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Evaluation of the incidence and clinical significance of WT-1 expression in uterine serous carcinoma☆

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ABSTRACT

Background: Wilms tumor gene 1 (WT1) expression is a hallmark of ovarian serous carcinoma and considered to be diagnostic marker of these tumors, differentiating them from uterine serous carcinoma (USC), historically thought to rarely express WT1. However, more recent data indicates a significant percentage of USC may express WT1. The clinical implications of WT1 positivity in USC remain unclear.

Methods: A multicenter retrospective analysis of patients with USC was conducted from 2000 to 2019. Inclusion criteria were patients who had undergone comprehensive surgical staging/tumor debulking with archival tissue available for WT1 assessment via immunohistochemistry (IHC). Chemosensitive patients were defined as those recurring >6 months from last platinum-based chemotherapy. Progression free survival (PFS) and overall survival (OS) analysis was performed using Kaplan-Meier estimates. Multivariate analysis (MVA) was performed using Cox proportional hazards model.

Results: WT1 status was evaluated in 61 patients with USC. 13 (21.3%) were positive for WT1 by IHC. Stage distribution included 32% stage I, 5% stage II, 25% stage III and 38% stage IV. There was no difference in the stage ($p = 0.158$), race ($p = 0.227$) or distribution of recurrence sites ($p = 0.581$) between WT1 positive and WT1 negative tumors. The majority of patients were chemosensitive (63%). Chemosensitivity was significantly improved in WT1 positive (92.3%) vs. WT1 negative tumors (55.8%) ($p = 0.016$). We observed a trend towards improved PFS among WT1 positive tumors (21 vs. 16-months, respectively) ($p = 0.544$). On MVA, stage ($p < 0.001$) and chemosensitivity ($p < 0.001$) were independent predictors of PFS.

Conclusions: WT1 positivity is observed in over 20% of USC. WT1 expression is associated with improved chemosensitivity which may contribute to improvements in PFS.

1. Introduction

Wilms' tumor 1 gene (WT-1) plays an important role in normal embryonic development of the urogenital system and other tissues derived from the mesoderm including the heart, spleen and adrenal glands (Hohenstein and Hastie, 2006). Additionally, WT-1 has been identified as a major contributor to carcinogenesis. Although the exact mechanism of WT-1 carcinogenesis remains unclear, studies have suggested that this gene plays a key role in the process of invasion and migration of malignant cells (Barbolina et al., 2008). The expression of WT-1 in a wide range of hematologic and solid tumors makes it an attractive potential prognostic indicator and focus for targeted-therapy. Clinical trials of WT-1 targeted vaccines have been published in both hematologic malignancies and solid tumors with ongoing trials investigating this therapy in treatment resistant gynecologic cancers (Keillholz et al., 2009; Takahashi et al., 2013; Taube et al., 2016; Di Stasi et al., 2015; Ohno et al., 2012).

Historically, WT-1 has been utilized as a marker to distinguish primary uterine serous carcinoma (USC) from high-grade serous ovarian carcinoma (HGSOC). Almost universal expression of WT-1 in HGSOC

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aids in the histologic diagnosis of these tumors compared to USC which is characteristically negative for WT-1 (Al-Hussaini et al., 2004; Goldstein, 2004a). Multiple single institution studies and meta-analysis have evaluated and validated this concept, demonstrating that over 90% of HSGOC expresses WT-1 versus a much smaller fraction of USC that expresses this marker (Heatley, 2005). However, current literature suggests that WT-1 may be more universally expressed among USC than what previous studies had indicated. Hedley and colleagues evaluated a cohort of 77 women with USC and found that 44% of the tumors expressed WT-1, which is strikingly higher than previously reported (Hedley et al., 2014).

