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Research Article

Clinicopathological evaluation of patients with SMILE, cervical intraepithelial neoplasia 3, and adenocarcinoma in situ

SMILE, servikal intraepitelyal neoplazi 3 ve adenokarsinoma in situ hastalarının klinikopatolojik değerlendirilmesi

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Abstract

Aim: To compare cervical biopsy diagnoses with final surgical pathology results among patients with SMILE, CIN3, and AIS, and to evaluate differences in clinicopathological features between these lesions.

Material and Methods: We performed a retrospective single-center analysis of patients diagnosed with SMILE (n=8), CIN3 (n=16), or AIS (n=14) who underwent surgical treatment. Clinical variables, high-risk HPV genotypes, cervical cytology findings, treatment modality, and pathological outcomes of surgical specimens were reviewed.

Results: AIS patients were significantly older and had higher BMI compared to SMILE and CIN3 groups, which showed similar demographic profiles. Comorbidities, particularly hypertension, were more frequent in AIS. HPV16 was the most common genotype overall, with HPV18 enriched in glandular lesions. LEEP + ECC was the most frequent surgical procedure across all groups. Histopathologic concordance was highest in CIN3, whereas SMILE and AIS showed more variable final excision outcomes, including cases of discordance between initial biopsy and definitive histology. Reoperation rates were highest in AIS and CIN3, while SMILE generally had favorable outcomes after a single excision.

Conclusion: Although the distribution of oncogenic HPV types and cytology findings were similar in SMILE, CIN3, and AIS, the agreement between biopsy and definitive surgical pathology was significantly different, highlighting diagnostic and management challenges especially for glandular lesions. The need for repeat surgical treatment was notably higher in AIS and CIN3 cases, underscoring the importance of thorough initial treatment and follow-up in these high-grade lesions.

Keywords: Cervical cytology, colposcopy, biopsy, concordance, cervical intraepithelial neoplasia, Adenocarcinoma in situ, SMILE

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Öz

Amaç: SMILE, CIN3 ve AIS tanılı hastalarda servikal biyopsi sonuçlarının konizasyon/histerektomi sonrası kesin patolojik tanılarla uyumunu ve klinik özelliklerdeki farklılıkları karşılaştırmak.

Gereç ve Yöntemler: Tek merkezli retrospektif bir çalışma kapsamında SMILE (n=8), CIN3 (n=16) veya AIS (n=14) tanısı alarak cerrahi tedavi uygulanmış hastaların klinikopatolojik verileri incelenmiştir. Hastaların HPV genotip sonuçları, sitoloji (Pap smear) bulguları, uygulanan cerrahi işlemler ve cerrahi örneklerin patoloji sonuçları retrospektif olarak incelendi.

Bulgular: AIS hastaları, benzer demografik profiller gösteren SMILE ve CIN3 gruplarıyla karşılaştırıldığında önemli ölçüde daha yaşlıydı ve daha yüksek BMI'ye sahipti. Eşlik eden hastalıklar, özellikle hipertansiyon, AIS'de daha sıktı. HPV16 genel olarak en yaygın genotipti ve HPV18 glandüler lezyonlarda daha sık saptandı. LEEP + ECC tüm gruplarda en sık uygulanan cerrahi prosedürdü. Histopatolojik uyum CIN3'te en yüksekti; buna karşın SMILE ve AIS, ilk biyopsi ile kesin histoloji arasındaki uyumsuzluk vakaları da dahil olmak üzere daha değişken nihai eksizyon sonuçları gösterdi. Tekrarlayan operasyon oranları AIS ve CIN3'de en yüksekti, SMILE genellikle tek eksizyondan sonra olumlu sonuçlar gösterdi.

Sonuç: SMILE, CIN3 ve AIS olgularında HPV tipleri ve sitoloji sonuçları benzer olsa da biyopsi ile cerrahi patoloji uyumu özellikle glandüler lezyonlarda (AIS ve SMILE) değişkenlik gösterebilir. AIS ve CIN3 olgularında cerrahi sınır pozitifliği veya yetersiz tedavi nedeniyle ikinci bir cerrahi girişime ihtiyaç duyma oranının yüksek oluşu, bu lezyonlarda tedavi planlanırken dikkatli olunması gerektiğini göstermektedir.

