. Demarquet E, Mancini J, Preaubert L, et al. Risk Factors of Post-Large Loop Excision of the Transformation Zone Recurrent High-Grade Cervical Intraepithelial Lesion: A Prospective Cohort Study. J Low Genit Tract Dis 2019;23:18-23.

20. Leguevaque P, Motton S, Decharme A, et al. Predictors of recurrence in high-grade cervical lesions and a plan of management. Eur J Surg Oncol 2010;36:1073-9.

21. Park JY, Lee SM, Yoo CW, et al. Risk factors predicting residual disease in subsequent hysterectomy following conization for cervical intraepithelial neoplasia (CIN) III and microinvasive cervical cancer. Gynecol Oncol 2007;107:39-44.

22. Park JY, Bae J, Lim MC, et al. Role of high risk-human papilloma virus test in the follow-up of patients who underwent conization of the cervix for cervical intraepithelial neoplasia. J Gynecol Oncol 2009;20:86-90.

23. Torné A, Fusté P, Rodríguez-Carunchio L, et al. Intraoperative post-conisation human papillomavirus testing for early detection of treatment failure in patients with cervical intraepithelial neoplasia: a pilot study. BJOG 2013;120:392-9.

24. Arbyn M, Redman CWE, Verdoost F, et al. Incomplete excision of cervical precancer as a predictor of treatment failure: a systematic review and meta-analysis. Lancet Oncol 2017;18:1665-79.

25. Costa S, De Nuzzo M, Infante FE, et al. Disease persistence in patients with cervical intraepithelial neoplasia undergoing electrosurgical conization. Gynecol Oncol 2002;85:119-24.

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