Studies in non-gynecologic malignancies have evaluated the prognostic significance of WT-1 expression and reported that positive expression of WT-1 is associated with poor prognosis and resistance to chemotherapy (Bergmann et al., 1997; Virappane et al., 2008). The literature regarding the significance of WT-1 expression in USC is scarce and based on small single institution reviews. Hedley and colleague evaluated the clinical outcomes in a cohort of 20 women with USC (9 WT-1 expressing and 11 WT-1 non-expressing tumors). Corresponding with the literature regarding WT-1 expression at other primary sites, they observed a significant decrease in disease-free survival among WT-1 expressing tumors versus those lacking expression (Hedley et al., 2014). In gynecologic malignancies, due to the almost universal expression of WT-1 among HGSOC, the prognostic implications of its baseline expression appear to be trivial. However, alterations in the level of expression in response to treatment have raised particular interest. A group of German investigators reported strong WT-1 expression in HGSOC was associated with both improved progression free and overall survivals relative to lower expression (Taube et al., 2016). Additionally, Casey et al. evaluated a cohort of WT-1 expressing HGSOC and observed a significant decrease in the intensity of WT-1 expression in patients achieving complete or partial response to chemotherapy (Casey et al., 2017). At present, further evaluation of USC is needed to clarify the incidence of positivity and prognostic significance of WT-1 expression in these tumors. The current study evaluates WT-1 expression in a cohort of women with USC managed with primary surgery to determine the clinical significance of WT-1 expression in this population.

2. Methods

2.1. Study population

A multicenter retrospective analysis of patients with USC was conducted from 2000 to 2019. Internal review board approval was obtained at all participating sites. Tumor registries were reviewed to identify all patients with USC who received primary surgical treatment with archival tissue available for immunohistochemical (IHC) assessment of WT-1 expression. In all cases, at the time of initial pathologic evaluation, the endometrium, fallopian tubes and ovaries were thoroughly evaluated to classify the endometrium as the primary site of serous carcinoma. TP53 immunostaining was carried out to aid in the differentiation of USC versus other endometrial histologies in certain cases. Mixed histology, including mixed serous-clear cell and mixed serous-endometrioid carcinoma were included if the serous component comprised at least 10% of the total tumor volume. The final pathologic diagnosis was confirmed by interdepartmental review conducted by two attending pathologists. Additionally, each case was reviewed at multidisciplinary tumor board conference to confirm correlation between the clinical and histologic findings. Primary surgical management was defined as total hysterectomy with or without bilateral salpingoophorectomy and comprehensive surgical staging for uterine carcinoma. Comprehensive surgical staging was defined as pelvic lymph node dissection with or without paraaortic lymph node dissection with or without omentectomy. Among those patients who received adjuvant chemotherapy, chemosensitive patients were defined as those with disease recurrence >6 months from their last platinum-based therapy. Key exclusion criteria included histology other than USC or serous components involving <10% of the tumor volume, absence of archival tissue for WT-1 assessment, and those who received neoadjuvant chemotherapy and/or preoperative pelvic radiation.

2.2. Acquisition of clinical data

Clinical and demographic data was obtained from a review of tumor registry, operative notes, pathology reports, and both inpatient and outpatient medical records. Data regarding the date of diagnosis, surgical procedures, types of adjuvant therapy, date and site of recurrence, chemotherapy regimen, number of chemotherapy cycles received, type of radiation therapy received, and date of death were extracted. Progression free survival (PFS) was defined as the time of surgery to the time of first recurrence. Overall survival (OS) was defined as the time of surgery to the time of death. Patients who were alive at the date of last follow up were censored.

2.3. Immunohistochemistry

All patients with USC were identified through a review of the tumor registries. Case diagnostic reports along with hematoxylin and eosin (H&E) slides were reviewed to verify the diagnosis, confirm endometrium as the primary site of origin, and to identify a representative tissue block to undergo IHC staining for WT-1. Tissue from surgical resection specimens was favored over biopsy materials. Sections of tumor involving the uterine corpus were given preference for IHC staining. Tissue blocks consisting of formalin-fixed paraffin-embedded sections were utilized to generate unstained slides. Using standard laboratory protocols, prediluted WT-1 antibody (clone 6F-H2, Roche Diagnostics, Indianapolis, IN) was used to stain the tissue sections via the Ventana BenchMark ULTRA System (Roche Diagnostics, Indianapolis, IN) after performing standard antigen retrieval. Immunoreactivity was detected using the OptiView DAB IHC Detection kit (Ventana Medical Systems Inc., Tucson, AZ). Appropriate positive and negative controls were included. The IHC slides were examined by 2 pathologists, and staining was considered to be positive if at least 1% of tumor cells demonstrated nuclear WT-1 immunoexpression.