Anahtar Kelimeler: Servikal sitoloji, kolposkopi, biyopsi, uyum, servikal intraepitelyal neoplazi, Adenokarsinoma in situ, SMILE

Introduction

Cervical cancer remains a significant women's health issue worldwide, but effective screening programs have made it largely a preventable disease. Central to prevention is the identification and treatment of precancerous cervical lesions before they progress to invasive carcinoma (1). Cervical intraepithelial neoplasia (CIN), particularly high-grade lesions (CIN2 and CIN3), and glandular dysplasias like adenocarcinoma in situ (AIS) represent critical precancerous stages with a substantial potential to evolve into cancer if left untreated (2). Accurate diagnosis of these lesions is therefore of paramount importance: prompt detection and appropriate management can interrupt the progression towards cervical cancer and dramatically improve patient outcomes (3).

Biopsy-based pathology from colposcopic examinations is the standard first step in diagnosing such lesions. However, because cervical pre-cancers can be multifocal or extend into endocervical glands, a limited biopsy may not always reflect the full extent or severity of the disease. In practice, an excisional procedure (such as a cone biopsy or loop excision) is often performed both to treat the lesion and to obtain a definitive histopathological assessment of the entire transformation zone (4-6). This approach not only removes the abnormal tissue but also allows pathologists to examine margins and detect any occult invasive carcinoma that the initial biopsy might have missed (7). Given the high stakes of missing an evolving cancer, ensuring concordance between the initial biopsy diagnosis and the final surgical pathology is a critical aspect of cervical precancer management. Notably, certain cervical lesions are known to have higher discordance rates. AIS in particular poses a challenge: because of its patchy distribution in the endocervical canal, a superficial biopsy might under-sample the lesion. Studies have shown that after an initial conservative excisional procedure for AIS, residual AIS or higher-grade disease is found in a considerable proportion of cases upon hysterectomy or repeat excision (8, 9). In one report, the risk of residual AIS after a cone biopsy was as high as 14–53%, far exceeding the residual disease risk seen with CIN (10). This high rate of residual or occult disease is why guidelines often recommend definitive surgery (hysterectomy) for AIS when future fertility is not required. Even for high-grade squamous lesions like CIN3, about 3–23% of cases may show some form of overdiagnosis or underdiagnosis (11). Therefore, understanding the patterns of concordance (or lack thereof) between biopsy and excisional histopathology can help identify which patients are at risk of having more extensive disease than initially thought.

This study aimed to evaluate the concordance between initial

biopsy-based cervical pathology diagnoses and the final histopathological outcomes after surgical excision for lesions diagnosed as SMILE, CIN3, or AIS.

Material and Methods

This study was designed as a single-center retrospective analysis. It was conducted at the Gynecologic Oncology Clinic of Başakşehir Çam and Sakura City Hospital. The study covered patients with a pathological diagnosis of SMILE, CIN3, or AIS between May 2020 and June 2025. Ethical approval was obtained from the Başakşehir Çam and Sakura City Hospital Ethics Committee (Date: 09.07.2025, Approval No: 2025-181). The study adhered to the principles of the Declaration of Helsinki. Due to its retrospective design, the requirement for informed consent was waived by the ethics committee.

Study Population

During the study period, patients who had cervical biopsies and available clinical follow-up data were retrospectively screened. The study included patients aged 18 years or older who had cervical biopsy records, complete clinical and pathological documentation, and a diagnosis of SMILE, CIN3, or AIS. A total of 8 SMILE, 14 AIS, and 16 CIN3 patients who met the inclusion criteria were included in the analysis.

Data Collection

Demographic characteristics (age, body mass index, parity, comorbidities, and menopausal status), laboratory parameters (including CA-125, CA19-9, CA15-3, CEA, complete blood count indices), and HPV status were extracted from medical records. Cervical cytology findings, biopsy-to-surgery intervals, and the type of surgical procedure were recorded.

