Cancer antigen 125 is associated with disease status in uterine carcinosarcoma

Malcolm Strachan Ross[1] (iD), Chelsea Kilpatrick Chandler[2],
Koji Matsuo[3], John Austin Vargo[4], Esther Elishaev[5],
Nalyn Siripong[6], Jessica Layne Berger[2], Joseph Leo Kelley III[2]
and Sarah Elizabeth Taylor[2]

Abstract

Uterine carcinosarcoma is a rare and aggressive tumor with poor outcomes. Cancer antigen 125 is routinely used to track the disease course of ovarian cancer and has been suggested as a biomarker in other aggressive forms of uterine cancer. We sought to characterize cancer antigen 125 as a potential biomarker of disease status in uterine carcinosarcoma. Clinical and pathological data were abstracted for patients who had surgical staging for a pathologically confirmed uterine carcinosarcoma at our institution from January 2000 to March 2014. Non-parametric tests were used to compare changes in cancer antigen 125. Elevated cancer antigen 125 (>35 U/mL) as a predictor of survival was assessed via Kaplan–Meier curves. Among the 153 patients identified, 66 patients had at least one paired measure of cancer antigen 125 drawn preoperatively, post-treatment, or at the time of disease recurrence, and 19 patients had cancer antigen–125 levels at all three time points. Analysis of the 51 patients with both preoperative and post-treatment values found a significant drop in cancer antigen 125 ($p < 0.001$). Among the 30 patients who had end-of-treatment and recurrence levels, a significant increase was noted ($p = 0.001$). There was no significant difference in cancer antigen–125 levels preoperatively compared to at recurrence among the 23 patients with levels at both time-points ($p = 0.99$). Elevated preoperative cancer antigen 125 was not associated with overall survival ($p = 0.12$); elevated post-treatment cancer antigen 125 was associated with a worse overall survival ($p < 0.001$). Based on this dataset, there seems to be utility in trending a cancer antigen–125 level in patients with uterine carcinosarcoma. A cancer antigen–125 level could predict recurrence and provide prognostic information regarding survival.

Keywords

Uterine carcinosarcoma, cancer antigen 125, survival

[1]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Magee-Womens Hospital, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
[2]Department of Obstetrics and Gynecology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
[3]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Southern California, Los Angeles, CA, USA
[4]Division of Radiation Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

[5]Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
[6]Clinical and Translational Science Institute, University of Pittsburgh, Pittsburgh, PA, USA

Corresponding author:
Malcolm Strachan Ross, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Magee-Womens Hospital, University of Pittsburgh Medical Center, 300 Halket Street, Pittsburgh, PA 15213, USA.
Emails: rossms@upmc.edu; m4lki3@gmail.com

Introduction

Uterine cancer is the most common gynecologic malignancy in the western hemisphere. Worldwide there are 353,000 incident cases with 68,000 deaths annually.[1,2] Uterine carcinosarcoma (UCS), formally known as malignant mixed mesodermal tumor, is a rare and aggressive subtype of endometrial cancer with both epithelial and mesenchymal components, accounting for 15% of all deaths due to uterine cancer.[3,4] Its incidence is reported as less than two per 100,000 women per year and accounts for more than 5% of endometrial carcinomas in recent years.[5–7] Typically, UCS presents as advanced disease and greater than 50% recur.[3,4,8–11] A combination of a low incidence and poor outcomes make it a hard pathologic entity to study in large numbers or prospectively.

Cancer antigen 125 (CA-125), also known as Mucin 16, is a 2–5 Kilo Da trans-membrane glycoprotein whose extracellular domain undergoes proteolytic cleavage and is released into the extracellular space.[11,12] The role of CA-125 for the initial work up and surveillance in ovarian cancer is well established.[13] However, the literature is less clear regarding its utility in the evaluation and monitoring of endometrial cancers. Currently, the National Comprehensive Cancer Network (NCCN) guidelines list CA-125 as optional for the work up of extra uterine disease and for surveillance in endometrial carcinoma. The same recommendation is made for type II endometrial cancers and UCS.[14]

In our single institution, retrospective study we sought to identify the utility of following patient's serum CA-125 level as a marker for treatment response and disease recurrence. We hypothesized that we would see a drop in CA-125 level after surgery and adjuvant treatment, and a rise between the end of treatment and time of recurrence. In addition, we sought to evaluate if an elevated preoperative CA-125 was associated with tumor-specific characteristics and worse overall survival.

