ONCOLOGY

Accuracy of preoperative endometrial sampling for the detection of high-grade endometrial tumors

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OBJECTIVE: This study was undertaken to evaluate the ability of preoperative endometrial sampling to accurately diagnose high-grade endometrial tumors.

STUDY DESIGN: Three hundred sixty endometrial cancer patients had preoperative endometrial sampling and hysterectomy specimens that underwent pathologic review at a single institution from 1995 to 2005. The sensitivity of Pipelle and curettage to diagnose high-grade endometrial tumors (grade 3 endometrioid adenocarcinoma, serous carcinoma, carcinosarcoma, clear cell carcinoma) was determined. Agreement between preoperative and hysterectomy diagnoses was measured by the Kappa statistic.

RESULTS: Sensitivity of Pipelle and curettage was 93.8% and 97% in patients with low-grade cancer and 99.2% and 100% in patients with high-grade cancer. Good agreement was observed between the preoperative and the hysterectomy histologic diagnoses (Kappa = 0.69), and between the preoperative and hysterectomy tumor grade (Kappa=0.78).

CONCLUSION: Preoperative endometrial sampling with Pipelle or curettage is sensitive and accurate for the diagnosis of high-grade endometrial tumors, including tumors with nonendometrioid histology.

Key words: endometrial biopsy, endometrial carcinoma, predictive testing

Uterine cancer is the most common gynecologic malignancy in the United States with an approximately 1 in 40 lifetime risk for women.[1] Women with uterine cancer often present with

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postmenopausal, perimenopausal, or irregular vaginal bleeding. Pipelle endometrial biopsy is a useful office procedure for the assessment of patients with abnormal uterine bleeding. It is a minimally invasive outpatient procedure that is less expensive and less time-consuming compared with curettage with or without hysteroscopy. Pipelle is the most accurate device for office endometrial sampling, compared with other devices (Vabra, Novak) or methods (lavage).[2] However, the impact of histologic type and grade on the accuracy of Pipelle is unknown. Very few studies in the literature have evaluated Pipelle biopsy by using the gold standard of hysterectomy for determining the accuracy of the biopsy results.[3-7] All these studies were limited by small numbers of patients with endometrial cancer, ranging from only 4 to a maximum of 65 patients. Moreover, none of the studies reported data on patients with nonendometrioid histology.

Although endometrioid adenocarcinoma (EA) is the most common histologic type of endometrial cancer, nonendometrioid types of endometrial cancer have a higher propensity for early metastasis and aggressive clinical behavior. These high-grade (HG) tumors include uterine papillary serous carcinoma (UPSC), carcinosarcoma (CS), and clear cell carcinoma (CCC). In contrast with well-differentiated endometrioid tumors, which are estrogen-driven and typically arise in the setting of hyperplastic endometrium, HG endometrial tumors are often estrogen-receptor negative and may arise from an atrophic endometrium.[8] In addition, UPSC and CS frequently arise from endometrial polyps.[9,10] These characteristics of HG tumors raise the concern about the accuracy of endometrial sampling using Pipelle or curettage. For example, the ability to obtain an adequate endometrial sample by Pipelle can be adversely affected by an endometrial thickness less than 5 mm.[11] False-negative Pipelle results also occur when tumors are localized to a polyp or a small surface area of the endometrium.[5] Curettage similarly has a poor detection rate for focal lesions, with reported failure rates of 38% to 100%.[12]

The accuracy of endometrial sampling in the diagnosis of HG uterine tumors is unknown. Accurate and early detection

	Unstaged	I	II	III	IV	Total
G1-G2 EA	24	162	11	8	2	207
G3 EA	3	17	2	2	3	27
CS	0	20	4	12	11	47
UPSC	5	31	5	11	15	67
CCC	1	5	1	3	2	12
Total	33	235	23	36	33	360

of HG tumors may be beneficial for allowing the benefit of maximal surgical intervention before extrauterine spread occurs. In addition, the detection of HG tumors would increase the likelihood of referral to a gynecologic oncologist. Conversely, a delayed diagnosis in patients with these HG subtypes may result in serious consequences, as the proportion of patients surviving 5 years significantly decreases with advancing stage.[13] The purpose of this study was to evaluate the accuracy of preoperative endometrial sampling to detect and accurately diagnose HG endometrial tumors, by using a large cohort of patients with endometrial cancer treated at a single institution.

