RESEARCH ARTICLE

CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2024.2024-39
Cyprus J Med Sci 2024;9(4):289-296

Early Detection of Endocervical Adenocarcinoma and Adenocarcinoma in Situ: Role of PAP Smear and HPV Screening Test

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Abstract

BACKGROUND/AIMS: Endocervical adenocarcinoma (ECA) accounts for 25% of cervical cancers and is clinically more aggressive than squamous cell carcinoma (SCC). Similarly, SCC and ECA can be treated without the formation of invasive tumors if precursor lesions are identified and treated accordingly. The objective of this study is to analyze the effectiveness of screening tests in the detection of endocervical adenocarcinoma in situ (AIS), which represents a precursor lesion of ECA.

MATERIALS AND METHODS: The study comprised a total of 121 cases, including 83 cases of ECA and 38 cases of AIS, diagnosed through histopathologically examination between 2020 and 2023 at our center. The clinical history, cytological findings, results of the high-risk human papillomavirus (hrHPV) test, and other pathological findings from the pathology reports of the patients aged 26 to 84 years were subjected to analysis.

RESULTS: A total of 22.2% of the cervical carcinoma cases diagnosed histopathologically at our center during the study period were ECA. The mean age of the ECA cases was 48.6 years while that of the AIS cases was 39 years. A positive association was observed between HPV and 94% of ECA cases. Among the 83 ECA cases, 56.6% had not undergone screening, and 88% had not undergone an hrHPV test. A total of 33 patients with AIS underwent a screening test, and 31 cases exhibited abnormalities in the smear. All 13 AIS cases that underwent hrHPV screening tested positive for hrHPV. A biopsy was performed in 33 of the 38 AIS cases based on the combined evaluation of the PAP smear and the hrHPV test results.

CONCLUSION: Our study emphasizes the effectiveness of the combined PAP smear and hrHPV screening tests in the early detection of ECA at the AIS stage, achieving a success rate of 96.9%.

Keywords: Adenocarcinoma in situ, endocervical adenocarcinoma, HPV screening test, PAP smear

To cite this article: Ekemen S, Erkanlı S. Early Detection of Endocervical Adenocarcinoma and Adenocarcinoma in Situ: Role of PAP Smear and HPV Screening Test. Cyprus J Med Sci. 2024;9(4):289-296

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Received: 11.05.2024
Accepted: 31.07.2024

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INTRODUCTION

Endocervical adenocarcinoma (ECA) accounts for a smaller proportion of cervical carcinoma cases comparing to squamous cell carcinoma (SCC); however, it still represents a significant portion, approximately 25%.[1-3] An aggressive tumor, it is particularly common in women aged 40-50.[4-6]

Although there was a remarkable reduction in SCC rates by up to 80% due to the human papillomavirus (HPV) vaccine and papanicolaou (PAP) smear test, the incidence of ECA showed a significant increase.[5,7] This increase may be attributed to differences in the etiology, morphology, and molecular characteristics of ECA and SCC.[5,8] Research indicates that adenocarcinoma in situ (AIS), the precursor lesion of ECA, can progress to invasive carcinoma over a span of at least 5 years.[9] Similar to the identification of precursor lesions of SCC, the detection of AIS through screening tests, such as PAP smears and high-risk human papillomavirus (hrHPV), can enable timely intervention before invasive tumors develop.[9]

The effectiveness of the PAP smear and HPV tests for detecting cervical squamous intraepithelial lesions (SIL) is well established. However, their efficacy in detecting ECA and its precursor lesions is limited by several factors.[9-11]

One of the main challenges in the diagnosis of ECA and AIS is the difficulty in obtaining an adequate sample.[12] Unlike squamous lesions, which are more easily accessible, ECAs may not be adequately sampled on PAP smears, leading to false-negative results. In addition, the cytological features of ECA and its precursor lesions can be difficult to interpret, leading to observer misinterpretation. Benign lesions may have characteristics similar to those of ECA or its precursors, further complicating the diagnostic process.[12]

Furthermore, because ECA and its precursor lesions frequently lack clinical symptoms, they are frequently identified incidentally during biopsy or hysterectomy procedures performed for other indications.[11]

In summary, although PAP smear and HPV tests are effective in detecting cervical SIL, their sensitivity and specificity for ECA and its precursor lesions are limited by sampling challenges, observer misinterpretation, and the asymptomatic nature of these lesions.