Methods

Study design

This was a single institution, retrospective study at Magee-Womens Hospital of the University of Pittsburgh Medical Center. Institutional Review Board approval was obtained prior to study initiation. Patients who had undergone staging or surgical debulking for pathologically confirmed UCS at our institution from January 2000 to March 2014 were identified using our institution's cancer registry. Histological evaluation was performed by a gynecologic pathologist to confirm UCS. Patients with incorrect histology and no hysterectomy were excluded.

We abstracted demographic information (age, race, and body mass index (BMI)) and clinical history (prior tamoxifen use, prior pelvic radiation therapy, neoadjuvant radiotherapy (NART), neoadjuvant chemotherapy (NACT), and the 2009 International Federation of Gynecology and Obstetrics (FIGO) cancer stage). Histological review included carcinoma component and grade, sarcoma component, tumor size, depth of myometrial tumor invasion, presence of lymphovascular space invasion (LVSI), cervical stroma and vaginal involvement, pelvic and para-aortic lymph node status, and the presence of omental disease, including grossly visible and microscopic lesions.

Treatment characteristics included extent of surgical staging, presence of residual disease, postoperative treatment (type of radiation, type and number of cycles of chemotherapy, combination and order of chemotherapy and radiation), and treatments for recurrences. For survival outcomes, progression-free survival (PFS) and overall survival (OS) were calculated based on date of surgery and dates of recurrence or death, respectively. If death and/or recurrence were not recorded, date of the last visit was used. Patient's disease status, if alive, was recorded at time of last documented clinical encounter. We compared survival outcomes between patients with elevated CA-125 at the end of primary treatment, defined/measured as a CA-125 value greater than 35 U/mL, and those who had normal CA-125. This value was chosen based on prior serum screening of women with an intact reproductive system.[15]

While following CA-125 level is not part of standard practice per NCCN recommendations, they are frequently monitored throughout treatment and during remission. Any CA-125 levels ordered preoperatively, after adjuvant chemotherapy and radiation, and at the time of recurrence were abstracted. We focused on three time-points: preoperatively, post-treatment, and at recurrence. When CA-125 levels were available at the end of adjuvant chemotherapy and after radiation, the CA-125 value taken at the later date was used as the end-of-treatment value.

Statistical analysis

To assess CA-125 as a biomarker for disease status, we ran non-parametric Wilcoxon signed-rank tests for differences in CA-125 levels at each of the different time points measured (preoperatively, at the end of treatment, and at recurrence). Because collection of CA-125 is not standard practice among patients with UCS, the comparisons between each set of time-points include a variable set of patients, which could introduce selection bias to our results. The data were re-analyzed, restricting our sample to complete case analysis (i.e. including only people with CA-125 values at all three time points). Selection bias was assessed for each comparison by looking for any important differences between people who were included and excluded from each analysis.

Wilcoxon rank-sum test and Kruskal–Wallis tests were used to evaluate whether preoperative CA-125 levels were associated with other measures of disease severity (simplified stage, carcinoma vs sarcoma predominance, homologous vs heterologous sarcoma component, tumor size greater than 5

cm, depth of invasion). Kaplan–Meier curves were constructed to compare survival outcomes among people with or without elevated CA-125 level preoperatively and at the end of treatment. For the initial analyses, CA-125 was considered elevated if the value was greater than 35 U/mL.[15] Additional Kaplan–Meier curves were constructed to compare survival outcomes among patients with an elevated CA-125 at the end of treatment, re-defined as <50% drop or value >35 U/mL, versus those with a normalized CA-125, re-defined as ≥50% drop or value <35 U/mL.[16] From this second Kaplan–Meier analysis, those without a preoperative CA-125 were excluded. Log-rank test was used to detect differences in Kaplan–Meier curves. A *p* value <0.05 was considered significant; all hypothesis were two-tailed. All statistical analysis was conducted in STATA 14 (StataCorp LP, College Station, TX).

