

Correlation of Cytology Pelvic Washings and Histopathologic Stage of Early (pT1/T2) Disease and Late Stage (pT3) Uterine Serous Carcinoma: Findings from a Single Institution Study

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ABSTRACT

Objective: Uterine Serous Carcinoma (USC) is an aggressive non-endometrioid subtype of endometrial carcinoma, often associated with extra-uterine spread and poor outcomes. Although peritoneal cytology was historically included in FIGO staging to detect occult disease, its prognostic relevance in USC remains uncertain. This study aimed to evaluate the correlation between pelvic washing cytology and final histopathologic stage in patients with serous endometrial carcinoma.

Methods: We conducted a retrospective review of 26 patients who underwent hysterectomy at our institution between 2010 and 2020. Pelvic washing cytology was classified as positive (atypical or malignant cells present) or negative, and histopathologic staging followed the CAP protocol. Low-grade disease was defined as pT1–pT2 and high-grade disease as pT3. Fisher’s exact test was used to assess the association between cytology and stage.

Results: Positive cytology was more frequent than in Stage 1 or 2 disease (93% **vs** 64%), but the difference was not significant using the Fischer exact test ($p=0.13$). Along with this, 7 cases out of 11 were staged as low grade but had positive malignant cells in their pelvic washes. One of the cases is presented as an example.

Conclusions: In this cohort, despite the diagnosis of low-grade serous carcinoma (pT1–pT2) in these seven cases, washing cytology revealed the presence of malignant cells suggesting that these are not truly low stage tumours. This conclusion is supported by recent studies that demonstrate that patients with low stage uterine cancers with positive peritoneal cytologies have been found to have significantly lower overall survival rates than patients with low stage tumours with negative peritoneal cytologies. Our findings suggest that larger, multicentre studies with standardized cytology protocols are needed to evaluate staging and risk stratification of low stage uterine cancers with positive cytologic findings.

Keywords: Cytology; Uterine serous carcinoma; Histopathology

INTRODUCTION

Endometrial carcinoma is the most common gynecologic malignancy in developed countries, with uterine serous carcinoma representing a highly aggressive non-endometrioid subtype [1]. Although it accounts for only a small proportion of all endometrial cancers, uterine serous carcinoma is associated with disproportionately high rates of extrauterine spread and recurrence, often presenting at an advanced stage despite minimal myometrial invasion. Accurate staging and risk stratification are therefore critical in guiding adjuvant therapy and predicting outcomes in these patients. Traditional staging systems rely primarily on histopathologic evaluation of the hysterectomy specimen and associated adnexa, with additional emphasis on myometrial and cervical invasion, lymph node involvement, and extrauterine dissemination [2]. This current investigation was prompted by clinical queries concerning a not infrequent occurrence of diagnosis of low stage (stages 1 and 2) serous uterine cancer accompanied with positive cytologic pelvic (intraperitoneal) washings. Thus we have undertaken a quality assurance study to determine the frequency of such findings and possible reasons for their occurrence.

Peritoneal cytology, obtained through pelvic washing at the time of surgery, historically served as a component of the International Federation of Gynecology and Obstetrics (FIGO) staging for endometrial carcinoma. Its intended role was to detect occult extra-uterine disease, particularly in high-risk histologic subtypes [3]. However, the prognostic significance of malignant cells in peritoneal washings has been controversial. Early studies suggested that positive cytology often is concurrent with other adverse features, such as serosal invasion or nodal metastasis, but may not independently predict outcomes [4]. Consequently, peritoneal cytology was removed from FIGO staging in 2009, though it continues to be documented in surgical reports because of its potential prognostic implications, particularly in non-endometrioid subtypes like serous carcinoma and clear-cell carcinoma [1,2].

Despite these changes, the clinical utility of peritoneal cytology in serous endometrial carcinoma remains uncertain. Several recent studies indicate that positive cytology in stage I serous or clear-cell carcinoma may be associated with earlier relapse, peritoneal dissemination, and worse overall survival, highlighting a possible role in risk stratification rather than formal staging [5,6]. Given the aggressive nature of serous carcinoma and its propensity for occult extrauterine spread, evaluating the correlation between pelvic washing cytology and final histopathologic stage may help clarify its relevance in contemporary practice.

To address this question, we conducted a retrospective correlation study evaluating the relationship between pelvic washing cytology and final histopathologic stage in patients with serous endometrial carcinoma. By reviewing archival pathology records from women who underwent hysterectomy at our institution, we sought to determine whether the presence of malignant cells in pelvic or peritoneal washings corresponds with low-grade (pT1–pT2) versus high-grade (pT3) disease.

