



## Perspective

# Selective applications of excisional surgical treatments of cervical precancers



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## ABSTRACT

Cervical precancers encompass high-grade squamous intraepithelial lesion and adenocarcinoma in situ. Treatment of precancerous lesions can reduce cervical cancer mortality and prevent the development of invasive cervical cancer. The choice of treatment regimen needs to follow the principle of individualization and should be based on a combination of factors, including the patient's age, fertility requirements, pregnancy status, pathological type, type of colposcopic transformation zone, patient's follow-up conditions, and the experience of the treating provider. This article presents an opinion regarding the appropriate indications for excisional surgery and total hysterectomy in the management of precancerous lesions of the cervix, with the aim of establishing standardized therapeutic approaches for the treatment of precancerous lesions of the cervix.

Cervical precancers include cervical intraepithelial neoplasia (CIN) 2, CIN3 and adenocarcinoma in situ (AIS). The concept of CIN was introduced in 1969 by Richart.<sup>1</sup> The classification of CIN is based on the histologic changes observed in the cytoplasm, nucleus, and tissues, ranging from mild to severe abnormalities. World Health Organization (WHO) revised the classification of female genital tumors in 2014, proposing the use of two grades: low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL).<sup>2</sup> According to this classification system, CIN1 is classified as LSIL, while CIN2 and CIN3 are classified as HSIL and are considered precursor lesions of squamous carcinoma of the cervix. CIN3 is widely recognized as a direct precursor requiring intervention, CIN2 is a histologic diagnosis that falls between CIN1 and CIN3. In the absence of any identifiable biological marker to accurately predict the regression of HSIL lesions, the classification of histologic HSIL as either CIN2 or CIN3 and subsequent differential management should be considered the most suitable approach.<sup>3</sup> AIS is considered a precancerous lesion of adenocarcinoma of the cervix, with a very high risk of progression to invasive adenocarcinoma if left untreated.

Cervical excisional treatment is recommended by clinical guidelines as an effective approach for managing precursor lesions as it provides

both diagnostic and therapeutic benefits. The literature suggests that the diagnosis of a biopsy may underestimate the final histologic findings in 11 %–47 % of cases.<sup>4,5</sup> Additionally, the risk of missing invasive carcinoma in CIN2 detected by cervical biopsy ranges from 0.5 % to 4.5 %<sup>6,7</sup> and the risk of missing invasive cancer in CIN3 detected by cervical biopsy can be as high as 7 %.<sup>6</sup> Meanwhile, it has been observed that more than 5 % of cases with HSIL may be detected in patients who have previously undergone cervical excisional treatment, along with coexisting AIS.<sup>8</sup>

Cervical excisional treatment including loop electrosurgical excision procedure (LEEP) or cold knife conization (CKC). In a meta-analysis of LEEP or CKC for the treatment of CIN, Jiang et al.<sup>9</sup> found no significant differences in recurrence rate, margin positivity, and residual lesions between the two procedures, indicating that the two treatments were equally effective. The incidence of LEEP is significantly lower than that of CKC in terms of complications such as bleeding, infection, cervical stenosis, and adverse pregnancy outcomes.<sup>9</sup> Currently, LEEP has become the mainstay of excisional surgery. Total hysterectomy is not a preferred treatment for precursor lesions and is performed only in certain special circumstances.

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## 1. Excisional treatment of high-grade squamous intraepithelial lesions

Although CIN2 and CIN3 are both classified as HSIL, their clinical prognosis exhibits significant heterogeneity in terms of biological behavior. Epidemiological evidence suggests that the biological behavior of CIN2 is more similar to that of CIN1 than to that of CIN3<sup>10</sup>. Recent meta-analyses have indicated that more than half of CIN2 lesions regress spontaneously, with a higher rate of regression in women aged 30 years and younger.<sup>11</sup> Kaiser Permanente Northern California (KPNC) enrolled 2417 patients aged 21–39 years with CIN2, with a median follow-up time of 48 months. They ultimately found that the risk of CIN2 progressing to CIN3+ was 18%.<sup>12</sup> Tainio et al. also found that untreated CIN2 progressed to CIN3+ in 14%, 18%, and 24% of cases at 12, 24, and 36 months, respectively.<sup>11</sup> Furthermore, the progression of CIN 2 to cervical cancer is observed in only a minimal 0.3% of cases.<sup>10</sup>

