Original Article on Endometrial Cancer

Impact of endometrial sampling technique and biopsy volume on the diagnostic accuracy of endometrial cancer

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Background: Histotype and tumor grading of endometrial cancer are the most important factors that have to be assessed by preoperative endometrial sampling, and their concordance with the final surgical and definitive histological findings is of paramount importance. We aim to compare histotype and tumor grading concordance of various endometrial sampling techniques (ESTs) and to investigate the role of endometrial volume biopsy.

Methods: We performed a retrospective analysis of patients with apparent early stage endometrial cancer collecting demographic, clinical data, type of EST, pathological characteristics of endometrial biopsies and final specimens. We classified ESTs as dilation and curettage (D&C), diagnostic hysteroscopy with D&C, outpatient hysteroscopy and operative hysteroscopy with or without D&C. Diagnostic and operative hysteroscopy were performed with Bettocchi's 5 mm hysteroscope. We evaluated concordance for histotype, and tumor grading, and we performed subgroup analysis based on the technique and final tumor grading. Concordance was classified from good, moderate, sufficient, fair, poor and none using Cohen k-statistic. Finally, we investigated the existence of independent risk factors for discordant tumor grading using multivariate binary logistic regression.

Results: We collected 148 patients and of these 131 (88.5%) were diagnosed with endometrioid histotype and 65 (44%), 46 (31%) and 37 (25%) respectively with well, moderate and poor differentiated tumors. Atypical hyperplasia (AH) was detected preoperatively in 28 patients (19%). Histotype concordance was fair (k=0.35) and tumor grading concordance was moderate (k=0.45); particularly, concordance was fair in well-differentiated cases (k=0.38); concordance was moderate in moderate- and poor-differentiated cases (k=0.52) and good (k=0.71). Operative hysteroscopy showed moderate concordance for histotype (k=0.41), while grading concordance was fair for G1 (k=0.41), moderate for G2 (k=0.58) and good for G3 (k=0.72), regardless the use of D&C. Preoperative volume biopsy did not impact the concordance of tumor grading, while the adoption of operative hysteroscopy (with or without D&C) decreased the risk of grading discordance in G3 tumors (HR 0.17; 95% CI: 0.03–0.94; P=0.04). Conversely, time elapsed from diagnosis to treatment in well-differentiated tumors increased the risk of discordant results (HR 1.06; 95% CI: 1.02–1.52; P=0.04).

Conclusions: Operative hysteroscopy demonstrated the best tumor grading concordance, especially in poor-differentiated tumors. The volume of biopsy did not affect the tumor grading concordance.

Keywords: Endometrial biopsy; endometrial cancer; grading; hysteroscopy

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Introduction

Endometrial cancer is the most common gynecological malignancy in developed countries with a cumulative risk, up to seventy-five years old, equal to 1.6% (1). So far, most of these cancers are diagnosed at an early stage, with low risk of recurrence, and do not require adjuvant therapy (2). However, approximately 20% of the patients have a worse outcome in terms of recurrence and survival (3), depending on prognostic factors such as myometrial infiltration (MI), lymph nodal status, histotype and tumor grading (4). Endometrial sampling is a fundamental step in preoperative workup (5,6) and it aims to predict the two latter aforementioned factors (7), to tailor the surgical approach (8,9) and lymph nodal staging (10). In fact, the risk of under- or overestimating an endometrial malignancy can lead to a wrong therapeutic approach (11).

Unfortunately, preoperative endometrial sampling was found to be only a modest predictor of the final diagnosis (12,13). In fact, several studies compared various endometrial sampling techniques (ESTs) evaluating their concordance with the final histology (14,15) and, currently, there is not clear evidence on which EST has the better diagnostic accuracy. Moreover, many limiting factors can interfere with the choice of the EST, such as pain uterine bleeding, cervical stenosis and contraindication to general anesthesia (16-19). Occasionally, the amount of tissue obtained is so minimal that diagnosis cannot be reached and furthermore, to date, specific quantitative criteria for an adequate endometrial sample have not been established yet as a standard of care (20,21).

The aim of our study is to compare the histotype and tumor grading concordance of preoperative endometrial sampling with the final specimen of endometrial cancer across different ESTs and to investigate the impact of endometrial volume biopsy in tumor grading concordance. We present the following article in accordance with the STROBE reporting checklist.

Methods

We performed a single center mono-institutional retrospective study, using a surgical electronic database, of consecutive patients who underwent preoperative endometrial sampling and subsequent surgical treatment for endometrial cancer, from January 2014 to December 2018 at the Department of Obstetrics and Gynecology of ASST Spedali Civili of Brescia, a tertiary northeastern university hospital in Italy. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional Review Board of the hospital approved this study (Protocol number 3398) and patients signed an informed consent.

Indeed, we excluded patients underwent preoperative endometrial biopsy at external institution and subsequently referred to our hospital for staging and treatment.

