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Review article

Adenocarcinoma *in situ* of the uterine cervix: Clinical practice guidelines from the Italian society of colposcopy and cervical pathology (SICPCV)

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ABSTRACT

Objective: to provide a practical tool for the evidenced-based management of adenocarcinoma *in situ* (AIS) of the uterine cervix, a challenging diagnosis encountered by colposcopists in their daily practice.
Methods: the proposed recommendations were drafted by the Italian Society of Colposcopy and Cervical Pathology (SICPCV) based on comprehensive reviews of previous guidelines, large uncontrolled studies, metanalysis, and sytematic reviews. The quality Level and the strength of the recommendations were graded and respectively expressed in Roman numbers (I–VI) and letters (A–E).
Results: Women with all subcategories of abnormal glandular cells and AIS on cervical citology should be offered colposcopy with endocervical sampling (Strength of recommendation: A). In women with cytological AIS and negative colposcopy or endocervical curettage, an excisional treatment under colposcopic guidance is recommended (Strength of recommendation: A). If immediate post-conization endocervical sampling is positive, further conization is indicated (Strength of recommendation: C). In women who desire to preserve fertility with positive cone margins, further conization should be performed (Strength of recommendation: B). If colposcopy is adequate, a cylindrical excision that includes the whole transformation zone and at least 1–1.5 cm of endocervix beyond the squamous-columnar junction should be performed (Strength of recommendation: B). If colposcopy is inadequate, it is recommended that conization includes the whole transformation zone with a depth of 20–25 mm (Strength of recommendation: B). Hysterectomy is the standard definitive treatment for AIS in women who do not wish to preserve fertility (Strength of recommendation: B).
Conclusion: the proposed recommendations should enable clinicians to correctly diagnose, treat and follow AIS patients, avoiding mismanagement.

Contents

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Introduction

The following recommendations are addressed to all medical professionals who deal with the diagnosis and treatment of adenocarcinoma *in situ* of the uterine cervix (AIS). They have been written by a group of physicians identified by the Clinical Practice Committee of Italian Society of Colposcopy and Cervical Pathology (SICPCV), who conducted an exhaustive review of the literature.

Although AIS does not represent a common neoplasm, recent epidemiological data from Western countries have shown an increase in the number of diagnoses when compared to squamous cervical carcinoma of the uterine cervix [1–5].

To date, AIS is the only precursor of invasive cervical adenocarcinoma [6], as endocervical glandular dysplasia (EGD), that includes all glandular lesions with minor cytological atypia, is no longer considered a precursor of neither AIS nor invasive cervical carcinoma [7]. EGD diagnosis is poorly reproducible, and management is not codified. The management of EGD will not be addressed in this review.

Definition and histopathology

AIS is an intraepithelial lesion, in which normally situated glands are in part or completely replaced by pre-malignant epithelium, that may degenerate into adenocarcinoma of the uterine cervix if not treated [8]. Cervical epithelium is usually devoid of intracellular mucin and may resemble endometrial epithelium [8], while at times glands are lined by intestinal epithelium containing goblet, neuroendocrine, and Paneth cells [9]. Pre-neoplastic glands do not extend beyond the deepest normal crypts: remaining above the lamina propria. AIS may affect the surface of the glands, where the epithelium is often single-layered, presenting with a sharp border when the lesion is detected on colposcopy [9]. However, AIS often hides in the crypts, accounting for frequent detection failures on colposcopy [9].

The most frequent cell types identified in AIS are endocervical (usual type), intestinal, endometrioid, and tubal respectively [8]. A stratified mucin-producing type has also been described, where the neoplastic cells of the squamous intraepithelial lesion contain intracellular mucin [8]. Although the stroma around AIS may be intensely inflamed, there is no desmoplastic reaction.

The pattern of AIS lesions varies, making the diagnosis of the full extent of the disease challenging. Endocervical-type lesions arise from glandular reserve cells of the squamous-columnar junction infected with oncogenic HPV, extending from the transformation zone to the endocervical canal. AIS may also present with "skip" lesions" in 10–15% of women (multifocal disease), with outbreaks that are separated by at least 2 mm of normal mucosa [10]. Finally, AIS may also be found in the upper endocervical canal, affecting the deeper portions of the endocervical clefts [8].