HPV plays a significant role in the diagnosis and classification of ECAs. Approximately 85% of ECAs are associated with HPV infection, whereas 15% do not.[7,13,14] Among HPV-associated ECAs, types 18, 16, and 45 are the most implicated.[7,13,14] Clinical features, P-16 expression, and HPV status play a main role in determining prognosis and treatment response.[3,7] Since 2020, the classification of ECAs has evolved to incorporate the HPV status, with tumors being categorized into HPV- associated and HPV-independent subtypes.[6,14] The incidence of ECA is higher in younger women, particularly around the age of 30, whereas the less common type, accounting for 15% of cases, is more prevalent in older individuals and tends to be more aggressive.[5] Precancerous lesions that precede ECA by 10-15 years provide a crucial window for detection and intervention.[5,11,14] Although the PAP test has relatively low sensitivity and specificity for the detection of ECA and precancerous lesions, approximately 90% of cases exhibit abnormal cytological findings.[9]

In the clinical approach, colposcopy examination and biopsy are recommended when encountering a high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells cannot be excluded, atypical glandular cells that are not otherwise specified (AGC, NOS), atypical endocervical cells that are neoplastic (AEC, FN), AIS smear results, and/or hrHPV positivity.[15,16]

Currently, few comprehensive studies have included both clinical and pathological analyses of ECA and its precursor lesion AIS, particularly in large case series. Although limited research is available, the World Health Organization predicts an increase in the incidence of these tumors in the future. Consequently, conducting clinical and pathological analyses of ECA and AIS in large case series is increasingly crucial to inform future research and clinical practice. Such studies can illuminate the difficulties encountered in the detection of ECA and facilitate the development of effective detection strategies.

The objective of this study was to investigate the efficacy of early diagnostic methods for ECA at the AIS stage. The aim of this study was to determine the benefit of using a PAP smear and high-risk HPV screening tests together in detecting AIS cases. Additionally, the study will identify the clinical features of ECA and AIS cases.

MATERIALS AND METHODS

Study Population and Ethics Approval

This retrospective study was approved on 28.03.2024 by Acıbadem University and Acıbadem Healthcare Institutions Medical Research Ethics Committee (ATADEK) under study number 2024-5/178.

The study included a total of 121 patients histopathologically diagnosed with AIS or ECA who presented to our laboratory with surgical specimens between January 2020 and January 2024. In this study, we evaluated whether PAP smears and HPV screening tests were performed before histopathological diagnosis, and the results of cases in which screening tests were performed were included in the analysis. The patients exhibited a wide age range, from 26 to 84 years, with a mean age of 46.6. Each case was analyzed for clinical history, clinical symptoms, biopsy type, smear results, HPV co-test results, HPV subtypes, and additional immunohistochemical studies utilized during the diagnostic phase before reaching a histopathological diagnosis.

Histopathological Samples and Immunohistochemistry

The specimens were fixed in 10% neutral-buffered formalin solution and processed using Tissue-Tek Vip® 6 AI (Sakura Finetek Japan Co., Ltd., Tokyo, Japan) to generate paraffin blocks. Subsequently, 3 µm-thick sections were from all blocks and subjected to hematoxylin and eosin (H&E) staining using a Shandon Gemini stainer (Epredia, USA). Immunohistochemical staining was then conducted using a Ventana Benchmark XT (Roche Diagnostics, Basel, Switzerland).[17]

Cytopathological Sampling and HPV Co-Test

The Thin Prep process used PreservCyt and CytoLyt solutions (Aptima, Canada) for specimen collection. Cytological preparations were performed using the ThinPrep technique (Cytyc Corp., Boxborough, MA, USA) with a ThinPrep 5000 automated processor utilized for processing. Any surplus materials were preserved in ThinPrep solution (Cytyc's ThinPrep PreservCyt medium). For hrHPV co-testing, the Aptima Panther test, which covers 14 hrHPV types (31, 33, 35, 39, 51, 52, 56, 58, 59, 66, 68) with type 16 detected individually, types 18/45 in combination, and the remaining 11 types collectively,[18] was employed.

