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## SPECIAL ARTICLE

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# Adenocarcinoma in Situ of The Uterine Cervix

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### ABSTRACT

Adenocarcinoma in situ (AIS) of the uterine cervix has been acknowledged as a precursor lesion of invasive adenocarcinoma. AIS is histologically characterized by the presence of endocervical gland lined by atypical endocervical epithelium resembling the cells of adenocarcinoma but has no evidences of stromal invasion. AIS occurs within the endocervical clefts, it is difficult to screen cytologically. Incorporating high-risk HPV-DNA testing into cytologic screening could better identify AIS lesion. For definitive diagnosis of AIS, cervical conization either with knife, electrical loop, or laser is required to ensure the exclusion of coexisting invasive adenocarcinoma. Hysterectomy remains the most preferred method of definite treatment. Conservative management by conization alone is only acceptable for whom preservation of fertility is an issue. The occurrences of recurrent or persistent disease for women treated for AIS are mostly noted during the first 3 years of follow-up emphasizing the necessity of extensive surveillance in this period.

**Keywords:** adenocarcinoma in situ, cervical conization, margin, residual lesion

### Introduction

Adenocarcinoma in situ (AIS) of the uterine cervix has been acknowledged as a precursor lesion of invasive adenocarcinoma owing to the following evidences: i) AIS is usually diagnosed in women approximately 5-10 years younger than those with invasive adenocarcinoma; ii) AIS frequently coexists with invasive adenocarcinoma on excisional specimens; iii) AIS has a similar human papillomavirus (HPV) types as have been noted in invasive adenocarcinoma and; iv) there are cases of untreated AIS that subsequently develop invasive adenocarcinoma<sup>(1)</sup>.

Nevertheless, the incidence of AIS is considerably low than that of invasive adenocarcinoma, indicating that AIS is difficult to be detected and treated prior to the development of invasive lesion. Management of AIS therefore remains the challenging issue. In this review, we summarized etiology, pathological characteristics, and screening and treatment strategy of AIS.

### Etiology

Similar to that of precursor lesions of invasive squamous cell carcinoma, the identification of high-risk HPV in almost all of AIS strongly suggests a significant

role of the virus in AIS oncogenesis<sup>(2-6)</sup>.

Table 1. displays the overall high-risk HPV positivity rate and HPV type distribution in women with AIS from previous studies<sup>(2-5)</sup>. Younger women tend to be infected with multiple types of HPV rather than that in older women<sup>(5)</sup>. The most common HPV types found in AIS lesion are HPV type 16 and 18, which account

for more than 90% of cases<sup>(2-5)</sup>.

Coexisting squamous intraepithelial lesions (SIL) are commonly found among AIS lesion ranging from approximately 30% to 90% which also partly depicts the similar etiology between these two types of cervical cancer precursors<sup>(4, 7, 8)</sup>.

**Table 1.** The overall high-risk HPV positivity rate and distribution of HPV types in women with AIS

Authors	Year	Number of patients	Overall positive rate	Distribution of HPV type
Rabelo-Santos et al <sup>(2)</sup>	2009	5	100%	HPV 16: 3 (60.0%) HPV 18: 2 (40.0%)
Quint et al <sup>(3)</sup>	2010	33	100%	HPV 16: 16 (48.5%) HPV 18: 8 (24.2%) HPV 16+18: 1 (3.0%) HPV 16+other: 6 (18.2%) HPV 35: 1 (3.0%) HPV 45: 1 (3.0%)
Ault et al <sup>(4)</sup>	2011	22*	95.5%	HPV 16: 7 (31.8%) HPV 18: 5 (22.7%) HPV 16+18: 1 (4.5%) HPV 16 + other: 4 (18.2%) HPV 18+other: 1 (4.5%) HPV 16+18+other: 3 (13.6%)
Andersson et al <sup>(5)</sup>	2013	22	95.5%	HPV 18/45: 13 (59.1%) HPV 16: 3 (13.6%) HPV 18/45+59: 2 (9.1%) HPV 16+18/45:1 (4.5%) HPV 16+18/45+33/53/58: 1 (4.5%) HPV 16+33/53/58: 1 (4.5%)

Abbreviation: HPV, human papillomavirus; AIS, adenocarcinoma in situ

\*One case was negative for 16/18/31/33/35/39/51/52/56/58/59, and had missing data about the positivity of type 45

## Pathological Characteristics

AIS is characterized microscopically by the presence of endocervical gland lined by atypical endocervical epithelium resembling the cells of adenocarcinoma but lacks desmoplastic stromal response around the involved glands which is the evidence of invasion by cancer. The AIS cells have elongated, prominent nuclei and are pseudostratified. Additionally, mitotic figures and apoptotic materials are frequently observed<sup>(9)</sup>.

