Original Article

Risk factors predicting pathological degradation after cervical excision in cervical intraepithelial neoplasia grade II P16-positive patients over 25 years old: a cross-sectional study

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Background: Cervical intraepithelial neoplasia (CIN) is a collective term for pre-cancerous lesions associated with cervical invasive carcinoma. Treatment options depend on the development and progression of the disease. Especially for patients with CINII grade who are aged 25 years and older and have fertility requirements, it is a clinical challenge to determine whether to proceed with conservative or excisional treatment. Excisional treatment increases the risk of overtreatment outcomes, such as cervical insufficiency, preterm labor, miscarriage, and premature rupture of membranes, in young women with childbearing potential. P16 immunohistochemical staining has greatly improved the consistency of CINII patient's diagnosis. The aim of this study was to analyze the risk factors predicting pathological degradation after cervical excision in cervical intraepithelial neoplasia grade II P16-positive patients over 25 years old, and to provide information to help optimize clinical treatments patients with CINII disease.

Methods: Single-factor and logistic regression models were used to analyze the risk factors for pathological downgrading in the CINII/P16-positive (+) group. The predicted probability of pathological downgrading in the CINII/P16(+) group of patients was calculated according to the logistic regression model to generate a new variable multi-indicator association for receiver operating characteristic (ROC) curve plotting to determine the predictive ability.

Results: A total of 248 women who met the inclusion and exclusion criteria were included. Statistical analysis showed that the CINII/P16(+) group had a higher pathological downgrading rate compared with the CINIII group after cold knife conization (CKC) (χ^2=6.26, P=0.012). Univariate factors showed that the differences were statistically significant when comparing age, number of biopsy-involved quadrants, menopausal status, and involvement of glands, respectively (P<0.05). In contrast, the differences were not statistically significant when comparing cytological findings, type of transformation zone, high-risk human papilloma virus (HR-HPV) testing, abortion status, pregnancy frequency, time from diagnosis to CKC and Ki67 percentage between the two groups. Multifactorial logistic regression showed that the extent of biopsy CINII involvement [odds ratio (OR), 1.589], menopausal status (OR, 4.031), and glandular involvement (OR, 5.549) were all independent risk factors for pathological downgrading in the CINII/P16(+) patient group (P<0.05). The order of significance of the areas under the ROC curve (AUCs) was as follows: combined multiple indicators (AUC 0.716) > gland involvement (AUC 0.625) > biopsy CINII involvement extent (AUC 0.614) > menopausal status (AUC 0.565).

Conclusions: A higher rate of pathological downgrading after CKC was found in CINII/P16-positive patients who were aged over 25 years. Overtreatment exists in patients with CINII/P16-positive diagnosis.

Independent factors for pathological downgrading were identified by the factors including if the lesion involved the gland, the extent of CINII involvement on biopsy, and menopausal status.

Keywords: Cervical intraepithelial neoplasia II (CINII); P16 immunohistochemical staining; overtreatment; patients aged 25 years or older

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Introduction

Cervical intraepithelial neoplasia (CIN) is a collective term for pre-cancerous lesions associated with morphologic squamous epithelium alterations related to human papilloma virus (HPV) infection which reflects a continuum in the development and progression of cervical cancer. There are different grades of CIN based on the extent of the disease: CINI, CINII, and CINIII. Currently, in the treatment of the disease, CINI is considered a histological diagnosis of benign viral replication. Even with persistent CINI, the chances of lesion progression are low, so most patients with CINI are able to achieve self-resolution and should be managed conservatively (1). In contrast, CINIII is considered a true precancerous lesion with a high risk of developing into invasive cervical cancer, and patients in this stage should consider excisional treatment as the best option (2). CINII represents the threshold of intervention, and there are different treatments in clinical management. Some hospitals adopt P16 immunohistochemical (IHC) staining as an indicator to stratify management, based on which, excisional treatment is used for CINII/P16-positive (+) patients and conservative treatment is used to treat patients with a CINII/P16-negative (–) diagnosis (3,4). However, a report has shown that using $P16^{IHC}$ staining for stratified management of CINII patients may also cause some lesion regression over time (5).