MATERIALS AND METHODS

This retrospective correlation study evaluated the relationship between pelvic washing cytology and final histopathologic stage in patients with serous endometrial carcinoma. Pathology records from women patients at the State University of New York Downstate Medical Centre University Hospital in Brooklyn, New York who underwent hysterectomy at our institution between 2010 and 2020 were reviewed. This study was prompted by the fact that our medical centre services a largely African American and West Indian population for which cancer rates are significantly higher than in the general population. A total of 65 cases were identified.

Thirty- nine cases were excluded due to: (1) absence of an available cytology specimen, (2) endometrial carcinoma subtype other than serous, or (3) diagnosis of primary ovarian cancer or a primary tumour of unknown origin. After excluding these cases, a total of 26 cases met inclusion criteria and were analyzed.

For each case, pelvic washing cytology reports were reviewed and classified as positive when atypical or malignant cells were present and negative when no malignant cells were identified. Corresponding hysterectomy specimens were staged according to the College of American Pathologists (CAP) protocol for endometrial cancer [7]. Low-grade disease was defined as pT1–pT2, indicating tumour confined to the uterus, including myometrial invasion (pT1a–c) or cervical stromal involvement (pT2). High-grade disease was defined as pT3 (pT3a–b), representing extension to the serosa, adnexa, vagina, and/or parametrium. No cases of pT4 disease were identified. Data was compiled using Microsoft Excel. Cytology classification (positive *vs* negative) and histopathologic stage (low-grade *vs* high-grade) were tabulated for all cases, and results were summarized in a 2 × 2 contingency table. Since our sample size was small, Fisher’s exact test was used to evaluate the correlation between cytology results and histopathologic stage. Counts were plotted using an online statistical tool [8].

RESULTS AND DISCUSSION

Table 1 summarizes the 26 cases that were retrieved. After plotting the counts in a 2 × 2 contingency table, **Table 2** shows that patients with stage 3 disease demonstrated a higher proportion of positive pelvic washing cytology compared with stage 1 and/or 2 disease (14/15 or 93% *vs* 7/11 or 64%). However, seven of the eleven cases with low grade disease had positive malignant cells in cytology and this difference did not reach statistical significance. The Fisher exact test yielded a p-value of 0.1279 ($p > 0.05$), indicating that the presence of malignant cells in pelvic or peritoneal washings did not significantly differ between early-stage (pT1–pT2) and advanced-stage (pT3) serous endometrial carcinoma in this cohort.

Table 1: Clinicopathologic characteristics of the cases. Summary of demographic and tumor characteristics for patients with serous endometrial carcinoma who had both pelvic washing cytology and concurrent hysterectomy histopathology available for review. Cytology results are categorized as positive (atypical or malignant cells identified) or negative (no malignant cells identified). Histopathologic staging follows CAP synoptic reporting criteria.

Case	Cytology Diagnosis	Cytology Category	Final Histopathologic Diagnosis	Pathologic Stage	Stage Category
1	Positive for malignant cells	Positive	High-grade mixed serous/endometrioid carcinoma	pT3a pNx pM1	HIGH
2	Positive; metastatic carcinoma	Positive	Carcinosarcoma (serous phenotype)	pT3a pN0 pM1	HIGH
3	Positive—ascitic fluid	Positive	High-grade serous adenocarcinoma	ypT3c	HIGH
4	Ascitic fluid—positive	Positive	Papillary serous carcinoma	ypT2 ypN1a ypM1	LOW
5	Metastatic adenocarcinoma	Positive	Serous carcinoma	ypT1a Nx M1	LOW
6	Ascitic fluid—positive	Positive	Serous carcinoma	pT3c pNx pMx	HIGH
7	Cannot rule out malignancy	Positive	Serous carcinoma	T2 Nx Mx	LOW
8	Adenocarcinoma—ascitic fluid	Positive	Serous adenocarcinoma	T3a Nx M1	HIGH
9	Pelvic wash—adenocarcinoma	Positive	Serous adenocarcinoma, papillary & solid	T2 N2 Mx	LOW

