Pathology Articles   Pathology and Laboratory Medicine

8-1-2021

Impact of positive cytology in uterine serous carcinoma: A reassessment

Logan Corey

Juliana Fucinari

Mohamed A. Elshaikh
Henry Ford Health, MELSHAI1@hfhs.org

Daniel Schultz
Henry Ford Health, DSCHULT2@hfhs.org

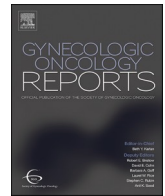Rami Mussallam

See next page for additional authors

Recommended Citation

Corey L, Fucinari J, Elshaikh M, Schultz D, Mussallam R, Zaiem F, Daaboul F, Fehmi O, Dyson G, Ruterbusch J, Morris R, Cote ML, Ali-Fehmi R, and Bandyopadhyay S. Impact of positive cytology in uterine serous carcinoma: A reassessment. Gynecol Oncol Rep 2021; 37:100830.

Authors

Logan Corey, Juliana Fucinari, Mohamed A. Elshaikh, Daniel Schultz, Rami Mussallam, Feras Zaiem, Fayez Daaboul, Omar Fehmi, Greg Dyson, Julie Ruterbusch, Robert Morris, Michelle L. Cote, Rouba Ali-Fehmi, and Sudeshna Bandyopadhyay

Research Report

Impact of positive cytology in uterine serous carcinoma: A reassessment

Logan Corey [a,b], Juliana Fucinari [c], Mohamed Elshaikh [d], Daniel Schultz [d], Rami Mussallam [e], Feras Zaiem [e], Fayez Daaboul [e], Omar Fehmi [f], Greg Dyson [a], Julie Ruterbusch [a], Robert Morris [a,b], Michelle L. Cote [a,c], Rouba Ali-Fehmi [a,*], Sudeshna Bandyopadhyay [e]

[a] Wayne State University, School of Medicine, Department of Oncology, Detroit, Michigan
[b] Karmanos Cancer Institute, Department of Gynecologic Oncology, Detroit, Michigan
[c] Karmanos Cancer Institute, Population Sciences and Disparities Research, Detroit, Michigan
[d] Henry Ford Health System, Detroit, Michigan
[e] Wayne State University, School of Medicine, Department of Pathology, Detroit, Michigan
[f] University of Michigan, Ann Arbor, Michigan

ARTICLE INFO

ABSTRACT

Objectives: The aim of this study was to evaluate the prognostic value of peritoneal cytology status among other clinicopathological parameters in uterine serous carcinoma (USC).

Methods: A retrospective study of 148 patients diagnosed with uterine serous carcinoma from 1997 to 2016 at two academic medical centers in the Detroit metropolitan area was done. A central gynecologic pathologist reviewed all available slides and confirmed the histologic diagnosis of each case of USC. We assessed the prognostic impact of various clinicopathological parameters on overall survival (OS) and endometrial cancer-specific survival (ECSS). Those parameters included race, body mass index (BMI), stage at diagnosis, tumor size, lymphovascular invasion (LVSI), peritoneal cytology status, receipt of adjuvant treatment, and comorbidity count using the Charlson Comorbidity Index (CCI). We used Cox proportional hazards models and 95% confidence intervals for statistical analysis.

Results: Positive peritoneal cytology had a statistically significant effect on OS (HR: 2.09, 95% CI: [1.19, 3.68]) and on ECSS (HR: 2.02, 95% CI: [1.06 – 3.82]). LVSI had a statistically significant effect on both OS (HR: 2.27, 95% CI: [1.14, 4.53]) and ECSS (HR: 3.45, 95% CI: [1.49, 7.99]). Black or African American (AA) race was also found to have a significant effect on both OS (HR: 1.92, 95% CI: [1.07, 3.47]) and ECSS (HR: 2.01, 95% CI: [1.02, 3.98]). Other factors including BMI and tumor size > 1 cm did not show a statistically significant impact on OS or ECSS.

Conclusions: Peritoneal washings with positive cytology and LVSI are important prognostic tools that may have a significant impact on overall survival in USC and can be used as independent negative prognosticators to help guide adjuvant treatment.

1. Background

Endometrial cancer (EC) is the most common gynecologic malignancy in the United States, but is one of the few common cancers that has not had improvement in overall survival (OS) since the mid 1970 s (Henley et al., 2018). The histopatholpogic diagnosis of epithelial endometrial cancer is heterogenous, but historically has been separated into only two groups. Type I EC is of endometrioid histology, has an overall favorable prognosis, and is associated with excess estrogen exposure and positive hormone receptor status. Type II EC encompasses most other histologic types, is usually higher grade than Type I EC, and has worse overall survival and higher recurrence rates (Lee et al., 2021). Despite these important differences, there is a singular staging system for EC, last revised by the International Federation of Gynecology and Obstetrics (FIGO) in 2009 (Pecorelli, 2009).

The FIGO categorization for EC underwent a major change in 2009, when positive peritoneal cytology was removed from the staging criteria due to uncertainty surrounding its prognostic significance (Tebeu et al., 2004; Mariani et al., 2009). Many of the studies that informed this change, though, did not consider potential differences according to

---

* Corresponding author.at: 4100 John R Street Detroit MI 48201.
 E-mail address: af7591@wayne.edu (R. Ali-Fehmi).

histologic classification. Some that did account for the histologic sub-type supported positive peritoneal cytology as a prognostic factor in the diagnosis and management of EC (Garg et al., 2013; Havrilesky et al., 2007). Other studies that accounted for histology maintained that cytology status had no definitive prognostic implication (Wethington et al., 2009).

