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Case Series

Molecular markers in uterine serous cancer: Correlation between endometrial biopsy and hysterectomy specimens

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ABSTRACT

Objectives: To measure the correlation of molecular biomarkers between biopsy and final pathology specimens in uterine serous cancer (USC) and to establish the overall prevalence of specific biomarkers among subjects with USC.

Methods: Twenty eight patients with a diagnosis of USC and sufficient biopsy and hysterectomy specimens were identified. IHC was used to measure the biomarker status of EGFR, phospho-AKT, ER, PR, Her2/neu, and PTEN in FFPE tissue. The presence or absence of individual biomarkers was then compared between a given subject's diagnostic biopsy specimen and final hysterectomy specimen.

Results: In the cohort identified, average age was 72 and average BMI was 29. 75% of patients had full lymphadenectomy performed. The average time from biopsy to surgery was 33 days (range 9–91 days). The distribution of disease was 61% stage I (n = 17), 14% stage II (n = 4), 22% stage III (n = 6) and 4% stage IV (n = 1). Biopsy and hysterectomy specimens agreed 67% of the time for phospho-AKT, 80% for ER, 73% for PR, 83% for EGFR, 100% for Her2/neu and 95% for PTEN loss.

Conclusions: The measurement of specific biomarkers correlated well between subjects' biopsy and hysterectomy specimens in women with USC as measured by a pathologist using routine clinical techniques. Preoperative diagnostic biopsy may be a useful tool for guiding neoadjuvant targeted therapy in USC.

Uterine serous carcinoma (USC) is an aggressive histologic type that accounts for 5–10% of all endometrial cancers(Boruta et al., 2009). Although USC comprises a small absolute number of all endometrial cancers, outcomes for patients with USC are far worse than patients with endometrioid-type endometrial cancers (EEC). In USC, up to 70% of patients present with tumor burden outside the uterus(Del Carmen and Rice, 2017).

Additionally, in those patients with disease confined to the uterus, the rate of recurrence is high and estimated to be between 30 and 80% (Del Carmen and Rice, 2017; Tropé et al., 2001). This is notably higher than EEC in which only 17% of patients present with disease outside of the uterus(Moore and Fader, 2011). Not surprisingly, survival is markedly different between EEC and USC, with an 80–90% 5-year-survival in patients with EEC compared to 50–80% for those patients with USC[4]. In light of this information, improved therapies for women with USC are needed.

Fortunately, progress has been made in the understanding of the specific pathways and biomarkers for endometrial cancer. There are distinct differences in the molecular make-up of Type I and II endometrial cancers. Type I endometrial cancers, those of endometrioid histology, are driven by excess estrogen and characteristically have a loss of *PTEN* and mutations in *PIK3CA, KRAS*, and *B-catenin*[5]. Type II endometrial cancers, including UPSC, are estrogen independent and characterized by alterations in *p53, Her2/neu, p16* and *E-cadherin*[5]. In both Type I and Type II endometrial cancers increased signaling in *PI3K/AKT/mTOR* pathways is associated with aggressive disease and poor prognosis(Slomovitz and Coleman, 2012). Activating mutations in *PI3K* drive the development of the tumor by loss of inhibition on mTOR, which then activates pathways for cell growth and proliferation (Slomovitz and Coleman, 2012; Rudd et al., 2011). Due to the poor prognosis in patients with USC, these patients with known *PI3KCA* mutations may benefit from treatment with inhibitors of the *PI3K/AKT/mTOR* pathway, or other targeted therapies, pre-operatively, and “phase 0” or “window” trials for endometrial cancer are promising. It is

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essential, however, to understand the accuracy of preoperative biopsy samples in diagnosing biomarker status in order to use these samples to direct therapy.