2.4. Statistical analysis

A one-way ANOVA test was used to compare the differences in mean age between cohorts. Differences in the frequencies of stage, race, chemosensitivity, and sites of disease recurrence were identified using Pearson's chi-square test. PFS and OS analysis was performed using Kaplan-Meier estimates. Multivariate analysis (MVA) was performed using Cox proportional hazards model. Statistical analysis was performed using SPSS version 26.0 (IBM, Armonk, New York) and significance was defined as $p < 0.05$.

3. Results

3.1. Patient characteristics

WT-1 status was evaluated in 61 patients with USC. We observed WT-1 positivity via IHC in 13 (21.3%) patients. Of these 61 patients, 56 had follow-up information available for review and were included in the final analysis. When considering only the 56 patients with follow up information, the WT-1 positivity rate increased to 30.2%. Ninety percent (90%) of the tumors were classified as pure USC and 10% were mixed histology. At the time of initial pathologic diagnosis, three cases created a diagnostic dilemma. Each of these three cases presented with widely metastatic disease in the abdomen. All three of these cases underwent WT-1 assessment at the time of initial pathologic evaluation as determined necessary by the pathologist. One was reported as positive and the other two were reported as negative. The critical feature used to

differentiate these uterine carcinomas from ovarian carcinomas was the diffuse involvement of the endometrial lining in all cases. There was no difference in the stage ($p = 0.158$), race ($p = 0.227$) or distribution of recurrence sites ($p = 0.581$) between the WT-1 positive and negative tumors (Table 2).

3.2. Adjuvant therapy

Of the 56 patients with follow up data available, the majority received chemotherapy with or without radiation (91.1%). Twenty-seven (48.2%) patients received chemotherapy alone, and 24 (42.9%) received a combination of chemotherapy with radiation including external beam radiation therapy or vaginal brachytherapy. Only 4 patients (7.1%) received radiation therapy alone and one patient underwent observation with no further adjuvant therapy. The mean time from surgery to start of chemotherapy was 34 days (Range 19–50 days). For those patients receiving combination chemoradiation, the mean time between modalities was 21 days (Range 14–35). Adjuvant therapy regimens were well balanced between the WT-1 positive and negative cohorts ($p = 0.331$). Of the patients receiving systemic chemotherapy, all received platinum-based therapy of which the most common regimen was carboplatin-paclitaxel (94.1%).

3.3. Recurrence patterns

Thirty-six (64.3%) patients recurred during the study period, 8 (61.5%) of the WT-1 positive cohort and 28 (65.1%) of the WT-1 negative cohort. The most common location of recurrence was the abdomen (57%) followed by the pelvis (30%) and extra-abdominopelvic sites (13%). The majority of patients recurred at multiple sites (71%), and the location of recurrence did not differ based on the WT-1 status ($p = 0.581$). However, we observed no isolated pelvic recurrences in the WT-1 positive cohort. All WT-1 positive patients with recurrent disease had at least one site of abdominal metastases.

3.4. Clinical treatment outcomes

The median follow-up was 34 months. For the entire cohort, the median PFS was 20 months and the median OS was 29 months. The median PFS and OS did not differ significantly based on the WT-1 status ($p = 0.544$ and $p = 0.759$, respectively). However, we did observe a trend towards improved PFS among WT-1 positive tumors (21 vs. 16 months, respectively) (Fig. 1). Chemosensitivity was significantly improved in the WT-1 positive (91.6%) vs. negative tumors (55.2%) ($p = 0.015$). On MVA, stage ($p < 0.001$) and chemosensitivity ($p < 0.001$) were independent predictors of PFS. Similarly, only stage ($p < 0.001$) and chemosensitivity ($p < 0.001$) were independent predictors of OS. Age, race and WT-1 status did not independently alter survival outcomes (Table 3).