All slides were examined and interpreted by experienced cytopathologists using a light microscope (Olympus BX51). PAP smears were evaluated in accordance with The Bethesda System for Reporting Cervical Cytology, 2016.[1,19,20]

In this study, specimens prepared and reported using the methods described above were used. The histological sections stained with H&E and immunohistochemical preparations of the cases were reviewed and analyzed along with the information provided in the pathology reports (SE). All images were captured using the latest version of Viracenter Digital Pathology's latest version.[21]

Statistical Analysis

Statistical analyses were conducted using the SPSS 21.0 software (IBM Corp., Armonk, NY, USA; licensed from Istanbul University, Türkiye). Results are presented as frequencies and percentages.

RESULTS

Biopsy Results

A total of 83 cases of ECAs were included in the study, representing 22.3% of the 372 cases of invasive cervical carcinoma diagnosed at our laboratory between January 2020 and January 2024. In addition, all 38 cases of AIS within this period (38 cases) were included.

The patients in our study cohort ranged in age from 26 to 84 years (mean 46.6). Among the patients, 31.4% (n=38) were diagnosed with AIS, with a mean age of 39 years, whereas 68.6% (n=83) were diagnosed with ECA, with a mean age of 48.6 years. Of the AIS cases, 92.1% were younger than 50 years old, with only 3 patients (7.9%) age of 50 years or older. For the ECA cases, 65% were younger than 50 years old, and 35% (n=29) were 50 years or older.

Diagnosis was made by cervical biopsy in 61.4%, endometrial curettage in 9.6%, hysterectomy 9.6% and loop electrosurgical excision procedure (LEEP) in 2.4% of ECA cases. ECA diagnosis was made in metastatic tissue in 14 cases (17%), of which 3 cases represented the first presentation. The procedures which AIS was diagnosed on were as follows: cervical biopsy (71.1%), LEEP (15.7%), hysterectomy (7.9%), and endometrial curettage (5.3%).

In 5% (n=6) of the 121 cases, non-ECA malignancy was also present. Additionally; endometrial polyps were observed in seven cases, leiomyomas in two cases, and pregnancy in two cases. Among the cases, 24% (n=29) exhibited accompanying SIL, with HSIL being the most common. One case of AIS was detected in a patient with SCC, and one case of ECA was accompanied by SCC.

In all cases, the primary clinical indication for biopsy was PAP smear abnormality and/or hrHPV positivity, which accounted for 45.5% (n=55). The other common clinical indications for biopsy, excluding cases in which biopsy was performed due to metastasis, smear, and HPV test results, were cervical hemorrhagic lesion (n=30), postmenopausal bleeding (n=12), abnormal uterine hemorrhage (n=5) and cervical polyp (n=5).

In ECA cases, the most common clinical indication for biopsy was cervical hemorrhagic lesions (accounting for 31.3%), followed by abnormal smears and/or HPV positivity (at a rate of 27.7%). In AIS cases, abnormal smears and/or HPV positivity were the primary clinical findings leading to sampling in 84.2% of cases.

In one patient with age of 51, hysterectomy was performed due to postmenopausal bleeding attributed to multiple leiomyomas, and AIS was an incidental finding (Figure 1). Graphic 1 displays the age, clinical complaint, and cytological findings following biopsy in patients with ECA and AIS. cases.