MATERIALS AND METHODS
Institutional Review Board exemption was obtained for this retrospective study. Patients treated at Montefiore Medical Center (MMC)/Albert Einstein College of Medicine (AECOM) for endometrial cancer from 1995-2005 were identified from our tumor registry. Three hundred sixty patients' preoperative endometrial samples and hysterectomy specimens underwent pathologic review at MMC/AECOM, and all these patients were included in this study. All study patients underwent hysterectomy at MMC/AECOM, and 278 of these patients also had frozen section evaluation of the uterus at the time of surgery. From the operative and pathology reports, the extent of surgical staging was determined and the International Federation of Gynecology and Obstetrics (FIGO) stage assignment confirmed.

Preoperative diagnoses were classified as negative, complex atypical endome-trial hyperplasia (CAH), grade 1 or grade 2 (G1-2) EA, grade 3 (G3) EA, CS, UPSC, CCC, or sarcoma. Postoperative diagnoses were G1-2 EA, G3 EA, CS, UPSC, or CCC. For statistical analyses of histologic type, G1-2 EA and G3 EA were combined into a single EA group. For statistical analyses of grade assignment, the preoperative and postoperative diagnoses were categorized as either low-grade (LG) or HG. LG included G1-2 EA, and HG included G3 EA, UPSC, CS, CCC, and sarcoma.

The Kappa statistic was used to measure the agreement between the preoperative and hysterectomy diagnoses, with respect to the histology and the grade of the tumor. For comparison, the agreement between the intraoperative frozen section and postoperative diagnoses was measured by using the same method. The sensitivity for detecting malignancy and the percentage of correct prediction of HG pathology for Pipelle, curettage, and frozen section were calculated. The final postoperative diagnosis for all patients was determined by the disease of the hysterectomy specimen.

RESULTS
Surgery and staging
The extent of surgical staging was as follows: 100% (360/360) of patients had total hysterectomy; 97.2% (350/360) of patients had bilateral salpingo-oophorectomy; 96.7% (348/360) of patients had peritoneal cytology; 90.8% (327/360) of patients had lymph node sampling, and 15.8% (57/360) had omental sampling. The distribution of FIGO surgical stage and histologic type on final pathology is shown in Table 1. Nonendometrioid histologic types were well represented in the study population and accounted for 35% (126/360) of the patients. The percentage of patients with advanced stage (III/IV) disease was lower in patients with EA, occurring in 5.5% and 20.8% of G1-2 EA and G3 EA patients, respectively. As expected, advanced stage disease was much more common in patients with nonendometrioid histology, occurring in 49%, 42%, and 45% of patients with CS, UPSC, and CCC, respectively. The omental sample was positive for carcinoma in 2 of 15 (13.3%) of the patients with LG cancer and 16 of 42 (38%) of the patients with HG cancer. In 9 of 153 (6%) of patients with HG cancer, the carcinoma was confined to an endometrial polyp without evidence of myometrial invasion.

Sensitivity of preoperative sampling to detect endometrial malignancy
The preoperative endometrial sample was compared with the final pathology (Table 2). In 349 of 360 patients, the preoperative endometrial sample detected a malignancy, yielding an overall sensitivity for detection of endometrial cancer of 96.9%. In 11 patients, the endometrial sampling failed to detect a malignancy; 5 of these patients had a preoperative diagnosis of CAH and 6 patients had a negative endometrial sample. All the patients falsely diagnosed with CAH were postmenopausal, and none had available pelvic ultrasound results. The overall sensitivity for the detection of endometrial malignancy was 95.2% in patients with LG cancer and 99.3% in patients with HG cancer.

Comparison of Pipelle vs curettage for the detection of endometrial malignancy
For the comparison of Pipelle vs curettage, 346 patients were included, of whom 253 patients underwent Pipelle and 93 patients underwent curettage. The method of endometrial sampling was not available for 14 patients. Comparison of Pipelle vs curettage revealed a sensitivity of 96.4% for pipelle vs 97.8% for curettage in the detection of cancer. Of the 9 patients with false-negative endometrial sampling by Pipelle, the final

TABLE 2
Preoperative sampling histology compared with final pathology

| Pre-operative Sample | Final pathology | | | | | | Total |
| | LG | | HG | | | | |
	G1 EA	G2 EA	G3 EA	CS	UPSC	CCC	
Negative	5 4P/1C	0	1 1P	0	0	0	6
CAH	5 4P/1C	0	0	0	0	0	5
G1 EA	120	21	3	4	2	1	151
G2 EA	21	28	9	0	1	0	59
G3 EA	1	3	10	0	14	0	28
CS	0	1	2	26	0	0	29
UPSC	0	1	1	0	49	0	51
CCC	1	0	1	0	1	11	14
Sarcoma	0	0	0	17	0	0	17
Total	153	54	27	47	67	12	360

P, pipelle; *C*, curettage.

diagnosis was G1 EA in 8 patients and G3 EA in 1 patient. Of the 2 patients with false-negative endometrial sampling by curettage, the final diagnosis was G1 EA for both. The sensitivity for the detection of malignancy by Pipelle was 93.8% in patients with LG cancer and 99.2% in patients with HG cancer. The sensitivity for the detection of malignancy by curettage was 97% in patients with LG cancer and 100% in patients with HG cancer.