The relative rarity of Type II EC makes prospective analysis of factors affecting survival and recurrences difficult, so most contemporary insight is derived from retrospective studies (Wethington et al., 2009; Han et al., 2014; Holman et al., 2017). There are even fewer studies that specifically evaluate the prognostic impact of cytology in uterine serous carcinoma (USC), the most commonly diagnosed histology of Type II EC. Therefore, we designed our study to interrogate the impact of positive peritoneal cytology with regard to other known prognostic factors of USC and hypothesize that cytology acts as an independent predictor of survival.

2. Methods

2.1. Case identification

Potential cases were identified from ongoing institutional studies at Henry Ford Health System (HFHS) and Karmanos Cancer Institute (KCI) in Detroit, Michigan, and were screened for eligibility using medical records and the Metropolitan Detroit Cancer Surveillance System (MDCSS). The MDCSS cancer registry has been active since 1973 as one of the founding registries of the Surveillance, Epidemiology, and End Results (SEER) Program, and provides active identification and follow up of malignant tumors diagnosed in the Metropolitan Detroit tri-county area (Wayne, Macomb, and Oakland counties). Inclusion criteria were female patients with endometrial cancer aged 21–79 at diagnosis, with FIGO stage I-III with serous histology type who received a hysterectomy at HFHS or KCI, with known peritoneal cytology results, and no receipt of neoadjuvant treatment (Fig. 1). Cases of mixed histology type and cases with < 10% serous component were excluded. Grade and histo-logic subtype of all included cases were re-evaluated microscopically and confirmed by a gynecologic pathologist (RAF), and were consistent with 5th edition of the World Health Organization Classification of Tu-mours of the Female Genital Tract ("Publication of the WHO Classifi-cation of Tumours, 5th Edition, Volume 4: Female Genital Tumours." n. d. Accessed April 3, 2021). This study was approved by the Wayne State University Institutional Review Board (043116M1E).

2.2. Outcomes

The primary endpoints assessed were endometrial cancer-specific survival (ECSS), with competing risk of other cause of death, and OS. Survival times were calculated from hysterectomy date to date of event or last follow-up, and deaths were confirmed through MDCSS and vital records. Endometrial cancer-specific death was determined using pri-mary cause of death codes from the death certificate in the MDCSS (ICD-10 codes: C53-C56) or from patient medical records.

2.3. Statistical analyses

Statistical analyses were performed using SAS 9.4 (Cary, NC), and an alpha of 0.05 was considered statistically significant. Distribution of clinical and demographic patient characteristics were compared be-tween patients with positive and negative cytology results using chi squared tests for categorical variables and Cochran-Armitage tests for ordinal variables. Cox proportional hazards regression with competing risks using the Fine-Gray test of significance was used to estimate the hazard of endometrial cancer-specific death with competing risk of other cause of death. Hazard ratios (HR) and 95% confidence intervals (CI) were computed. Each model was tested for proportionality of haz-ards, and the presented models did not violate the proportional hazards
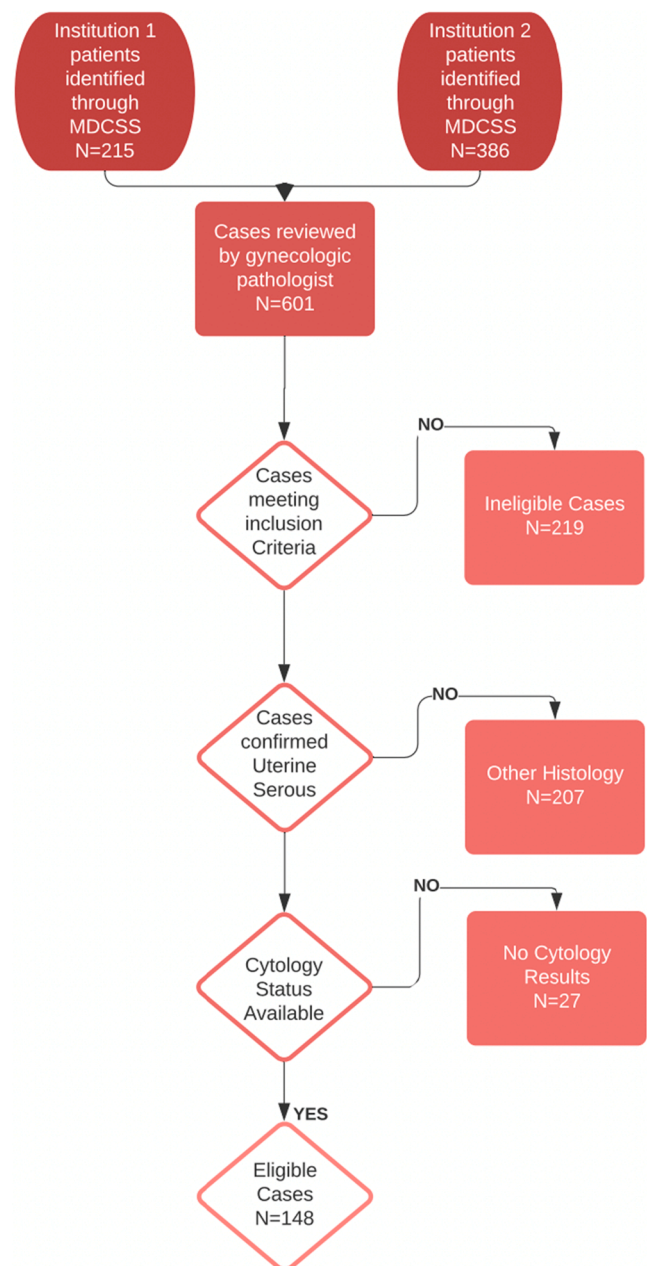

Fig. 1. Flow chart of eligible cases.

assumption.