Results

Patient characteristics

After query of the cancer registry and expert review of histology, 153 patients were identified. Median age was 65 years old (range = 40–87), median BMI was 34.6, the majority of patients were Caucasian (88.9%), 14 (9.2%) patients had a history of tamoxifen treatment, six (3.9%) patients had a prior history of pelvic radiation therapy, five (3.3%) received neoadjuvant radiation, and four (2.6%) received neoadjuvant chemotherapy. All patients underwent a bilateral salpingo-oophorectomy, 121 (79.0%) underwent a pelvic lymph node dissection, 109 (71.2%) had a para-aortic lymph node dissection, and 106 (69.3%) had an omentectomy.

Seventy-two (47.7%) had stage I, 21 (13.9%) stage II, 30 (19.9%) stage III, and 28 (18.5%) had stage IV disease. Most (94.1%) had no gross residual disease at the end of surgical resection. On pathological review, 102 (66.2%) had a tumor size greater than 5 cm, 78 (50.7%) had depth of invasion greater than 50%, and 97 (65.5%) had LVSI (Table 1). Seventeen (14.0%) of those patients who had pelvic lymph node dissection had nodal involvement. For those patients who had para-aortic nodal dissection, 11 (10.1%) were noted to have nodal involvement. Postoperatively, 84 (54.9%) received radiation, 111 (72.6%) patients received chemotherapy, and 58 (37.9%) received chemo-radiation. Median follow-up time was 29.6 (range = 0.9–151.9) months. Of the 84 patients who received adjuvant radiation, nine (10.7%) received vaginal brachytherapy only, 69 (82.1%) received pelvic external-beam radiotherapy (69.6%, *n* = 48, of which included vaginal brachytherapy boost), and six (7.1%) received extended-field external-beam radiotherapy to pelvis plus para-aortics (66.6%, *n* = 4, of which included vaginal brachytherapy boost). Of the 111 patients receiving chemotherapy, the majority, 98 (88.3%), got doublet therapy, followed by 11 (9.9%) receiving single agent and two (1.8%) receiving triplet therapy. The most common doublet was carboplatinum with a taxane, 63 (56.8%), followed by ifosfamide with a taxane, 23 (20.7%) (Table 2). Given the multitude of different adjuvant chemotherapy, radiation, and

Table 1. Demographic and clinical characteristics of patients.

Total patients	153
Median age	65.0 (15)
BMI	34.6

Variables	*n* (%)
Race	
Caucasian	136 (88.9%)
African American	14 (9.1%)
Asian	3 (2.0%)
Tamoxifen	14 (9.2%)
History of pelvic radiation	6 (3.9%)
Neoadjuvant radiation	5 (3.3%)
Neoadjuvant chemotherapy	4 (2.6%)
Surgery	
Bilateral salpingo-oophorectomy	153 (100%)
Pelvic lymphadenectomy	121 (79.1%)
Para-aortic lymphadenectomy	109 (71.2%)
Omental sampling	106 (69.3%)
Postoperative treatment	
Radiation	84 (54.9%)
Vaginal brachytherapy	9 (10.7%)
Pelvic EBRT ± Brachytherapy	69 (82.1%)
EFRT ± brachytherapy	6 (7.1%)
Chemotherapy	111 (72.6%)
Chemotherapy + radiation	58 (37.9%)
Recurrence	70 (45.8%)
Lymphovascular space invasion	97 (65.5%)
Depth of invasion (>50%)	78 (50.7)
Tumor size (>5 cm)	102 (66.2%)
FIGO stage	61 (39.6%)
I	72 (47.7%)
II	21 (13.9%)
III	30 (19.9%)
IV	28 (18.5%)

CA-125 levels	*n*	Median (IQR)
Preoperative	79	29 (51)
End of treatment	74	8 (10)
Time of recurrence	37	30 (118)

Descriptive statistics were reported as number (%) or median (IQR). BMI: body mass index; EBRT: external-beam radiotherapy; EFRT: extended-field external-beam radiotherapy to pelvis plus para-aortics; IQR: interquartile range.

chemo-radiation combinations, as well as the availability of CA-125 level at different treatment points, it was not possible to evaluate for a trend in CA-125 by specific treatment type.