Menopausal status was determined based on clinical documentation indicating amenorrhea for 12 months or more without identifiable pathological or physiological causes. Patients positive for HPV 16 or 18 were classified into the HPV 16 and 18 group, whereas those infected with high-risk HPV types other than 16 or 18 were categorized as HPV others. According to the 2014 Bethesda System, cytological findings were categorized as atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), or atypical squamous cells in which a high-grade lesion could not be excluded (ASC-H).

Surgical management consisted of excisional procedures tailored to the initial diagnosis and patient characteristics. These included loop electrosurgical excision procedure (LEEP), cold-knife conization, total laparoscopic hysterectomy (TLH), pelvic lymph node dissection (PLND), and bilateral salpingo-oophorectomy (BSO). Secondary surgical procedures, when performed, were also reviewed with respect to type and histopathological outcome. In accordance with the World Health Organization (WHO) guidelines, histopathological classification included benign lesions, cervical intraepithelial neoplasia, and adenocarcinoma in situ (12).

Statistical Analysis

Data analysis was conducted with IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). The normality of the data distribution was evaluated using the Shapiro–Wilk test. Descriptive statistics were presented as means ± standard deviations (SD) or medians with interquartile ranges (IQR) for continuous variables, and as frequencies and percentages for categorical variables. Group comparisons were conducted using the chi-square test or Fisher's exact test for categorical variables, and ANOVA test (post-hoc: Benferroni test) or Kruskal–Wallis test (post-hoc: Dunn test) for continuous variables, as appropriate. A p-value of <0.05 was considered statistically significant for all analyses.

Results

The mean age of the study participants was 44.2 ± 11.4 years, with the vast majority in the premenopausal stage. Cervical biopsy results via colposcopy or endocervical curettage (ECC) confirmed the diagnoses of SMILE in 8 patients, AIS in 14 patients, and CIN3 in 16 patients. Patient age differed significantly across groups, with AIS patients being older on average compared to SMILE and CIN3 groups (SMILE: 40.8 ± 13.3 vs. AIS: 51.2 ± 15.4 vs. CIN3: 37.7 ± 9.1, $p = 0.018$). Body mass index was also significantly higher in the AIS group ($p = 0.001$). Although the overall prevalence of comorbidities did not differ, hypertension was more frequent in AIS group ($p = 0.041$). Reproductive history revealed higher parity among AIS group. In terms of laboratory findings, median CA-125 was elevated in AIS group compared to the other groups ($p = 0.032$). Hematologic indices showed higher neutrophil counts in SMILE and higher lymphocyte counts in AIS group ($p = 0.045$ and $p = 0.040$, respectively), whereas hemoglobin, platelet counts, and other tumor markers did not differ significantly (Table 1).

Table 1. Distribution of demographic and clinical findings.

Variables	SMILE n=8	AIS n=14	CIN3 n=16	p
Age, years	40.8 ± 13.3	**51.2 ± 15.4**	37.7 ± 9.1	0.018*
BMI, kg/m2	23.9 ± 2.8	**29.4 ± 6.2**	23.9 ± 4.3	0.001*
Postmenopausal, n (%)	1 (12.5)	4 (28.6)	2 (12.5)	
Comorbidity				
No	6 (75.0)	7 (50.0)	13 (81.2)	0.212
Yes	2 (25.0)	7 (50.0)	3 (18.8)	
Hypertension	0	**4 (28.6)**	0	0.041*
Diabetes mellitus	0	3 (21.4)	2 (12.5)	0.414
Thyroid diseases	0	2 (14.3)	2 (12.5)	0.665
Others	2 (25.0)	2 (14.3)	0	0.097
Gravida ≥1, n (%)	5 (62.5)	13 (92.9)	10 (62.5)	0.107
Parity ≥1, n (%)	4 (50.50)	**13 (92.9)**	9 (56.3)	0.034*
Abortus ≥1, n (%)	1 (12.5)	0	3 (18.8)	0.240
Curettage ≥1, n (%)	0	0	0	-
Laboratory findings				
CA-125, U/mL	7.5 (7.2-12.5)	**16.0 (10.9-25.3)**	9.6 (7.8-15.9)	0.032*
CA 19-9, U/mL	13.3 (12.1-16.0)	11.6 (4.9-16.7)	10.8 (6.7-22.4)	0.846
CA 15-3, U/mL	14.6 (10.9-16.1)	13.1 (7.2-22.6)	18.6 (14.4-21.1)	0.581
CEA, ng/mL	1.1 (1.0-2.5)	1.5 (1.2-2.5)	1.5 (1.2-3.1)	0.095
Hemoglobin, g/dL	12.7 ± 0.9	13.1 ± 0.5	12.8 ± 1.6	0.902
WBC, $\times10^3$/µL	7.9 ± 2.0	8.0 ± 2.3	7.4 ± 1.9	0.604
Platelets, $\times10^3$/µL	212 (198-280)	280.0 (219-313)	256.0 (245-360)	0.782
Neutrophils, $\times10^3$/µL	**5.1 (4.1-6.1)**	4.1 (3.3-6.0)	4.3 (3.3-5.4)	0.045*
Lymphocytes, $\times10^3$/µL	**1.7 (1.6-1.9)**	2.6 (1.9-3.0)	2.2 (1.7-2.5)	0.040*
Monocytes, $\times10^3$/µL	0.6 (0.4-0.7)	0.5 (0.4-0.8)	0.5 (0.4-0.6)	0.541