The Cox proportional hazards models estimating ECSS (with competing risk of other cause of death) were created by including all variables of interest, then excluding variables individually by highest p-value until remaining variables were statistically significant. We built a Cox proportional hazards model for ECSS and OS using the receipt of any adjuvant treatment within six months of index surgery (versus surgery only with no adjuvant treatment within six months) as our treatment variable. To correct for potential confounding factors, variables were individually reintroduced into the model, and were included if any statistically significant covariates had a change in beta estimate of 10% or more. Treatment site and age group at diagnosis were included as model strata to account for the expectation of different baseline hazards among these subgroups. Potential interaction effects between factors were investigated. Variables included in the final models were: patient race (categorical), FIGO stage at diagnosis (ordinal), categorization of tumor size into < 1.0 cm and 1.0 cm or greater (ordinal), comorbidity

count as an unweighted count of comorbidities included in the Charlson Comorbidity Index (ordinal) (Charlson et al., 1987), cytology results (categorical), lymphovascular invasion (categorical), and adjuvant treatment type (yes or no). For the purposes of our study, adjuvant treatment is defined as patients who received radiation therapy (vaginal brachytherapy, external beam radiation, or both), chemotherapy, or both chemotherapy and radiation within 6 months of undergoing surgery. Analyses of the impact of specific individual treatment types were beyond the scope of this project. These data were abstracted from medical records.

3. Results

3.1. Patient characteristics

One hundred and forty-eight patients (148) with USC met initial inclusion criteria, of whom nearly 70% were Black or African American patients (AA). There was no statistically significant difference in the rate of positive cytology between the two racial groups (Table 1). Two-thirds (65%) of patients were diagnosed with early stage (Stage I/II) USC, and

Table 1
Selective descriptive statistics by peritoneal cytology results among 148 uterine serous carcinoma patients, diagnosed 1996–2016 at Henry Ford Hospital or Karmanos Cancer Institute.

Variable	Total (N = 148)	Positive Cytology (n = 33)	Negative Cytology (n = 115)	P Value[1]
Patient Race				
White	45 (30.4)	13 (39.4)	32 (27.8)	0.20
Black/African American	103 (69.6)	20 (60.6)	83 (72.2)	
Age at Diagnosis				
<50 years	10 (6.8)	4 (12.1)	6 (5.2)	
50 – 59 years	28 (18.9)	6 (18.2)	22 (19.1)	
60 – 69 years	72 (48.6)	11 (33.3)	61 (53.0)	
70 + years	38 (25.7)	12 (36.4)	26 (22.6)	
Stage at Diagnosis				
I	80 (54.1)	15 (45.5)	65 (56.5)	0.50
II	17 (11.5)	4 (12.1)	13 (11.3)	
III	51 (34.4)	14 (42.4)	37 (32.2)	
LVSI[2]				
Absent	65 (46.8)	11 (36.7)	54 (49.5)	0.21
Present	74 (53.2)	19 (63.3)	55 (50.5)	
Tumor Size				
<1.0 cm	105 (70.9)	21 (63.6)	84 (73.0)	0.29
1.0 + cm	43 (29.1)	12 (36.3)	31 (27.0)	
Comorbidity Count[3]				
None	79 (53.7)	62 (54.4)	17 (51.5)	0.73
1	35 (23.8)	26 (22.8)	9 (27.3)	
2+	33 (22.4)	26 (22.8)	7 (21.2)	
Treatment				
Surgery Only	49 (33.1)	14 (42.4)	35 (30.4)	—[4]
Chemo Only	26 (17.6)	8 (24.2)	18 (15.7)	
EBRT Only	14 (36.8)	2 (6.1)	12 (10.4)	
VB Radiation only	15 (39.5)	2 (6.1)	13 (11.3)	
EBRT + VB	9 (23.7)	0 (0.0)	9 (7.8)	
Chemo + Radiation	35 (23.6)	7 (21.1)	28 (24.4)	
Lymphadenectomy				
No	15 (10.1)	7 (21.1)	8 (7.0)	
Yes	133 (89.9)	26 (78.8)	107 (93.0)	
Recurrence Status[5]				
No Recurrence	81 (55.5)	13 (39.4)	68 (60.2)	0.04
Recurrence	52 (35.6)	14 (42.4)	38 (33.6)	
Never Disease-Free	13 (8.9)	6 (18.2)	7 (6.2)	

[1] Chi squared test used for categorical variables, and Cochran-Armitage trend test used for ordinal variables
[2] $N_{unknown} = 9$, [3]$N_{unknown} = 1$
[4] Chi square test invalid when any cell count = 0
[5] $N_{unknown} = 2$

there was no significant difference in cytology results when stratified by 2009 FIGO Stage at diagnosis (p = 0.50). There was, however, a significant association between cytology result and distribution of documented recurrence (p = 0.04): of the 52 cases with recurrence, 14 had positive cytology at time of surgery (27%), and of the 81 patients without recurrence, 13 had positive cytology at the time of surgery (16%). Positive cytology was not significantly associated with BMI, co-morbidity count, tumor size or lymphovascular space invasion (LVSI).

3.2. Overall survival and endometrial cancer specific survival

The Cox proportional hazard model for ECSS with competing risk of other cause of death (Table 2) included race, FIGO stage at diagnosis, comorbidity count, cytology results, LVSI, and receipt of adjuvant therapy. Hazard ratios reported for individual variables are corrected for all other variables included in the model. When corrected for all other variables in the model, positive LVSI, positive cytology results, AA race, and comorbidity count were predictive of worse ECSS and OS. In this model AA women had 2.01 times the hazard of endometrial cancer-related death than that of white women (HR 2.01; 95% CI (1.02, 3.98); p = 0.04). Patients with positive peritoneal cytology results had HR of 2.02 for ECSS compared to patients with negative peritoneal

Table 2
Cox proportional hazards models for endometrial cancer specific death (ECSS) with competing risk of other cause of death, and for overall survival/death by any cause* – with site of treatment and age category at diagnosis as strata.