In the clinical setting, most patients with endometrial cancer present with post-menopausal bleeding and undergo a diagnostic procedure to sample the endometrial lining. This is traditionally done prior to definitive surgery with a hysterectomy either through outpatient biopsy or traditional dilation and curettage (D&C) in the operating room. Both of these procedures are highly sensitive with over 99% of malignancies diagnosed(Dijkhuizen et al., 2000). Additionally, if molecular alterations in the biopsy specimen are representative of alterations seen in the entire tumor, targeted neoadjuvant therapies could be used and tailored to molecular biomarkers as a result of the endometrial biopsy (Thangavelu et al., 2013).

It is currently unknown whether molecular markers in endometrial biopsy specimens correlate with biomarkers in final pathology hysterectomy specimens. Additionally, for this to be clinically relevant, it is essential for these biomarkers to be identifiable by clinically available pathology methods rather than specialized research laboratory techniques. For preoperative treatment with targeted agents to be effective and acceptable, molecular alterations in the biopsy specimen must be representative of alterations seen in the entire tumor. Therefore, using routinely performed pathology methods, we aim to determine if molecular markers in endometrial biopsy specimens showing a histologic diagnosis of USC are accurate predictors of the molecular markers tested in final hysterectomy specimens in untreated patients. Secondly, we aim to establish the overall prevalence of specific biomarkers of interest among subjects with USC based on routine clinical pathology methods.

1. Materials and methods

This was a retrospective cohort study whose aim was to measure the correlation of molecular biomarkers between biopsy and final pathology specimens in USC as well as to establish the overall prevalence of specific biomarkers of interest among subjects with USC based on routine clinical pathology methods. The study was approved by the Women and Infants Hospital institutional review board and was funded by the Rhode Island Foundation (Grant Number 30133892).

Seventy three patients with USC were identified from the institutional pathology database from January 2010 through December 2013. Thirty six patients were excluded because either endometrial biopsy or hysterectomy specimens were not available for molecular testing. This left thirty seven patients with pathologically proven USC who had both endometrial biopsy and hysterectomy specimens available for molecular testing.

Eligible subjects had undergone hysterectomy at Women and Infants Hospital (WIH) and were diagnosed on final pathology as having a papillary serous uterine carcinoma. Subjects must also have had a preoperative diagnosis of USC based on a diagnostic procedure reviewed at WIH (either D&C or endometrial biopsy). The patient identifiers were replaced by serial numbers for all cases. The master list was not available to the pathologist when the slides were reviewed by the pathologist.

Immunohistochemistry on 5-μm sections was used to measure the biomarker status of six markers significant in endometrial carcinoma including *phospho*-AKT, ER, PR, EGFR, Her2 and PTEN. These markers were chosen for their potential utility in choosing targeted therapy and for comparison to previously reported papillary serous cohorts. The following laboratory analysis was performed by the department of pathology using formalin fixed paraffin embedded (FFPE) archived surgical specimen blocks. The antibodies used were the following: Dako's Estrogen Receptor, Rabbit clone EP1, # IR084, Dako's Progesterone Receptor, Mouse clone PgR 636, # IR068, Dako's PTEN, Mouse clone 6H2.1, # M3627, Dako's c-erbB-2, Polyclonal Rabbit, # A0485, Dako's EGFR Kit # K1494, Cell Signaling's Phospho-Akt, Rabbit clone (Ser473) (736E11). Complete tissue sections were dewaxed in a 60^{O} C oven for one hour. The pre-treatment process of deparaffinization, rehydration, and antigen retrieval took place in a Dako PT Link module, with a Tris/EDTA buffer pH 9. Slides were blocked for peroxidase for 5 min and incubated at room temperature with primary antibody for 20 min. Dako EnVision FLEX polymer was applied for 20 min at room temperature as secondary antibody. The slides were then incubated with Dako's Liquid DAB chromogen-substrate system for 10 min. Finally, slides were counter-stained with hematoxylin. Two stained slides from each case for each antibody (one representative slide of the biopsy and one representative slide from the hysterectomy) were blindly scored according to the system described elsewhere (Quddus et al., 1999). One pathologist (MRQ) reviewed and scored the slides based on the intensity and extent of staining patterns. After completion of scoring the slides blindly, the results of the biopsy and hysterectomy were matched and tabulated.

