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Detection and correlation of pre-operative, frozen section, and final pathology in high-risk endometrial cancer

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Summary

Purpose: To evaluate sensitivity and specificity of pre-operative and frozen section pathologic evaluation (FSA) in predicting high-risk (HR) histology endometrial cancer. *Materials and Methods:* A retrospective analysis was performed on all patients diagnosed with endometrial cancer at a single institution. Medical records were abstracted for baseline characteristics, surgical reports for staging, and final histology was confirmed by a gynecologic pathologist. *Results:* 868 patients were identified. Of these, 118 had Grade 3 endometrioid, 36 clear cell carcinoma (CCC), 47 carcinosarcoma (CS), and 84 uterine papillary serous carcinoma (UPSC) histology. Endometrial biopsy (EMB) had an overall sensitivity of 90%, 77% for low grade, 78% for HR, with a specificity of 0%. For dilation and curettage (D&C), overall sensitivity was 85%, 69% for low grade, and 77% for HR. Specificity was 33%. Sensitivities for combined pre-operative testing for G3 endometrioid, CCC, CS, and UPSC were: 56%, 28%, 72%, and 60%, respectively. For frozen section analysis (FSA), overall sensitivity was 77%, and 67% for low and high grade. For G3 endometrioid, CCC, CS, and UPSC, sensitivities were 57%, 20%, 74%, 32%, respectively. Specificity was 95%. FSA identified an additional six patients (8%) with UPSC, CCC or CS that were pre-operatively low risk, providing an 8% improvement in sensitivity but decreased specificity. *Conclusions:* Pre-operative EMB and D&C are overall very sensitive for detecting endometrial cancer; however, sensitivity decreases with HR histology. Pre-op testing will miss 28% of HR diagnoses and FSA provides an opportunity to identify some patients with UPSC, CCC, and CS. If pre-operative results suggest HR cancer, the surgeon should proceed with comprehensive surgical staging without an FSA.

Key words: D&C; Pipelle; Frozen section; Endometrial cancer.

Introduction

Endometrial cancer is the most common gynecologic malignancy with 52,630 new cases and 8,590 deaths in the United States in 2014 [1]. The incidence of endometrial cancer is rising, particularly as the obesity rate rises in this country. The gold standard for diagnosing endometrial cancer is a dilation and curettage (D&C), although it has largely been replaced by the Pipelle endometrial biopsy (EMB), which is a simpler in-office procedure. Several studies have demonstrated an equivalent ability to detect malignancy. Dijkhuizen *et al.* reviewed nearly 8,000 patients, comparing tissue obtained from Pipelle EMBs and D&Cs to final hysterectomy specimens for a diagnosis of malignancy, and found a 99% and 91% detection rate in postmenopausal and premenopausal women, respectively [2].

However, there is limited data on the ability of pre-operative sampling or frozen section analysis (FSA) methods to accurately predict high-risk (HR) histology on final hysterectomy specimens. In a retrospective review of 360 patients, Huang *et al.* published a 99% sensitivity for detecting HG disease with a Pipelle and 100% sensitivity with a D&C when compared to the final surgical specimens [3]; however the role of FSA was not addressed. The objective of this study was to evaluate sensitivity and specificity of both pre-operative testing (EMB and D&C) and FSA in predicting HR histology endometrial cancer.

Materials and Methods

Following IRB approval, the authors performed a retrospective analysis of all patients with endometrial cancer between January 2001 to December 2009. Electronic medical records were abstracted for baseline characteristics including demographics, presentation, method of diagnosis, and surgical procedure performed. All surgeries were performed by a Board-Certified gynecologic oncologist. Pathology reports were reviewed for pre-operative diagnosis including grade and/or histology, intra-operative frozen analysis, and final analysis. In all cases, final histology was confirmed by gynecologic pathologists. SAS v. 9.2 statistical software was used. Using the final surgical pathology as the gold standard, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for EMB, D&C and FSA were computed.

Results

There were 868 patients identified with endometrial cancer. Twenty-eight patients had benign final pathology, and five were unstaged as they were determined not to be operable candi-

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Table 1. — *Breakdown of patients by stage and histology according to final histopathology.*

Stage	G1 Endo	G2 Endo	G3 Endo	CCC	CS	UPSC	Total
1A	213	211	62	23	20	36	565
1B	14	61	36	6	12	17	146
II	8	32	15	6	7	15	83
III	1	8	3	1	5	10	28
IV	0	2	2	0	3	6	13
Total	236	314	118 (14%)	36 (4%)	47 (6%)	84 (10%)	835

Table 2. — *Summary of detection rates of pre-operative sampling for each grade and histology.*