Considering the relatively high rate of CIN2 regression<sup>13</sup> and the low rate of progression<sup>14</sup> in young women, it may be appropriate to consider observation as the preferred approach for patients under the age of 25<sup>3,15</sup>. However, treatment may also be considered for this age group.<sup>3,15</sup> On the other hand, patients over 24 years of age may also be managed conservatively (which involves closely monitoring the patient through cervical cytology, HPV testing, and colposcopy instead of immediate surgical intervention) if they prioritize their concern about future fertility over tumor progression and meet the eligibility criteria, including adequate colposcopy and negative endocervical curettage (ECC) for CIN2+ or ungraded CIN.<sup>3</sup> The guidelines recommend treatment if CIN2 persists for more than 24 months or if the lesion expands into the endocervix.<sup>3,16,17</sup> The determination of whether to treat CIN2 or opt for conservative management is most effectively made through consultation with the patient. This decision should be made after a comprehensive discussion of the benefits and harms associated with each approach, with the aim of striking a balance between fertility preservation and the treatment of precursor lesions.

CIN3 is recognized as a direct precursor to cervical cancer. The true malignant potential of CIN3 was confirmed by a study in New Zealand, which found that the risk of progression from untreated CIN3 to invasive carcinoma over a follow-up period of more than 30 years was 31%.<sup>18</sup> According to national guidelines,<sup>3,17,19,20</sup> excisional treatment is the recommended intervention for CIN3. In Germany, a conservative strategy can be used for women up to the age of 24 with histopathologically confirmed CIN3, provided the entire lesion can be evaluated by colposcopy and does not contain any atypical glandular components, and an invasive process must be excluded with a high degree of certainty.<sup>16</sup> Treatment should be initiated if the CIN3 persists for more than 12 months or if the lesion expands into the endocervix.<sup>16</sup>

There is no consensus on the feasibility of conservative management for HSIL that is not categorized. If CIN3 cannot be excluded, managing the patient as if CIN3 is present is preferred.<sup>3</sup> Cervical excisional treatment was considered safest for patients.

Excisional treatment enables the comprehensive evaluation of histologic specimens for pathological analysis, thereby aiding in the identification of higher-grade lesions or glandular lesions. The margin status can also be indicated by it, serving as a predictive factor and providing a foundation for managing residual or recurrent CIN2+. Excisional treatment offers the advantage of removing lesions while preserving the anatomy and function of the cervix without requiring more extensive surgery. The treatment is typically associated with a high success rate. Invasive carcinoma can be ruled out when the excision specimen shows negative margins and more than 87% of patients are followed up without more surgery.<sup>21</sup>

## 2. Excisional treatment of adenocarcinoma in situ

About 15% of AIS cases coexist with invasive adenocarcinoma.<sup>22</sup> The incidence of AIS is low but has been gradually increasing in recent years.

Most AIS lesions are found in the transformation zone of the uterine cervix. 85% of these lesions are unicentric, while 6.5%–15% can be multifocal and discrete.<sup>23</sup>

Diagnostic excision is strongly advised for all patients with a histopathologic diagnosis of AIS through cervical biopsy. This procedure is necessary to validate the diagnosis and assess the extent of the disease. Additionally, it is crucial to exclude invasive adenocarcinoma before proceeding with the final treatment plan. Early opinions suggested that CKC tends to obtain more comprehensive specimens and achieve greater depths compared to LEEP. A meta-analysis of 18 studies found that LEEP had a higher rate of positive margins (44.0%) compared to CKC (28.8%, RR = 1.55, 95% CI 1.34–1.80).<sup>24</sup> However, there was no significant difference in the residual lesion rate (LEEP 9.1% vs. CKC 11.0%) and recurrence rate (LEEP 7.0% vs. CKC 5.6%).<sup>24</sup> Therefore, both LEEP and CKC are considered viable surgical procedures for AIS. It is crucial to prioritize the preservation of the resection specimen's integrity and the interpretability of the margins to obtain precise information regarding the margins' status and the staging of invasive adenocarcinoma. CKC is preferred if LEEP does not achieve complete resection.<sup>3</sup>