Covariate	Endometrial Cancer Specific Survival (ECSS)		Overall Survival (OS)	
	HR (CI)	P Value	HR (CI)	P Value
Race				
White	Ref		Ref	
Black/African American	2.01 (1.02, 3.98)	0.04	1.92 (1.07, 3.47)	0.03
FIGO Stage				
I	Ref		Ref	
II	1.93 (0.76, 4.90)	0.17	1.71 (0.73, 4.02)	0.22
III	1.89 (0.87, 4.11)	0.11	2.05 (1.07, 3.92)	0.03
Comorbidity Count	1.42 (1.11, 1.81)	<0.01	1.44 (1.16, 1.79)	<0.01
Cytology Results				
Negative	Ref		Ref	
Positive	2.02 (1.06, 3.82)	0.03	2.09 (1.19, 3.68)	0.01
Lymphovascular Invasion				
Absent	Ref		Ref	
Present	3.45 (1.49, 7.99)	<0.01	2.27 (1.14, 4.53)	0.02
Adjuvant Therapy				
Surgery Only	Ref		Ref	
Received adjuvant therapy	0.65 (0.36, 1.20)	0.17	0.74 (0.44, 1.25)	0.27

Early Stage (2009 FIGO I/II)				
Adjuvant Therapy	Total(N = 97)	1997–2008 (n = 52)	2009–2016 (n = 45)	P value
Observation	32 (33.0)	17 (32.7)	15 (33.3)	0.23
Chemo Only	19 (19.6)	14 (26.9)	5 (11.1)	
Radiation Only	25 (25.8)	11 (21.2)	14 (31.1)	
Combination	21 (21.6)	10 (19.2)	11 (24.4)	
All Stages (2009 FIGO I-III)				
Adjuvant Therapy	Total(N = 148)	1997–2008 (n = 77)	2009–2016 (n = 71)	P value
Observation	49 (33.1)	27 (35.0)	22 (31.0)	<0.01
Chemo Only	26 (17.6)	20 (26.0)	6 (8.5)	
Radiation Only	38 (25.7)	19 (24.7)	19 (26.8)	
Combination	25 (23.6)	11 (14.3)	24 (33.8)	

*N = 133 for both models

cytology results (HR 2.02; 95% CI (1.06, 3.82); p = 0.03, Fig 2). Each additional comorbidity resulted in a 40% higher hazard of death on average (HR 1.42; 95% CI (1.11, 1.81); p < 0.01). In this multivariate model, 2009 FIGO stage at diagnosis and adjuvant therapy did not have a statistically significant effect on ECSS. When evaluating effect of stage OS, only 2009 FIGO stage III had a statistically significant effect (HR 2.05; 95% (1.07, 3.92); p = 0.03). Peritoneal cytology, LVSI and race all remained statistically significant prognosticators in the cox hazard models for ECSS and OS.

3.3. Rates of adjuvant treatment

We found there is a statistically significant difference between the distribution of adjuvant therapy type between patients diagnosed before and after 2009 (Table 3). Observation only was the most common before 2009 (35.0%), while the most common adjuvant therapy after 2009 was combination chemotherapy and radiation (33.8%). We further compared treatment patterns for those with 2009 FIGO early stage disease with positive cytology before and after 2009 and found no significant differences in treatment modality (data not shown).

4. Discussion

In this study, we report that peritoneal cytology is a prognostic factor after a diagnosis of uterine serous carcinoma (USC). Specifically, we found that positive peritoneal cytology resulted in 2.02 two times the hazard of ECSS compared to patients with negative cytology on multivariate analysis. Despite the surfeit of studies analyzing the impact of peritoneal washings on endometrial cancer, most studies focus on endometrioid type and the impact of cytology among patients diagnosed with USC remains unclear (Tebeu et al., 2004; Garg et al., 2013; Kiess et al., 2012; Fadare et al., 2005; Turner et al., 1989; Kadar et al., 1992). Our data are consistent with a study by Han et al. that described cytology as an independent prognostic factor in non-endometrioid cancers (Han et al., 2014). However, Dr. Han's study was limited to only 14 patients with uterine serous cancer and the cohort consisted entirely of Korean patients.

In addition to independently prognosticating worse survival, positive peritoneal cytology was associated with significantly higher rates of recurrence than negative cytology (27% vs 16%, p = 0.04). This is of particular importance because recurrences of USC are usually fatal, which is in contrast to the recurrences seen in low risk EC, which are believed to be generally salvageable (Haltia et al., 2014; van den Heerik et al., 2021). Historical arguments for omission of peritoneal cytology in

Table 3
Distribution of adjuvant therapy by year of diagnosis (pre-2009 changes to FIGO stage classification) among USC cases.

Early Stage (2009 FIGO I/II)			
Adjuvant Therapy	Total (N = 97)	1997–2008 (n = 52)	2009–2016 (n = 45)	P value
Observation	32 (33.0)	17 (32.7)	15 (33.3)	0.23
Chemo Only	19 (19.6)	14 (26.9)	5 (11.1)	
Radiation Only	25 (25.8)	11 (21.2)	14 (31.1)	
Combination	21 (21.6)	10 (19.2)	11 (24.4)	
All Stages (2009 FIGO I-III)			
Adjuvant Therapy	Total(N = 148)	1997–2008(n = 77)	2009–2016(n = 71)	P value
Observation	49 (33.1)	27 (35.0)	22 (31.0)	<0.01
Chemo Only	26 (17.6)	20 (26.0)	6 (8.5)	
Radiation Only	38 (25.7)	19 (24.7)	19 (26.8)	
Combination	25 (23.6)	11 (14.3)	24 (33.8)	

staging of EC largely came from studies overrepresenting Type I EC. For instance, Fadare et al., reporting a rate of<5% of patients with early stage EC with positive peritoneal cytology, argued against upstaging EC based on positive peritoneal washings alone (Fadare et al., 2005). Of note, that study included only one case of USC with positive cytology. In the present study we found that 19.5% of early stage (I/II) USC would be upstaged based on positive peritoneal washing status using the 1988 FIGO categorization. Larger studies evaluating impacts of types of adjuvant treatment on early stage USC with positive cytology is needed.

