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Original Article

High-grade Serous Carcinomas Identified in Cervical Biopsies: A Clinicopathologic Study Supporting the Exclusion of Cervical Serous Carcinoma from World Health Organization Classification

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Abstract

Background and objectives: High-grade serous carcinoma is a rare diagnosis in cervical biopsies. Cervical serous carcinoma is no longer recognized as a primary cervical tumor in the 2020 World Health Organization classification. This study aimed to characterize the clinicopathologic, immunohistochemical, and molecular features of high-grade serous carcinoma identified in cervical or endocervical biopsies, to assess tumor origin and ensure accurate classification. ***Methods:*** Fifty-nine cases originally diagnosed as "serous carcinoma" or "high-grade serous carcinoma" in cervical or endocervical biopsies from 2013 to 2023 were retrospectively reviewed. Clinical data, radiologic findings, and follow-up information were analyzed. Histologic features and immunohistochemical profiles were re-evaluated. Targeted next-generation sequencing was performed on a subset of cases. ***Results:*** The majority of tumors (96%) were determined to originate from the endometrium (n = 47) or the tubo-ovarian region (n = 4), with only one case confirmed as a primary cervical carcinoma. Morphologic patterns varied and could mimic human papillomavirus-associated adenocarcinoma. All tumors showed aberrant p53 expression and diffuse p16 positivity. WT-1 was expressed in all tubo-ovarian tumors but in only 12% of endometrial cases. Estrogen receptor and progesterone receptor were frequently positive in endometrial tumors; human epidermal growth factor receptor 2 was positive in 31% of cases. Molecular analysis confirmed tumor protein p53 mutations and other alterations typical of uterine serous carcinoma. ***Conclusions:*** High-grade serous carcinoma identified in cervical biopsies is overwhelmingly secondary to upper genital tract tumors, most commonly of endometrial origin. A small subset of endocervical adenocarcinomas may mimic serous carcinoma. These findings support the exclusion of primary cervical serous carcinoma from the current World Health Organization classification and emphasize the importance of accurate diagnosis for appropriate management.

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Introduction

Serous carcinoma is a highly aggressive malignancy that can arise from various Müllerian-derived organs, including the endometrium, ovaries, fallopian tubes, and peritoneum.[1,2] It accounts for approximately 50% of all malignant ovarian tumors and about 10% of endometrial cancers.[1–5]

Although serous carcinoma may occasionally be identified in cervical biopsies, primary serous carcinoma of the uterine cervix is exceedingly rare.[6–8] The 2020 World Health Organization (WHO) classification no longer recognizes it as a distinct subtype of cervical adenocarcinoma.[9] It is now accepted that most serous tumors involving the cervix represent metastases or direct extensions from primary serous carcinomas originating in other parts of the female genital tract, such as the endometrium, fallopian tubes, ovaries, or peritoneum. Nonetheless, a few case series have reported primary cervical serous adenocarcinoma, asserting that the diagnosis was made only after meticulous exclusion of spread from other gynecologic sites.[10–15]

The entity formerly referred to as serous carcinoma of the uterine cervix was first described in 1992 and is reported to have a bimodal age distribution, with peak incidence occurring before age 40 and after age 54 (range: 27–79 years; mean: 52 years).[10,15] Some studies have proposed that cervical serous carcinoma may represent a morphological variant of human papillomavirus (HPV)-associated endocervical adenocarcinoma.[6] However, among the limited number of reported cases, HPV DNA has only rarely been detected.[16]

It has been speculated that cervical serous carcinoma, like its endometrial counterpart, may be driven by mutations in the tumor protein p53 (hereinafter referred to as *TP*53) gene.[10,12] Histologically, it is indistinguishable from serous

Keywords: High-grade serous carcinoma; Cervical biopsy; Endometrial carcinoma; p53; WT-1; Human papillomavirus; HPV; HPV-independent adenocarcinoma; WHO classification.

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carcinoma of the endometrium.[10–15] These tumors typically exhibit complex papillary structures and tufts lined by pleomorphic, hobnail cells with high-grade nuclei. Alternatively, they may demonstrate stromal invasion by glands with slit-like lumina, lined by highly atypical epithelial cells, some displaying smudgy nuclei. High mitotic activity is frequently observed.[4,6]

Prognostically, premenopausal patients and those with HPV-associated endocervical adenocarcinoma generally have better outcomes than those with HPV-independent tumors exhibiting aberrant p53 expression.[12] In larger case series, this histologic variant has been associated with poor outcomes when diagnosed at advanced stages. However, patients with stage I disease appear to have a prognosis similar to that of more common forms of cervical adenocarcinoma.[10–12]

To further explore the origin and better characterize serous carcinoma involving the cervix, we conducted a retrospective review of all cases diagnosed as serous carcinoma in cervical biopsies from our pathology archives over a 10-year period.