Additional demographic data was obtained from patient medical records including age at diagnosis, race/ethnicity, BMI, stage of cancer, surgicopathologic factors (including depth of myometrial invasion, lymphovascular space invasion, cervical or adnexal involvement), whether or not a lymphadenectomy was performed, adjuvant therapy received, time to relapse, and location of recurrence.

Proportions, means, medians, and ranges were computed for all demographic data. The intensity and extent of staining for each biomarker was categorized as positive if greater than zero or negative if equal to zero. Percent of specimens that agreed for each biomarker were also calculated, along with binomial 95% confidence intervals and unweighted kappa statistics. Fisher's exact test was used to compare agreement by other characteristics.

2. Results

The last thirty seven patients with pathologically proven USC were identified who had both endometrial biopsy and hysterectomy specimens available for molecular testing. There were 9 patients unevaluable due to inability to reobtain their preoperative biopsies from outside facilities for further testing, leaving a total of 28 evaluable patients. Table 1 shows the patients' characteristics. The mean age of diagnosis was 72.5 years (range, 58–92 years) and the mean body mass index (BMI) was 29.1 kg/m2 (range, 19.1–38.5 kg/m2). Time from biopsy to hysterectomy was a mean of 32.6 days (range, 9–91 days). In this cohort of patients, the majority had early stage disease with 61% having stage I, 14% stage II, 22% stage III, and 4% having stage IV disease. Depth of invasion was > 50% in 46.4%, cervical and adnexal involvement was present in 28.6% and 10.7% respectively. Pelvic lymphadenectomy was performed in 75% of patients and para-aortic lymphadenectomy was performed in 53.5% of patients.

Each biopsy specimen was evaluated for specific biomarkers with the following results: *phospho-AKT* was present in 13/19 (68%), *ER* was

Table 1
Characteristics of patients with UPSC.

Characteristics	Value (n = 28)
Age at diagnosis, mean (range), yrs	72.5 (58–92)
BMI, kg/m2	29.1 (19.1–38.5)
Time from biopsy to hysterectomy, days	32.6 (9–91)
FIGO stage	
I	17 (61%)
II	4 (14%)
III	6 (22%)
IV	1 (4%)
Histopathological characteristic	Number (%)
Depth of invasion > 50%	13 (46%)
Cervical involvement	8 (29%)
Adnexal involvement	3 (11%)

Table 2
Biomarker positivity in biopsy and hysterectomy specimens.

	Biopsy specimen		Hysterectomy specimen		Traditional reported values from literature
	#stained	%positive	#stained	%positive	
P-AKT +	13/19	68%	11/24	46%	20–42%(Network et al., 2013)
ER +	15/21	71%	15/24	63%	19–44%(Kuderer et al., 2017; Wolff et al., 2013)
PR +	9/20	45%	10/24	42%	19–24%(Mentrikoski and Stoler, 2014)
EGFR +	9/20	45%	5/20	75%	50–80%(Buza et al., 2013)
Her2/neu +	20/20	100%	25/25	100%	18–80%(Del Carmen and Rice, 2017; Mentrikoski and Stoler, 2014; Fader et al., 2018; Network et al., 2013)
Loss of PTEN	0/19	0%	0/24	0%	0–11%(Mentrikoski and Stoler, 2014; Network et al., 2013)

present in 15/21 (71%), *PR* was present in 9/20 (45%), *EGFR* was present in 9/20 (47%), *Her2/neu* was present in 20/20 (100%), and PTEN loss was present in 0/19 (100%) of evaluated samples. Similarly, in the hysterectomy specimens; *phospho-AKT* was present in 11/24 (46%), *ER* was present in 15/24 (63%), *PR* was present in 10/24 (42%), *EGFR* was present in 5/20 (75%), *Her2/neu* was present in 25/25 (100%), and *PTEN* loss was present in 0/24 (0%) of evaluated samples. **(**Table 2**).**