In response to the 2009 FIGO endometrial staging changes, two of the largest population-based studies evaluating the impact of peritoneal washings in EC were undertaken by Garg et al in 2013 and Seagle et al in 2018, using the SEER database and NCDB, respectively (Garg et al., 2013; Seagle et al., 2018). Consistent with our study, Garg et al concluded that positive peritoneal cytology was an independent predictor of survival in patients diagnosed with early EC, independent of histology. However, a major limitation to this study was an inability to include LVSI as a covariate (Garg et al., 2013). LVSI is an established prognostic factor in EC and should be accounted for as a possible confounding variable when evaluating other prognostic factors, such as the stage and impact of positive cytology. As such, a large multi-institutional report by Zhong et al evaluated the impact of cytology status on USC and also failed to account for LVSI; and also neglected to include the impact of any type of treatment in multivariate analysis (Zhong et al., 2018). The study performed by Seagle et al. also evaluated early stage EC of multiple histologies and found positive cytology was associated with decreased overall survival, even in low-grade EC, and that adjuvant chemotherapy was associated with increased survival (Seagle et al., 2018). However, the impact of adjuvant treatment was not stratified by stage at diagnosis and serous histology was not individually evaluated. Our present study had comparable results to these studies that showed a hazard ratio for death significantly worse in the positive cytology group versus the negative cytology group. We were also able to show that positive cytology remained an independent negative prognostic factor even when considering stage at diagnosis in our multivariate models.

A major strength of our study compared to the aforementioned larger, population-based studies was our ability to have every case reviewed by a pathologist specialized in gynecologic histology. A noted limitation in the SEER and NCDB databases is the difficulty of confirming correct histologic diagnosis, especially among rarer cancers (Duggan et al., 2016). We have previously demonstrated there is moderate interobserver variability between general pathologists when diagnosing high grade endometrial cancer, with serous histology type among the most misclassified. This variability is reduced when the specimen is read by a gynecologic-specific pathologist (Thomas et al., 2016) and we believe addressing this in our design adds to the robustness of our study.

Most of the patients in our study (65%) were diagnosed with early
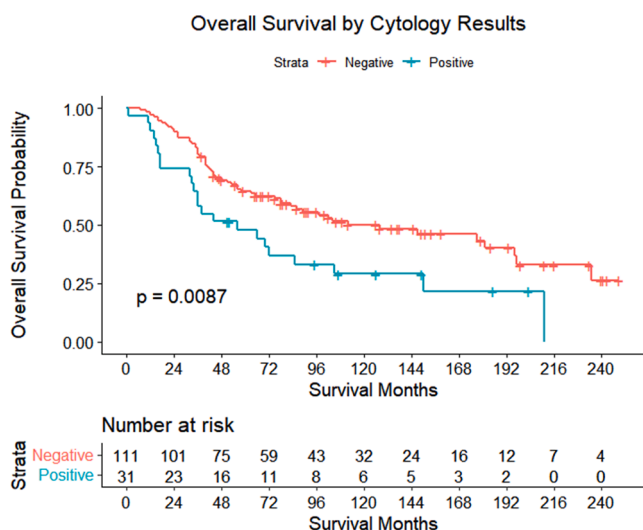

Fig. 2. Kaplan-Meier Graph of Overall Survival.

stage disease. Although patients with early stage EC have better outcomes than patients with more advanced stage, high-grade non-endometrioid EC still have recurrence rates nearing 30% (Fader et al., 2016). A study of 206 patients with early stage USC by Fader et al found that the presence of any percentage of serous histology and increasing substage correlated with increased recurrence rates, but that patient age, tumor size, and lymphovascular space invasion did not (Fader et al., 2009). Our study adds to Dr. Fader's analysis to include the presence or absence of positive cytology documented for every study participant. When factoring in cytology status, we found that LVSI was a significant predictor for worse survival outcomes in USC for both ECSS (HR 3.45) as well as overall survival (HR 2.27) in our multivariate hazard models. This finding differs from Dr. Fader's findings, and was not able to be evaluated in Dr. Garg's study, mentioned above (Garg et al., 2013).

Investigators have previously shown that for non-invasive USC, vaginal brachytherapy reduced the risk of vaginal recurrence while systemic chemotherapy and pelvic radiation therapy provided no extra benefit (Mahdi et al., 2015; Mahdi et al., 2015). However, for invasive USC, systemic therapy seems to provide better outcomes (Havrilesky et al., 2007; Fader et al., 2009) and there are data from retrospective studies that suggest the need for multimodal treatment in all invasive stages of uterine serous cancer (Kiess et al., 2012; Fader et al., 2016; Sood et al., 2003). Unfortunately, the exact type of adjuvant treatment is unclear (Havrilesky et al., 2007; Kiess et al., 2012; Mahdi et al., 2015; Mahdi et al., 2015; Kelly et al., 2005; Chang-Halpenny et al., 2013; Koh et al., 2018). To evaluate the impact of treatment of any type on USC patients with positive cytology, we created a model analyzing the impact of adjuvant treatment type. Unfortunately, after reducing our sample size to patients with known peritoneal cytology result, LVSI status, and receipt of treatment within six months of surgery, we did not have a large enough sample size to compare individual treatment types (chemotherapy versus radiation therapy versus chemoradiation) and their effects on survival in patients with positive peritoneal cytology status. Therefore, we combined receipt of any adjuvant treatment (VB, EBRT, chemotherapy, or any combination thereof) into the "treatment" group, and all patients without adjuvant treatment into the "no treatment" group (Table 2). In this model, when all variables were accounted for, positive peritoneal cytology was independently associated with worse OS (HR 2.02) and ECSS (HR 2.09) compared to those with negative peritoneal cytology.