Of the 83 cases, of ECA, 94% (78 cases) were associated with HPV infection. Among these, 68 were of the usual type and 10 were of the mucinous type (Figure 2, 3). In contrast, 6% (n=5) of the ECA cases were independent of HPV infection, with four cases of gastric type and one case of clear cell type.

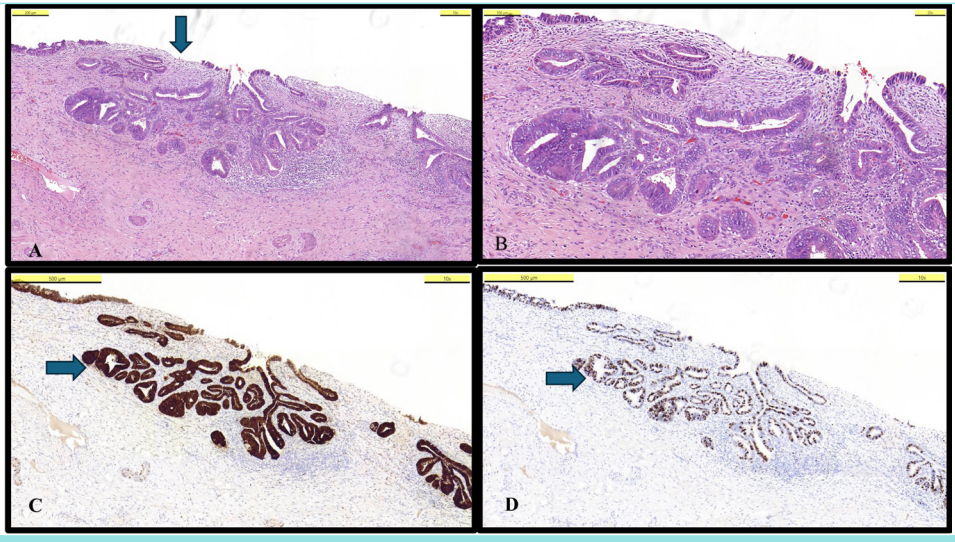


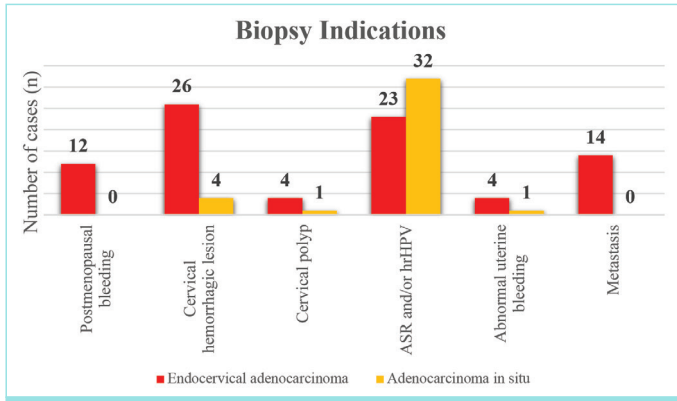
Figure 1. A 52-year-old patient with incidentally detected adenocarcinoma in situ (AIS) in hysterectomy material. (A) AIS area hematoxylin and eosin (H&E), (B) magnified view of the area marked by the arrows in A (H&E) and (C) diffuse strong positive expression in the AIS area with P-16 antibody (indicated by an arrow, (D) high positivity in the AIS area with Ki-67 antibody indicated by an arrow. The patient did not have a papanicolaou smear and human papillomavirus screening test.

Smear Test Results

Periodic smear tests were conducted in 24.8% of the cases (n=30). Among these, cytological abnormalities were also present in 33.3% (n=10) of the previous smear tests, with atypical squamous cells of undetermined significance (ASCUS) being the most common abnormality (n=7). In one patient aged 59 years and diagnosed with ECA, the previous smear result indicated ASCUS, whereas the latest smear test was negative for intraepithelial lesion or malignancy and negative for hrHPV.