Of the 153 patients, 79 (51.6%) had a CA-125 drawn preoperatively (median = 28 U/mL, inter-quartile range (IQR) = 51), 74 (48.4%) had a post-treatment level (median = 8 U/mL, IQR = 10), 37 (24.2%) had a level at the time of disease recurrence (median = 30 U/mL, IQR = 118), and 19 (12.4%) had a level at all three time points (Table 1). Because CA-125 levels were not collected at all time points

nor among all women, we assessed for selection bias by evaluating for the following differences in patient characteristics between people with and without both preoperative and end-of-treatment CA-125 levels: age ($p = 0.096$), carcinoma versus sarcoma predominance ($p = 0.563$), stage ($p = 0.181$), size greater than 5 cm ($p = 0.975$), depth of invasion >50% ($p = 0.951$), patient weight ($p = 0.233$), and LVSI ($p = 0.563$). A similar analysis was performed for those with and without both end-of-treatment and recurrence CA-125 levels: age ($p = 0.141$), carcinoma versus sarcoma predominance ($p = 0.632$), stage ($p = 0.248$), size greater than 5 cm ($p = 0.778$), depth of invasion >50% ($p = 0.136$), patient weight ($p = 0.3313$), and LVSI ($p = 0.242$).

Table 2. Description of adjuvant therapy.

Adjuvant therapy	*n*
Radiation	84
Vaginal brachytherapy alone	9
Pelvic EBRT + vaginal brachytherapy boost	48
Extended-field EBRT + vaginal brachytherapy	4
Pelvic EBRT alone	21
Extended field alone	2
Chemotherapy	111
Doublet	98
Carboplatinum/taxane	63
Ifosfamide/taxane	23
Cisplatinum/ifosfamide	10
Cisplatinum/taxane	1
Gemcitabine/taxane	1
Single agent	11
Ifosfamide	4
Carboplatinum	3
Cisplatinum	1
Taxane	1
Liposomal doxorubicin	1
Adriamycin	1
Triple agent TAP	2
Chemotherapy + radiation	58

TAP: cisplatinum, adriamycin, paclitaxel; EBRT: external-beam radiotherapy.

Analysis of the 51 patients with both pre (median = 29 U/mL, IQR = 49) and post-treatment values (median = 11 U/mL, IQR = 13) found a significant drop in CA-125 ($p < 0.001$). In the 30 patients who had end-of-treatment (median = 10 U/mL, IQR = 17) and recurrence CA-125 levels (median = 30 U/mL, IQR = 167), a significant increase was noted ($p = 0.001$). There was no significant trend in the 23 patients who had CA-125 drawn preoperatively (median = 38 U/mL, IQR = 109) and at time of recurrence (median = 43 U/mL, IQR = 167, $p = 0.99$). In patients with all three time points, there was a significant difference between end-of-treatment (median = 14 U/mL, IQR = 6) and recurrence CA-125 level (median = 60, IQR = 212, $p = 0.014$) but not between preoperative (median = 31 U/mL, IQR = 44) and end-of-treatment levels (median = 14 U/mL, IQR = 68, $p = 0.073$) or recurrence (median = 60 U/mL, IQR = 212, $p = 0.445$) CA-125 levels (Table 3).

An elevated preoperative CA-125 level was present in 28 (36%) patients. Elevation in preoperative CA-125 was significantly associated with stage IV disease ($p = 0.003$). No other tumor characteristics were found to be statistically significantly associated with an elevated preoperative CA-125 level (Table 4).

Survival

With a median follow-up time of 29.6 (range = 0.9–151.9) months, 70 (45.8%) patients had recurrence. Median PFS was 18.9 months (range = 0.5–166.6 months) and OS was 29.2 months (0.9–166.6 months) for the study population. Log-rank test of the Kaplan–Meier curves found that an elevated CA-125, defined as a value >35 U/mL, at the end of treatment was associated with a worse OS ($p < 0.001$; Figure 1). However, an elevated preoperative CA-125 level did not show the same statistically significant association ($p = 0.12$). When an elevated CA-125 at the end of treatment was re-defined as a <50% drop between pre and post-treatment values or a value >35 U/mL, there were 21 total patients who met this criteria for evaluation; 15 of which had <50% drop but CA-125 < 35 U/mL and six that met both criteria. When a normalized CA-125 was redefined as