Prediction of histologic type and grade by endometrial sampling
The final histology was EA (G1, G2, or G3) in 234 patients, CS in 47 patients, UPSC in 67 patients and CCC in 12 patients. Endometrial sampling predicted the correct histologic diagnosis in 302 of 360 (83.9%) of patients (Table 2). The endometrial sample histology showed good agreement with the final hysterectomy specimen histology (Kappa = 0.69). The corresponding Kappa statistics for patients who underwent sampling by curettage or Pipelle was 0.81 vs 0.66, respectively.

The final pathology was categorized as HG in 153 patients (42.5%) of whom 132 (86.3%) patients had a concordant HG endometrial sample. Of the remaining 21 patients, 20 patients had a G1-2 EA endometrial sample, and 1

patient had a false-negative sample. Two hundred seven patients had LG cancer on final pathology, of whom 190 patients (91.8%) had a LG endometrial sample. Seven of the LG patients had a HG endometrial sample, and 10 had CAH or a negative sample. The preoperative sample was lower grade than the final pathology in 20 of 360 (5.6%) and CAH or negative in 11 of 360 (3.1%) of patients. The preoperative sample was higher grade than final pathology in 7 of 360 (1.9%) of patients. There was excellent agreement between the grade of the preoperative sample and the tumor grade at final histologic diagnosis (Kappa = 0.78). The corresponding Kappa statistics for patients who underwent sampling by D&C or Pipelle was 0.87 vs 0.75, respectively. Among patients with a HG preoperative endometrial sample, 46% had UPSC and 31% had CS on final pathology (Table 2).

In 95% of patients with a HG preoperative sample, HG cancer was confirmed on final pathology. In 90.5% of patients with a LG preoperative sample, LG cancer was confirmed on final pathology, whereas the remaining 9.5% had HG cancer on final pathology. The results when analyzing Pipelle

and curettage separately are summarized in Table 3.

Accuracy of frozen section diagnosis
Frozen section predicted the correct final histologic type in 224 of 278 (80.6%) of patients, compared with 80.2% by Pipelle and 92.5% by curettage (Table 3). For patients who had frozen section evaluation, the final pathologic diagnoses were HG in 109 patients, of whom 94 patients (86.2%) had a HG frozen section, 6 patients (5.5%) had a false-negative frozen section, and 9 patients (8.3%) had a LG frozen section. The final pathology was LG in 169 patients, of whom 155 patients (91.7%) had a LG sample, 3 patients (1.8%) had a false-negative frozen section; whereas, 11 patients (6.5%) had a HG sample. The frozen section diagnosis was lower grade than the final pathology in 9 of 278 (3.2%) of patients, and negative or CAH in 9 of 278 (3.2%). The frozen section diagnosis was higher grade than the final pathology in 11 of 278 (4.0%) of patients.

Preoperative sampling and frozen section had similar accuracy ($P = .39$ by χ^2 analysis), when compared with the final pathology with regard to histologic type and tumor grade (Table 3).

TABLE 3
Comparison of the accuracy of endometrial sampling vs frozen section

	Curettage n = 93	Pipelle n = 253	Frozen section n = 278
Concordant histology and grade with final pathology	75 (80.6%)	159 (62.8%)	179 (64.4%)
Concordant histologic type with final pathology	86 (92.5%)	203 (80.2%)	224 (80.6%)
Concordant grade with final pathology	88 (94.6%)	221 (87.4%)	249 (89.6%)
Lower grade than final pathology	2 (2.2%)	17 (6.7%)	9 (3.2%)
Hyperplasia or negative compared with final pathology	2 (2.2%)	9 (3.6%)	9 (3.2%)
Higher grade than final pathology	1 (1.1%)	6 (2.4%)	11 (4.0%)
Sensitivity of detecting HG final histology	92.3%	85.7%	86.1%
Positive predictive value of a HG sample	96%	94.6%	89.5%

Eighty-two of 360 patients (23%) did not have frozen section evaluation at the time of surgery. The decision to perform frozen section was at the discretion of the attending physician. A comparison of the grade distribution for patients who did and those who did not have frozen section reveals a trend ($P = .06$) toward higher grade tumors in the group who did not have frozen section. A comparison of the histologic type distribution demonstrated that the group not having frozen section was overrepresented by nonendometrioid types ($P < .01$ by χ^2 analysis). Therefore, patients with a HG diagnosis preoperatively, in whom the frozen section would be unlikely to affect the intraoperative management, were less likely to undergo frozen section evaluation intraoperatively.