Pre-sampling smear tests were conducted in 57% of the cases. Among these, smear tests were performed in 86.8% (n=33) of AIS cases and 43.4% (n=36) of ECA cases prior to biopsy. Distribution of PAP-smear and hrHPV test results according to final diagnoses are presented in Tables 1, 2, respectively.

The most common smear result observed before biopsy was HSIL (18.8%), followed by ASC-H (17.4%) in all cases in which a smear test



Graphic 1. Biopsy indications by diagnosis.

ASR: Abnormal smear results, hrHPV: High risk human papillomavirus.

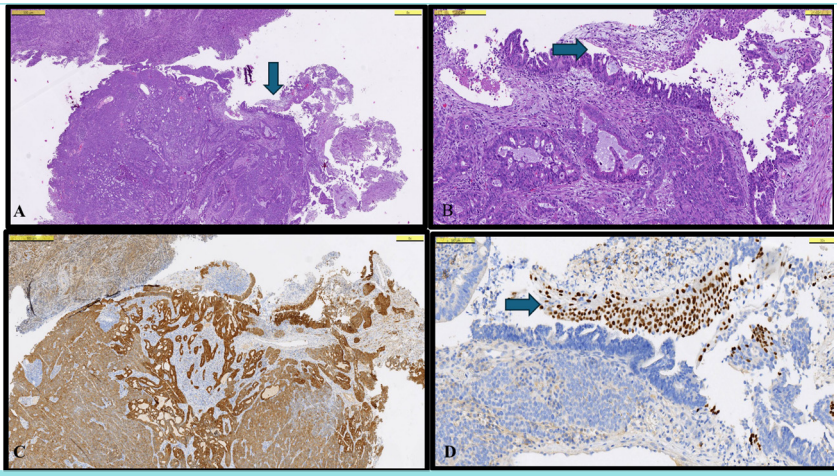


Figure 2. Cervical biopsy material from a 75-year-old patient with postmenopausal bleeding. (A) Endocervical adenocarcinoma (ECA) hematoxylin and eosin (H&E), (B) Magnified view of the area marked by the arrows in A (H&E) and (C) Diffuse strong positive staining in tumor with P-16 antibody, (D) Negative staining of the ECA area with P40 antibody, positive staining in high-grade squamous intraepithelial lesion area. The patient did not have a papanicolaou smear and human papillomavirus screening test.

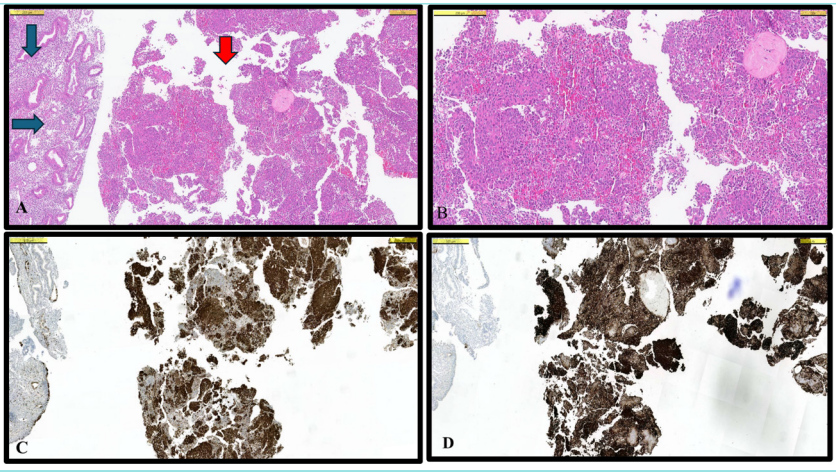


Figure 3. Histories of abnormal uterine bleeding in a 47-year-old woman who underwent hysteroscopic polypectomy material. (A) Blue arrows indicate endometrial polyp areas, and red arrows indicate ECA areas hematoxylin and eosin (H&E). (B) Magnified view of the red arrows in A (H&E). (C) Diffuse strong positive staining of tumors with P-16 antibody. (D) Diffuse strong positive staining of the tumor with CEAm antibody. The tumor location in the patient was ER (-), PR (-). The patient did not have a papanicolaou smear and human papillomavirus screening test.

was performed prior to biopsy. ASCUS (27.3%) was the most common smear result in AIS cases, whereas HSIL and NLIM (22.2%) were the most common smear results in ECA cases. The distribution of the smear results based on biopsy results is shown in Table 3.