There were 18 samples that underwent *phospho-AKT* staining in both biopsy and hysterectomy sample, agreement in intensity was 61.1% (CI 35.7–82.7) and in extent of staining was 66.7% (CI 41.0–86.7). *ER* staining was performed in both biopsy and hysterectomy of 20 samples, agreement in both intensity and extent was 80% (CI 56.3–94.3). Nineteen samples underwent *PR* staining in both biopsy and hysterectomy sample, agreement in both intensity and extent of staining was 73.7% (CI 48.8–90.9). *EGFR* staining was performed in both the biopsy and hysterectomy sample in 18 patients, agreement in both intensity and extent of staining was 83.3% (CI 58.6–96.4). Twenty samples underwent both *Her2/neu* staining in both biopsy and hysterectomy sample, agreement in intensity and extent of staining was 100% (CI 83.2–100). *PTEN* staining was performed in both biopsy and hysterectomy sample in 18 patients, agreement in intensity was 100% (CI 83.2–100) and in extent of staining was 95% (CI 75.1–99.9). (Table 3).

Agreement between biopsy and hysterectomy sample, in terms of both intensity and extent of staining, did not vary based on stage of disease. Staining in both stage 1&2 samples was compared to that in stage 3&4 samples for the 7 different tumor markers evaluated. Difference in the percent agreement between the two groups varied from 0 to 23.1% with *P values* of 0.52–1.0.

In three cases, the biopsy specimen was unable to be stained or interpreted for any of the six biomarkers of interest and in an additional three cases, the biopsy specimen was unable to be stained or interpreted for EGFR only.

3. Discussion

In this study we examined pre-operative endometrial biopsy specimens and post-operative hysterectomy specimens of 28 women with USC. We correlated biomarker staining of seven distinct pathologic markers in these specimens. Her2/neu was positive in 100% of the biopsy and hysterectomy specimens examined with 100% correlation between biopsy and hysterectomy specimens. There was no loss of PTEN in any of the biopsy or hysterectomy specimens. *Phospho*-AKT, ER, PR and EGFR showed a more variable staining pattern. Correlation in the staining pattern between biopsy and hysterectomy specimens for these four markers was also variable at 67% for *phospho*-AKT, 80% for ER, 73% for PR and 83% for EGFR.

In multiple human cancers pathologic biomarker positivity predicts response to targeted therapies and guides treatment. For example, in lung cancer, tumors that stain positive for EGFR mutations respond to tyrosine kinase inhibitors such as gefitinib, erlotinib and others (Lilenbaum and Horn, 2016). In breast cancer, tumors that stain positive for Her2/neu either on biopsy and/or on final surgical specimen respond well to treatment with targeted agents like trastuzumab and pertuzumab(Slamon et al., 2001; Slamon et al., 2011; Baselga et al., 2012),Her 2/neu staining by immunohistochemistry (IHC) and by FISH is standardized in breast pathology with consensus guidelines initially published in 2007 by the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) and updated in 2014 (15). However, no such standards currently exist for staining gynecologic specimens for these biomarkers. As an increasing number of targeted therapies (and their correlative biomarkers) are studied, agreement is necessary between researchers regarding definitions of biomarker positivity and negativity. This problem is not unique to immunohistochemistry but is representative of a new era of precision medicine and has recently been identified as an issue in commercial next generation sequencing, with poor concordance when patients were analyzed on two separate platforms(Kuderer et al., 2017).

Table 3
Extent of biomarker staining agreement between biopsy and hysterectomy.

Marker	Concordant biopsy and hysterectomy		Discordant biopsy and hysterectomy			
	Bx + /Hyst +	Bx-/Hyst-	Bx + /Hyst-	Bx-/Hyst +	Agreement (95% CI)	Kappa (p)
(a)						
P-AKT	8	4	4	2	67% (41–87%)	0.31 (p = .09)
ER	11	5	3	1	80% (56–94%)	0.57 (p = .005)
PR	6	8	3	2	73% (49–91%)	0.47 (p = .02)
EGFR	5	10	3	0	83% (59–96%)	0.65 (p = .002)
Her2/neu	20	0	0	0	100% (83–100%)	n/a
PTEN loss	19	0	1	0	95% (75–100%)	n/a
(b) Intensity of biomarker staining agreement between biopsy and hysterectomy						
P-AKT	8	3	5	2	61% (36–83%)	0.18 (p = .2)
ER	11	5	3	1	80% (56–94%)	0.57 (p = .005)
PR	6	8	3	2	74% (49–91%)	0.47 (p = .02)
EGFR	5	10	3	0	83% (57–96%)	0.65 (p = .002)
Her2/neu	20	0	0	0	100% (83–100%)	n/a
PTEN loss	19	0	0	0	100% (82–100%)	n/a