In some European countries and the United States, substituting the prospective treatment with surgical treatment for CINII patients who are over 25 years of age and have fertility requirements has been reported for many years (6). There are two main treatments available for female patients who are aged 25 years and above and have a fully visible colposcopic zone of transformation if they have fertility requirements (7). Although cervical conization is a relatively simple and safe treatment, excisional treatment increases the risk of adverse pregnancy outcomes, such as cervical insufficiency, preterm labor, miscarriage, and premature rupture of membranes, in young women with childbearing potential (8-10). $P16^{IHC}$ has greatly improved the consistency of CINII patient's diagnosis (5). From our clinical experience, it is common to observe pathological downgrading in some CINII/P16(+) patients. In this paper, we analyzed the risk factors predicting pathological degradation after cervical excision in cervical intraepithelial neoplasia grade II P16-positive patients over 25 years old, and to provide information to help optimize clinical treatments for patients with CINII disease. We present this article in accordance with the STROBE and STARD reporting checklists (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1745/rc)

Highlight box

Key findings

- The identified independent factors for pathological degradation after cervical ex-cision in cervical intraepithelial neoplasia grade II P16 (CINII/P16)-positive patients over 25 years old were uninvolved glands, lower number of biopsy-involved quadrants, and non-menopausal status.

What is known and what is new?

- Over-treatment exists in high-grade squamous intraepithelial lesion (CINII/III) patients.
- It is crucial to distinguish the management between CINII and CINIII patients. The rate of pathological degradation was 27.0% which has been identified in CINII/P16-positive patients who are aged 25 years and above.

What is the implication, and what should change now?

- We suggest that for CINII/P16-positive patients who are aged 25 years and above with the identified risk factors, especially young women who have fertility requirements, informed follow-up after biopsy should be given priority.

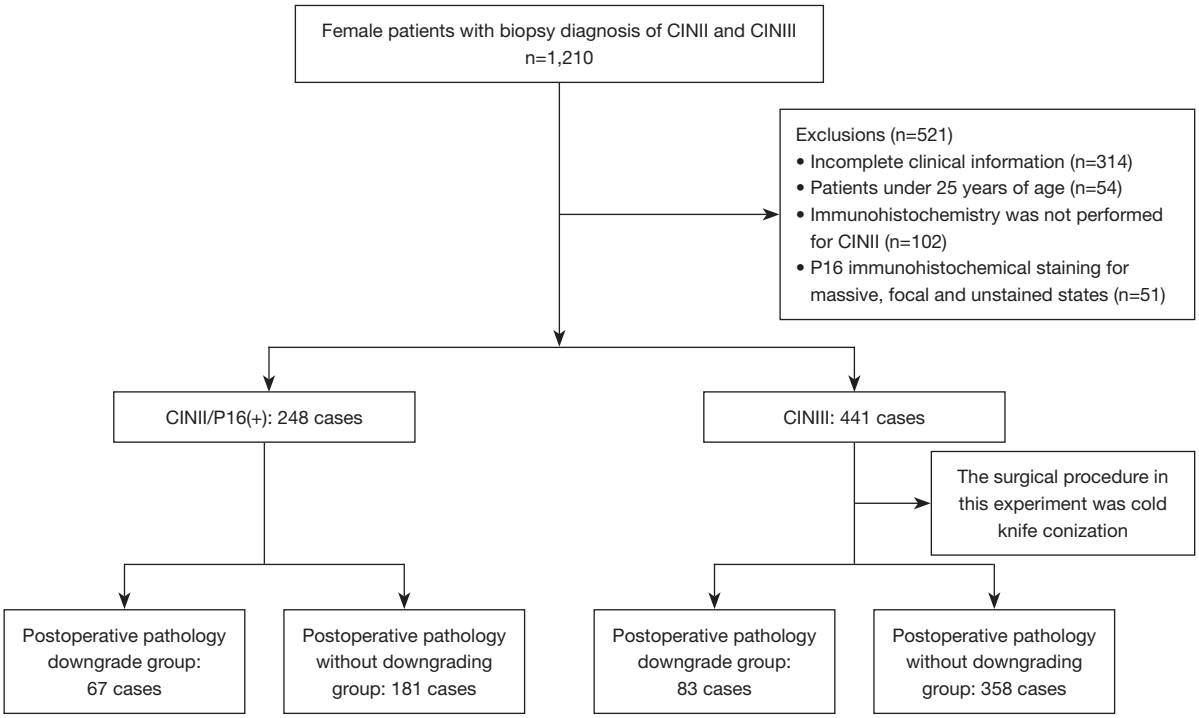

Figure 1 Flow chart. CIN, cervical intraepithelial neoplasia.