Another notable finding was the absence of SILs in the biopsy results of AIS or ECA, despite the presence of squamous cell abnormalities on the smear in 16 cases. In seven AIS cases with ASCUS on smear, only AIS was identified on biopsy. Similarly, in nine ECA cases with smear results indicating ASC-H (n=5), HSIL (n=3), and ASCUS (n=1), no SIL was observed in the biopsy specimens.

HPV Test Results

HPV testing was performed in 23 (19%) of all cases. Of the 10 ECA cases that underwent HPV testing (12% of all ECA cases), half tested positive for HPV. The mean ages of patients who underwent HPV testing were 37 years in AIS cases and 47.8 years in ECA cases. The distribution of HPV test results according to the final biopsy diagnosis is shown in Table 2. All 13 AIS cases that underwent HPV screening (34.2% of all AIS cases) tested positive for hrHPV.

The most common subtype detected in the 23 cases that underwent HPV testing was HPV type 16, present in 12 cases (52.2%).

Cervical biopsy was performed in a total of nine cases because of hrHPV positivity, including two cases with NLIM smear results (one ECA, one AIS), five cases with ASCUS (one ECA, four AIS), and two cases with LSIL (one ECA, one AIS).

DISCUSSION

A total of 372 cases were diagnosed with cervical carcinoma in our laboratory during the period when the study cases were selected. The prevalence of ECA cases was 22.2%, with 83 cases identified. This prevalence rate was consistent with the 25% prevalence rate reported in the literature.[1,3,7]

The age range for ECA is typically reported to be between 40 and 50 years.[4,5] In our study cohort, the mean ages were 48.6 years for ECA cases and 39 years for AIS. Considering the recognized progression of AIS to invasive tumors over a period of at least 5 years, the mean age of our AIS cases was also consistent with the literature.[9] Only 3 cases of ECA were under the age of 30 years. Among them, two cases (aged 26 and 29) were diagnosed with HPV-associated usual-type ECA based on metastatic tissue. The third case (aged 29) was diagnosed using LEEP material obtained from an HSIL smear result. In these patients, HPV-associated usual-type ECA and accompanying HSIL were detected. Unfortunately, all three of these young patients did not undergo HPV

Table 1. Distribution of PAP-smear results according to final diagnosis

	Abnormal, n (%)	Negative, n (%)	N/A, n (%)	Total, n (%)
Endocervical adenocarcinoma	28 (33.8)	8 (9.6)	47 (56.6)	83 (68.6)
Adenocarcinoma in situ	31 (81.6)	2 (5.3)	5 (13.1)	38 (31.4)
Total	59 (48.7)	10 (8.3)	52 (43)	**121 (100)**

N/A: Non-applicable.

Table 2. Distribution of hrHPV results according to the final diagnosis

	Positive, n (%)	Negative, n (%)	N/A, n (%)	Total, n (%)
Endocervical adenocarcinoma	6 (7.2)	4 (4.8)	73 (88)	83 (68.6)
Adenocarcinoma in situ	13 (34.2)	0	25 (65.8)	38 (31.4)
Total	19 (15.7)	4 (3.3)	98 (81)	**121 (100)**

N/A: Non-applicable, hrHPV: High-risk human papillomavirus.