Table 3. Evaluation of CA-125 level at different points in disease course.

	n	Preoperative	End of treatment	Recurrence	Difference	*p* value
Preoperative vs end of treatment						
All available	51	29 (49)	11 (13)		−12 (33)	<0.001
Complete case	19	31 (44)	14 (68)		−12 (34)	0.0073
End of treatment vs recurrence						
All available	30		10 (17)	30 (167)	7 (46)	0.001
Complete case	19		14 (6)	60 (212)	8 (94)	0.014
Preoperative vs recurrence						
All available	23	38 (109)		43 (167)	1 (130)	0.999
Complete case	19	31 (44)		60 (212)	5 (120)	0.445

Descriptive statistics were reported as number (*n*) or median (interquartile range).

a drop ≥50% drop between pre and post-treatment or a value <35 U/mL, there were 30 total patients included, all of which met both criteria. By these new definitions, a log-rank test of Kaplan–Meier curves found that an elevated CA-125 at the end of treatment remained a predictor of OS ($p = 0.112$) when compared to a normalized CA-125 (Figure 2). There were 21 patients excluded from this repeat analysis as they were missing preoperative CA-125 levels.

Table 4. Analysis of possible associations of preoperative CA-125 level with other patient–tumor characteristics.

	n	Median (IQR)	p value
Stage	79		0.003
I	38	20 (21)	
II	9	23 (47)	
III	14	27 (31)	
IV	18	115 (427)	
Carcinoma vs sarcoma predominance	53		0.6
Carcinoma	25	31 (49)	
Sarcoma	28	26 (51)	
Heterologous vs homologous component	54		0.6
Heterologous	11	31 (143)	
Homologous	43	29 (52)	
Depth of invasion	77		0.6
≥50%	53	29 (67)	
<50%	26	22 (25)	
Tumor size	79		0.5
≥5 cm	53	31 (50)	
<5 cm	26	21 (41)	
LVSI	77		0.6
No	24	23 (34)	
Yes	53	29 (50)	

Median and IQR of CA-125 level.
LVSI: lymphovascular space invasion; IQR: interquartile range.

Discussion

In one of the largest retrospective, multi-institutional studies of the significance of histological pattern on survival outcomes, Matsuo et al.[17] found that 615 of 906 (67.9%) total patients had a CA-125 level collected, demonstrating that while CA-125 is being monitored, it is not done routinely. To our knowledge, there are no large studies that specifically evaluate the trend of CA-125 levels throughout the disease course of UCS. However, there is some literature assessing the role of CA-125 levels in endometrial and more specifically type II endometrial carcinoma.

A recent multi-institutional, retrospective chart review sought to define patterns of surveillance in patients with high-grade and type II endometrial cancer including carcinosarcoma. In their cohort of 254 patients, 36% of patients experienced a recurrence; the majority (56%) of which were diagnosed by symptoms and only 10% by CA-125.[18] While Hunn et al. demonstrated a small number of individuals were found to have recurrence based on rise in CA-125, Duk et al.[19] found that, when looking at all endometrial cancers, an elevated CA-125 correlated with advanced stage and that levels paralleled the disease course. Although they did not specify endometrial histology type, Jhang et al.[20] showed that an elevated preoperative CA-125 correlated with advanced stage, lymph node status, myometrial invasion, and LVSI. This was also confirmed in early stage patients with FIGO grade I–II disease, where an elevated preoperative CA-125 was found to correlate with poor prognostic pathological features.[21] To further build on this data, a retrospective review of 125 patients, with all histology types, found that CA-125 was elevated in patients
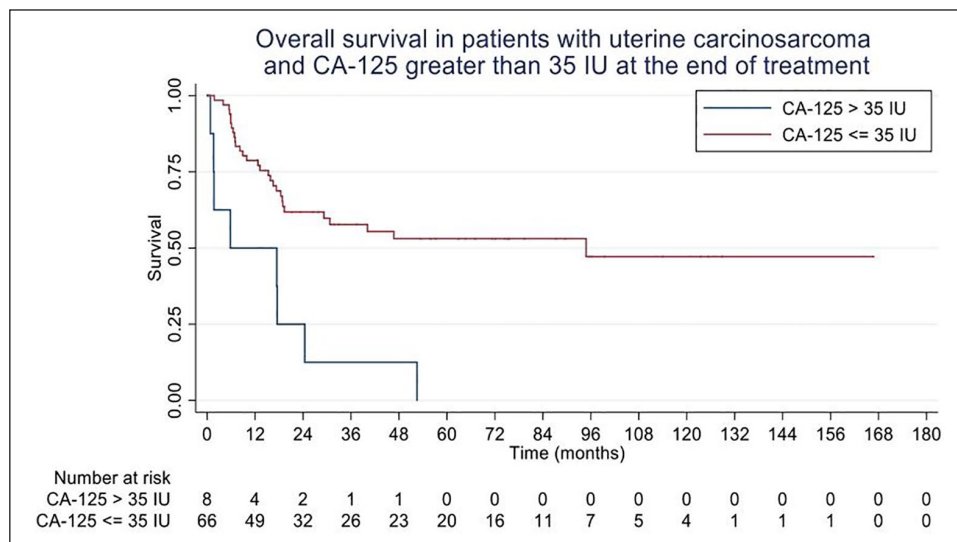