Methods

Participants

This study was conducted retrospectively. We collected clinical data from patients treated in the period from January 2018 to December 2021 at Baoding No.1 Central Hospital, Hebei Province, China. The standards of exclusion were as follows:

- Incomplete clinical information;
- Patients under 25 years of age;
- Immunohistochemistry was not performed for CINII;
- P16 immunohistochemical staining for massive, focal and unstained states.

A total of 689 women who met the inclusion and exclusion criteria were included. Among them, 248 patients aged 25 years or older had been diagnosed with CINII with colposcopy-guided pathological spot biopsy and had undergone a line of IHC staining and cervical conization, and 441 patients were diagnosed with CINIII (*Figure 1*). The CINII/P16(+) group was further divided into a pathological downgrading subgroup and a pathological non-downgrading subgroup based on whether the patients' pathology was downgraded (CINI or chronic cervicitis) or not after cold knife conization (CKC). The postoperative pathology of the CINII/P16(+) group included 15 cases of chronic cervicitis, 52 cases of CINI, 175 cases of CINII–III, and 6 cases of adenocarcinoma in situ (AIS) of the cervix and squamous carcinoma of the cervix. All cases had complete clinical data and follow-up data, and initial colposcopic cervical biopsy results of CINII and CINIII. Patients had also undergone further IHC staining and cervical conization for CINII.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the Baoding No.1 Central Hospital (Date: 2021/11/22; No. [2021]039), and all included patients were informed and signed the informed consent form.

Variable items

The patients' age, ThinPrep cytologic test (TCT), human papilloma virus (HPV) infection typing, transformation zone type, Ki67 percentage, cervical biopsy pathology results, pregnancy frequency, number of abortions, biopsy lesion involvement quadrant status, CKC pathology results and time from diagnosis to CKC were collected in the two groups, respectively.

Inspection method

Cervical cytology examination was performed by TCT production, Pap staining, microscopic observation, and application of The Bethesda System (TBS) reporting system for the results. Cobas 4800 HPV test was used to analyze the samples. This is a qualitative test device for detection of HPV DNA that amplifies target DNA in cervical epithelial cells by real-time polymerase chain reaction (PCR) and nucleic acid hybridization to detect quantitative HPV genotyping tests (type 21) [real-time fluorescence quantitative polymerase chain reaction (RT-fluorescence qPCR) method] to detect the virus in specimens in microscopic amounts. The method can detect 18 HR-HPV types, including HPV16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82, and 3 low-risk HPV types, 6, 11, and 81. Colposcopy was performed using a SLC-2000 electronic colposcope from Shenzhen Jinkowei (Shenzhen, China). All biopsies were sent to two pathologists in our pathology department for simultaneous reading and unified diagnosis. If the results from the two pathologists were inconsistent, the diagnosis was determined by a third senior physician or sent to a province-level hospital for consultation. The degree of lesion was determined by a senior pathologist. P16 and Ki67 IHC staining were performed for CINII patients for further diagnosis, with postoperative pathology ≤ low-grade squamous intraepithelial lesion (LSIL) being defined as the pathology downgrading group, and postoperative pathology ≥ high-grade squamous intraepithelial lesion (HSIL) being defined as the pathology non-downgrading group (11-13). P16 staining was performed on the pathological sections using a Roche BenchmarkGX immunohistochemistry instrument (Roche, Basel, Switzerland), and a Nikon ECLIPSE light microscope (Nikon Corporation, Minato-ku Tokyo, Japan) to classify P16 diffuse strong positive staining, focal positive staining, and no staining. Diffuse strong positive staining for P16 was further classified as P16 positive and partial, focal, punctate. No staining was defined as P16 negative (14).

Treatment method

CKC of the cervix: All patients were treated within 5–7 days after menstruation, with routine leucorrhea checks and abstinence from sexual intercourse 1 day before the procedure. The patient was placed in a cystotomy position, and routinely disinfected with a towel that was coated with 5% Lugol's iodine solution (EDAN, Shenzhen, China). The cervical area was exposed after intravenous anesthesia, and the exact location and extent of the lesion was determined. Sturmdorf suture was used to close the cervix. The excised tissues were sent for pathological examination. The resection standard was decided according to the type of transformation zone: type I transformation zone was resected with a resection length of 7–10 mm; type II transformation zone was resected with a resection length of 10–15 mm; type III transformation zone was resected with a resection length of 15–25 mm (15). The length of resection was 15–25 mm.