Table 1
Frequency of WT-1 expression in uterine serous carcinoma and high grade serous ovarian carcinoma.

Author	USC	HGSOC
Al-Hussaini et al. (2004)[b]	5/25; 20%	36/38; 95%
Acs et al. (2004)[b]	10/16; 63%	24/28; 86%
Cooseman et al. (2007)[c]	7/9; 78%	X
Dupont et al. (2004)[a]	3/9; 33%	X
Egan et al. (2004)[a]	2/31; 7.5%	X
Eusher et al. (2003)[a]	0/9; 0%	10/12; 83%
Goldstein (2004a)[a]	0/18; 0%	X
Hashi et al. (2003)[a]	0/5; 0%	25/25; 100%
Hedley et al. (2014)[b]	34/77; 44%	X
McEachron[*b]	? 13/61; 21.3%	X
Ohno et al. (2009)[c]	64/70; 91%[x]	X
Wang et al. (2003)[d]	3/9; 33.3%	16/25; 64%
Zhang[d]	5/8; 63%	19/21; 91%

HGSOC: High grade serous ovarian carcinoma; *USC*: Uterine serous carcinoma; *X*: Not reported.

[*] Current report.

[x] Included all endometrial adenocarcinoma histologies.

[a] WT-1 positivity diagnosed by presence of moderate to strong nuclear expression.

[b] WT-1 positivity diagnosed by presence or absence of nuclear expression.

[c] WT-1 positivity diagnosed by presence of cytoplasmic expression without regard to nuclear expression.

[d] WT-1 positivity diagnostic criteria unknown.

Table 2
Clinical and pathologic characteristics based on WT1 status.

	All Patients (N = 56)	WT1 Positive (N = 13)	WT1 Negative (N = 43)	*p*-Value[*]
Age at surgery Mean (range)	67 (57–81)	69 (59–75)	67 (57–81)	$p = 0.311$
	N (%)	N (%)	N (%)	
Race				
African American	54 (96)	13 (100)	41 (95)	$p = 0.227$
Caucasian	1 (2)	0 (0)	1 (2.5)	
Other	1 (2)	0 (0)	1 (2.5)	
Stage				
I	18 (32)	5 (39)	13 (30)	$p = 0.158$
II	3 (5)	0 (0)	3 (7)	
III	14 (25)	6 (46)	8 (19)	
IV	21 (38)	2 (15)	19 (44)	
Recurrence site[**]				
Abdomen	26 (57)	7 (58)	19 (56)	$p = 0.581$
Pelvis	14 (30)	3 (25)	11 (32)	
Distant	6 (13)	2 (17)	4 (12)	
Chemosensitive[^]	33 (65)	12 (92)	21 (55)	$p = 0.016$
Chemoresistant	18 (35)	1 (8)	17 (45)	

[*] Statistical significance was defined as $p < 0.05$.

[**] The majority of patients recurred a multiple locations simultaneously, percentages based on total number of recurrence sites.

[^] Chemosensitive defined as recurrence >6 months from last platinum-based chemotherapy.