10	Ascitic fluid—positive	Positive	Serous carcinoma	T3c N1 Mx	HIGH
11	Pelvic wash—negative	Negative	Uterine serous carcinoma	T3b N1 Mx	HIGH
12	Ascitic fluid—positive	Positive	Serous carcinoma	T1a N1 M1	LOW
13	Ascitic fluid—positive	Positive	Serous carcinoma	T3a Nx M1	HIGH
14	Peritoneal fluid—negative	Negative	Serous carcinoma	T2 N1 Mx	LOW
15	Peritoneal fluid—positive	Positive	Serous carcinoma	T3a N1 M1	HIGH
16	Peritoneal fluid—positive	Positive	Serous carcinoma	T3 Nx M1	HIGH
17	Pelvic wash—negative	Negative	Serous carcinoma	T1a N0 Mx	LOW
18	Pelvic wash—negative	Negative	Serous carcinoma	T1a N0 Mx	LOW
19	Pelvic washing—positive	Positive	Serous carcinoma	T1b N2a Mx	LOW
20	Reactive mesothelial cells	Negative	Serous carcinoma	T1a N0 Mx	LOW
21	Pelvic washing—positive	Positive	Serous carcinoma	T3b N1a Mx	HIGH
22	Pelvic fluid positive; ascitic fluid positive	Positive	Serous carcinoma	T3a Nx M1	HIGH
23	Pelvic wash—atypical cells	Positive	Uterine serous carcinoma	T1a N0 Mx	LOW
24	Atypical cells—ascitic fluid	Positive	Uterine serous carcinoma	T3a N0 Mx	HIGH
25	Ascitic fluid—positive	Positive	Metastatic serous carcinoma involving myometrium	pT3c pNx pM1	HIGH
26	Ascitic fluid—positive	Positive	High-grade endometrial carcinoma	pT3c pN0 pMx	HIGH

Table 2: 2 × 2 Contingency table comparing cytology and surgical stage.

Results			
	Cytology Pos	Cytology Neg	Marginal Row Totals
Low SS	7	4	11
High SS	14	1	15
Marginal Column Totals	1	5	26 (Grand Total)

The Fisher exact test statistic value is 0.1279. The result is not significant at $p < .05$.

Although our analysis did not demonstrate a statistically significant correlation between malignant peritoneal cytology and advanced (pT3) disease, this result must be interpreted in the context of the broader, somewhat equivocal literature. Historically, peritoneal cytology was included in FIGO staging, but its prognostic value has been controversial. Early large cohort studies found that positive cytology accompanied with other high-risk features such as extrauterine disease and high-grade histology, is the driver of adverse outcomes [3]. These observations contributed to the removal of peritoneal cytology from FIGO staging in 2009 [4] and its continued exclusion in more recent staging systems [7].

However, recent studies in non-endometrioid subtypes such as serous and clear-cell carcinoma have re-examined the role of malignant cytology. Huh et al. [5], reported that patients with stage 1 disease with positive peritoneal cytology had significantly shorter progression-free and overall survival and were more likely to experience peritoneal recurrence. Similarly, Suh, Kim, and Lee [6] found that positive cytology was associated with earlier

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relapse and worse survival even in multivariable analyses. These conclusions have been confirmed in other more recent large-scale studies [2,9]. Major factors in determining overall survival were positive peritoneal cytologies and lymphovascular invasion. Importantly, overall survival in the African American patient population was significantly lower than the overall mean survival [2], a finding of direct relevance to our study, given that our patient population is predominantly African-American and West Indian.

Our study also suggests that another possible factor in determination of overall survival is tumour grade. Cases with positive peritoneal cytologies showed high grade though localized tumours. An example is shown in **Figures 1 and 2**. **Figure 1** shows the malignant cells in cytology where the cells are clustering and overlapping. **Figure 2A-2B** shows the high-grade features of the corresponding histopathologic specimen with infiltrating nests of glandular tumour cells with slit-like spaces. Higher power (**Figure 2B**), shows papillary features, pleomorphic cells with prominent nucleoli with some mitotic activity. This finding highlights the probable importance of tumour grade that, together with positive cytology, may carry meaningful implications in high-risk non-endometrioid subtypes. From the data in **Table 1**, a majority of the cancers (15 of the 26) were staged as "Mx" (metastasis not determined). Of the remaining 11 cancers, three low grade tumors with positive peritoneal washings were staged as M1 (presence of metastasis) and eight high grade tumors were also staged as M1. Thus, every M1 case was positive for peritoneal involvement including all of the low-grade tumors, for which metastasis was evaluated, making tumor metastasis an important factor in ultimate staging.

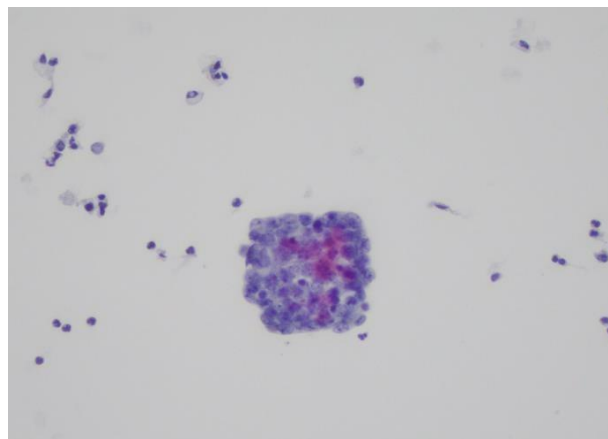


Figure 1: Papstain. 400x. Clustering and overlapping of cells from pelvic wash.