Materials and methods

Case selection and histology review

With Institutional Review Board approval, a total of 59 cases diagnosed as "serous carcinoma" on cervical biopsies between 2013 and 2023 were identified by searching the pathology databases at our institution. Available prior or concurrent Pap smears and subsequent surgical resection specimens were reviewed in conjunction. Histologic evaluation was independently performed by two pathologists. Clinical history, demographic information, treatment, and follow-up data were obtained from medical records.

Immunohistochemistry

Immunohistochemical analysis was performed on selected formalin-fixed, paraffin-embedded (FFPE) tissue blocks containing representative tumors. The antibody panel included p53 (clone DO7, Bio-Rad), p16 (clone E6H4, Biocare Medical), estrogen receptor (ER; clone SP1, Roche), progesterone receptor (PR; clone 16, Biocare Medical), WT1 (clone 6F-H2, Abnova), and human epidermal growth factor receptor 2 (HER2)/neu (clone EP3, Abcam/Epitomics). Staining was visualized using the Ultraview Universal DAB Detection Kit, followed by counterstaining with hematoxylin and bluing reagent (Ventana). Appropriate positive and negative controls were used for all immunohistochemistry procedures.

p53 staining was categorized as "aberrant" (diffuse strong nuclear staining in >80% of tumor cells, complete absence of staining, or cytoplasmic staining) or "wild-type" (heterogeneous nuclear staining in <80% of tumor cells). p16 staining was recorded as positive with "block-type" staining (diffuse nuclear and cytoplasmic staining in all tumor cells) or as negative/non-block-type. ER and PR were considered positive if ≥1% of tumor cell nuclei showed staining. WT1 positivity was defined as diffuse nuclear staining; cytoplasmic or absent staining was interpreted as negative. HER2/neu was evaluated using the 2018 clinical trial criteria for endometrial serous carcinoma and scored as 3+ (positive), 2+ (equivocal), or 1+/0 (negative), according to American Society of Clinical Oncology (ASCO)/College of American Pathologist (CAP) guidelines. Equivocal cases (2+) were referred for HER2 fluorescence *in situ* hybridization (FISH) testing.

HER2/neu (ERBB2) FISH

HER2 gene amplification was assessed using the Abbott Molecular PathVysion HER2 DNA Probe Kit on FFPE tissue sections. Direct image analysis was employed, with control slides run concurrently to ensure assay validity. HER2 FISH results were interpreted using endometrial carcinoma criteria: positive if the HER2/CEP17 ratio was ≥2.0 or if the average HER2 copy number was ≥6.0 signals per cell.[17,18]

High-risk HPV testing

Detection of high-risk HPV DNA (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) was performed using the Roche cobas 6800 HPV Test System on cervical specimens. Results below the manufacturer-defined threshold were considered negative.

Targeted next-generation sequencing (NGS)

Selected cases underwent comprehensive genomic profiling using the FoundationOne CDx assay (Cambridge, MA) on FFPE tumor tissue. DNA extraction was performed according to standard protocols, followed by testing as per the manufacturer's instructions. The assay detects substitutions, insertions/deletions (indels), copy number alterations, and selected gene rearrangements across 324 cancer-related genes. In addition, it assesses genomic signatures, including microsatellite instability and tumor mutational burden. All immunostains and molecular tests were performed as part of the clinical work-up.

Statistical analysis

Fisher's exact test was conducted using GraphPad Prism (version 9; La Jolla, CA) to compare proportions of positive immunohistochemical markers between carcinomas of presumed tubo-ovarian and endometrial origin.

Results

Demographic and clinical features

A total of 59 cases with an initial diagnosis of "serous carcinoma" or "high-grade serous carcinoma" based on cervical or endocervical biopsies were included in the study. Detailed demographic and clinical characteristics are summarized in Table 1. Patients ranged in age from 27 to 97 years, with a median age of 69 years.

The most common presenting symptom was abnormal uterine bleeding, reported in 48 patients (81%). Twenty-one patients (36%) presented with a cervical mass or grossly visible lesion, with tumor sizes ranging from microscopic foci to 6 cm (mean: 4 cm). Eleven patients (19%) underwent colposcopy and endocervical curettage or biopsy due to a prior abnormal Pap smear. Including concurrent Pap smears performed at the time of biopsy, 36 of 40 patients (90%) had an abnormal Pap smear either prior to or at the time of cervical biopsy. Among these, 12 cases were attributed to squamous cell abnormalities (atypical squamous cells of undetermined significance or atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion, n = 11; squamous cell carcinoma, n = 1), while 24 showed glandular abnormalities (atypical glandular cells, n = 12; adenocarcinoma, n = 12). All 13 Pap smears with available high-risk HPV testing were negative.