4. Discussion

In our study cohort of 61 patients with USC, we observed WT-1 expression in 21.3% of the tumors. This corresponds with several previously published small scale reports (Al-Hussaini et al., 2004; Casey et al., 2017) (Table 1). However, our observed incidence of WT-1 positivity is notably lower than that reported by Hedly et al, who observed 44% of USC expressing WT-1. Importantly, these authors employed a similar criterion to classify tumors as WT-1 positive by designating tumors as positive based on any degree of nuclear expression (Hedley et al., 2014). At present, several variations in the methods of reporting WT-1 positivity in USC have limited the interpretation of existing literature. Based on the reporting criteria in HGSOC, we and many other authors would consider only the nuclear expression to represent WT-1 positivity (Köbel et al., 2009). However, other authors have considered WT-1 expression to include those tumors with only cytoplasmic staining for WT-1 in the absence of nuclear staining. This method designates 78–91% of USC as WT-1 positive and is considered by many to be inaccurate but nevertheless has clouded the literature (Ohno et al., 2009; Cooseman et al., 2007). Additionally, variation exists in the quantification of the intensity of nuclear staining, with some authors reporting any nuclear staining as positive expression and others requiring moderate or strong nuclear staining to classify tumors as WT-1 positive (Table 1). Low intensity staining of WT-1 has been reported in the nuclei of normal cells; therefore, some suggest that quantification of the degree of nuclear staining is the key for classification (Goldstein, 2004a, 2004b, Egan et al., 2004; Goldstein and Uzieblo, 2002). This highlights the importance of standardization of diagnostic approaches, especially in the setting of molecular markers with prognostic potentials.