Risk factors and clinical presentation

Like invasive cervical adenocarcinoma, AIS is associated with high-risk HPV infection and persistence [1,11–13], as well as exposure to oral contraceptives [12]. The spread of oncogenic HPV could only account for the increasing incidence of endocervical adenocarcinomas, as tubal or intestinal variants are not as strictly related to the infection, while endometrioid types have no associations with HPV [14]. Recent reports have also described cases of negative HPV in older women with intestinal AIS [15–17].

A meta-analysis that included 1278 women showed that the average age at AIS diagnosis is 36.9 years [20]; most cases occur between age 32 and 40 [10–13,15–18], with almost 70% of the cases affecting women less than 35 years of age [19].

Although AIS is generally asymptomatic, some patients may report vaginal bleeding. Bleeding may not directly reflect the presence of AIS, but it can prompt colposcopy with cervical and endocervical biopsy that can eventually identify AIS [21].

AIS diagnosis is a clinical challenge considering the low sensitivity of cytology and colposcopy for glandular intra-epithelial lesions [18,19]. Retrospective studies showed that the sensitivity of cytology to identify women later diagnosed with AIS reached 50–69% for glandular lesions, 26–31% for squamous lesions,15% for mixed squamous and glandular lesions, while it failed to identify any lesions 4% of the times [22,23]. When cytology detects atypical glandular cells (AGC) favor neoplasia, 29% of the subjects present pre-invasive or invasive lesions on histology [24]. Approximately 50% of AIS are unexpected findings on biopsies or conizations performed for high grade or invasive squamous lesions [25,26]. As many as 5% of women undergoing conization for high-grade SIL, may present with a concomitant AIS [19], while AIS has also been detected on specimens from histerectomies performed for benign pelvic pathology or abnormal uterine bleeding [19].

Methods

The guidelines here presented are the result of a specific methodological process defined during a satellite meeting of the 2018 SICPCV National Congress through the following phases: 1) designation of a group of national experts in AIS diagnosis and treatment (expert drafters) to draft the guidelines 2) literature search on Medline, PubMed, EMBASE, and the Cochrane Library for articles published until March 2019 using the keywords “AIS”, “adenocarcinoma *in situ*” and “cervix”; 3) formulation of clinical themes used to develop the guidelines.

The Level of Quality and Strength of Recommendations (Fig. 1) were defined according to the criteria suggested by the Methodological Manual of the National Guidelines System [27], and respectively expressed in Roman numbers (I to VI) and letters (A to E).

The recommendations here presented were approved by the Scientific Committee of the SICPCV (April 2019), and are now endorsed by the SICPCV.

Results

Diagnostic work-up

All women with abnormal cervical cytology due to glandular lesions should undergo colposcopy with endocervical sampling; triage by reflex HPV testing is not recommended [28]. AIS has no colposcopic features that can differentiate it from other cervical lesions. Cytological slide review may be considered in young women with negative colposcopy and negative histology, before performing an excisional treatment. Excisional treatment is