Based on subsequent hysterectomy, salpingo-oophorectomy, and imaging, most cases of serous carcinoma identified at the cervix were determined to originate from the endometrium (n = 47), including endometrial serous carcinoma (n = 40), endometrial carcinosarcoma (n = 4), and mixed endometrial serous and endometrioid carcinoma (n = 3). Four cases were of tubo-ovarian origin. Only one case lacked

Table 1. Clinical and pathologic features of cases with serous carcinoma present at the cervix (n = 59)

Feature	Count (n)	Percentage (%)
Media age at diagnosis (range)	69 (27–97)	
Clinical presentation		
Cervical mass/polyp	21	36%
Abnormal vaginal bleeding	48	81%
Abnormal Pap smear	11	19%
Others	9	15%
Biopsy sites		
Endocervical or cervical biopsy only	22	37%
Cervical and endometrial biopsy	37	63%
Recent Pap smear results		
NILM	4	7%
ASCUS/ASC-H	11	19%
AGC	12	20%
Adenocarcinoma	12	20%
Squamous cell carcinoma	1	2%
NA	19	32%
HPV status in Pap smear		
Negative	13	22%
NA	46	78%
Final diagnosis in surgical resection		
Endometrial serous carcinoma	40	67%
Endometrial carcinosarcoma	4	7%
Endometrial mixed serous and endometrioid carcinoma	3	5%
Tubo-ovarian high-grade serous carcinoma	4	7%
Cervical primary carcinoma	1	2%
NA	7	12%
Tumor origin and other sites of involvement		
Vaginal involvement	5	9%
Lower uterine segment involvement	23	39 %
Endometrial involvement	42	71 %
Myometrial involvement	24	41%
Tubo-ovarian involvement	23	39%
Peritoneal involvement	19	31%
Lymph node metastasis	12	20%
Adjuvant treatment		
Chemotherapy	34	58%
Brachytherapy/pelvic radiation	6	10%
Follow-up		
Death of disease	29	49%
Death of other diseases	3	5%
Alive with disease	9	15%
Alive, free of disease	18	30%

AGC, atypical glandular cells; ASCUS/ASC-H, atypical squamous cells of undetermined significance/atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion; HPV, human papillomavirus; NA, not available; NILM, negative for intraepithelial lesion or malignancy.

Table 2. Morphologic features of serous carcinoma at the cervix

Features	(n = 38)
Architecture	
Papillary	31 (82%)
Micropapillary	14 (37%)
Fibrovascular core	29 (76%)
Psammoma bodies	3 (8%)
Growth pattern	
Slit-like space	27 (71%)
Glandular-like space	31 (82%)
Solid growth	17 (45%)
Discohesive	28 (74%)
Cytology	
Cytoplasm amount	
Abundant	10 (26%)
Moderate	7 (18%)
Scant	21 (55%)
Cytoplasm texture	
Eosinophilic	25 (66%)
Both eosinophilic and clear	13 (20%)
Prominent nucleoli	36 (95%)

evidence of tumor at any other anatomical site and was diagnosed as a primary cervical serous carcinoma.

In addition to the cervix, tumor involvement was frequently observed in other anatomical regions, including the endometrium, myometrium, or tubo-ovarian tissue, as well as the vagina (n = 5), lower uterine segment (n = 23), and peritoneum (n = 19). Lymph node metastasis was present in 12 cases.

During a median follow-up of 56 months, 34 patients received chemotherapy, and six underwent brachytherapy or pelvic radiation. More than half of the patients died during the follow-up period, 29 due to disease progression and three from other causes. Of the surviving patients, nine were living with disease, while 18 had no evidence of disease. Among 17 cases with serous carcinoma confined to endometrial polyps or with minimal uterine involvement, 11 patients remained disease-free at follow-up, suggesting that early-stage disease was associated with a favorable prognosis.

Histological features of high-grade serous carcinoma at the cervix

All tumor slides were re-reviewed for histologic classification and pathologic features. For cases with available Pap smears (n = 40), endometrial biopsies (n = 37), and hysterectomy and salpingo-oophorectomy specimens (n = 49), a comprehensive assessment was performed in conjunction with immunohistochemical and radiologic data.

Pathologic findings are detailed in Table 2. Papillary architecture was identified in 82% (31/38) of cases, while micropapillary features were observed in 37% (14/38). Fibrovascular cores were present in 76% (29/38), and psammoma bodies were rare (8%, 3/38). Glandular architecture was the most frequent growth pattern (82%, 31/38), followed by slit-like spaces (71%, 27/38) and discohesive cells (74%, 28/38). A solid growth pattern was seen in 45% (17/38) of cases.