Unfortunately, differentiation between early invasion of adenocarcinoma and AIS may be problematic in some cases. Recent study of Jordan et al<sup>(10)</sup> reported that  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) might be a useful surrogate histopathologic marker in identifying early invasive glandular lesion. Increased  $\alpha$ -SMA expression in the periglandular stroma was associated with invasive adenocarcinoma. In this study, approximately 30% of women who were initially diagnosed with AIS were upstaged to invasive adenocarcinoma by means of  $\alpha$ -SMA overexpression<sup>(10)</sup>. Standard biologically relevant cut-off value for  $\alpha$ -SMA staining however is not established.

Most cases of AIS are of endocervical type, commonly referred to “usual” or “conventional” type. The malignant cells in endocervical type AIS are non mucin-secreting epithelium. However, an involved endocervical gland may be lined by mucin-producing malignant glandular epithelium, the so-called “goblet cells”, which is the characteristic of the intestinal type AIS. Because of its rarity, only few reports regarding clinical and histological characteristics of intestinal type AIS are available<sup>(8,11)</sup>. In recent study of Howitt et al<sup>(8)</sup>, women with intestinal type AIS were approximately 10 years older than those with endocervical type AIS (44.5 years versus 32.6 years). Additionally, in comparison with that of endocervical type AIS, women with intestinal type AIS had a lower rate of encountering coexisting SIL (29% versus 46%) and of HPV positivity (67% versus 100%) indicating that a small subset of intestinal type AIS may occur through a non-HPV infection pathway which might explain the existence of high-risk HPV negative AIS that has been reported previously<sup>(4,5)</sup>.

The rate of negative biomarkers for HPV infection in intestinal type AIS was substantially observed among older women<sup>(8)</sup>. Therefore, further research investigating the alternative pathogenesis among high-risk HPV-negative intestinal type AIS is mandatory for comprehensive cervical cancer prevention.

## Screening for adenocarcinoma in situ

Because AIS lesion frequently occurs within the endocervical clefts rather than at the surface as SIL, it is difficult to screen cytologically. In the authors' previous study, the combining of Pap smear and colposcopy procedures had a sensitivity of only 61% in detecting AIS lesions, supporting what is known about the limitations of conventional methods in detecting AIS lesion<sup>(7)</sup>.

Theoretically, endocervical curettage (ECC) might be a useful investigation tool to detect AIS lesion. However, in our recent study, approximately 40% of women who found to have residual AIS after initial cervical conization had normal ECC results<sup>(12)</sup>. ECC is therefore not helpful in detecting AIS. Several studies also support this notion<sup>(13-15)</sup>. As mentioned earlier, AIS lesion is frequently extends deep in the endocervical clefts and invagination within the endocervical stroma, it might not be exposed to the curettage instrument in some cases.

Recently, in the clinical trials of quadrivalent HPV vaccine, 22 women participating in these trials were found to have AIS. Among these women, only 2 had concomitant cytology results suggesting glandular abnormality. In addition, colposcopy also failed to diagnose AIS in all cases. Interestingly, almost all of AIS lesions (96%) were however found to be positive to high-risk HPV<sup>(4)</sup>. These findings have provide strong support for incorporating high-risk HPV-DNA testing into cytologic screening to better identify women at risk of harboring AIS lesion.

## Diagnosis and Treatment

Colposcopic features of glandular lesion including AIS have been categorized into 5 patterns: i) lesions overlying columnar epithelium not contiguous with the squamo-columnar junction; ii) lesions with large

gland openings; iii) papillary lesion; iv) lesion exhibiting epithelial budding and v) variegated red and white lesions<sup>(16)</sup>. However, Ostor et al<sup>(17)</sup> reported that among 90 women with AIS, only 19 (21.1%) women were reported to have colposcopic findings suggesting cervical glandular abnormality. This might be due to the fact that the colposcopic appearances of AIS as mentioned earlier are quite similar to the benign metaplastic process which is why these lesions are often overlooked<sup>(18)</sup>.

For definitive histologic diagnosis of AIS, cervical conization, an excision of the entire cervical transformation zone, is required to ensure the exclusion of coexisting invasive adenocarcinoma. Management of AIS after cervical conization requires meticulous consideration owing to the uncertain risk of harboring residual lesion and disease severity.