Statistical analysis

The statistical software SPSS 23.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. All measurement values were expressed as mean ± standard deviation ($\bar{x} \pm s$), and the values were compared using the χ^2 test. Multifactorial unconditional logistic regression was used to analyze the correlations between pathological degradation of CINII and age, TCT, HPV infection typing, transformation zone type, Ki67 percentage, number of pregnancies, number of abortions, time from diagnosis to CKC, and biopsy lesions involvement quadrant. Odds ratio (OR) values and 95% confidence intervals (CIs) were calculated. P values less than 0.05 were considered statistically significant. The predictive probability of the combination of multiple indicators was calculated by logistic regression model, the receiver operating characteristic (ROC) curve was plotted, and the predictive ability of risk factors for the appearance of pathological downgrading in the CINII/P16(+) group was assessed. *Figure 1* summarizes the research methods and procedures used in this study.

Results

A total of 689 women who met the inclusion and exclusion criteria were included. Among them, 248 patients aged 25 years or older had been diagnosed with CINII, and 441 patients were diagnosed with CINIII. *Table 1* shows that among 248 cases in the CINII/P16(+) group, there were 15 cases of the normal cervix/chronic cervicitis, 52 cases of CINI, 181 cases of CINII and above. Among 441 cases in the CINIII(+) group, there were 17 cases of normal cervix/chronic cervicitis, 66 cases of CINI, 358 cases of CINII and above. *Table 2* shows that the difference in pathological downgrading rate between the CINII/P16(+) group and

Table 1 Pathological diagnosis after conization in two groups of patients (cases)

Group	Total number of cases	Chronic cervicitis/ normal cervix	CINI	CINII	CINIII	AIS	SCC
CINII/P16 positive group	248	15	52	110	65	4	2
CINIII group	441	17	66	37	279	18	24

CIN, cervical intraepithelial neoplasia; AIS, adenocarcinoma in situ; SCC, squamous cell carcinoma.

Table 2 Pathological downgrading after conization in two groups of CINII patients

Group	Pathological findings after conization		Pathological downgrading rate (%)	χ^2	P value
	Cervicitis or CINI	CINII, CINIII or higher grade lesions			
Total number of cases	150	539	21.77	6.26	0.012
CINII/P16(+) group, cases (%)	67 (44.7)	181 (33.6)	27.01		
CINIII group, cases (%)	83 (55.3)	358 (66.4)	18.82		

CIN, cervical intraepithelial neoplasia.

CINIII was statistically significant.

Among 248 cases in the CINII/P16(+) group, there were 67 cases of pathological downgrading and 181 cases of pathological non-downgrading. Univariate factors showed that the differences were statistically significant when comparing age, number of biopsy-involved quadrants, menopausal status, and involvement of glands, respectively (P<0.05). In contrast, the differences were not statistically significant when comparing cytologic findings, type of transformation zone, high-risk human papilloma virus (HR-HPV) testing, time from diagnosis to CKC, abortion status, pregnancy frequency, and percentage of Ki67 in both (*Table 3*). The factors with P<0.05 in the univariate analysis, namely, age, number of biopsy-involved quadrants, menopausal status, and glandular involvement were then included in the multivariate logistic regression analysis. The results showed that the number of biopsy-involved quadrants (OR, 1.589), menopausal status (OR, 4.031), and glandular involvement (OR, 5.549) were independent factors influencing the pathological downgrading of CINII/P16(+) patients (all P<0.05) (*Table 4*).

ROC curve and prediction analysis showed that the ability order of predicting the diagnostic efficacy of CINII/P16(+) patients presenting with pathological downgrading was as follows: multiple indicator combination [area under the curve (AUC) 0.716] > glandular involvement (AUC 0.625) > number of quadrants involved in the lesion (AUC 0.614) > menopausal status (AUC 0.565) (*Figure 2*).