Cytologically, prominent nucleoli (95%, 36/38) and atypical mitoses (87%, 33/38) were the most common features. Cytoplasmic volume was semi-quantified as low (scant), moderate (apparent but not abundant), or high (abundant). Cytoplasmic volume was scant in 55% (21/38), moderate in 18% (7/38), and abundant in 26% (10/38). Cytoplasmic staining was eosinophilic in 66% (25/38) and a combination of eosinophilic and clear in 20% (13/38). Representative features are illustrated in Figure 1.

In endocervical curettage specimens, tumor cells were often scant and deceptively subtle, potentially mimicking benign endocervical glandular epithelium at low magnification (Fig. 2). However, at higher magnification, these cells exhibited high-grade cytologic features with aberrant p53 expression. Tumor cells were observed colonizing or clinging to benign endocervical or squamous epithelium.

Association between tumor origin and immunohistochemistry markers

Immunohistochemical findings and their correlation with tumor origin are summarized in Table 3. All tested cases demonstrated aberrant p53 expression and diffuse p16 positivity, regardless of tumor origin.

ER and PR expression were frequently positive in tumors of endometrial origin (ER: 81%, 17/21; PR: 75%, 15/20) but were negative in the one tested tubo-ovarian tumor. WT1 was negative in the majority of endometrial-origin tumors (88%, 36/41), while all four tubo-ovarian tumors showed WT1 positivity. The one primary cervical carcinoma tested negative for WT1.

HER2 immunohistochemistry was performed in 29 endometrial-origin cases, of which 70% (20/29) tested negative. The primary cervical case was also negative for HER2.

None of the 13 Pap smears with available high-risk HPV testing were positive.

Serous carcinoma confined to the cervix

One case featured serous carcinoma-like cells confined to the cervix. Histologically, the radical hysterectomy specimen predominantly showed usual-type endocervical adenocarcinoma with a minor serous carcinoma-like component (Fig. 3). Immunohistochemistry revealed diffuse p16 expression and aberrant p53 overexpression in both components.

Targeted NGS

Targeted NGS was performed on five cases, all of which were confirmed to be of endometrial origin. Detailed molecular findings are provided in Table S1. The most common alteration was a missense mutation in *TP53*, detected in all cases. Other frequent mutations included *PIK3CA* or *PIK3R1* (4/5 cases), *BCL2* amplification (2/5), and single instances of *PPP2R1A*, *FBXW7*, *EGFR*, *KRAS*, *RAD21*, and *CCNE1* alterations. All sequenced tumors were microsatellite stable and exhibited low tumor mutational burden (4–7 mutations/Mb), consistent with typical molecular features of endometrial serous carcinoma.

Discussion

Serous carcinoma of the cervix was excluded from the 2020 WHO classification due to a lack of convincing evidence supporting its existence as a true primary cervical tumor.[9] Historically, this diagnosis was based on morphological resemblance to serous carcinoma in other parts of the female genital tract.[8,10–14] However, it has since become evident