Data are mean ± SD, median (IQR) or numbers (percentages). * P-value <0.05 shows statistical significance. Groups highlighted in bold represent those with statistically significant differences compared to other groups. Abbreviations: AIS: Adenocarcinoma in situ, CA-125: Cancer antigen 125, CA 19-9: Cancer antigen 19-9, CA 15-3: Cancer antigen 15-3, CEA: Carcinoembryonic antigen, CIN-3: Cervical intraepithelial neoplasia grade 3 WBC: White blood cell.

HPV-16 represented the most prevalent genotype, particularly among CIN3 group, although the overall distribution of HPV genotypes was not statistically different between groups (p=0.181). Cervical cytology demonstrated no significant variation across categories ranging from ASCUS to HSIL/ASC-H (p = 0.147). The interval from biopsy to surgical intervention was similar among groups (median 6–9 weeks, p = 0.795). Surgical approach differed significantly (p = 0.018): LEEP ± ECC predominated in all groups. Histopathology from primary procedures varied significantly (p < 0.001), with CIN3 predominantly diagnosed as high-grade intraepithelial neoplasia, AIS group as adenocarcinoma in situ, and SMILE group showing a heterogeneous spectrum including benign and endocervical adenocarcinoma (Table 2).

The requirement for reoperation varied significantly, being more frequent in AIS and CIN3 groups compared with SMILE group (p = 0.011). The distribution of secondary procedures also differed (p = 0.040): CIN3 patients most commonly underwent repeat LEEP, whereas AIS cases were more likely to undergo hysterectomy-based procedures. Histopathological findings at reoperation did not differ significantly among groups (p = 0.334), with outcomes ranging from benign changes to residual CIN and adenocarcinoma, underscoring the heterogeneous pathological spectrum observed after secondary interventions (Table 3).

Table 2. Distribution of HPV status, cervical cytology, and initial surgical findings among study groups.

Variables	SMILE n=8	AIS n=14	CIN3 n=16	p
HPV, n (%)				
Negative	3 (37.5)	3 (21.4)	1 (6.2)	
HPV-16	4 (50.0)	8 (57.1)	10 (62.5)	
HPV-18	0	2 (14.3)	1 (6.2)	0.181
Others	0	1 (7.1)	4 (25.0)	
Unknown	1 (12.5)	-	-	
Cervical cytology, n (%)				
Negative	3 (37.5)	4 (28.6)	2 (12.5)	
ASCUS	1 (12.5)	7 (50.0)	2 (12.5)	
LSIL	2 (25.0)	0	4 (25.0)	0.147
HSIL	1 (12.5)	2 (14.3)	4 (25.0)	
ASC-H	1 (12.5)	1 (7.1)	4 (25.0)	
Time from biopsy to procedure, weeks	9 (7-12)	8 (6-12)	6 (4-15)	0.795
Surgery type, n (%)				
LEEP + ECC	4 (50.0)	7 (50.0)	**14 (87.5)**	0.018*
Conization + ECC	1 (12.5)	2 (14.2)	1 (6.2)	
TLH + BSO + PLND	0	1 (7.1)	0	
None⁂	3 (37.5)	4 (28.6)	1 (6.2)	
Histopathology, n (%)				
Benign	1 (12.5)	1 (7.1)	0	<0.001*
CIN2	0	1 (7.1)	1 (6.2)	
CIN3	2 (25.0)	0	**14 (87.5)**	
AIS	0	**7 (50.0)**	0	
Endocervical adenocarcinoma	2 (25.0)	1 (7.1)	0	
Unknow≠	3 (37.5)	4 (28.6)	**1 (6.2)**	