We also found a significant difference in adjuvant treatment when comparing prescribing patterns prior to and following the 2009 FIGO changes (Table 3). We believe the shift in adjuvant treatment is most likely attributed to the contemporary publications and does not reflect provider reactions to the alterations in the 2009 FIGO staging classifications (Zakem et al., 2019).

Finally, nearly 70% of the 148 patients included in our study identified as Black or African American (AA) on record review. AA women with EC have worse outcomes than other races (Cote et al., 2015; Dubil et al., 2018). AA patients are more likely to present with less favorable subtypes and higher-grade tumors (Long et al., 2013) and, in congruence with our study, AA race has been identified as an independent risk factor for worse outcomes in high grade EC (Rauh-Hain et al., 2015; Sud et al., 2018). AA women account for nearly 14% of the US population and 27.5% of uterine cancers diagnosed (U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on, 2019). Despite this, the AA population is often underrepresented in both retrospective and prospective trials of high grade and serous EC (Han et al., 2014; Fader et al., 2016; Wright et al., 2009). The large proportion of AA patients in our study greatly adds to the limited data on the AA population with USC.

The present study has several limitations inherent to its retrospective design, especially selection bias in regards to adjuvant treatment type. The treatment groups were not matched for all known variables in the models, including presence of or extent of lymphadenectomy. However, nearly all (90%) of patients did undergo lymph node dissection, helping

to dampen this possible bias. We were also limited by sample size and did not have adequate power to evaluate the impact of specific treatment types on outcomes of patients with positive peritoneal cytology. Therefore, we are unable to recommend which treatment type is most beneficial for a patient with USC with positive peritoneal washings. Additionally, as a hospital-based study based at two large urban academic cancer referral centers, our results have limited generalizability. The patients in this study had access to specialists in gynecologic oncology, as well as specialists in pathology and radiation oncology, making application of our outcomes to community hospitals limited.

In conclusion, our study is one of the largest multi-institutional studies to specifically look at prognostic value of peritoneal cytology results in USC. When accounting for age, comorbidities, race, stage, LVSI, tumor size, and receipt of adjuvant treatment, peritoneal cytology had approximately two times the risk of death compared to patients with negative cytology. We also found it interesting that there was no association between stage or presence of LVSI and positive cytology, indicating cytology can be evaluated independently from these other common risk factors. We strongly agree that the optimal staging of tumors should reflect their specific biology and patterns of spread, and also inform prognostication relative to the tumor type (Zaino, 2009). The present study provides compelling data that positive peritoneal cytology at any stage of USC is an independently poor prognostic indicator. To further refine our understanding of the implication of peritoneal cytology status in USC, randomized controlled trials should be designed to include peritoneal cytology results in serous cancer as an important adverse risk factor, especially when studying early stage uterine serous carcinoma.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Henley, S.J., Miller, J.W., Dowling, N.F., Benard, V.B., Richardson, L.C., 2018. Uterine Cancer Incidence and Mortality - United States, 1999–2016. MMWR Morb. Mortal. Wkly Rep. 67 (48), 1333–1338.

Lee, E.K., Fader, A.N., Santin, A.D., Liu, J.F., 2021. Uterine Serous Carcinoma: Molecular Features, Clinical Management, and New and Future Therapies. Gynecol. Oncol. 160 (1), 322–332.

Pecorelli, S., 2009. Revised FIGO Staging for Carcinoma of the Vulva, Cervix, and Endometrium. Int. J. Gynaecol. Obst.: Off. Organ Int. Fed. Gynaecol. Obst. 105 (2), 103–104.

Tebeu, P.-M., Popowski, Y., Verkooijen, H.M., Bouchardy, C., Ludicke, F., Usel, M., Major, A.L., 2004. Positive Peritoneal Cytology in Early-Stage Endometrial Cancer Does Not Influence Prognosis. Br. J. Cancer 91 (4), 720–724.

Mariani, A., Dowdy, S.C., Podratz, K.C., 2009. New Surgical Staging of Endometrial Cancer: 20 Years Later. Int. J. Gynaecol. Obst.: Off. Organ Int. Fed. Gynaecol. Obst. 105 (2), 110–111.

Garg, G., Gao, F., Wright, J.D., Hagemann, A.R., Mutch, D.G., Powell, M.A., 2013. Positive Peritoneal Cytology Is an Independent Risk-Factor in Early Stage Endometrial Cancer. Gynecol. Oncol. 128 (1), 77–82.

Havrilesky, L.J., Cragun, J.M., Calingaert, B., Alvarez Secord, A., Valea, F.A., Clarke-Pearson, D.L., Berchuck, A., Soper, J.T., 2007. The Prognostic Significance of Positive Peritoneal Cytology and Adnexal/serosal Metastasis in Stage IIIA Endometrial Cancer. Gynecol. Oncol. 104 (2), 401–405.

Wethington, S.L., Barrena, N.I., Medel, J.D., Wright, Thomas Herzog, J., 2009. Prognostic Significance and Treatment Implications of Positive Peritoneal Cytology in Endometrial Adenocarcinoma: Unraveling a Mystery. Gynecol. Oncol. 115 (1), 18–25.

Han, K.H., Park, N.H., Kim, H.S., Chung, H.H., Kim, J.W., Song, Yong Sang, 2014. Peritoneal Cytology: A Risk Factor of Recurrence for Non-Endometrioid Endometrial Cancer. Gynecol. Oncol. 134 (2), 293–296.