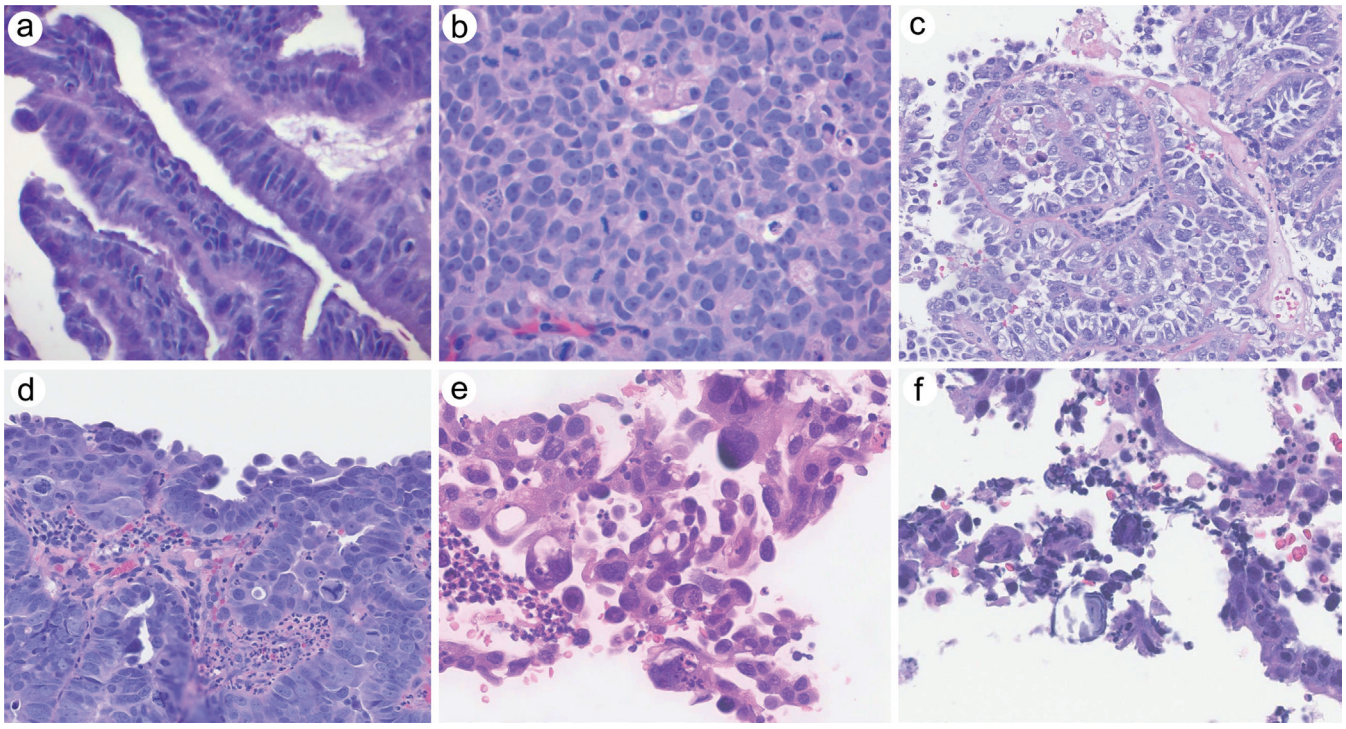

Fig. 1. Variable morphologic features of high-grade serous carcinoma involving the cervix. (a) Papillary growth pattern with columnar, pseudostratified tumor cells. This morphology can mimic HPV-associated usual-type endocervical adenocarcinoma. (b) Solid growth composed of round to ovoid tumor cells, with frequent mitotic figures including atypical mitoses. (c) Papillary architecture with hobnailing high-grade tumor cells and clear cytoplasm, which requires distinction from clear cell carcinoma. (d) Infiltrating glandular tumor cells with hyperchromatic, "smudgy" nuclei. Conspicuous mitoses, including atypical forms, and apoptosis are present. (e) Discohesive tumor cells with marked nuclear pleomorphism. (f) Loosely cohesive tumor cells associated with psammoma bodies. Magnification: a-f: 400×.

that most of these cases represent either endometrial or tubo-ovarian serous carcinomas that secondarily involve the cervix, or, alternatively, HPV-associated endocervical adenocarcinomas that exhibit serous-like architecture or cytomorphologic features.[9,15] In the current study, the vast majority of cases (50 of 52, 96%) initially diagnosed as serous carcinoma in cervical biopsies were later confirmed to be of upper genital tract origin, predominantly from the endometrium. Only one case exhibited features suggestive of a primary cervical tumor, and even these were ultimately reclassified as usual-type endocervical adenocarcinoma with focal serous-like morphology. These findings support and further strengthen the rationale for removing serous carcinoma from the list of recognized primary cervical carcinomas in the WHO classification.

Diagnosing serous carcinoma in cervical specimens can present significant challenges due to its wide morphological spectrum, which includes papillary, glandular, and solid architectural patterns, as well as variation in nuclear pleomorphism and cytoplasmic features.[4,7,10–12,19,20] In our cohort, immunohistochemical work-up was often initiated based on high-grade cytologic features, and many tumors were designated as "serous carcinoma" or "high-grade serous carcinoma" owing to their aberrant p53 expression.[21–24] In cervical adenocarcinomas, particularly those associated with high-risk HPV infection, p53 immunostaining typically shows a wild-type (scattered or weak heterogeneous) pattern. Abnormal p53 expression, including diffuse overexpression or complete absence (null pattern), is rare but may be seen in a subset of non-HPV-associated adenocarcinomas, such as gastric-type or mesonephric tumors. Therefore, interpretation of aberrant p53 staining in cervical lesions should be contextualized with HPV status and morphologic subtype to avoid misclassification, as diffuse p53 positivity alone does not necessarily exclude HPV-associated endocervical adenocarcinoma.[21–23]