⁂ indicates patients who declined surgery, were not operated on because of pregnancy, or did not return for follow-up. ≠ There was no histopathological evaluation for patients who could not undergo surgery. * P-value <0.05 shows statistical significance. Groups highlighted in bold represent those with statistically significant differences compared to other groups. Abbreviations: AIS: Adenocarcinoma in situ, ASC-H, atypical squamous cells—cannot exclude HSIL; ASCUS, atypical squamous cells of undetermined significance; BSO, bilateral salpingo-oophorectomy; CIN2/3, cervical intraepithelial neoplasia grade 2/3; ECC, endocervical curettage; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LEEP, loop electrosurgical excision procedure; LSIL, low-grade squamous intraepithelial lesion; PLND, pelvic lymph node dissection; TLH, total laparoscopic hysterectomy.

Table 3. Surgical procedures and histopathological results of patients requiring a second surgery.

Variables	SMILE n=8	AIS n=14	CIN3 n=16	p
Need for second surgery, n (%)	**1 (12.5)**	6 (42.9)	7 (43.8)	0.011*
Procedure type, n (%)				
None	7 (87.5)	8 (57.1)	9 (56.2)	0.040*
Type 2 Hysterectomy + BSO + PLND	**1 (12.5)**	0	0	
TAH + BS	0	**3 (21.4)**	0	
TAH + BSO	0	**2 (14.3)**	0	
RH + BPP-LND	0	1 (7.2)	0	
reLEEP	0	0	**6 (37.6)**	
TLH + BSO	0	0	1 (6.3)	
Histopathology, n (%)				
Benign	0	3 (21.4)	2 (12.5)	0.214
CIN1	0	1 (7.2)	0	
CIN2	0	1 (7.12)	2 (12.5)	
CIN3	0	0	3 (18.8)	
Endocervical adenocarcinoma	1 (12.5)	1 (7.2)	0	

Data are mean ± SD, median (IQR) or numbers (percentages). * P-value <0.05 shows statistical significance. Groups highlighted in bold represent those with statistically significant differences compared to other groups. Abbreviations: BPP-LND, bilateral pelvic para-aortic lymph node dissection; BSO, bilateral salpingo-oophorectomy; CIN1/2/3, cervical intraepithelial neoplasia grade 1/2/3; PLND, pelvic lymph node dissection; reLEEP, repeat loop electrosurgical excision procedure; RH, radical hysterectomy; TAH, total abdominal hysterectomy; TLH, total laparoscopic hysterectomy.

Discussion

Our findings indicate that patients with AIS were significantly older and had higher BMI compared to those with SMILE or CIN3. Notably, the SMILE and CIN3 groups showed similar age and BMI distributions. This pattern aligns with epidemiologic data from the past decade: AIS tends to be diagnosed in women of later reproductive age, whereas high-grade squamous lesions like CIN3 are often detected in younger women (13). Moreover, women with obesity have an elevated risk of cervical cancer (14), and some studies have specifically noted that excess body weight may contribute to a greater proportion of cervical cancer cases (15). In contrast, the SMILE and CIN3 groups' younger age and lower comorbidity profiles are consistent with their epidemiology (16). We found a higher frequency of medical comorbidities in AIS patients – particularly hypertension – while the SMILE and CIN3 groups had comparatively lower comorbidity rates. This disparity is in line with the older age and higher BMI of the AIS cohort. Advanced age and obesity are naturally associated with greater comorbidity burdens, including hypertension and diabetes (17). One report noted that hypertension and hyperglycemia were positively correlated with more aggressive behavior (local invasion) in early cervical cancer (18).