COMMENT

Pipelle is a convenient and acceptable outpatient method for evaluating abnormal uterine bleeding.[2] However, its use for detecting HG endometrial tumors has not been previously described in the literature. In the current study, we found that preoperative endometrial sampling by Pipelle or curettage was sensitive and accurate for the diagnosis of HG endometrial tumors, including nonendometrioid histologic types.

The fact that many HG tumors are not estrogen driven and may arise in an atrophic endometrium or a polyp may, hypothetically, adversely impact the ability of Pipelle to detect these cancers. However, we found that the Pipelle demonstrated a sensitivity of 99.2% in patients

with HG cancer, compared with 93.8% in patients with LG cancer. This was comparable to the sensitivity of curettage, which was 100% in patients with HG cancer and 97% in patients with LG cancer. In addition, we observed excellent agreement between the preoperative histology and grade and the final pathology.

The accuracy of preoperative endometrial sampling was similar to the frozen section in predicting the final pathology. Frozen section did not appear to add clinically useful information in the majority of the patients, suggesting that the additional cost and time associated with performing a frozen section might be avoided in patients with HG endometrial tumors diagnosed by their preoperative endometrial sampling. In fact, we already observed a trend in clinical practice in which patients with HG tumors diagnosed preoperatively were less likely to have intraoperative frozen section requested by the attending physician. Because a 29-52% incidence of endometrial cancer has been reported in women with CAH on preoperative sampling, frozen section may be useful to identify an invasive cancer in these patients, particularly in postmenopausal patients.[14-19]

We identified 6 patients who were found to have endometrial cancer on their hysterectomy specimens, despite having had negative preoperative endometrial sampling. Four of these patients had persistent postmenopausal bleeding in conjunction with abnormal imaging findings, which included a complex adnexal mass in 2 patients, a complex uter-

ine mass in 1 patient, and marked thickening of the endometrial echo to greater than 20 mm in 1 patient. Clearly, the high sensitivity of endometrial sampling to detect a malignancy does not obviate the need for definitive surgery in patients whose further evaluation demonstrates highly abnormal findings. The other 2 patients presented with postmenopausal bleeding with uterine enlargement and leiomyomata.

Of note, we found that preoperative endometrial sampling more often underestimated rather than overestimated the grade of final pathology. Of patients with a HG preoperative sample, 95% of these patients' final pathology was indeed HG. In addition, approximately 10% of patients with a LG preoperative sample were subsequently found to have a HG tumor on final pathology. Furthermore, the majority of patients with a HG preoperative endometrial sample were found to have a nonendometrioid histologic type on final pathology. These cancers have a propensity for extrapelvic metastases. More than one third of our patients with HG endometrial cancer presented with extrauterine disease. In addition, the subset of HG patients who underwent omental sampling during their initial surgery had a 38% incidence of omental metastases, thereby supporting the concept of extended surgical staging in patients with HG endometrial pathology on the preoperative endometrial sampling, as has been proposed by others.[8,20-22] These findings substantiate the importance of involving a gynecologic oncologist in the management of all

patients with a preoperative diagnosis of endometrial cancer.

The strengths of the current study include the large cohort size, the inclusion of a substantial number of patients with nonendometrioid tumor types, and the consistency afforded by a single institution study. A limitation of this study design is the possibility that some patients undergoing Pipelle or curettage could have had a subsequent hysterectomy performed at an outside facility, which could result in a discrepancy between the calculated sensitivity and actual sensitivity of endometrial sampling. However, our institution is by far the dominant health care provider in its service area— Bronx and southern Westchester—and the existing practice pattern is for generalists to refer patients within our institution. Moreover, the gynecologic oncologists employed by this institution do not routinely perform surgeries at outside facilities, which further decreases the likelihood of patients being excluded from the study because of having surgery elsewhere.