Initial pathology reports frequently included comments suggesting that potential primary tumor sites include the endometrium, tubo-ovarian complex, and, rarely, the cervix. Some earlier cases (n = 4, diagnosed between 2013 and 2019) were initially reported as "cervical serous carcinoma," but subsequent radical hysterectomy revealed that these were actually endometrial serous carcinomas arising in endometrial polyps (n = 3) or tubo-ovarian serous carcinomas associated with serous tubal intraepithelial carcinoma (n = 1). Upon further histologic and clinical correlation, these findings were interpreted as secondary involvement from an upper tract serous carcinoma, most consistent with either surface colonization or artifactually displaced fragments rather than invasive cervical disease. Several such cases demonstrated features such as surface epithelial involvement of the endocervix without stromal invasion, supporting the interpretation of glandular colonization rather than a primary cervical origin. Radiologic imaging is often helpful in identifying the primary tumor site when serous carcinoma is diagnosed in a cervical biopsy; however, early-stage endometrial serous carcinoma often arises within polyps in an atrophic endometrium background,[5] and serous tubal intraepithelial carcinoma lesions can be missed on imaging. Importantly, 11 patients in our study underwent cervical biopsy due to abnormal findings in Pap smears. In total, 90% of patients with recent Pap smear results had abnormalities, underscoring the importance of routine cervical cytologic screening in detecting these aggressive yet elusive malignancies.

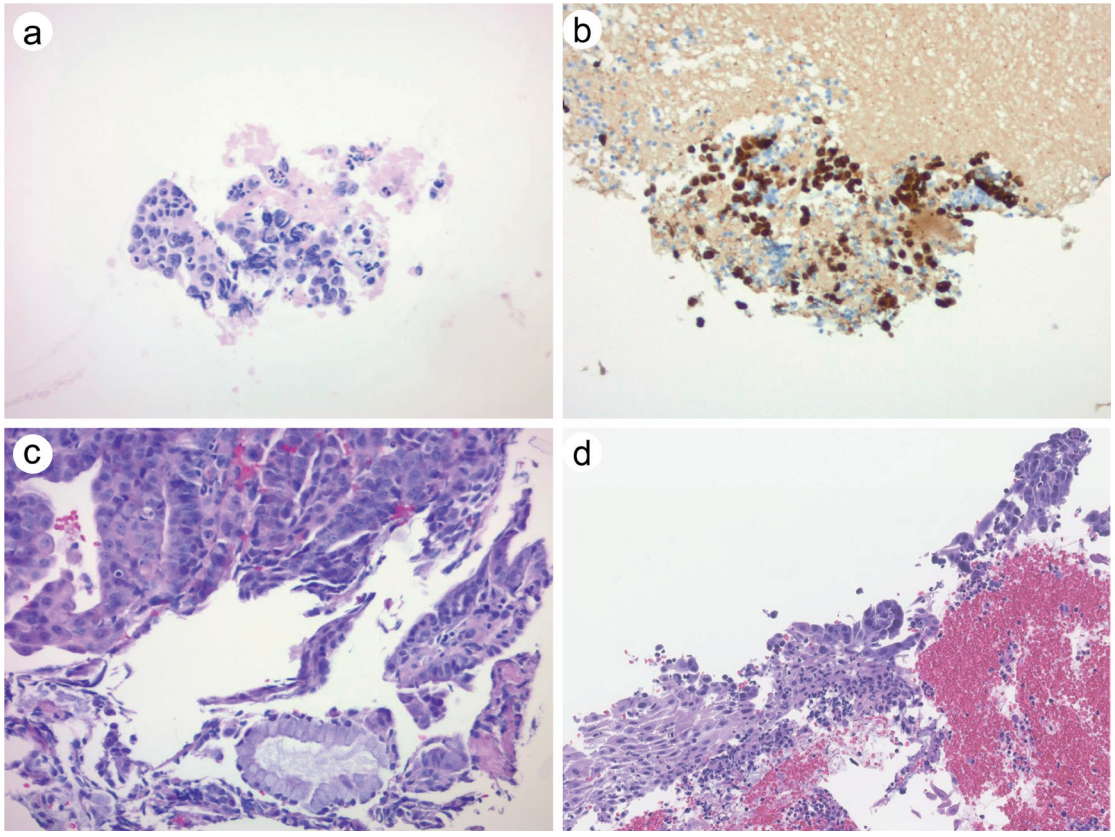

Fig. 2. Subtle histologic features of high-grade serous carcinoma involving the cervix. (a) Scant tumor cells with high-grade morphology, which can be easily overlooked (magnification of 100×). (b) p53 immunostaining shows diffuse overexpression (aberrant pattern) in the same tumor cell group shown in panel a (magnification of 100×). (c) Tumor cells admixed with benign endocervical glandular epithelium (magnification of 200×). (d) Tumor cells colonizing benign squamous epithelium (magnification of 100×).