Table 3. Biopsy correlations between PAP-smear tests

	AIS, n (%)	ECA, n (%)	Total, n (%)
NILM	2 (6)	8 (22.2)	10 (14.5)
ASCUS	9 (27.3)	1 (2.8)	10 (14.5)
LSIL	2 (6)	1 (2.8)	3 (4.4)
HSIL	5 (15.2)	8 (22.2)	13 (18.8)
ASC-H	6 (18.2)	6 (16.6)	12 (17.4)
AGC, NOS	6 (18.2)	3 (8.3)	9 (13)
AEC, FN	0	6 (16.7)	6 (8.7)
AIS	3 (9.1)	1 (2.8)	4 (5.8)
ECA	0	2 (5.6)	2 (2.9)
Total	33 (47.8)	36 (52.2)	100 (69)

NILM: Negative for intraepithelial lesion or malignancy, ASCUS: Atypical squamous cells of undetermined significance, LSIL: Low grade squamous intraepithelial lesion, HSIL: High grade squamous intraepithelial lesion, ASC-H: Atypical squamous cells - cannot exclude high grade squamous intraepithelial lesion, AGC: Atypical glandular cell, NOS: Not otherwise specified, AEC: Atypical endocervical cell, FN: Favor neoplastic, AIS: Adenocarcinoma in situ, ECA: Endocervical adenocarcinoma.

testing or undergo a prior smear test. In the review by Rivera-Colón and Zheng[5], it was mentioned that typical AIS can present around the age of 15, and these patients may develop ECA at a young age.

Although the sensitivity and specificity of the PAP smear test for the detection of AIS and ECA are known to be low, smear abnormalities have been reported in up to 90% of cases, as demonstrated in a study by Niu et al.[9]. In our study, smear abnormalities were observed in 94% (31/33) of AIS cases, 77.8% (28/36) of ECA cases, and 85.5% (59/69) of all cases. Unfortunately, 42.1% of our patients did not undergo a pre-biopsy smear test, and 75.2% did not undergo periodic smear tests in previous years.

A notable observation in the smear results was the presence of squamous epithelial abnormalities in 16 cases, despite the absence of SIL on biopsy. These abnormal smear results included ASCUS in patients with AIS and ASC-H and HSIL in patients with ECA.

Research by Liu et al.[22] suggests that ASCUS results, especially when accompanied by hrHPV positivity, may indicate an increased risk of carcinoma or precancerous lesions. Similarly, in a study by Bamanikar et al.[23], ASCUS was found to be the most common abnormal smear result in cervical cancer cases.

The absence of SILs accompanying AIS and ECA in our cases may be attributed to the difficulty in accurately characterizing the abnormal cellular changes observed in ASCUS and ASC-H. It is plausible that the HSIL results indicated glandular involvement in squamous epithelial lesions. However, it is important to note that our study included a limited number of ECA and AIS cases, which limits the depth of our analysis on this issue. Further research with a larger sample size is warranted to explore this issue comprehensively.

A similar result was observed for the hrHPV test. In 81% of all cases and 88% of ECA cases, hrHPV testing was not performed. In cases where hrHPV testing was performed, 82.6% of 23 cases and 100% of 13 AIS cases tested positive for hrHPV. This positivity rate is similar to that reported by Bruehl et al.[24], who reported a positivity rate of 92.7%. However, it is important to note that our study may not reflect the true prevalence rates because of the limited number of patients tested.

In contrast, the low number of hrHPV tests performed (n=23), biopsies were performed and in 9 cases the diagnosis was made based on hrHPV positivity, even in cases in which the smear results did not require a cervical biopsy. In one case of HPV-associated usual-type ECA (58 years old), periodic smear tests, the most recent smear test, and the hrHPV test were negative. However, biopsy was performed in this case due to the clinical finding of a cervical hemorrhagic lesion. The negative result of the periodic smear test in this case could be attributed to the difficulty in sampling the lesion because of its deep location. Nevertheless, the negativity of the hrHPV test is interesting because the tumor was associated with HPV.