Discussion

In this study, the probability of pathological downgrading in CINII/P16(+) patients who were aged 25 years or older was 27.01%, which is consistent with the rate in other reports (12,16). The reasons for the appearance of downgraded postoperative pathology could be as follows: (I) smaller lesions, with CINII lesions already being removed at the time of biopsy (17); (II) low diagnostic concordance of CINII, even though P16 IHC staining has greatly improved the diagnostic concordance of CINII, the correctness of the diagnostic results has still not reached 100% (14); (III) long interval between biopsy and conization, lesion fading, and so on (13).

It has been reported that young age, long interval between biopsy and conization, uninvolved glands, unproductive, low grade cytologic findings, and small lesion size are all predictive factors for the appearance of pathological downgrading in HSIL (CINII/CINIII) (11). However, CINII is not the same as CINIII in terms of risk of progression to carcinoma, natural regression, and prognosis, and the biological significance of HSIL/CINII downgrading is still unclear. A retrospective analysis of 1,659 patients with HSIL (CINII and III) by Guo *et al.* found that age of 18–24 years, biopsy results of CINII, uninvolved glands, and cytologic non-HSIL findings were the outcomes of pathologic downgrading (18). It has even been suggested that CINII lesions may represent a mixture

Table 3 Results of univariate analysis affecting pathological downgrading after conization in CINII/P16(+) patients

Category	Total number of cases	Pathology downgrading group, cases (%)	Pathology non-downgrading group, cases (%)	χ^2/T	P value
Cytology results				2.114	0.833
NILM	46	14 (20.9)	32 (17.7)		
ASC-US	101	24 (35.8)	77 (42.5)		
LSIL	65	20 (29.9)	45 (24.9)		
ASC-H	20	6 (9.0)	14 (7.7)		
HSIL	15	3 (4.5)	12(6.6)		
CA	1	0 (0.0)	1(0.6)		
Age				6.560	0.01
25–40 years	115	40 (59.7)	75 (41.4)		
>40 years	133	27 (40.3)	106 (58.6)		
Number of quadrants involved in biopsy				4.732	0.03
Single point accumulation	158	50 (74.6)	108 (59.7)		
Two or more points cumulative	90	17 (25.4)	73 (40.3)		
Transformation zone type				0.001	0.976
Type I/II	207	56 (83.6)	151 (83.4)		
Type III	41	11 (16.4)	30 (16.6)		
HPV typing				0.707	0.401
Without 16/18 type	67	33 (24.8)	34 (29.6)		
Type 16/18 included	181	100 (75.2)	81 (70.4)		
Menopausal status				3.860	0.049
Non-menopausal	181	55 (82.1)	126 (69.6)		
Menopausal	67	12 (17.9)	55 (30.4)		
Pregnancy times				0.075	0.784
≤2	96	25 (37.3)	71 (39.2)		
>2	152	42 (62.7)	110 (60.8)		
Abortion situation				0.621	0.431
No history of abortion	112	33 (49.3)	79 (43.6)		
History of abortion	136	34 (50.7)	102 (56.4)		
Ki67 percentage (%)		55.30±2.13	52.75±1.40	0.962	0.337
Gland involvement				14.122	<0.001
Yes	70	7	63		
No	178	60	118		
Time from diagnosis to CKC (d)		44.40±7.69	33.27±2.14		0.058

Data are presented as mean ± standard deviation or number (frequency). CIN, cervical intraepithelial neoplasia; NILM, negative for intraepithelial lesion or malignancy; ASC-US, atypical squamous cells of unknown significance; LSIL, low-grade squamous intraepithelial lesion; ASC-H, atypical squamous cells, cannot exclude high-grade lesion; HSIL, high-grade squamous intraepithelial lesion; CA, cancer; HPV, human papillomavirus; CKC, cold knife conization.

Table 4 Results of multifactorial analysis affecting pathological downgrading after conization in CINII/P16(+) patients

Category	B	SE	Wald	OR (95% CI)	P value
Age	0.333	0.214	2.421	1.717 (0.896–2.980)	0.120
Lesion involvement quadrant	0.463	0.211	4.833	1.589 (1.051–2.400)	0.028
Menopausal status	1.394	0.562	6.262	4.031 (1.341–12.120)	0.013
Recurrent glandular condition	1.714	0.443	14.971	5.549 (2.329–13.220)	<0.001

CINII, cervical intraepithelial neoplasia II; SE, standard error; OR, odds ratio; CI, confidence interval.