Table 3. Immunohistochemical findings and association with tumor origin sites

	Endometrium (n = 47)	Tubo-ovary (n = 4)	Cervix (n = 1)	Unknown (n = 7)
p53				
Aberrant	47	4	1	7
Wild type	0	0	0	0
p16				
Positive	22	2	1	5
Negative	0	0	0	0
ER				
Positive	17	0	–	3
Negative	4	1	–	2
PR				
Positive	15	0	–	1
Negative	5	1	–	0
WT-1				
Positive	5	4	0	1
Negative	36	0	1	1
HER2				
Positive	9	–	0	1
Negative	20	–	1	3

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

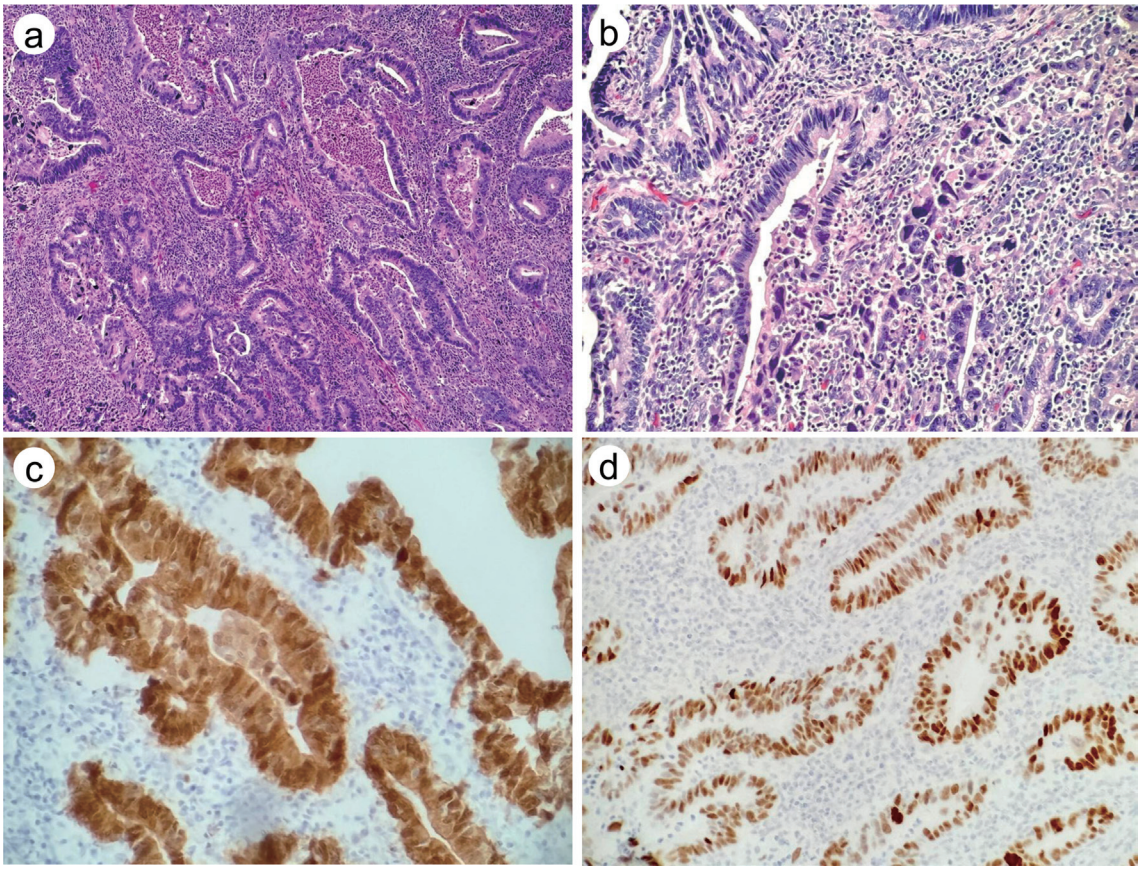

Fig. 3. Histologic and immunohistochemical findings of a cervical adenocarcinoma with serous-like features. (a) The predominant histology of the tumor is usual-type endocervical adenocarcinoma (magnification of 100×). (b) A minor serous carcinoma-like component is seen within the usual-type endocervical adenocarcinoma (magnification of 100×). (c) Immunostaining shows diffuse p16 positivity in both components (magnification of 200×). (d) p53 immunostaining demonstrates an aberrant overexpression pattern in both the usual-type and serous-like elements (magnification of 200×).