	FINAL PATHOLOGY						
	LG		HG				
EMB/D&C	G1	G2	G3	CCC	CS	UPSC	Total
G1	50/27	40/22	3/1	2/0	1/0	1/0	97/50
G2	13/8	56/33	13/4	2/0	0/0	4/3	88/48
G3	2/2	7/9	25/16	0/1	5/2	7/2	46/32
CCC	1/0	4/2	2/0	5/4	0/0	2/2	14/8
CS	0/1	0/0	1/0	0/0	19/2	0/1	20/4
UPSC	1/1	2/3	1/4	3/0	2/0	25/12	34/20
Total	176 / 108		123 / 54				
Sensitivity	77% / 69%		78% / 77%				90% / 85%
	57%/ 47%	47%/ 45%	56%/ 57%	38%/ 67%	72%/ 50%	62%/ 55%	
Pre-op Sensitivity	53%	30%	56%	26%	72%	60%	
Specificity	0%						

dates, leaving 835 patients in the final analysis; 118 (14%) had Grade 3 endometrioid, 36 (4%) had clear cell carcinoma (CCC), 47 (6%) had carcinosarcoma (CS), and 84 (10%) had uterine papillary serous carcinoma (UPSC) (Table 1). For all patients with endometrial cancer, 711 (82%) were Stage 1, 83 (10%) Stage 2, 28 (3%) Stage 3, and 13 (2%) Stage 4. For those with HG disease, the breakdown was: Stage 1: 212 (79%), Stage 2: 42 (15%), Stage 3: 19 (7%), and Stage 4: 11 (4%).

For pathology analysis, 338 (40.5%) of patients had an EMB, 197 (23.6%) had a D&C, and 630 (75.4%) had a FSA. Sensitivities for EMB and D&C were 77% and 69% for LG and 87% and 77% for HG, respectively (Table 2). For G3, CCC, CS, and UPSC, the sensitivities for EMB and D&C were 56% / 57%, 38% / 67%, 72% /50%, and 63% / 55%, respectively. The combined sensitivities for pre-operative sampling of these HG histologies were 56%, 26%, 72%, and 60%, respectively. The overall sensitivity for malignancy was 90% for EMB and 85% for D&C; specificity was 0%.

The overall sensitivity of FSA was 67% for both LG and HG. For each G3, CCC, CS, and UPSC, the sensitivities were 57%, 20%, 74%, and 32%, respectively. The overall specificity of FSA was 95% (Table 3).

Table 3. — *Summary of detection rates of frozen section analysis for each grade and histology.*

	FINAL PATHOLOGY						
	LG		HG				
FROZEN	G1	G2	G3	CCC	CS	UPSC	Total
G1	81	62	4	2	1	2	153
G2	18	12	19	6	0	13	168
G3	1	10	46	10	8	17	92
CCC	0	1	2	5	0	0	8
CS	0	0	0	0	25	0	25
UPSC	0	2	2	0	0	19	23
Total	410		199				
Sensitivity	67%		67%				77%
	42%	52%	57%	20%	74%	32%	
Specificity	95%						

Table 4. — *Sensitivity and Specificity of pre-operative sampling and FSA for CCC, CS, and UPSC.*

Pre-op Screen Alone	Path Results		
	Positive	Negative	Total
Positive	55	15	70
Negative	21	292	313
Total	76	307	383
Sensitivity	72.37%		
Specificity	95.11%		
PPV	78.57%		
NPV	93.29%		
Accuracy	90.60%		

Only frozen on pre-op negatives to catch False Negatives

Pre-op + Frozen Screen	Path Results		
	Positive	Negative	Total
Positive	61	19	80
Negative	15	288	303
Total	76	307	383
Sensitivity	80.26%		
Specificity	93.81%		
PPV	76.25%		
NPV	95.05%		
Accuracy	91.12%		

In a subset analysis of CCC, CS, and UPSC, the sensitivity for pre-operative screening alone was 72%, and specificity was 95% (Table 4). When a FSA was combined with the pre-operative sampling, an additional six patients were identified to have HG histology, which would have been missed by the initial testing alone. The sensitivity improved to 80% but specificity decreased to 93% (Table 5).

Discussion

In the present study, we found that pre-operative EMB and D&C are sensitive for diagnosing endometrial cancer, in-

Table 5. — *The ten patients where FSA identified patients with true high grade histology but pre-op testing was low grade.*

Patient	Pre-op Histology	Frozen Histology	Frozen DOI	Final Histology
1	G3 Endo	UPSC	<50%	UPSC
2	G1 Endo	CS	>50%	CS
3	G3 Endo	CS	None	CS
4	G3 Endo	CS	>50%	CS
5	G3 Endo	CS	None	CS
6	Benign	CCC	>50%	CCC
7	G1 Endo	CCC	>50%	G3 Endo
8	G3 Endo	UPSC	>50%	G3 Endo
9	G2 Endo	UPSC	<50%	G2 Endo (DOI >50%)
10	G1 Endo	UPSC	<50%	G2 Endo (DOI <50%)