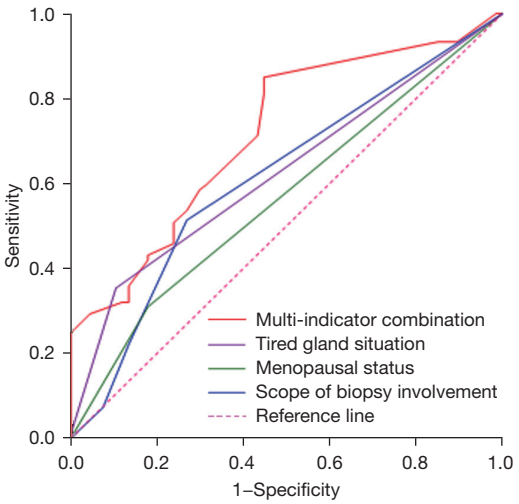

Figure 2 ROC curves of each index and multiple indexes combined to predict CINII/P16(+) female patients over 25 years of age. ROC, receiver operating characteristic; CINII, cervical intraepithelial neoplasia II.

of HPV infection (i.e., CINI) and cancer precursors (CINIII). Therefore, it is necessary to differentiate the study of pathological downgrading between CINII and CINIII. In this paper, we only analyzed the causes of postoperative pathological downgrading in the CINII patients who are over 25 years old. The results were consistent with the appearance of pathological downgrading in HSIL (CINII/CINIII). Furthermore, our study has found that the absence of gland involvement, the small extent of CINII involvement on biopsy, and the absence of menopause were considered as predictors of pathological downgrading in CINII/P16(+) patients.

This study has shown that the possibility of overtreatment to some patients exists. Standardized biopsy itself has a certain therapeutic effect. This study shows that some CINII patients can achieve recovery of lesions within a certain period of time through biopsy. For this group of patients, follow-up observation after biopsy is sufficient, and immediate cervical conization is not feasible and may cause overtreatment.

A study reported that gland involvement was an independent factor for pathological downgrading in 1,499 HSIL (CINII and CINIII) cases (19). This study also found that gland involvement was an independent factor for pathological downgrading in CINII/P16(+) patients. The number of quadrants involved in the biopsy was also found to correlate with pathological downgrading in this experiment. The possible reason for this may be that the lack of involvement of glands indicates superficial lesions, and the involvement of 1 quadrant indicates that the lesions are limited and have not yet spread to other quadrants or the cervical canal, which makes it easier to remove the lesions during biopsy.

This study showed that the number of involved quadrants of the biopsy lesion, the involvement of the gland, and the menopausal status were all independent factors for the occurrence of lesion downgrading.

The combined AUC of multiple indicators was 0.716 (>0.7) which is greater than the individual AUC of each indicator. The probability of pathological downgrading was as high as 71.6% if the above three factors were combined. Therefore, clinicians should fully evaluate the feasibility of conservative treatment for women with an age of over 25 years, uninvolved glands, few quadrants of lesion involvement and non-menopausal women, especially those with fertility requirements, and maintain close follow-up to reduce the occurrence of overtreatment.

This study had the following limitations: since this study was a retrospective analysis, no time factor was used to analyze the downgrading of CINII/P16(+) patients. A large sample may be needed to confirm the optimal follow-up time after biopsy. Also, the accuracy of biopsy may be compromised when colposcopy is inadequate, which may lead to higher-level missed lesions and decreased accuracy in the number of quadrants involved in biopsy. We also noted

that the report did not discuss the risk of undertreatment of cancer. As CINII was not separated from CINIII in the surgical specimen outcome, it was not clear what percentage of CINII was, in fact, a missing CINIII diagnosis that should be treated anyway, and why it is acceptable to have overtreatment in CINIII but not in cases of CINII. The report focuses on the downgrading of CINII/P16 positive but does not make a counterpoint evaluating the risk of CINIII or carcinoma underdiagnosis at biopsy. Therefore, the patient and the gynecologist lack the full risk evaluation.

Conclusions

This study revealed that the rate of pathological degradation in CINII/P16(+) patients who were aged 25 years or older was 27.01%. It is crucial to distinguish the management between CINII and CINIII patients. The independent factors for the occurrence of pathological degradation were uninvolved glands, lower number of biopsy-involved quadrants, and non-menopausal status. We suggest that for patients with these factors, especially young women who have fertility requirements, informed follow-up after biopsy should be given priority, which can avoid the occurrence of overtreatment in some degree.