This is the first study to comprehensively evaluate the sensitivity and accuracy of preoperative endometrial sampling in patients with HG and nonendometrioid tumor types. Our results demonstrate that Pipelle performs well for the detection of these cancers, with a sensitivity that compares favorably with the sensitivity in patients with EA. In addition, our findings define the accuracy of the endometrial sample in predicting the final histology and grade, which may be useful for guiding the preoperative counseling and management of patients undergoing surgery for endometrial cancer. ■

REFERENCES
1. Cancer facts and figures. American Cancer Society; 2006.
2. Dijkhuizen FP, Mol BW, Brolmann HA, Heintz AP. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis. Cancer 2000;89:1765-72.
3. Antoni J, Folch E, Costa J, et al. Comparison of cytospat and pipelle endometrial biopsy instruments. Eur J Obstet Gynecol Reprod Biol 1997;72:57-61.
4. Ferry J, Farnsworth A, Webster M, Wren B. The efficacy of the pipelle endometrial biopsy in detecting endometrial carcinoma. Aust N Z J Obstet Gynaecol 1993;33:76-8.
5. Guido RS, Kanbour-Shakir A, Rulin MC, Christopherson WA. Pipelle endometrial sampling: sensitivity in the detection of endometrial cancer. J Reprod Med 1995;40:553-5.
6. Stovall TG, Photopulos GJ, Poston WM, Ling FW, Sandles LG. Pipelle endometrial sampling in patients with known endometrial carcinoma. Obstet Gynecol 1991;77:954-6.
7. Zorlu CG, Cobanoglu O, Isik AZ, Kutluay L, Kuscu E. Accuracy of pipelle endometrial sampling in endometrial carcinoma. Gynecol Obstet Invest 1994;38:272-5.
8. Jordan LB, Abdul-Kader M, Al-Nafussi A. Uterine serous papillary carcinoma: histopathologic changes within the female genital tract. Int J Gynecol Cancer 2001;11:283-9.
9. Bague S, Rodriguez IM, Prat J. Malignant mesonephric tumors of the female genital tract: a clinicopathologic study of 9 cases. Am J Surg Pathol 2004;28:601-7.
10. Trahan S, Tetu B, Raymond PE. Serous papillary carcinoma of the endometrium arising from endometrial polyps: a clinical, histological, and immunohistochemical study of 13 cases. Hum Pathol 2005;36:1316-21.
11. Elsandabesee D, Greenwood P. The performance of Pipelle endometrial sampling in a dedicated postmenopausal bleeding clinic. J Obstet Gynaecol 2005;25:32-4.
12. Epstein E, Valentin L. Managing women with post-menopausal bleeding. Best Pract Res Clin Obstet Gynaecol 2004;18:125-43.
13. Hamilton CA, Cheung MK, Osann K, et al. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. Br J Cancer 2006;94:642-6.
14. Trimble CL, Kauderer J, Zaino R, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer 2006;106:812-9.
15. Horn LC, Schnurrbusch U, Bilek K, Hentschel B, Einenkel J. Risk of progression in complex and atypical endometrial hyperplasia: clinicopathologic analysis in cases with and without progestogen treatment. Int J Gynecol Cancer 2004;14:348-53.
16. Hunter JE, Tritz DE, Howell MG, et al. The prognostic and therapeutic implications of cytologic atypia in patients with endometrial hyperplasia. Gynecol Oncol 1994;55:66-71.
17. Janicek MF, Rosenshein NB. Invasive endometrial cancer in uteri resected for atypical endometrial hyperplasia. Gynecol Oncol 1994;52:373-8.
18. Kurman RJ, Kaminski PF, Norris HJ. The behavior of endometrial hyperplasia: a long-term study of "untreated" hyperplasia in 170 patients. Cancer 1985;56:403-12.
19. Widra EA, Dunton CJ, McHugh M, Palazzo JP. Endometrial hyperplasia and the risk of carcinoma. Int J Gynecol Cancer 1995;5:233-5.
20. Saygili U, Kavaz S, Altunyurt S, Uslu T, Koyuncuoglu M, Erten O. Omentectomy, peritoneal biopsy and appendectomy in patients with clinical stage I endometrial carcinoma. Int J Gynecol Cancer 2001;11:471-4.
21. Quinlivan JA, Petersen RW, Nicklin JL. Accuracy of frozen section for the operative management of endometrial cancer. BJOG 2001;108:798-803.
22. Kristensen G, Trope C. Endometrial cancer: the management of high-risk disease. Curr Oncol Rep 2004;6:471-5.