Figure 1. An elevated CA-125 >35 U/mL at the end of treatment is associated with a worse overall survival ($p < 0.001$).
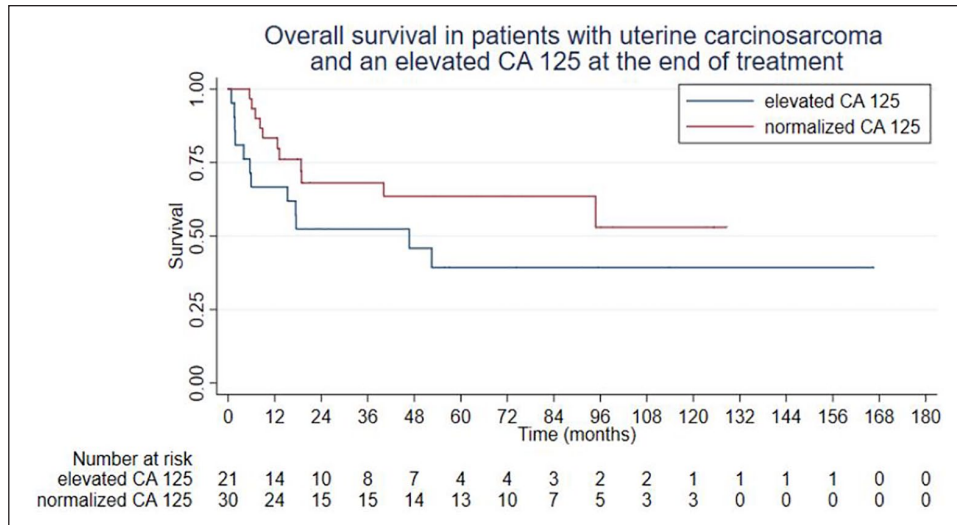
Figure 2. An elevated CA-125 (re-defined) remains a predictor of overall survival ($p < 0.112$).

who had a pelvic, abdominal, and pulmonary but not vaginal recurrence and concluded that CA-125 may play a role in surveillance.[22] Rose et al.[23] looked at low, medium, and high risk endometrial cancer in 266 patients with 1101 post-treatment assays and found that in patients with high-risk disease 94% that experienced a recurrence had an elevated CA-125.

In one of the largest studies of uterine papillary serous carcinomas (UPSC) to date, preoperative CA-125 was found to correlate with stage of disease and risk of death.[24,25] In a review of UPSC by Boruta et al.,[24] they concluded that CA-125 may be a useful marker for disease but should not be used alone. Conversely, Price et al.[26] reviewed 220 serum specimens from 16 patients with serous endometrial carcinoma undergoing adjuvant therapy and noted that all five patients that died of disease had clinical or radiographic evidence of tumor that was not preceded by an elevated CA-125.