Holman, L.L., Pal, N., Iglesias, D.A., Soliman, P.T., Balakrishnan, Nyla, Klopp, A., Broaddus, R.R., Fleming, N.D., Munsell, M.F., Lu, K.H., Westin, S.N., 2017. Factors

Prognostic of Survival in Advanced-Stage Uterine Serous Carcinoma. Gynecol. Oncol. 146 (1), 27–33.

"Publication of the WHO Classification of Tumours, 5th Edition, Volume 4: Female Genital Tumours." n.d. Accessed April 3, 2021. https://www.iarc.who.int/news-events/publication-of-the-who-classification-of-tumours-5th-edition-volume-4-female-genital-tumours/.

Charlson, M.E., Pompei, P., Ales, K.L., MacKenzie, C.R., 1987. A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation. J. Chron. Dis. 40 (5), 373–383.

Kiess, A.P., Damast, S., Makker, V., Kollmeier, M.A., Gardner, G.J., Aghajanian, C., Abu-Rustum, N.R., Barakat, R.R., Alektiar, K.M., 2012. Five-Year Outcomes of Adjuvant Carboplatin/paclitaxel Chemotherapy and Intravaginal Radiation for Stage I-II Papillary Serous Endometrial Cancer. Gynecol. Oncol. 127 (2), 321–325.

Fadare, Oluwole, M. Rajan Mariappan, Denise Hileeto, Sa Wang, Jessica N. McAlpine, and David L. Rimm. 2005. "Upstaging Based Solely on Positive Peritoneal Washing Does Not Affect Outcome in Endometrial Cancer." Modern Pathology: An Official Journal of the United States and Canadian Academy of Pathology, Inc 18 (5): 673–80.

Turner, D.A., Gershenson, D.M., Atkinson, N., Sneige, N., Wharton, A.T., 1989. The Prognostic Significance of Peritoneal Cytology for Stage I Endometrial Cancer. Obst. Gynecol. 74 (5), 775–780.

Kadar, N., Homesley, H.D., Malfetano, J.H., 1992. Positive Peritoneal Cytology Is an Adverse Factor in Endometrial Carcinoma Only If There Is Other Evidence of Extrauterine Disease. Gynecol. Oncol. 46 (2), 145–149.

Haltia, U.-M., Bützow, R., Leminen, A., Loukovaara, M., 2014. FIGO 1988 versus 2009 Staging for Endometrial Carcinoma: A Comparative Study on Prediction of Survival and Stage Distribution according to Histologic Subtype. J. Gynecol. Oncol. 25 (1), 30–35.

Heerik, Anne Sophie V. M. van den, Nanda Horeweg, Stephanie M. de Boer, Tjalling Bosse, and Carien L. Creutzberg. 2020. "Adjuvant Therapy for Endometrial Cancer in the Era of Molecular Classification: Radiotherapy, Chemoradiation and Novel Targets for Therapy." International Journal of Gynecological Cancer: Official Journal of the International Gynecological Cancer Society, October. https://doi.org/10.1136/ijgc-2020-001822.

Seagle, B.-L.L., Alexander, A.L., Lantsman, T., Shahabi, S., 2018. Prognosis and Treatment of Positive Peritoneal Cytology in Early Endometrial Cancer: Matched Cohort Analyses from the National Cancer Database. Am. J. Obst. Gynecol. 218 (3), 329.e1–329.e15.

Zhong, X., Wang, J., Kaku, T., Wang, Z., Li, X., Wei, L., 2018. Prognostic Factors of Uterine Serous Carcinoma-A Multicenter Study. Int. J. Gynecol. Cancer: Offi. J. Int. Gynecol. Cancer Soc. 28 (6), 1138–1144.

Duggan, M.A., Anderson, W.F., Altekruse, S., Penberthy, L., Sherman, M.E., 2016. The Surveillance, Epidemiology, and End Results (SEER) Program and Pathology: Toward Strengthening the Critical Relationship. Am. J. Sur. Pathol. 40 (12), e94–e102.

Thomas, Sumi, Hussein, Yaser, Bandyopadhyay, Sudeshna, Cote, Michele, Hassan, Oudai, Abdulfatah, Eman, Alosh, Baraa, Guan, Hui, Soslow, Robert A., Ali-Fehmi, Rouba, 2016. Interobserver Variability in the Diagnosis of Uterine High-Grade Endometrioid Carcinoma. Arch. Pathol. Lab. Med. 140 (8), 836–843.

Fader, A.N., Java, J., Tenney, M., Ricci, S., Gunderson, C.C., Temkin, S.M., Spirtos, N., Kushnir, C.L., Pearl, M.L., Zivanovic, O., Tewari, K.S., O'Malley, D., Hartenbach, E. M., Hamilton, C.A., Gould, N.S., Mannel, R.S., Rodgers, W., Walker, J.L., 2016. Impact of Histology and Surgical Approach on Survival among Women with Early-Stage, High-Grade Uterine Cancer: An NRG Oncology/Gynecologic Oncology Group Ancillary Analysis. Gynecol. Oncol. 143 (3), 460–465.

Fader, A.N., Starks, D., Gehrig, P.A., Secord, A.A., Frasure, H.E., O'Malley, D.M., Tuller, E.R., Rose, P.G., Havrilesky, L.J., Moore, K.N., Huh, W.K., Axtell, A.E., Kelley, J.L., Zanotti, K.M., 2009. An Updated Clinicopathologic Study of Early-Stage Uterine Papillary Serous Carcinoma (UPSC). Gynecol. Oncol. 115 (2), 244–248.

Mahdi, Haider, Elshaikh, Mohamed A, DeBenardo, Robert, Munkarah, Adnan, Isrow, Derek, Singh, Sareena, Waggoner, Steven, Ali-Fehmi, Rouba, Morris, Robort T., Harding, Jarod, Moslemi-Kebria, Mehdi, 2015. Impact of Adjuvant

Chemotherapy and Pelvic Radiation on Pattern of Recurrence and Outcome in Stage I Non-Invasive Uterine Papillary Serous Carcinoma. A Multi-Institution Study. Gynecologic Oncology 137 (2), 239–244.