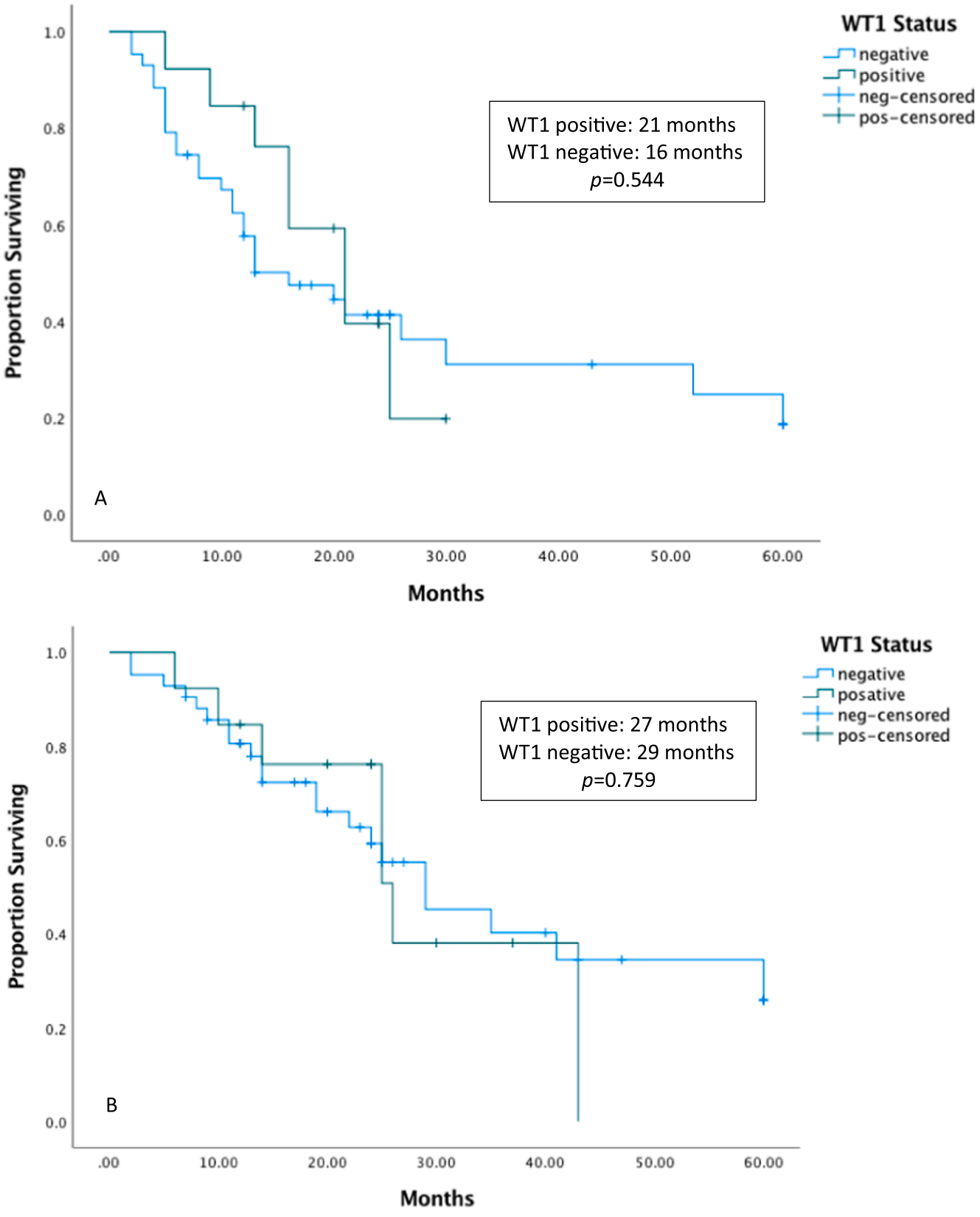

Fig. 1. Kaplan–Meier survival analysis based on WT-1 status. (A) Progression Free Survival Analysis; (B) Overall Survival Analysis.

When the existing literature is filtered and only those studies utilizing the same criteria as the current report are considered, WT-1 expression is consistently reported in at least one-fifth of tumors (Table 1).

In the current study, we observed improved chemosensitivity in WT-1 expressing USC. Multiple studies in both gynecologic and non-gynecologic malignancies have evaluated the prognostic significance of WT-1 expression with mixed conclusions. Bergman et al. evaluated WT-1 expression in acute myeloid leukemia and found that the

Table 3
Multivariate analysis for PFS and OS.

Variable	PFS			OS		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age (per year)	1.033	0.97–1.10	0.345	0.965	0.89–1.04	0.327
Race	1.941	0.34–11.07	0.456	2.283	0.48–10.77	0.297
Stage*	0.071	0.02–0.21	<0.001	0.077	0.02–0.35	<0.001
WT1 status	0.269	0.09–0.85	0.067	0.442	0.17–1.123	0.087
Chemosensitivity^	12.2	12.9–34.1	<0.001	17.83	4.88–55.07	<0.001

OS: Overall survival; *PFS:* Progression free survival.
* Stage I vs. all other stages.
^ Chemosensitivity defined as recurrence >6 months from last platinum-based chemotherapy.

expression of WT-1 correlated with tumor relapse and worse survival versus those with no expression (Bergmann et al., 1997). A recent meta-analysis of 13 studies evaluating WT-1 expression in gynecologic malignancies, including 10 ovarian and 3 endometrial cancer studies, concluded that WT-1 expression was associated with worse progression free and disease specific survivals relative to WT-1 negative tumors. However, this review also identified significant heterogeneity among the included studies primarily due to the different diagnostic criteria used to classify tumors as WT-1 expressing, limiting its applicability and making it difficult to draw clear conclusions (Lu et al., 2018). In contrast to these observations, Taube et al. evaluated a cohort of 207 patients with HGSOC and reported WT-1 expression as a favorable prognostic indicator associated with improved progression free and overall survivals. Importantly, these authors quantified the levels of WT-1 expression and correlated the degrees of expression with survival time and observed an improvement in survival proportional to the amount of WT-1 positive cells (Taube et al., 2016).

Literature regarding the prognostic implications of WT-1 expression specifically in USC is limited. Dupont and colleagues evaluated the clinical implications of WT-1 expression in 130 endometrial cancers noting a trend towards inferior survival in WT-1 expressing tumors. However, this review included only 9 USC and was not designed to specifically evaluate the outcomes in this population (Dupont et al., 2004). Similarly, Hedley et al. evaluated the WT-1 expression in 20 patients with USC. They observed a statistically significant decrease in disease-free survival in WT-1 expressing tumors compared to those not expressing WT-1, 15 vs. 38-months, respectively. However, the majority of these tumors were early-stage diseases, and the overall validity of this study is limited by the small sample size of only 20 patients (Hedley et al., 2014).

