Correlation between Low-Grade Cervical Squamous Intraepithelial Lesion and Ki-67 Positive Index: Post-Print

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Abstract

Objective: To investigate the correlation between low-grade cervical intraepithelial neoplasia (CIN I) and the Ki-67 proliferation index positivity rate.

Methods: One hundred patients diagnosed with low-grade cervical intraepithelial neoplasia by cervical biopsy in our hospital' s gynecology outpatient clinic were enrolled. Immunohistochemical Ki-67 detection was performed concurrently. Without any intervention, repeat pathological biopsy and immunohistochemical Ki-67 detection were conducted after six months. Pre- and post-treatment pathological and immunohistochemical Ki-67 results were compared to statistically analyze disease progression in patients.

Results: Initial cervical biopsy diagnosed 100 patients with CIN I, with concurrent Ki-67 positivity index detection. These 100 CIN I patients were stratified into three groups based on Ki-67 positivity rate: 88 cases with <3% positivity, 10 cases with 3%-10% positivity, and 2 cases with >10% positivity; the difference was statistically significant ($P<0.05$). Second biopsy pathology demonstrated essentially no disease progression in patients with Ki-67 positivity rate <3%; among the 10 patients with 3%-10% positivity, 8 progressed to CIN II; and both patients with >10% positivity progressed to CIN III.

Conclusion: The Ki-67 positivity index directly determines the clinical outcome of patients with low-grade cervical squamous intraepithelial neoplasia; higher positivity indices correlate with increased likelihood of progression to CIN II or CIN III.

Full Text

Preamble

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Title

Correlation between Cervical Low-grade Squamous Intraepithelial Lesion and Ki-67 Positive Index

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Abstract

Objective: To investigate the correlation between cervical low-grade intraepithelial neoplasia (CIN I) and the positive index of cell proliferation marker Ki-67.

Methods: A total of 100 patients diagnosed with cervical low-grade intraepithelial neoplasia by cervical biopsy in our hospital' s gynecology outpatient clinic were selected. Immunohistochemical Ki-67 detection was performed simultaneously. Without any treatment, pathological biopsy and immunohistochemical Ki-67 detection were repeated after six months. The results of the initial and follow-up pathology and immunohistochemical Ki-67 were compared to track patient outcomes.

Results: Among the 100 patients initially diagnosed with CIN I by cervical biopsy, Ki-67 positive index was simultaneously detected. The 100 CIN I patients were divided into three intervals based on Ki-67 positive rate: 88 cases with <3%, 10 cases with 3%-10%, and 2 cases with >10%. The differences were statistically significant (P<0.05). Patients with Ki-67 positive rate <3% showed essentially no disease progression on the second biopsy. Among the 10 patients with 3%-10% positive rate, 8 progressed to CIN II. Both patients with >10% positive rate progressed to CIN III.

Conclusion: The Ki-67 positive index directly determines the outcome of patients with cervical low-grade squamous intraepithelial lesions; higher positive indices are more likely to progress to CIN II or CIN III.

Keywords: cervical; low-grade squamous intraepithelial neoplasia; moderate squamous intraepithelial neoplasia; severe squamous intraepithelial neoplasia; Ki-67; positive index

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Introduction

Currently, domestic research on the correlation between cervical low-grade squamous intraepithelial lesions (CIN I) [1] and immunohistochemical cell proliferation indices remains limited [2]. This study focuses on investigating cervical CIN I in combination with immunohistochemical cell proliferation index (Ki-67), utilizing Ki-67 as a single monitoring parameter for CIN I [3]. By detecting the positive index of atypical squamous epithelium in cervical biopsies and combining this with clinical follow-up tracking, we aimed to understand disease outcomes more precisely, guide early clinical intervention and treatment, and provide definitive diagnostic and therapeutic evidence for cervical precancerous lesions. The findings are reported as follows.

Materials and Methods

1.1 General Information

From January 2014 to October 2016, 100 patients diagnosed with cervical low-grade squamous intraepithelial lesions in our hospital were enrolled, and Ki-67 was detected in all patients. **Inclusion criteria:** patients with pathological diagnosis of CIN I by cervical biopsy, aged 18-45 years, married or sexually active adult women. **Exclusion criteria:** patients who did not cooperate with follow-up visits after six months or could not be contacted.

Reagents: Ki-67 produced by Guangzhou Ankaili. **Equipment:** Anping immunorepair instrument. **Pathology equipment:** sampling station, dehydrator, embedding machine, microtome, slide spreader, staining machine.

1.2 Detection Methods

(1) Patients diagnosed with CIN I by cervical biopsy simultaneously underwent Ki-67 detection according to immunohistochemical operating procedures; (2) Ki-67 positive index was divided into three intervals: 0%-3%, 3%-10%, and >10%; (3) After six months, cervical biopsy was performed on the same site with immunohistochemical Ki-67 detection; (4) Initial and follow-up pathological results were compared to track patient outcomes.

1.3 Observation Indicators

Observation indicators included: Ki-67 positive intervals; monitoring for fever, bleeding, and other adverse reactions after the second cervical biopsy; and assessing recovery status through gynecological examination one week post-procedure.

1.4 Statistical Methods

SPSS 17.0 software was used for statistical analysis. Chi-square analysis was employed to compare count data of Ki-67 index across different positive inter-

vals, with pairwise comparisons conducted. P<0.05 was considered statistically significant.