Table 6. — *Summary of the literature on the role of FSA in endometrial cancer.*

Author	Year	Findings
Quinlivan [7]	2001	• 88.6% accuracy for grade • 5% suboptimal surgery based on FSA
Frumovitz [8]	2004	• If no invasion - inaccurate in 72% of cases • 26% of FS with DOI <50% will be upstaged
Case [9]	2006	• 28% upgraded, 46% if no invasion • 58% correlation for grade • Clinically relevant upgrading 11%
Celik [5]	2008	• 68-98% concordance • Pre-op: 95% accuracy for histology, 90% grade • FSA: 92% accuracy for grade, 98% accuracy for histology, 43% sensitivity for pre-op and intra-op assessments
Turan [10]	2012	• 89% concordance overall, decreases with grade
Mariani [6]	2012	• 97.8% accuracy rate (Mayo: "gold standard")

cluding those with HG disease. The overall detection rate for HR histology was 78%. CS had the highest sensitivity followed by UPSC, G3 endometrioid, and CCC. Furthermore, the authors determined that pre-operative sampling was equivalent to FSA for CS and G3 endometrioid, but has a higher detection rate for UPSC and CCC. However, pre-operative testing alone will miss 28% of HR diagnoses, and FSA provides an opportunity to identify those patients with UPSC, CCC, and CS, although limited at 8%.

The distribution of each histologic subtype was as expected. The rates of G3 endometrioid, UPSC, CS, and CCC were all similar to the published data of the distribution of the disease [4]. The incidence of UPSC is approximated to be 10%, CCC: 4%, and CS: 4%.

The present sensitivities for detection of LG and HG were lower when compared to published data. Huang *et al.* found a 99% and 100% sensitivity for HG on EMB and D&C, respectively, and 94% and 97% for LG on EMB and D&C [3]. Celik *et al.* found a 95% pre-operative accuracy rate for histology and 90% for grade in all endometrial cancers [5]. This may be attributed to variation in the present pre-operative sampling methods as they are often done at outside facilities, and oncology cases are subsequently referred to our institution.

The variation in accuracy and limitations of FSA are well-established in the literature (Table 6). Mariani *et al.* found a 97.8% accuracy rate for determining grade and histology at the Mayo Clinic [6]. However, several other studies from various institutions were not as favorable. Quinlivan *et al.* found an 88.6% accuracy for grade and a 5% rate of suboptimal surgical management based on FSA [7]. Frumovitz *et al.* found inaccuracies in 72% of cases in which there was no invasion, and that 26% of FSA with a depth of invaion (DOI) less than 50% will be upstaged [8]. Similarly, in a blinded analysis, Case *et al.* found a 58% correlation for grade, and 28% of all patients were upgraded on final and of those with no invasion, 46% were upgraded. There was a clinically relevant rate of 11% in those who were upgraded [9]. Celik *et al.* documented a 92% accuracy rate for grade and 43% sensitivity rate for detecting endometrial cancer on FSA, which they attributed to a lower detection rate of those with G3 [5].

The variation in FSA accuracy, particularly in endometrial adenocarcinoma, has been attributed to the number of sections obtained by the pathologist. Fanning *et al.* [11] recommended a minimum of four sections be obtained with a 95% accuracy rate for DOI. Kucera *et al.* found an 80% rate with three sections performed in Stage 1 endometrioid carcinoma [12]. With only one to two sections obtained, the rate decreases to 72% [13]. The concern with FSA in HG disease is the failure to notice focal tumor zones. At the present institution, only one section is performed, and this may attribute to the present lower sensitivity for detecting HG cancer. Additionally, whereas all the present pre-operative and final hysterectomy pathology are reported by a gynecologic pathologist, some of the FSAs are interpreted by non-gynecologic pathologists, which may also contribute to the lower sensitivities.

Because pre-operative testing alone will miss 28% of HR diagnoses, we recommend that FSA be considered in cases that the pre-operative assessment indicates LG histology for determining the role of comprehensive surgical management. If pre-operative results suggest HR cancer, the surgeon should proceed with comprehensive surgical staging, including lymph node dissection without an FSA. In fact, an Society of Gynecologic Oncology (SGO) survey found that only 31% of gynecologic oncologists frequently rely on FSA for intra-operative decision-making [14]. In these cases, FSA does not provide additional useful information, and increases the operative time and cost.

One of the strengths of this study is that to our knowledge, it is the largest series to elucidate the challenges in identifying HR histology. It is also the first study to report the utility of both pre-operative and intra-operative pathologic assessment in predicting individual HR histologies. The data is also relevant to those practicing where FSA is not readily available, and surgeons can appropriately rely on pre-operative testing for their surgical planning. Additionally, all of the present pre-operative samples were compared to final hysterectomy specimens and thus had an internal control. As this was a single institution study, there was improved consistency in final pathology reporting, minimizing inter-observer variability, which has been reported to be as high as 40% in the GOG 167 study [15].

Moving forward, the potential role of MRI, CA-125, and HE4 for improved prediction of HR endometrial cancer may be clarified, and the role of sentinel lymph node biopsy will need further exploration as to its intra-operative benefit. Tumor profiling and genomic analysis of preoperative biopsies may also play a role in clarifying which patients may require comprehensive staging.

Conclusion

Pre-operative EMB and D&C are both sensitive methods for diagnosing endometrial cancer, including those with HG disease. However, pre-operative testing will miss a portion of high grade cases, and in certain circumstances frozen section may provide additional clinical benefit.

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