Similar to the larger studies including a variety of type II endometrial carcinoma, in UCS, preoperative CA-125 has been shown to be significantly associated with extra-uterine disease, deep myometrial invasion, and serous histology in the epithelial component.[27] In addition, Peters et al. first demonstrated the utility of CA-125 to detect recurrent or metastatic disease in patients with ovarian or UCS. In this limited study of seven patients, they found that CA-125 correlated with the clinical course of the disease.[28] However, more recently, Thomakos et al.[29] performed a retrospective chart review of 37 patients with pre and postoperative tumor markers and found no significant prognostic association with CA-125, CA 15-3, CA 19-9, or CEA (carcinoembryonic antigen). These mixed results pose the ongoing question of the utility of CA-125 in UCSs.

In this analysis, we found that staging surgery combined with adjuvant chemotherapy and/or radiation may lead to a significant drop in CA-125 levels. We were also able to show that there was a significant change in a patient's CA-125 level from the end of treatment compared to time of recurrence. As one might expect, there was no significant difference between preoperative and recurrence CA-125 levels. Evaluating CA-125 levels in patients with a measure at all three time points ($n = 19$, 12.4%) is the least biased analysis but also has the lowest statistical power. The results from this analysis suggest that there is a potential difference between preoperative and end-of-treatment CA-125 levels, a significant decrease in end-of-treatment CA-125 levels when compared to levels at time of recurrence; and again, as expected, no difference when comparing preoperative and time of recurrence CA-125 levels. In addition, we showed that an elevated CA-125 level at the end of treatment was significantly associated with a worse OS. In our data set, an elevated preoperative CA-125 level was not statistically associated with OS ($p = 0.12$); however, this is a limited data set and this association warrants further investigation.

One important limitation of this study was the potential for selection bias, because CA-125 levels were not collected at all time points nor among all women in the study. For example, if CA-125 levels were captured only among women who were likely to show a response (drop) in CA-125, then we will have overestimated the success of CA-125 as a good biomarker. We found no differences between those who had and did not have CA-125 values across measured variables of age, weight, carcinoma grade, carcinoma versus sarcoma predominance, tumor size, depth of invasion, or LVSI. In addition, the way that end-of-treatment CA-125 was defined could have introduced bias as there are many different types of adjuvant therapy.

While retrospective in nature, this data set contains a large number of patients for such a rare disease. The

demographic, surgical, pathologic evaluation is exhaustive and completes with a CA-125 levels at multiple different points throughout the disease course. In addition, all pathology was reviewed and verified by a pathologist trained in the evaluation of gynecologic malignancies.

Conclusion

While measuring a serum CA-125 level causes little to no physical harm to patients, there is a psychological impact of serial serum testing. It is well known that CA-125 can be falsely elevated in the setting of ovulation, infection, inflammatory conditions, medical co-morbidities, and post radiation. This should be taken into account when ordering a CA-125 for unclear indications as multiple studies have noted false positives in patients with endometrial cancer.[21,26]

These data suggest that it is worthwhile to pursue the use of CA-125 as a biomarker for cancer stage/severity in a more deliberate and prospective manner. Preoperative CA-125 correlates with advanced stage disease, surveillance CA-125 can predict possible recurrence, and an elevated end-of-treatment CA-125 is associated with a worse OS.

Author contributions

All authors reviewed the manuscript and approved the final version. M.S.R. helped develop the clinical question and performed the majority of the chart abstraction and literature review, and he is the primary writer and editor of the manuscript. C.K.C. assisted with chart abstraction and editing of the manuscript. This is an off-shoot of a multi-institution, retrospective study initiated by Dr. K.M. In this specific project, K.M. assisted with writing and editing of the manuscript. N.S. performed the statistical analysis for this project. E.E. is a trained gynecologic pathologist who performed the pathologic review of specimens of patients in this retrospective study. J.L.B. assisted with formulation of the clinical question, as well as writing and editing of the manuscript. J.L.K. assisted with formulation of the clinical question, writing, and editing. S.E.T. formulated the clinical question, assisted with statistical analysis, and played a major role in manuscript revisions.

Ethical approval

Ethical approval for this study was obtained from the University of Pittsburgh Institutional Review Board (PRO14040179).

Informed consent

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ORCID iD

Malcolm Strachan Ross https://orcid.org/0000-0001-7696-0663

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