Immunohistochemical biomarkers can aid in determining tumor origin. While WT-1 has traditionally been considered a marker more specific for tubo-ovarian serous carcinoma, recent studies show that up to 36–64% of uterine serous carcinomas may express WT-1.[2,25–27] Thus, although a positive WT-1 stain is not exclusive to tubo-ovarian tumors, a negative result can be highly informative. In our series, WT-1 negativity was observed in nearly all endometrial origin tumors, yielding a negative predictive value approaching 100% for excluding tubo-ovarian origin. ER expression in uterine serous carcinoma is variably reported, with positivity rates ranging from 10% to 50%.[2] In our study, ER was positive in 75% of cases, a discrepancy that may reflect differences in the immunohistochemical thresholds used to define positivity.[28] We adopted a ≥1% nuclear staining cut-off, which may have contributed to the higher positivity rate observed. HER2/neu status also holds therapeutic relevance in endometrial serous carcinoma, with overexpression and/or amplification seen in 25–35% of cases in prior studies. In our cohort, 31% of endometrial serous carcinomas involving the cervix were HER2-positive, consistent with these published findings.[17,18] These immunohistochemical markers, when interpreted in the appropriate clinical and histological context, are valuable tools for distinguishing primary sites in serous carcinoma.

A single case in our series was initially interpreted as primary cervical serous carcinoma. Following hysterectomy and bilateral salpingo-oophorectomy, no tumor was identified in the endometrium, fallopian tubes, or ovaries. Histologically, the tumor consisted predominantly of usual-type endocervical adenocarcinoma with a minor component of serous carcinoma-like morphology. The immunohistochemical profile demonstrated diffuse p16 expression and aberrant p53 overexpression in both components. While p16 positivity suggests the possibility of HPV association,[19,20] the aberrant p53 pattern raises the possibility of an HPV-independent pathway. This case illustrates the complexity of assigning tumor origin based solely on morphology and highlights the need for integrating histologic, immunophenotypic, and molecular features in diagnosis.

Our findings align with recent studies that have demonstrated similar trends. One investigation of 10 cervical carcinomas with serous-like morphology concluded that these tumors were better classified as endocervical adenocarcinomas with serous features, rather than true serous carcinomas.[12] Similarly, another recent study involving six cases concluded that serous carcinomas identified in cervical biopsies all originated from the upper genital tract.[29] Taken together, these studies, along with our data, provide strong evidence supporting the exclusion of primary cervical serous carcinoma as a distinct diagnostic entity.

Interestingly, we identified a subset of endometrial serous carcinomas arising in polyps or with minimal uterine serous carcinoma, without evidence of myometrial or cervi-

cal invasion. Among 17 such cases, 11 patients remained disease-free at follow-up, suggesting that early-stage disease confined to endometrial polyps may be associated with a favorable prognosis. A prior study of 13 cases originally diagnosed as cervical serous carcinoma noted better outcomes in premenopausal patients and poorer outcomes in postmenopausal individuals. In our cohort, however, prognosis was more clearly associated with disease stage rather than patient age at diagnosis, further emphasizing the importance of early detection and staging.[5,30]

There are limitations to our study. As a retrospective analysis, it is subject to inherent biases, including evolving terminology and treatment approaches over time. Additionally, the number of cases with confirmed tubo-ovarian or primary cervical origin was small, limiting our ability to fully assess the utility of immunohistochemical or molecular biomarkers in definitively determining tumor origin across all cases. Furthermore, in 12% of cases, the diagnosis was based on biopsy findings, and biopsy and subsequently resection were not performed. Nevertheless, the consistent clinicopathologic and molecular findings across our cohort provide meaningful insight into the true nature of serous carcinoma involving the cervix.

Conclusions

Our study demonstrates that serous carcinoma identified in cervical biopsy specimens almost always originates from the upper genital tract, particularly the endometrium or fallopian tubes/ovaries. A minority of cases may represent endocervical adenocarcinomas with serous-like features, which should not be classified as primary cervical serous carcinoma. To our knowledge, this is one of the largest series studies of serous carcinoma at the cervix and offers a comprehensive analysis integrating morphologic and molecular pathology. Accurate diagnosis is essential to guide appropriate clinical management. Our findings further support the exclusion of primary cervical serous carcinoma from the WHO classification and underscore the importance of integrating histopathologic, immunohistochemical, and clinical data to accurately determine tumor origin.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Study concept and design (VKM, TS), acquisition of data (VKM, TS), analysis and interpretation of data (VKM, TS), and drafting of the manuscript (TS). Both authors have made significant contributions to this study and have approved the final manuscript.

Ethical statement

This study was conducted in accordance with the ethical standards of the Helsinki Declaration (as revised in 2024). All specimens from the patients in this study were obtained with appropriate consents and approval from the institutional review board of Yale University (Institutional Review Board No. 2000026494). The requirement for individual consent for this retrospective analysis was waived.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to the sensitive nature of the clinical data and the potential for patient re-identification, de-identified data will be shared in compliance with institutional and ethical guidelines, and only for research purposes. Requests for data access will require a signed data use agreement.

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