High-risk human papillomavirus (HR-HPV) infection was ubiquitous in these high-grade lesions, but the distribution of HPV genotypes differed notably between squamous and glandular dysplasias. Consistent with global data, HPV16 was the single most common type across all lesion categories (19). However, AIS showed a marked enrichment of HPV18 relative to CIN3 and SMILE. A large multi-state analysis reported HPV18 in 38% of AIS cases, compared to only ~5% of CIN3 lesions (20). These genotype differences have practical implications. First, they underscore the importance of prophylactic HPV vaccination: the bivalent and quadrivalent vaccines (covering 16/18) target the vast majority of oncogenic HPV in AIS (21).

Cervical cytology findings at diagnosis also differed among the lesion types. By definition, CIN3 lesions are usually detected after an abnormal squamous cytology (high-grade squamous intraepithelial lesion, HSIL). AIS and SMILE, in contrast, often elude early detection by Pap smear. Glandular

neoplasms lack the overt abnormal exfoliative patterns of squamous lesions, and Pap tests have relatively low sensitivity for AIS (22, 23). Studies estimate roughly 30–60% of AIS cases are first identified on excisional specimens obtained for an unrelated HSIL or abnormal screening test (24). One report noted that when AIS accompanies a HSIL, the directed biopsy frequently shows only CIN3, with the AIS component "masked" until the cone excision is examined histologically (24). SMILE lesions often yield subtle findings on Pap smears. A retrospective cytology review showed SMILE cases often lacked the classic clues of AIS – for instance, SMILE typically did not exhibit the nuclear feathering or prominent nucleoli that cytopathologists associate with glandular lesions (25). In that study, SMILE's cytology overlapped with AIS but with only very slight abnormalities, leading to under-calls or benign interpretations in several cases (25). Despite the presence of histologically confirmed high-grade lesions in several patients with SMILE, nearly 38% of individuals in this group demonstrated normal cytology.

Across patients with SMILE, CIN3, and AIS, loop electrosurgical excision with endocervical curettage (LEEP + ECC) was the most frequently employed surgical approach, reflecting its role as the standard excisional management for high-grade cervical intraepithelial lesions (26-28). Notably, the SMILE and AIS groups showed a lower relative proportion of cases treated with LEEP + ECC, a finding explained by a higher fraction of patients in these cohorts who did not undergo immediate surgery. In these instances—often due to pregnancy or patient refusal of treatment —the absence of surgical intervention or loss to follow-up reduced the apparent use of LEEP + ECC in SMILE and AIS groups despite it remaining the predominant modality overall. This nuance is important in interpreting inter-group differences, as it underscores that patient factors (e.g. pregnancy) rather than a true shift toward alternative procedures accounted for the discrepancy. When excisional treatment was performed, it facilitated thorough histopathologic evaluation and high concordance between initial biopsy and final pathology, in line with reported rates for severe dysplasia (e.g. ~98% concordance for biopsy-proven CIN3 on LEEP) (29). By removing the lesion and adjacent transformation zone, LEEP + ECC provides a specimen for comprehensive analysis – confirming the diagnosis and often revealing any coexistent pathology. In our study, the vast majority of CIN3 cases had no unexpected findings on conization – initial colposcopic biopsy of CIN3 was confirmed on the excised specimen in nearly all cases. On the other hand, AIS and SMILE showed more complex pathology on final surgical specimens. The need for reoperation differed significantly across the lesion types. CIN3 patients had the lowest reoperation rate: most were cured by a single LEEP. In contrast, SMILE cases had a lower requirement for a second surgery.

Several limitations of our study should be considered when interpreting the results. First, this was a retrospective, single-center analysis, which may introduce selection bias and limit the generalizability of the findings to other populations or screening settings. The limited numbers reduce statistical power and precision in comparing outcomes between groups. Furthermore, outcomes including patient mortality could not be thoroughly assessed because of the retrospective nature of the study. Finally, we focused on clinicopathological factors and did not incorporate molecular analyses such as p16 expression patterns that could provide mechanistic insights. Despite these limitations, our study provides valuable comparative data on SMILE, CIN3, and AIS lesions, but the results should be interpreted with caution and verified in larger, multi-center cohorts.