Another important consideration is the technical and interpretive challenge of peritoneal cytology. Cytologic evaluation has limitations, including sampling variability, indistinct cell morphology, and possible reactive mesothelial changes, which can complicate interpretation [1]. Moreover, even when malignant cells are detected, their prognostic relevance may depend on the context of other risk factors. The CAP protocol acknowledges this controversy: although cytology is no longer part of formal surgical staging, results should still be documented because their significance is not fully resolved [7].

In light of our findings and the existing literature, the absence of a statistically significant correlation in our study may reflect several factors, including our relatively small sample size, the inherent biological aggressiveness of serous carcinoma regardless of stage, and variability in cytologic sampling or processing. Malignant peritoneal cytology in high-risk tumours such as serous carcinoma must be considered as a major factor for decisions concerning treatment [positive cytology would require postoperative adjunct radiation and/or chemotherapy [10]

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rather than simple observation] and risk stratification. If peritoneal involvement can be regarded as metastasis, then re-staging should be considered. Future larger, multicentre studies with standardized sampling and cytologic protocols are needed to confirm that peritoneal cytology should be reintegrated into prognostic models or treatment decision algorithms [5,6].

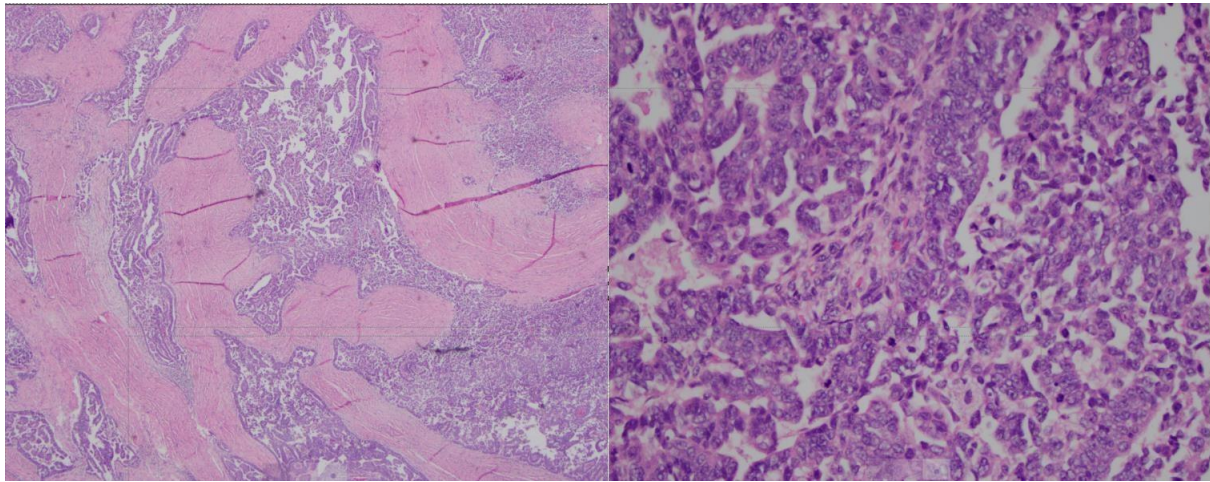


Figure 2A: H&E 100x and B: 1000x. Both figures show infiltrating glandular sheets of tumour cells with slit-like spaces.

Figure 2B: Figure 2B shows papillary-like growth of atypical hyperchromatic, pleomorphic cells with prominent nucleoli and mitotic activity.

CONCLUSION

In conclusion, our study found no statistically significant association between positive peritoneal cytology and advanced stage (pT3) in patients with serous endometrial carcinoma. Although our sample size is relatively small and given the known variability in cytologic sampling, our findings nonetheless suggest that peritoneal cytologic studies are vital in all cases of serous uterine carcinoma especially in populations with major risk factors such as in our patient population. Our results justify larger, multicentre studies with standardized cytology protocols to definitively verify the role of peritoneal cytology in risk stratification, guiding adjuvant therapy and possible staging.

DISCLOSURE

None of the authors of this paper have any real or perceived conflicts of interest concerning any aspects of the work presented in this paper.

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