Of interest, a recent large meta-analysis including 1616 patients with endometrial cancer, specifically 307 with USC, analyzed WT1 expression and its prognostic implications. Though the authors note that there was significant heterogeneity between studies, they report 21% of USC express WT1, aligning with our results. Similarly to the aforementioned reports, these authors reported worse overall, disease-specific and progression free survival across the entire cohort of endometrial cancer patients expressing WT-1. Additionally, when looking only at cases of USC, the authors observed a significant decline in OS with WT-1 expression (Angelico et al., 2020). Although the results of current study do not replicate these findings, it is important to again note that the reports by Hedley et al. and Dupont et al. represent only 29 patients in total and therefore the results are difficult to generalize to the population as a whole. Additionally, Angelico et al. acknowledge several key limitations to their report including differences in reporting of WT-1 expression and the grouping of different survival statistics together to generate outcome data.

At present, there is active investigation of WT-1 peptide vaccines in the treatment of myelodysplastic syndromes and acute myeloid leukemia, two conditions which typically demonstrates high levels of WT-1 expression. In this population, WT-1 vaccination was associated with a normalization and reduction in the WT-1 expression, correlating with improved progression free survival (Di Stasi et al., 2015). As a result, there are currently multiple phase I/II trials investigating WT-1 vaccination in this population (ClinicalTrials.gov Identifier: NCT02550535; NCT01266083). Additionally, a phase II Japanese trial evaluated WT-1 peptide vaccine in patients with gynecologic malignancies progressing on prior traditional systemic therapy (Miyatake et al., 2013). The observed stable disease in 40% of patients with minimal toxicity and concluded that this strategy warrants further large-scale investigation. Currently, there is a phase I study currently enrolling investigating the WT1 vaccine in combination with nivolumab for recurrent ovarian cancer (ClinicalTrials.gove Identifier: NCT02737787). This is of relevance to the current report, as we have highlight a significant proportion of USC will express WT1 and therefore be potential candidates for WT1-targetting strategies.

Our results shed important light on the significance of baseline WT-1 expression in USC. Although our survival analysis did not reach statistical significance, we believe that the observed 5-month improvement in PFS represents a clinically meaningful finding in a disease with a poor prognosis. We did not observe a difference in OS based on the WT-1 status which we believe is due to the aggressive tumor biology of USC that ultimately leads to recurrence in the majority of patients. Initial WT-1 expression is associated with improved sensitivity to chemotherapy leading to a prolonged time to first recurrence, therefore extending the PFS interval. However, once tumor recurs, it inevitably behaves the same as those non-WT-1 expressing tumors. Therefore, the identification of WT-1 positivity initially at the primary surgery serves as a surrogate for improved disease-free survival, however, recurrences seem to behave independent of the WT-1 status. Assessment of the WT-1 status post-treatment would better clarify this hypothesis and improve the utility of WT-1 as a predictive biomarker.

In summary, we observed WT-1 expression in 21.3% of USC. These results compare favorably to the available literature and emphasize the need for standardized reporting of WT-1 expression. In the setting of an advanced high-grade serous malignancy of uncertain ovarian or endometrial origin, negative WT-1 expression suggests endometrial primary, while positive WT-1 expression requires further investigation to classify the primary site. Additionally, WT-1 expression holds prognostic significance as the pre-treatment expression is associated with improved PFS and chemosensitivity. Further evaluations of the post-treatment expression are warranted to explore the full potential of WT-1 as a predictive biomarker. The major limitation to this study is its retrospective nature and small sample size. Additionally, we were not able to evaluate tumors for WT-1 expression in the post-chemotherapy or recurrent setting which would a be an area of future interest. Despite these limitations, the current study suggests that WT-1 status is predictive of improved response to chemotherapy.

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Institutional review board statement

This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review board of SUNY Downstate Medical Center.

Informed consent statement

Not applicable as this is a retrospective review.

Data availability statement

Data is available upon reasonable request.

CRediT authorship contribution statement

Jennifer McEachron: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Agha Wajdan Baqir:** Writing – original draft. **Nancy Zhou:** Data curation, Writing – review & editing. **Absia Jabbar:** . **Raavi Gupta:** . **Daniel Levitan:** Conceptualization. **Yi-Chun Lee:** Conceptualization, Writing – review & editing, Supervision, Project administration.

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.

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