In conclusion, this study provides a clinicopathological comparison of patients with SMILE, CIN3, and AIS, highlighting key differences in age, body mass index, comorbidities, and clinical outcomes. While LEEP + ECC emerged as the most frequent surgical approach across all groups, AIS patients were distinguished by older age, higher BMI, and greater comorbidity burden, particularly hypertension. Need for second surgery were more common in AIS and CIN3, whereas SMILE patients generally had favorable outcomes after a single excision. These findings underscore the importance of individualized management strategies and vigilant follow-up, with special attention to older AIS patients who may carry higher risks.

Ethical Approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by the Başakşehir Çam and Sakura City Hospital Ethics Committee (Date: 09.07.2025, Approval No: 2025-181).

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Conflicts of Interest

Authors declare that they have no conflicts of interest.

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Authors' Contribution

Concept – I.S., Design- I.S., Data collection and/or processing – I.S., H.S.A., G.S., Y.A.Y., E.D.T., and I.T.Y. Analysis and/or interpretation - I.S., H.S.A., G.S., Y.A.Y., E.D.T., and I.T.Y. Writing – I.S., Critical review –H.S.A., G.S., Y.A.Y., E.D.T., and I.T.Y. All authors read and approved the final version of the manuscript.

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References

1. Mishra GA, Pimple SA, and Shastri SS. An overview of prevention and early detection of cervical cancers. Indian J Med Paediatr Oncol. 2011;32(3):125-32.
2. Smedts F, Ramaekers FC, and Hopman AH. The two faces of cervical adenocarcinoma in situ. Int J Gynecol Pathol. 2010;29(4):378-85.
3. Gupta S, Nagtode N, Chandra V, and Gomase K. From Diagnosis to Treatment: Exploring the Latest Management Trends in Cervical Intraepithelial Neoplasia. Cureus. 2023;15(12):e50291.
4. Martin-Hirsch PP, Paraskevaidis E, Bryant A et al. Surgery for cervical intraepithelial neoplasia. Cochrane database of systematic reviews. 2013;2013(12):CD001318.
5. Ramirez SI and Lutzkanin A. Management of cervical dysplasia using office loop electrosurgical excision procedure. Primary Care: Clinics in Office Practice. 2021;48(4):583-95.
6. Lili E, Chatzistamatiou K, Kalpaktsidou-Vakiani A, Moysiadis T, and Agorastos T. Low recurrence rate of high-grade cervical intraepithelial neoplasia after successful excision and routine colposcopy during follow-up. Medicine. 2018;97(4):e9719.
7. Wu Q, Jiang Y, Ding J, Xia L, and Xu H. Clinical predictors of residual disease in hysterectomy following a loop electrosurgical excision procedure for cervical intraepithelial neoplasia grade 3. BMC Pregnancy and Childbirth. 2022;22(1):971.
8. Schaafsma M, Schuurman TN, Bekkers RLM, et al. The risk for residual AIS/CIN3+ after the first conservative surgical procedure for cervical adenocarcinoma in situ - A Dutch retrospective cohort study. Gynecol Oncol. 2025;200:44-50.
9. Delli Carpini G, Cicoli C, Bernardi M, Di Giuseppe J, Giannella L, and Ciavattini A. Clinical Outcomes of Cervical Adenocarcinoma In Situ According to Conservative or Demolitive Treatment: A Systematic Review and Meta-Analysis. Cancers (Basel). 2025;17(11)
10. Liu J, Wang Y, Wan X, et al. Comparison of the safety between cervical conization and hysterectomy for patients with cervical adenocarcinoma in situ. Journal of Gynecologic Oncology. 2022;34(1):e8.
11. Stuebs FA, Dietl AK, Behrens A, et al. Concordance Rate of Colposcopy in Detecting Cervical Intraepithelial Lesions. Diagnostics (Basel). 2022;12(10):2436.
12. Höhn AK, Brambs CE, Hiller GGR, et al. Classification of Female Genital Tumors. Geburtshilfe Frauenheilkd. 2021;81(10):1145- 537.
13. Teoh D, Musa F, Salani R, Huh W, and Jimenez E. Diagnosis and Management of Adenocarcinoma in Situ: A Society of Gynecologic Oncology Evidence-Based Review and Recommendations. Obstet Gynecol. 2020;135(4):869-78.
14. Clarke MA, Befano B, Wentzensen N, et al. Associations of obesity with post-treatment risks of cervical precancer and cancer. Am J Obstet Gynecol. 2025;233(1):40 e1-40 e16.
15. Park IS, Kim SI, Han Y, et al. Risk of female-specific cancers according to obesity and menopausal status in 2.7 million Korean women: Similar trends between Korean and Western women. Lancet Reg Health West Pac. 2021;11:100146.
16. Strojan Flezar M, Nedelko N, Poljak M, Ostrbenk Valencak A, and Gutnik H. Stratified Mucin-Producing Intraepithelial Lesion (SMILE) of the Uterine Cervix: High-Risk HPV Genotype Predominance and p40 Immunophenotype. Cells. 2021;10(8)
17. Huang X, Zhao Q, Yang P, et al. Metabolic Syndrome and Risk of Cervical Human Papillomavirus Incident and Persistent Infection. Medicine (Baltimore). 2016;95(9):e2905.
18. Shen T, Zhao J, Li W, et al. Hypertension and hyperglycaemia are positively correlated with local invasion of early cervical cancer. Front Endocrinol (Lausanne). 2023;14:1280060.
19. Luo Q, Zeng X, Luo H, et al. Epidemiologic characteristics of high-risk HPV and the correlation between multiple infections and cervical lesions. BMC Infect Dis. 2023;23(1):667.
20. Cleveland AA, Gargano JW, Park IU, et al. Cervical adenocarcinoma in situ: Human papillomavirus types and incidence trends in five states, 2008-2015. Int J Cancer. 2020;146(3):810-18.