The 2019 American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines recommend an excision length of at least 10 mm, which can be increased to 18–20 mm for patients without fertility requirements.<sup>3</sup> The 2019 Italian guidelines<sup>25</sup> recommend a depth of excision of at least 10–15 mm when squamocolumnar junction (SCJ) is visible and 20–25 mm when SCJ is invisible. The depth of excision should be determined based on factors such as the patient's age, fertility needs, and colposcopy features. A sampling of the cervical canal is performed during excision surgery to assess for residual disease. The marginal status of the excised tissue of the cervix is a predictor of residual lesions, recurrence, and progression. Positive margins have been found to be correlated with residual AIS ranging from 49.3% to 52.8% and invasive carcinoma ranging from 5.2% to 5.9%.<sup>26,27</sup> Nevertheless, it should be noted that negative margins exhibit a relatively low negative predictive value, as residual AIS is observed in less than 10% of cases,<sup>3</sup> and invasive carcinoma is detected in only 0.6%–0.7%.<sup>26,27</sup>

## 3. Total hysterectomy for HSIL and AIS

It is equally effective as a total hysterectomy in preventing the progression of CIN2 and CIN3 to invasive carcinoma. Additionally, close follow-up after treatment is also comparable to total hysterectomy in preventing invasive carcinoma.<sup>28,29</sup> Despite this, it is not advisable to use total hysterectomy as the primary approach for treating precursor lesions. The clinical scenario presents a range of complexities and variations. For instance, challenges may arise when performing cervical excisional treatment or when there is incomplete resection during the initial surgery for postmenopausal HSIL. Additionally, difficulties may arise in achieving effective postoperative follow-up in certain special groups or specific conditions. In such cases, it becomes crucial to determine a safer management strategy for HSIL that prioritizes the well-being of the patient. Furthermore, the unique pathological characteristics of AIS and the value of cervical excisional treatment in this context have become important considerations in clinical practice. It is imperative to acknowledge that there is still a prevalent tendency to excessively recommend hysterectomy as a precautionary measure against cancer, leading to potential overtreatment or surgical complications. In the context of managing cervical cancer precursor lesions, the urgent resolution of the issue lies in the standardization of excisional treatment procedures and the determination of the appropriate extent of total hysterectomy.

Total hysterectomy can benefit women as follows: (1) After menopause, there are physiological changes such as cervical volume reduction, loss of vault, and vaginal stenosis. These changes can result in a narrow surgical space and unclear anatomy, making it unsafe to perform cervical excisional surgeries. (2) It minimizes the risk of cervical excisional treatment and is better followed up by observing the vagina rather than a

narrowed cervix. The more aggressive treatment of total hysterectomy can be selectively recommended for postmenopausal HSIL patients who no longer have reproductive needs. Patients may benefit from this form of aggressive intervention rather than just follow-up after conservative treatment. (3) Hysterectomy remains the established therapeutic approach for individuals with AIS who do not desire future pregnancy. (4) Hysterectomy can be beneficial when combined with other gynecologic conditions.