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Footnote

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Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1745/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1745/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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the Baoding No.1 Central Hospital (Date: 2021/11/22; No. [2021]039), and all included patients were informed and signed the informed consent form.

References

1. Moscicki AB, Shiboski S, Hills NK, et al. Regression of low-grade squamous intra-epithelial lesions in young women. Lancet 2004;364:1678-83.
2. Montz FJ. Management of high-grade cervical intraepithelial neoplasia and low-grade squamous intraepithelial lesion and potential complications. Clin Obstet Gynecol 2000;43:394-409.
3. Wei L, Zhao Y, Shen D, et al. Expert consensus on cervical cancer screening and abnormal management issues in China (I). Chinese Clinical Journal of Obstetrics and Gynecology 2017;18:190-2.
4. Wei LH, Shen DH, Zhao FH, et al. Expert consensus on issues related to cervical cancer screening and abnormal management in China (II). Chinese Clinical Journal of Obstetrics and Gynecology 2017;18:286-8.
5. Miralpeix E, Genovés J, Maria Solé-Sedeño J, et al. Usefulness of p16(INK4a) staining for managing histological high-grade squamous intraepithelial cervical lesions. Mod Pathol 2017;30:304-10.
6. Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. J Low Genit Tract Dis 2020;24:102-31.

7. Zhao C, Bi H, Zhao Y, et al. Chinese expert consensus on the management of high-grade intraepithelial lesions of the uterine cervix. Chinese Clinical Journal of Obstetrics and Gynecology 2022;23:220-4.
8. Blomfield PI, Buxton J, Dunn J, et al. Pregnancy outcome after large loop excision of the cervical transformation zone. Am J Obstet Gynecol 1993;169:620-5.
9. Samson SL, Bentley JR, Fahey TJ, et al. The effect of loop electrosurgical excision procedure on future pregnancy outcome. Obstet Gynecol 2005;105:325-32.
10. Sadler L, Saftlas A. Cervical surgery and preterm birth. J Perinat Med 2007;35:5-9.
11. Poomtavorn Y, Tanprasertkul C, Sammor A, et al. Predictors of Absent High-grade Cervical Intraepithelial Neoplasia (CIN) in Loop Electrosurgical Excision Procedure Specimens of Patients with Colposcopic Directed Biopsy-Confirmed High-Grade CIN. Asian Pac J Cancer Prev 2019;20:849-54.
12. Bradbury M, Rabasa J, Murcia MT, et al. Can We Reduce Overtreatment of Cervical High-Grade Squamous Intraepithelial Lesions? J Low Genit Tract Dis 2022;26:20-6.
13. Zhang L, Li Q, Zhao M, et al. Discrepancies between biopsy-based and excision-based grading of cervical intraepithelial neoplasia: the important role of time between excision and biopsy. Int J Gynecol Pathol 2015;34:221-7.
14. Darragh TM, Colgan TJ, Cox JT, et al. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Arch Pathol Lab Med 2012;136:1266-97.
15. Zhao C, Liu J, Li M, et al. Operation specification of conical hysterectomy. Chinese Clinical Journal of Obstetrics and Gynecology 2021;22:218-9.
16. Nam K, Ryu A, Jeon S, et al. Clinical significance of a negative loop electrosurgical excision procedure biopsy in patients with biopsy-confirmed high-grade cervical intraepithelial neoplasia. J Low Genit Tract Dis 2015;19:103-9.
17. Livasy CA, Moore DT, Van Le L. The clinical significance of a negative loop electrosurgical cone biopsy for high-grade dysplasia. Obstet Gynecol 2004;104:250-4.
18. Guo Y, Wang Y, Peng Q, et al. Absence of high-grade cervical intraepithelial neoplasia in conization specimens from patients with colposcopic biopsy-confirmed high-grade cervical intraepithelial neoplasia: Retrospective study of 1695 cases. Front Oncol 2022;12:980884.
19. Tian PF, Zhang HF, Cao CC, et al. Analysis of factors influencing pathological downgrading after cervical high-grade squamous intraepithelial lesion biopsy and cervical conization. Chinese Clinical Journal of Obstetrics and Gynecology 2023;24:140-3.

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