21. Braaten KP and Laufer MR. Human Papillomavirus (HPV), HPV-Related Disease, and the HPV Vaccine. Rev Obstet Gynecol. 2008;1(1):2-10.

22. Miller RA, Mody DR, Tams KC, and Thrall MJ. Glandular Lesions of the Cervix in Clinical Practice: A Cytology, Histology, and Human Papillomavirus Correlation Study From 2 Institutions. Arch Pathol Lab Med. 2015;139(11):1431-6.

23. Lashmanova N, Braun A, Cheng L, Gattuso P, and Yan L. Endocervical adenocarcinoma in situ-from Papanicolaou test to hysterectomy: a series of 74 cases. J Am Soc Cytopathol. 2022;11(1):13-20.

24. Bruno MT, Valenti G, Cassaro N, et al. The Coexistence of Cervical Intraepithelial Neoplasia (CIN3) and Adenocarcinoma In Situ (AIS) in LEEP Excisions Performed for CIN3. Cancers (Basel). 2024;16(5):847.

25. Schwock J, Ko HM, Dube V, et al. Stratified Mucin-Producing Intraepithelial Lesion of the Cervix: Subtle Features Not to Be Missed. Acta Cytol. 2016;60(3):225-31.

26. Yang EJ, Kim NR, Choi JY, Kim WY, and Lee SJ. Loop electrosurgical excision procedure combined with cold coagulation for cervical intraepithelial neoplasia and adenocarcinoma in-situ: a feasible treatment with a low risk of residual/recurrent disease. Infect Agent Cancer. 2020;15:58.

27. Bruno MT, Cavallaro AG, Fiore M, et al. Endocervical Curettage and Extended HPV Genotyping as Predictors of Residual Disease After Hysterectomy in Postmenopausal Women Previously Treated with LEEP for CIN3: A Multivariate Analysis. Cancers (Basel). 2025;17(13): 2264.

28. Khunnarong J, Bunyasontikul N, Tangjitgamol S. Treatment Out- comes of Patients With Cervical Intraepithelial Neoplasia or In- vasive Carcinoma Who Underwent Loop Electrosurgical Excision Procedure. World J Oncol. 2021;12(4):111-8.

29. Inal HA, Han O, Ozturk Inal Z, Eren Karanis MI, and Kucukosmanoglu I. Evaluation of concordance between loop electrosurgical excisional procedure and cervical colposcopic biopsy results. J Turk Ger Gynecol Assoc. 2024;25(1):13-17.

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