However, the incidence of hemorrhage, infection, and other complications is significantly higher with total hysterectomy than with other treatments for CIN. In 9.2 % of cases, cervical lesions can extend into the vagina and develop vaginal intraepithelial neoplasia (VaIN).<sup>30</sup> Total hysterectomy alone will not be sufficient to eliminate all lesions that extend into the vagina. These lesions could spread in the context of the scar on the cuff, which can make subsequent treatment less effective.<sup>31</sup> It has been established that the risk of vaginal cancer or vaginal intraepithelial lesions is significantly elevated over a period of at least 15 years in individuals who undergo total hysterectomy for CIN compared to those who undergo total hysterectomy for other indications.<sup>32</sup>

A retrospective study by Cao et al.<sup>33</sup> which included 1449 patients with HSIL diagnosed by colposcopy cervical sampling found that the menopausal group had a higher risk of cervical cancer compared to the non-menopausal group (9.4 % vs. 3.8 %). These lesions have a higher likelihood of being ignored during colposcopy, and the inability to perform cervical excisional surgery diminishes its significance in excluding or diagnosing invasive carcinoma of the cervix. Consequently, the diagnosis of cervical cancer may be missed, leading to the dilemma of insufficient surgical intervention. The confirmation or exclusion of the diagnosis of microscopic invasive carcinoma combined with HSIL and the staging of cervical cancer can be best achieved through surgical means. It is crucial for patients and their families to be fully informed about the potential risks associated with surgery and the possibility of postoperative pathologic upgrading. Prior to undergoing surgery, patients should be provided with comprehensive information to make informed choices and explicit consent should be obtained.

### 3.1. Indication of total hysterectomy for HSIL<sup>3,15,17,19,34–36</sup>

- (1) Patients who struggle with cervical excisional treatment, especially postmenopausal individuals with cervical atrophy, may be considered for total hysterectomy instead of cervical excisional treatment.
- (2) Total hysterectomy is acceptable if there is evidence of residual HSIL lesions or when the patient is over 50 years old and repeat cervical excisional treatment is not possible due to positive endocervical margins.
- (3) Patients who are unable to undergo adequate follow-up, including those who receive multiple treatments and those who develop untreatable cervical stenosis and vaginal stenosis, may be considered for total hysterectomy after providing informed consent.
- (4) Postmenopausal patients with negative margins after cervical excisional treatment may undergo a total hysterectomy if they do not wish to preserve their fertility.
- (5) Conservative treatment of extensive HSIL of the uterine cervix with VaIN is challenging. Total hysterectomy with resection of the involved vaginal fornix can be accepted.
- (6) Total hysterectomy may be accepted for medical reasons along with other indications for uterine resection. These indications may include symptomatic fibroids, uterine prolapse, endometriosis, or intractable menorrhagia.

### 3.2. Indication of total hysterectomy for AIS

Total hysterectomy is widely regarded as the definitive treatment for AIS without fertility concerns<sup>15,17,25,37</sup>

- (1) In cases of AIS where there is no desire to preserve fertility and negative surgical margins for excisional treatment, total hysterectomy is the preferred approach.
- (2) Individuals who are unable to achieve negative margins through multiple resections may opt for a modified radical hysterectomy or a total hysterectomy alone. It is not advisable to preserve reproductive function in such cases.
- (3) Total hysterectomy at the end of labor is the recommended approach for individuals with AIS who have preserved reproductive function and have tested positive for HPV or abnormal cytologic/histologic results during surveillance.

## 4. Follow-up after surgical treatment for patients with cervical precancers

### 4.1. Follow-up after excision of HSIL

There is a potential risk of residual or recurrent lesions, estimated to be approximately 8 %~16 %, after treatment for HSIL. Additionally, individuals with these lesions have a 2–5 times higher risk of developing invasive cervical cancer compared to the general population.<sup>38,39</sup> Furthermore, there is a significantly elevated risk of developing tumors associated with HPV. So, long-term follow-up should be performed after treatment. Risk factors associated with the persistence or recurrence of HSIL following treatment include age  $\geq 50$  years, positive margins, and abnormal cytology or HPV testing during postoperative follow-up. Numerous studies have demonstrated that postoperative HPV testing can greatly enhance sensitivity in detecting residual or recurrent HSIL<sup>40–42</sup> and that the first post-treatment follow-up time point is 6 months after the surgery. It is recommended to perform HPV testing or combined screening, and if either test yields a positive result, the patient should be referred for colposcopy.