Compared with loop electrosurgical excision procedure (LEEP), a most common conization procedure in the current gynecological practice, cold-knife conization (CKC) is generally favored over LEEP for women with AIS owing to this conization technique provides a greater depth and larger volume of conization specimens, resulting in a lower rate of positive margins<sup>(12,15,19,20)</sup>. In our previous study, women with AIS who had undergone LEEP were an approximately 4 times more likely to have positive conization margins than among those undergoing CKC<sup>(12)</sup>. However, 2012 Updated Consensus Guidelines of the American Society for Colposcopy and Cervical Pathology (ASCCP) allow any diagnostic excision modality to be used for AIS lesion with strictly keeping specimen intact and margin interpretable and avoiding fragmentation of the specimens. Thus, this requires use of larger loop than that applied for SIL lesion if LEEP technique is to be chosen<sup>(21)</sup>.

In the literature, women with positive conization margins have a high rate of residual lesion ranging from 23% to 70%<sup>(13, 17, 19, 20, 22-28)</sup>. In the meta-analysis of 1278 women with AIS, a positive conization margins is associated with a significant increase in the risk of residual lesion with an odds ratio (OR) of 4.01 (95% confidence interval [CI], 2.62-6.33)<sup>(29)</sup>. As pointed out in those studies, conization margin status is a most useful

factor for determining risk of residual disease found on subsequent surgical specimens.

Despite a lower risk of residual disease, a finding of uninvolved conization margin status however is not fully protective against residual lesion, which has been reported to range widely from 0% to 45%<sup>(12-14, 17, 19, 20, 23, 25-28)</sup>. In our opinion, the differences in pathologic processing and sampling of conization specimens might be a cause of a wide variation in incidence of residual lesion among women with AIS who had negative conization margins.

In the authors' previous report<sup>(12)</sup>, by strictly following a standard sampling technique and adhering to criteria that needs the presence of normal cervical epithelium at the margins to ascertain a negative margin status, the high negative predictive value of negative conization margins in determining residual lesion was demonstrated. No AIS cases in whom the conization margins were negative had residual lesion on subsequent surgery. This result reaffirms the necessity of extensive sampling and examination of the conization specimens as has been previously proposed by Ostor et al<sup>(17)</sup> who also found that no residual lesion was noted in any hysterectomy specimens obtained after extensively sampled conization specimens revealed negative margins. Adherence to standard processing methods and criterion for margin status determination therefore is required if the high predictive value of conization margin status for the risk of residual lesion is to be achieved.

Noteworthy is that the status of conization margins also has been noted to a helpful factor predicting the risk of harboring invasive lesion in the residual cervix. In a meta-analysis of 33 previous studies, residual invasive adenocarcinoma was more commonly associated with positive conization margins compared to those with uninvolved margins (5.2% and 0.1%, respectively)<sup>(29)</sup>. Recently, Costales et al<sup>(20)</sup> reported that women with AIS in whom the conization margins were positive carried a higher risk of harboring invasive cervical lesion than those with negative margins (7.7% and 1.9%, respectively).

Some AIS lesions might be incidentally noted on LEEP specimens and might raise worrisome

about predictive value of LEEP margin status for risk of residual disease. In our previous study<sup>(12)</sup>, LEEP margin status was significantly associated with the risk of residual lesion similar to that of CKC. No residual lesion was observed in any of subsequent surgical specimens obtained from women who had free margins of initial LEEP specimens. In our perspective, a high predictive value of negative conization margin status for risk of residual disease in women with AIS could be obtained, if standard sampling methods and criterion for determining the conization margin status is strictly adhered, irrespective of the conization method.

As per the most recent ASCCP guidelines, hysterectomy remains the most preferred treatment in women with AIS to ensure exclusion of residual lesion particularly residual invasive disease. Conservative management is only acceptable for whom preservation of fertility is an issue<sup>(21)</sup>. Because of a high rate of residual lesion up to 70% in women with positive conization margins, achieving negative margins is strongly recommended if conservative management is chosen. If conservative management is planned and conization margin status is positive, the preferred management is repeat conization, if technically feasible to obtain free resection margins which results in a lower risk of residual disease<sup>(21)</sup>.