Mahdi, H., Rose, P.G., Elshaikh, M.A., Munkarah, A., Isrow, D., Singh, S., Waggoner, S., Ali-Fehmi, R., Morris, R.T., Harding, J., DeBenardo, R., 2015. Adjuvant Vaginal Brachytherapy Decreases the Risk of Vaginal Recurrence in Patients with Stage I Non-Invasive Uterine Papillary Serous Carcinoma. A Multi-Institutional Study. Gynecol. Oncol. 136 (3), 529–533.

Fader, A.N., Drake, R.D., O'Malley, D.M., Gibbons, H.E., Huh, W.K., Havrilesky, L.J., Gehrig, P.A., Tuller, E., Axtell, A.E., Zanotti, K.M., 2009. Platinum/taxane-Based Chemotherapy with or without Radiation Therapy Favorably Impacts Survival Outcomes in Stage I Uterine Papillary Serous Carcinoma. Cancer 115 (10), 2119–2127. https://doi.org/10.1002/cncr.24247.

Sood, Brij M., Jones, Joan, Gupta, Sajel, Khabele, Dineo, Guha, Chandan, Runowicz, Carol, Goldberg, Gary, Fields, Abbie, Anderson, Patrick, Vikram, B., 2003. Patterns of Failure after the Multimodality Treatment of Uterine Papillary Serous Carcinoma. Int. J. Radiat. Oncol. Biol. Phys. 57 (1), 208–216.

Kelly, M.G., O'Malley, D., Hui, P., Dziura, J., McAlpine, J., Azodi, M., Rutherford, T.J., Schwartz, P.E., 2005. Improved Survival in Surgical Stage I Uterine Papillary Serous Cancer (UPSC) Treated with Adjuvant Platinum-Based Chemoradiation. J. Clin. Oncol. 23 (16_suppl), 5023. https://doi.org/10.1200/jco.2005.23.16_suppl.5023.

Chang-Halpenny, Christine N., Natarajan, Sathima, Hwang-Graziano, Julie, 2013. Early Stage Papillary Serous or Clear Cell Carcinoma Confined to or Involving an Endometrial Polyp: Outcomes with and without Adjuvant Therapy. Gynecologic Oncology 131 (3), 598–603.

Koh, W.-J., Abu-Rustum, N.R., Bean, S., Bradley, K., Campos, S.M., Cho, K.R., Chon, H.S., Chu, C., Cohn, D., Crispens, M.A., Damast, S., Dorigo, O., Eifel, P.J., Fisher, C.M., Frederick, P., Gaffney, D.K., George, S., Han, Ernest, Higgins, S., Huh, W.K., Lurain, J.R., Mariani, A., Mutch, D., Nagel, C., Nekhlyudov, L., Fader, A.N., Remmenga, S.W., Reynolds, R.K., Tillmanns, T., Ueda, S., Wyse, E., Yashar, C.M., McMillian, N.R., Scavone, J.L., 2018. Uterine Neoplasms, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology. J. Nat. Compre. Cancer Net.: JNCCN 16 (2), 170–199.

Zakem, S.J., Robin, T.P., Smith, D.E., Amini, A., Stokes, W.A., Lefkowits, C., Fisher, C.M., 2019. Evolving Trends in the Management of High-Intermediate Risk Endometrial Cancer in the United States. Gynecol. Oncol. 152 (3), 522–527.

Cote, M.L., Ruterbusch, J.J., Olson, S.H., Lu, K., Ali-Fehmi, R., 2015. The Growing Burden of Endometrial Cancer: A Major Racial Disparity Affecting Black Women. Cancer Epidemiol. Biomark. Prev. 24 (9), 1407–1415. https://doi.org/10.1158/1055-9965.EPI-15-0316.

Dubil, E.A., Tian, C., Wang, G., Tarney, C.M., Bateman, N.W., Levine, D.A., Conrads, T.P., Hamilton, C.A., Maxwell, G.L., Darcy, K.M., 2018. Racial Disparities in Molecular Subtypes of Endometrial Cancer. Gynecol. Oncol. 149 (1), 106–116.

Long, B., Liu, F.W., Bristow, R.E., 2013. Disparities in Uterine Cancer Epidemiology, Treatment, and Survival among African Americans in the United States. Gynecologic Oncology 130 (3), 652–659.

Rauh-Hain, J.A., Buskwofie, A., Clemmer, J., Boruta, D.M., Schorge, J.O., del Carmen, M. G., 2015. Racial Disparities in Treatment of High-Grade Endometrial Cancer in the Medicare Population. Obst. Gynecol. 125 (4), 843–851.

Sud, S., Holmes, J., Eblan, M., Chen, R., Jones, E., 2018. Clinical Characteristics Associated with Racial Disparities in Endometrial Cancer Outcomes: A Surveillance, Epidemiology and End Results Analysis. Gynecol. Oncol. 148 (2), 349–356.

U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2019 submission data (1999-2017): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; www.cdc.gov/cancer/dataviz, released in June 2020.

Wright, J.D., Fiorelli, J., Schiff, P.B., Burke, W.M., Kansler, A.L., Cohen, C.J., Herzog, T. J., 2009. Racial Disparities for Uterine Corpus Tumors: Changes in Clinical Characteristics and Treatment over Time. Cancer 115 (6), 1276–1285.

Zaino, R.J., 2009. FIGO Staging of Endometrial Adenocarcinoma: A Critical Review and Proposal. Int. J. Gynecol. Pathol.: Off. J. Int. Soc. Gynecol. Pathol. 28 (1), 1–9.