Results

2.1 Secondary Pathological Biopsy Results and Ki-67 Positive Index

Among the 88 cases with initial cervical biopsy immunohistochemical Ki-67 <3%, all second biopsy results remained CIN I (88%). Of the 10 cases with initial Ki-67 of 3%-10%, 8 patients showed CIN I on second biopsy while 2 progressed to CIN II. Both patients (2 cases) with initial Ki-67 >10% progressed to CIN III on second biopsy. Chi-square test revealed statistically significant differences in patient distribution across different Ki-67 positive intervals (P<0.05), and significant differences in CIN I patient outcomes within different Ki-67 positive intervals (P<0.05, Table 1). Higher positive intervals were associated with greater likelihood of progression to CIN II or CIN III.

Table 1 Secondary cervical biopsy pathological results in CIN I patients (n)

2.2 Safety and Follow-up Observation

After secondary cervical biopsy, patients with pathological results of CIN I were advised to undergo regular follow-up; patients with CIN II and CIN III results were managed according to routine gynecological practice, receiving cervical conization surgery with postoperative regular follow-up required. After the second cervical biopsy, minor vaginal bleeding was observed, but no fever or bleeding occurred after three days. One-week postoperative gynecological examination confirmed that all patients had returned to their preoperative status.

Discussion

Cervical biopsy is one of the diagnostic methods for positive two-cancer screening and serves as an important means for cervical precancerous diagnosis, widely adopted by most domestic hospitals [3]. For patients with high-risk human papillomavirus (HPV) infection, before cervical biopsy, gynecological examination requires visual inspection of the cervix at 1-12 o' clock positions, with main indicators including smoothness, color, and endocervical mucosal surface conditions. The cervical surface is wiped with 3% acetic acid, and biopsy sites are determined only when abnormalities are detected. Most patients with pathological CIN I results require no treatment, as lesions may regress or remain non-progressive, while only a minority progress to CIN II or CIN III [4]. Research indicates that CIN I patients are closely associated with HPV infection. Once infected, the cervical epithelium becomes infected from outside to inside, with superficial epithelial cells easily eroded by HPV virus, resulting in koilocytic

changes, gradual nuclear enlargement, and even irregular nuclear membrane changes [5]. This study focused on detecting the cell proliferation index Ki-67 in cervical CIN I patients while conducting follow-up with second pathological biopsy and Ki-67 detection to monitor disease progression, employing combined pathological biopsy and immunohistochemistry to monitor CIN I patients.

The transmission routes of high-risk HPV infection are complex, often associated with unprotected sexual history. Following infection, high-risk HPV primarily remains latent within cervical epithelium. When physical condition declines, particularly before and after menstruation when resistance markedly decreases, conditions favor viral replication and proliferation. Over time, as viral load reaches certain levels, nuclear enlargement, irregular nuclear membranes, and koilocytic changes or apoptosis in cervical squamous epithelial cells occur [6]. Ki-67 immunohistochemical staining can label most cells outside the G0 phase [7], thus serving as a cell proliferation index. Higher Ki-67 positive rates indicate greater proportions of cells in the proliferative cycle and faster cell growth. In pathological reports, the proportion of Ki-67 positive cells is commonly used to express cell proliferation status. Tumor cells exhibit slowed division, relatively prolonged cell cycles, and increased numbers of proliferating cells. Utilizing this characteristic, immunohistochemical Ki-67 labeling readily detects tumor cells, with the primary distinction between tumor and normal cells being the proportion of positive cells [8]. In normal tissues, most cells exist in a non-proliferative state, resulting in extremely low Ki-67 positive cell proportions (<3%). This project employed Ki-67 labeling for cervical intraepithelial lesion cells to distinguish normal from abnormal cells and determine disease outcomes by detecting Ki-67 positive index in patient cervical epithelial cells [9].

The pathological diagnosis of CIN I primarily involves enlarged nuclei and mild atypia in the lower one-third region of cervical squamous epithelium, with focal koilocyte formation, mostly accompanied by high-risk HPV infection [10]. Since some high-risk HPV-positive patients spontaneously clear the virus over time, corresponding cervical CIN I patients tend toward self-limitation. For patients with persistent high-risk HPV positivity, regular follow-up is essential, utilizing detection methods including liquid-based cytology screening, HPV testing, HPV E6/E7 mRNA detection, and cervical biopsy [11]. This study selected CIN I patients and detected Ki-67 positive rates in biopsy specimens. Through classified observation and re-examination of different positive rates, we found that higher Ki-67 positive rates correlated with poorer patient outcomes, with high positive rate patients progressing toward CIN II or CIN III. This research demonstrates that regular biopsy with Ki-67 detection in CIN I patients can effectively guide medication use and necessary therapeutic interventions [12], precisely preventing cervical cancer while avoiding overtreatment. CIN I patients with Ki-67 positive index <5% can be managed with observation and follow-up, while those with Ki-67 positive index >10% should receive timely necessary interventions such as LEEP cervical conization to prevent cervical cancer development [13].

Ki-67 has been widely used as an antigen marker for cell proliferation status, expressed in actively proliferating cells [14]. Ki-67 expression is associated with breast cancer development and progression, serving as an adverse prognostic factor with important reference value for breast cancer diagnosis, treatment, and prognosis evaluation [15]. Ki-67 is believed to be involved in maintaining cell proliferation, though its functional mechanisms remain unclear. Research data indicate that Ki-67 proliferation index is closely related to tumor differentiation degree, invasion, metastasis, and prognosis, representing an important reference basis in tumor research [16].

Cervical CIN I patients monitored with Ki-67 proliferation index can effectively track disease development and outcomes, precisely detecting the metabolic activity of CIN lesion cells, controlling cervical cancer from its source, and effectively blocking further deterioration of lesion cells [17-20]. This protects women's health and improves quality of life while reducing cervical cancer incidence and preventing overtreatment, warranting clinical promotion and application.

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Note: Figure translations are in progress. See original paper for figures.