Although the presence of positive margins after treatment for HSIL is considered a risk factor for residual or recurrent disease, it is not recommended to perform repeat excisional surgery in these patients.<sup>3</sup> Re-excisional surgery should be limited to individuals who have a high risk of retaining residual lesions. Several authoritative guidelines<sup>15,43,44</sup> have been established to address the issue of balancing the potential harm caused by excessive treatment and the risk of missing lesions in the clinical management of abnormal cervical cytology. These guidelines aim to provide recommendations for healthcare professionals in order to achieve this balance effectively. For individuals who are over 50 years old and exhibit a positive endocervical margin are classified as being at a high risk for residual lesions. Therefore, it is recommended that these patients undergo repeat excisional surgery.

The 2019 ASCCP guideline<sup>3</sup> suggests that HPV-based screening should be conducted annually for the initial three years following surgery. Negative tests conducted annually during the initial 3-year period may extend the follow-up interval to once every 3 years for at least 25 years.

### 4.2. Follow-up after excision of AIS

Currently, there is a lack of evidence regarding the optimal surveillance strategy for fertility-preserving AIS. The 2019 ASCCP guideline proposes that co-testing and ECC surveillance be conducted every 6 months for at least 3 years.<sup>3</sup> Annual co-testing and ECC for at least 2 years may be recommended following negative results. Individuals who have consistently tested negative for a period of 5 consecutive years during follow-up may be eligible for long-term screening follow-up every 3 years. It is worth noting that the results of HPV tests have been found to be the most reliable indicator of disease recurrence.<sup>45,46</sup> Therefore, it is considered appropriate to continue monitoring patients who have consistently negative results in both HPV testing and ECC after child-bearing. For individuals who have received positive results from HPV tests or abnormal cytology/histology results, it may be advisable to

consider undergoing a hysterectomy once they have completed their childbearing.

#### 4.3. Follow-up after total hysterectomy

Wiener et al.<sup>47</sup> estimated the cumulative incidence of VaIN after total hysterectomy for CIN or AIS to be 0 %, 0.8 %, and 2.0 % at 10, 15, and 20 years of follow-up, respectively. The potential explanation for this phenomenon is the coexistence of CIN or cervical cancer can coexist with VaIN. Following surgery, these lesions can present as scar tissue on the vaginal cuffs, remaining inactive for extended periods. However, there is a risk of progression to invasive carcinoma.<sup>31</sup> Therefore, it is essential to conduct follow-up after total hysterectomy treatment of HSIL or AIS of the uterine cervix. However, there is currently a lack of substantial evidence in this regard. The Chinese expert consensus on elective application of hysterectomy (2022 edition)<sup>35</sup> recommends that the initial follow-up visit should be conducted 6 months after surgery based on HPV testing. If the result is negative, the test will be repeated in 12 months. If negative again, long-term follow-up is recommended every 3–5 years. If the result is positive, referral for colposcopy is recommended for prompt detection of VaIN or vaginal cancer, with particular attention to evaluating the corners of the dissection on both sides.

In conclusion, cervical excisional surgery is a preferred treatment for HSIL. This treatment option allows for the removal of lesions while maintaining the anatomy and function of the cervix, without requiring extensive surgery. The success rate of this treatment is generally high. It is crucial to consider all the advantages and disadvantages before performing a total hysterectomy for the treatment of precursor lesions. Strict regulation of the indications for total hysterectomy is necessary, and patients should be informed of the possible risks involved. Total hysterectomy may be considered as an alternative for specific groups, particularly postmenopausal women. To confirm the diagnosis of AIS, diagnostic excisional surgery is imperative since invasive carcinoma cannot be ruled out in the absence of this procedure. Hysterectomy remains the standard treatment for AIS patients who do not have fertility needs. However, cervical excisional treatment with negative margins is a viable alternative for AIS patients that preserves future fertility.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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