## Follow-up in women with AIS

Long-term follow-up is required for women with AIS undergoing conservative management. In updated ASCCP guidelines, a combination of cytology and high-risk HPV-DNA testing, the so-called “cotesting”, and colposcopy with endocervical sampling has been recommended as a surveillance tool<sup>(21)</sup>. Costa et al<sup>(30)</sup> reported that a finding of negative cytology result, negative high-risk HPV-DNA testing, and fully visibility of transformation zone on colposcopic examination during surveillance among women with AIS managed conservatively with conization alone increase the probability of disease clearance.

In the recent report by Li and Zhao<sup>(28)</sup>, at a median follow-up time of 40 months, only 1.4% of women with AIS in whom the conization margins were negative had residual AIS during follow-up after

conservative management with conization alone. The authors concluded that if a negative resection margins is obtained, conservative management with conization alone is appropriate for patients with AIS who desire future childbearing<sup>(28)</sup>.

Not only a status of conization margins, but the results of high-risk HPV-DNA testing performed during follow-up periods are also reported to be significant factors predicting the outcome of conservatively treated AIS. Positive high-risk HPV testing at any time point during follow-up for conservatively treated AIS increases risk of disease recurrence almost 3-fold (adjusted OR, 2.72; 95% CI, 1.08-6.87). In addition, positive high-risk HPV-DNA testing is a single most powerful for predicting disease progression to invasive adenocarcinoma with an OR of 3.74 (95% CI, 1.84-7.61)<sup>(30)</sup>. These findings emphasize the necessity of adding high-risk HPV-DNA testing into the surveillance investigation tools.

The risk of developing invasive cervical cancer among women who have been treated for cervical cancer precursor lesions, irrespective of treatment method, evolves over a period of at least 10 years<sup>(31)</sup>. In the literature, the occurrences of recurrent or persistent disease for women treated for AIS are mostly noted during the first 3 years of follow-up emphasizing the need of extensive surveillance in this surveillance period<sup>(20,30)</sup>.

## Conclusion

Cervical conization is required for diagnosis of AIS to ensure the exclusion of coexisting invasive adenocarcinoma. CKC seems to be more appropriate than LEEP due to a lower rate of involved margins. Hysterectomy remains the most preferred definite treatment. Treatment by conization alone is acceptable for whom fertility preservation is an issue. Long-term follow-up is required for women with AIS using a combination cytology and high-risk HPV-DNA testing and colposcopy with endocervical sampling as a surveillance tool.

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## Adenocarcinoma in Situ ของปากมดลูก

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รอยโรค adenocarcinoma in situ (AIS) ของปากมดลูกเป็นรอยโรคก่อนมะเร็งปากมดลูกชนิด adenocarcinoma ลักษณะทางเนื้อเยื่อวิทยาของรอยโรค AIS คือ การมีเซลล์ที่คล้ายเซลล์ของ adenocarcinoma อยู่ภายในเยื่อบุต่อม แต่ยังไม่มีการลุกลามเนื้อเยื่อstroma เนื่องจากรอยโรค AIS อยู่ภายในแอ่งหรือร่องของปากมดลูกจึงทำให้การตรวจคัดกรองด้วยเซลล์วิทยาตรวจพบได้ยาก และการตรวจด้วยกล้องคอลโปสโคปีวินิจฉัยได้ยาก การตรวจคัดกรองโดยการผนวกการตรวจหาเชื้อ HPV ร่วมกับการตรวจทางเซลล์ วิทยาช่วยให้ตรวจหารอยโรค AIS ได้มากขึ้น การวินิจฉัยโรคที่แน่นอนของรอยโรค AIS ต้องได้จากการตัดปากมดลูกออกเป็นรูปกรวย ซึ่งอาจจะตัดด้วยมีด ห่วงลวดไฟฟ้า หรือเลเซอร์ก็ได้ ทั้งนี้เพื่อให้แน่ใจว่าไม่มีมะเร็งระยะลุกลามชนิด adenocarcinoma อยู่ร่วมในรอยโรคด้วย การรักษาที่แนะนำมากที่สุดสำหรับรอยโรค AIS คือ การตัดมดลูกออก ส่วนการรักษาแบบอนุรักษ์โดยการตัดปากมดลูกออกเป็นรูปกรวย ยอมรับให้ปฏิบัติเฉพาะกรณีที่ต้องการพิทักษ์ภาวะเจริญพันธุ์ไว้เท่านั้น การกลับเป็นซ้ำและการคงอยู่ของรอยโรค AIS ภายหลังจากการรักษาโดยส่วนใหญ่จะเกิดขึ้นในช่วง 3 ปีแรก จึงจำเป็นต้องตรวจติดตามผู้ป่วยอย่างใกล้ชิดในช่วงดังกล่าว