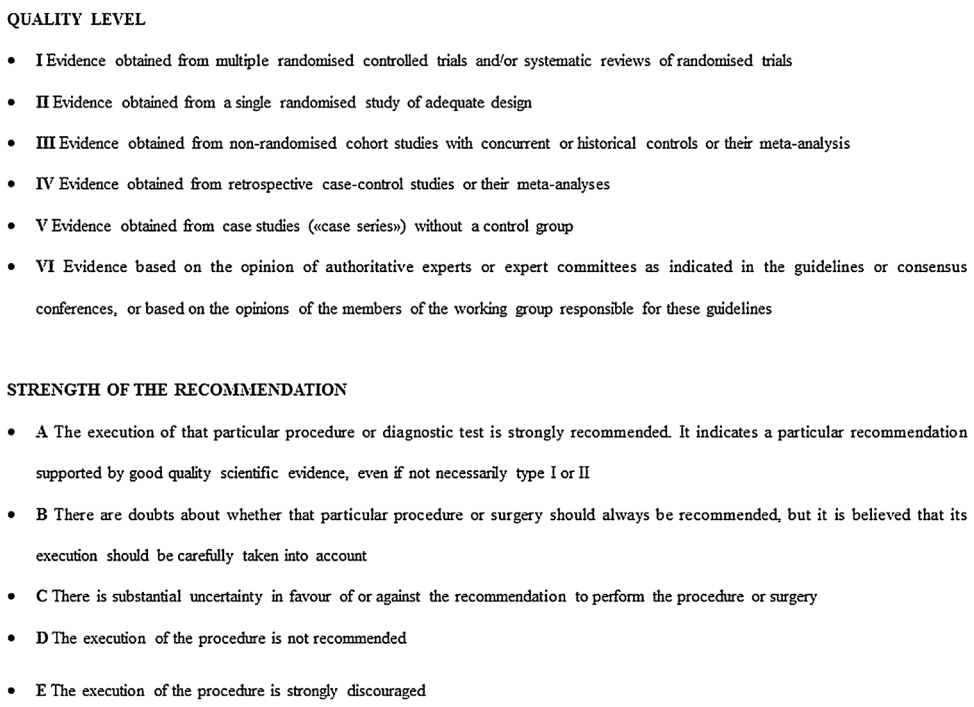

Fig. 1. Quality level and Strength of the Recommendations – Grading (Italian National Health Institute - National Standard Guidelines 2002).

necessary to confirm the diagnosis, to assess margin status, and to exclude an invasive disease [19].

Recommendations:

- For women with all subcategories of AGC and AIS, except atypical endometrial cells, colposcopy with endocervical sampling is recommended regardless of HPV testing results ***(Level of evidence: II - Strength of recommendation: A)*** [28–30].
- In women with cytological AIS and negative colposcopy and/or negative ECC, a diagnostic excisional procedure under colposcopic guidance is recommended ***(Level of evidence: II - Strength of recommendation: A)*** [28,31–33].
- The type of diagnostic excisional procedure used should provide an intact specimen with interpretable margins ***(Level of evidence: II - Strength of recommendation: B)*** [28,34].

Conservative management

In women who want to preserve fertility, cervical conization is the best therapeutic option [28]. Since women with AIS are usually of childbearing age, fertility sparing approaches should be considered. However, patients should be informed that surveillance for AIS has not been proven as effective in preventing progression to invasive disease [28,35]: AIS can be multifocal, colposcopic changes can be minimal, and sensitivity to detect residual disease or adenocarcinoma can therefore be limited [28]. Furthermore, invasive cancer cannot be excluded without a diagnostic excisional procedure [28].

Conization may be performed using one of the following techniques: loop electrosurgical excision procedure (LEEP), laser conization, or cold knife conization (CKC). There is no evidence that the technique used may affect outcomes [36]. A recent meta-analysis showed no significant difference in the rate of residual disease during post-treatment follow-up between women undergoing LEEP or CKC [37]. Likewise, laser conization revealed equal effectiveness when compared to other surgical techniques, with greater respect for healthy tissues [19].

ECC should be performed immediately after conization, especially in women considering fertility preservation [28,38]. If post-treatment ECC is positive further treatment is recommended as 77% of cases present residual AIS on the hysterectomy specimen [38,39].

Cone margin status in women with AIS is an essential clinical-pathological feature to consider [10,19,22,26,40]. The presence of positive cone margins was associated with residual disease in 49.3% of women with AIS [36]. However, a complete cervical excision may have limited negative predictive value: negative cone margins do not necessarily ensure the complete excision of AIS [36]. Previous studies, with a follow-up of 12–120 months, showed that conizations with negative margins had a recurrence risk of 3%; conversely, positive cone margins presented a 17% recurrence rate [36]. Finally, the risk of carcinoma after conservative treatment was reported as being less than 1%. Therefore, in women who desire to preserve fertility despite positive cone margins, further conization could be offered.

As the goal of excisional treatment is to have negative cone margins, a cone depth of 10–25 mm should be obtained, according to the guidelines on colposcopic adequacy [41]. A cone depth of 20–25 mm has been associated with negative cone margins [41]. However, such cone dimensions increase the rate of cervical stenosis and adverse pregnancy outcomes [42]. Given the histopathological features of AIS, 3–10 mm of healthy tissue from the lesion to the cone apex have been reported to decrease the possibility of residual satellite lesions [43].

Recommendations:

- If AIS is suspected, conization may be performed using one of the following techniques: LEEP, CKC or laser conization. There is no definitive evidence that conization technique may affect outcomes ***(Level of evidence: III – Strength of recommendation: B)*** [36].

- If immediate post-conization ECC is positive, further conization is indicated ***(Level of evidence: V – Strength of recommendation: C)*** [31,44].
- In women who desire to preserve fertility with positive cone margins, further conization should be performed ***(Level of evidence: III – Strength of recommendation: B)*** [20,31].
- If colposcopy is adequate, a cylindrical excision (type 3 conization) should be performed, including the entire transformation zone and at least 10–15 mm of endocervix beyond the squamous-columnar junction ***(Level of evidence: III – Strength of recommendation: B)*** [45].
- If colposcopy is inadequate, a type 3 conization including the entire transformation zone with a depth of 20–25 mm should be performed ***(Level of evidence: III – Strength of recommendation: B)*** [45,46].