Furthermore, the ability of biomarkers to predict response to targeted therapies in gynecologic cancers is less well known. Many gynecologic clinical trials in the future will study targeted therapies by using neoadjuvant treatment and comparing preoperative biopsy and final hysterectomy specimen to evaluate tumor response. We must first understand the correlation between preoperative biopsy and hysterectomy.

This is the first study to attempt to correlate pre-operative pathologic markers in UPSC with post-operative tumor specimens. Her2/neu also correlated well and while Her2/neu positivity was somewhat higher in our study than previously described in USC, this marker is known to be subject to significant variation in staining and interpretation both within and between specimens, and what constitutes positive and negative is not defined for USC(Mentrikoski and Stoler, 2014; Buza et al., 2013). In our study positive was defined as at least 1+ staining for both intensity and extent of staining as qualitative scoring/reporting of immunopositivity is standard practice. This marker deserves further investigation and perhaps standardization of what constitutes Her2/neu positivity particularly given that Herceptin, a Her2/neu receptor blocker, has recently been shown to improve progression free survival when combined with standard chemotherapy in women with advanced or recurrent USC[17]. *phospho*-AKT, ER, PR and EGFR showed a more variable staining patterns and lower correlation between biopsy and hysterectomy specimens. This could be due to a relatively low sample size, to variation within the tumor or to biomarker degradation over time in older specimens. For many of our tumor specimens, biopsy specimens were only available as slides obtained from outside institutions and tumor sampling was incomplete, which may have altered these observations if significant tumor heterogeneity was present. This does reflect clinical practice and clinical trial enrollment, however, with referral to tertiary care centers for specialized treatment. A larger tumor biopsy specimen may be less susceptible to tumor heterogeneity and procure more tissue for testing; uterine curettage may potentially be more useful in guiding neoadjuvant therapy than a standard office endometrial biopsy. Additionally one of the limitations of our study was the fact that we only had one pathologist review and score the stained slides.

Furthermore, when biopsy and hysterectomy specimens are both able to be stained, they agree and thus we can presume that the pre-operative biopsy or D&C is reasonably accurate. However, in six of our cases at least one biomarker was unable to be stained and in three cases none of the biomarkers were able to be stained on the pre-operative specimens. This may be due to tissue processing and the fact that this study was retrospective, and samples had been collected and processed 1–4 years prior and many in outside labs. It is possible that if specimens were tested for molecular markers at the time of initial processing, more consistent staining for these markers would result.

Clearly more work is needed to standardize IHC for these markers in gynecologic cancers. However, this is an exciting area of study with considerable growth in the future to allow for better treatment planning, expanded treatment options, and hopefully, improved patient survival outcomes. New treatment paradigms may also allow for treatment of advanced stage patients with targeted neoadjuvant therapies, improving symptom control and helping to minimize surgical morbidity. Although we do not yet understand the extent to which biomarker positivity may be able to predict response to targeted treatments such as inhibitors of the PI3K/mTOR pathway or Her2/neu receptor, our results lay the groundwork for future study.

None of the authors have any potential conflicts of interest to report.

Author Contributions: Drs. Lokich and Mathews were involved with study design, data analysis and writing of the manuscript. Dr. Kole was involved with data analysis and writing of the manuscript. Dr. Raker performed statistical analysis and helped with editing of the manuscript. Dr. Quddus performed all pathologic studies and interpretation and helped with editing of the manuscript.

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