Giannella et al.[25] and Tjalma and Depuydt[26] reported that cancer rates are higher in association with HPV infection and that hrHPV testing may yield negative results in cases of HPV infection. Tjalma and Depuydt[26] showed that 8.3% of HPV 16 and 27.9% of HPV 18 genotypes could not be detected by hrHPV testing. In addition, some studies have suggested that test negativity may occur due to low viral load in latent infections and the presence of low-risk HPV types that are undetectable by testing but still have oncogenic potential.[27,28]

Although HPV 18 is the subtype most commonly associated with ECA in the literature, we found that HPV 16 was the causative type in 57.9% (11/19) of our HPV-positive cases.[7,15,23]

Among patients with AIS, 86.4% (n=33) had undergone periodic smear tests, and 34.2% (n=13) had hrHPV screening tests. Of the 31 AIS cases with smear abnormalities, 25 had smear results indicating the need for biopsy. The smear results of the other seven patients did not contain biopsy indications, including ASCUS (n=5), LSIL (n=1), and NLIM (n=1). Nevertheless, these cases were hrHPV-positive, and therefore biopsy was indicated. The HPV test was not performed on an AIS case whose smear result of NLIM. This patient was diagnosed with AIS with a prediagnosis of endocervical polyp. Among the five AIS cases without periodic screening tests, two were detected incidentally in hysterectomy specimens obtained for other reasons. In the remaining three cases, cervical sampling was performed because of the presence of cervical hemorrhagic lesions.

Mitchell et al.[29] showed that increasing the frequency of smear screenings can reduce the incidence of ECA. Zhao et al.[30] demonstrated that long-term and periodic screenings can detect abnormal findings and be effective in the early detection of curable lesions, even in cases with negative smear and negative hrHPV test results. Unfortunately, in our study, only 24.8% of the 121 patients had periodic smear results in the last 5 years.

Study Limitations

In this study, the number of patients with AIS was limited. Nonetheless, the interpretation of the AIS results is consistent with the existing literature. It is known that the number of AIS cases is limited in many studies in the literature. Therefore, the results from more comprehensive studies with a higher case count may provide further insight into elucidating and preventing the development of ECA.

CONCLUSION

Our study highlights the potential for early detection of ECA at the AIS stage through the combined use of PAP smear and hrHPV screening tests. The use of both screening methods demonstrated a success rate of 96.9% in detecting AIS cases in our study cohort. In addition, consideration of deep sampling of endocervical tissue in cases with cervical hemorrhagic lesions (such as postcoital bleeding) and a history of postmenopausal bleeding may aid in early diagnosis.

We recommend the use of PAP smear and HPV screening tests according to guidelines starting from the onset of sexual activity. Furthermore, we advocate for the inclusion of HPV vaccinations in routine immunization programs, administered to the young population, without gender discrimination, ideally before the age of 25 years. We expect that these proactive measures will significantly contribute to the prevention and early detection of cervical cancer, ultimately improving patient outcomes.

MAIN POINTS

- It is evident from our study that screening tests are not employed to the fullest extent in the clinical histories of patients with ECA. A combined approach using both smear and HPV screening tests was effective in detecting 84.6% of AIS cases.
- In our cases, the smear results demonstrated a high prevalence of cytological abnormalities in both ECA and AIS although these were not specific.
- High-risk HPV positivity, particularly HPV 16 positivity, was significantly elevated in our cases.
- The combined use of both screening tests enabled the detection of AIS cases prior to the development of invasive tumors.

ETHICS

Ethics Committee Approval: This study was approved by the Acıbadem University and Acıbadem Healthcare Institutions Medical Research Ethics Committee (ATADEK) (approval number: 2024-5/178, date: 28.03.2024).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: S.E., S.E., Concept: S.E., Design: S.E., S.E., Data Collection and/or Processing: S.E., S.E., Analysis and/or Interpretation: S.E., S.E., Literature Search: S.E., Writing: S.E.

Acknowledgements: We would like to express our sincerest gratitude to Prof. Sadık Toprak for his invaluable statistical analysis support, Prof. Ümit İnce for their laboratory and data assistance, and Prof. Elife Kimiloğlu for constructive criticism of the revised manuscript. Their contributions and guidance were instrumental in the successful completion of this study.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study had received no financial support.

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