Post-conization follow-up

There are no definitive data about the optimal surveillance for women undergoing conization for AIS: long-term follow-up is required especially for women undergoing conservative treatment.

It is reasonable to recommend colposcopic evaluation with cytological and high-risk human papillomavirus (HPV) testing every 6 months for the first 2 years, and then every 12 months for the following 3 years [35]. Then, the cytological follow-up should be continued every 12 months indefinitely. Brushing of the cervical canal or ECC should be performed on each clinical evaluation. Post-conization HPV positivity is a valid predictor of disease relapse and progression [28,47], especially if the specific AIS histotype and the pre-treatment HPV status are also taken into consideration [47]. Women with recurrent AIS or high-grade squamous dysplasia should be offered further cervical conization before hysterectomy [35].

There is no recommended specific time interval between treatment and future pregnancies. It is reasonable to wait at least a 6–12 months before planning a pregnancy if follow up remains negative. AIS in pregnant women is very rare; however, management should be the same as for squamous cervical lesions: colposcopy, cervical cytology and cervical biopsies can be perform while ECC is unacceptable [28]. Obstetric outcomes for women managed conservatively for AIS are the same as for women subjected to conization for other indications: the rate of miscarriage and preterm birth are respectively 22% and 5.7% if conization was performed for AIS [48].

Definitive treatment

Hysterectomy represents the standard definitive treatment of AIS [28]. For women with cervical AIS who do not wish to preserve fertility, a total extrafascial hysterectomy without bilateral oophorectomy is recommended [28,49,50]. Hysterectomy should also be considered if cone margins remain positive on the subsequent cervical conization, and in women poorly compliant to follow-up [49,50]. After completion of childbearing, definitive treatment could also be offered, even if the supporting data are inconsistent [51]. In perimenopausal/menopausal women, conservative treatment should be considered only after adequate counselling about AIS recurrence rate and possible incomplete diagnostic follow-up due to cervical stenosis [51,52]. Hysterectomy represents a definitive surgical approach, as invasive adenocarcinoma after removal of the uterus is anecdotal [53,54].

Women with invasive adenocarcinoma on histology after hysterectomy should be managed according to the current guidelines. Post-hysterectomy follow-up for AIS is not standardized. It is reasonable to recommend colposcopy, cervical cytology and and high-risk human HPV testing every 6 for the first 2 years, and then every 12 months for the following 3 years. Colposcopy can effectively identify possible residual disease or early disease progression (such as high-grade vaginal intraepithelial neoplasia or invasive carcinoma in HPV related cases).

Recommendation:

- Hysterectomy is the standard definitive treatment for AIS in women who do not wish to preserve fertility ***(Level of evidence: II – Strength of recommendation: B)*** [20,28,31].

Discussion

Both the diagnosis and the treatment of AIS continue to challenge practicing clinicians. Mismanagement of AIS may not be uncommon: as this lesion is less common than squamous precancerous cervical lesions, physicians who rarely deal with AIS may be unfamiliar with the appropriate diagnostic workup and treatment.

Colposcopy with endocervical curettage represents the appropriate initial diagnostic approach to AIS. Colposcopy is performed to rule out the presence of advanced disease, and to evaluate cervical anatomical variants that may contraindicate conisation as an outpatient. The subsequent diagnostic step consists in an excisional treatment under colposcopic guidance, even if the initial assessment or preoperative histology were both negative. Conization can not only provide an adequate sample of cervical tissue to analyse, but it can also treat the patient removing the entire lesion.

Conservative treatment should be performed, especially in women who want to preserve fertility: conisation should remove the entire lesion and provide a specimen with negative margins. Subsequently, close surveillance should be provided with Pap test, HPV testing, and colposcopy for up to 5 years after conization. Instead, extrafascial hysterectomy is the definitive treatment for AIS, being usually offered to women who had completed childbearing. Post surgical follow up should be the same as the one offered after conservative management.

In conclusion, we presented a pragmatic approach to diagnose and treat AIS, based on a consensus on the available evidence. It should also be emphasized that these guidelines have not been conceived to make a significant advance in the management of the AIS. We detailed the most common scenarios related to AIS, that colposcopists may encounter in their daily practice, in order to provide practicing clinicians with practical guidelines that can help them minimize mismanagement. New studies are awaited to gather evidence that could further substantiate AIS management.

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