We collected demographic data such as age at surgery, parity, BMI, presence of abnormal uterine bleeding (AUB) and the type of endometrial sampling. At our institution, we adopted a specific EST based on detailed criteria, according to the clinical presentation. In fact, we classified ESTs as follows: (I) dilatation and curettage (D&C), performed in case of active uterine bleeding that usually prevents the view of the cavity; (II) outpatient biopsy with 5 mm Bettocchi's hysteroscope, using either micro scissors and/or forceps (22), performed in case of anesthesiological contraindication; (III) diagnostic hysteroscopy with 5 mm Bettocchi's hysteroscope followed by D&C, performed in case no suspicious endometrial area was found for selective biopsy; (IV) operative hysteroscopy with cervical dilatation, using saline solution for uterine distention and resectoscope, performed in all the remaining cases and, finally; (V) operative hysteroscopy with cervical dilatation, performed as previously mentioned and followed by D&C, in case of subjective impression of scanty material obtained after resectoscopic biopsy. All procedures, except outpatient hysteroscopy, were performed under general anesthesia. Final surgical treatment included peritoneal cytology, hysterectomy and bilateral salpingo-oophorectomy with or without nodal staging, namely with sentinel lymph node biopsy or pelvic and/or aortic lymphadenectomy based on preoperative imaging and biopsy histology and grading. Endometrial tissue obtained by different ESTs was sampled and entirely submitted for histological examination; the sampling method included a description of the macroscopic features of the tissue (consistency, color, presence of blood cot and mucus) and measurement of its amount. Of note, a standardized and reproducible method to assess tissue amount was performed: tissue fragments obtained by biopsy were measured as a three-dimension (height, width and depth in millimeters) tissue aggregate; subsequently, a total tissue volume was calculated and expressed as cubic centimeters (cc). A detailed clinical history including patients' age, symptoms, menopausal status, date of onset of the last menstrual cycle, length of menstrual cycle, and hormonal therapy was provided for pathological evaluation.

Table 1 Clinical characteristics of the patients

Variables	n=148
Age	
Mean (range)	64.6 [21–95]
Median (IQR)	65 [57–73]
BMI	
Mean (range)	27.9 (13.9–49)
Median (IQR)	27.2 (23–31.7)
Menopause	135 (91.2%)
AUB	121 (81.8%)
DM	26 (17.6%)
Tamoxifen use	5 (3.3%)
Abnormal ultrasound findings	109 (74%)
Endometrial thickness ≥5 mm	84 (57%)
Suspicious lesion or polyp	25 (17%)
Myometrial invasion ≥50%	79 (53.4%)
Final histotype	
Endometrioid	131 (88.5%)
Non endometrioid	17 (11.5%)
Serous	8 (5.4%)
Carcinosarcoma	3 (2%)
Undifferentiated	2 (1.4%)
Other	3 (2%)
Clear cell	1 (0.7%)
Endometrial sampling techniques	
D&C	13 (8.8%)
Diagnostic hysteroscopy with D&C	17 (11.4%)
Office hysteroscopy	40 (27%)
Operative hysteroscopy	58 (39.2%)
Operative hysteroscopy with D&C	20 (13.5%)
Endometrial biopsy volume (cc)	
Mean (range)	4.5 (0.5–25)
Median (IQR)	3.5 (1.5–6)
Time from diagnosis to treatment (days)	
Mean (range)	45 [4–232]
Median (IQR)	39 [31–57]

Data is presented as n (%) where not specified. IQR, inter quartile range; BMI, body mass index; AUB, abnormal uterine bleeding; DM, diabetes mellitus; D&C, dilation and curettage; cc, cubic centimeters.

Dedicated gynecological pathologist analyzed preoperative endometrial tissue and final uterine surgical specimen and classified histological findings according to the criteria of WHO Classification of Female Genital Tract Tumors (23-25). Of note, at our Hospital Institution, the same pathologist analyzed both the preoperative biopsy and the final specimen from hysterectomy of every single case, reducing the bias of interobserver agreement in assessing tumor grade/histology. The minimum criteria adequacy for the endometrial biopsy was the presence of 10 endometrial strips for postmenopausal women (according to Sakhadari's study are sufficient to exclude a malignant process, with a negative predictive value close to 100%) and the presence of at least one intact endometrial tissue fragment containing both glands and stroma for premenopausal ones (26).

We performed standard descriptive statistic calculating sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and accuracy for histotype and tumor grading diagnosis. We evaluated the concordance for histotype and tumor grading between endometrial sampling and final histology using Cohen k-statistic. Subsequently, we performed subgroup analysis clustered for the aforementioned ESTs and for each final tumor grade, namely well (G1), moderate (G2) and poor (G3) differentiated. The conventional Choen k-value scheme was applied for agreement as follows: <0 for "none", 0–0.19 for "poor", 0.2–0.39 for "fair", 0.4–0.59 for "moderate", 0.6–0.79 for "good" and 0.8–1 for "excellent" (27). Finally, we performed a multivariate binary logistic regression to investigate the impact of various factors on tumor grading concordance between endometrial biopsy and final specimen. We included as risk factors: age, BMI, menopausal status, ultrasound endometrial thickness in millimeters, suspect of MI at ultrasound greater than 50%, the type of EST, the volume of the endometrial biopsy in cubic centimeters and time elapsed from diagnosis to treatment in days. We used IBM SPSS Statistics for Windows, Version 23.

Results

We identified 148 patients and clinical characteristics are shown in *Table 1*; of note, 135 (91.2%) patients were in menopause and 121 (81.8%) presented with AUB as initial symptom. Most of the patients underwent operative hysteroscopy (n=58; 39.2%) and office hysteroscopy (n=40; 27%), while diagnostic hysteroscopy with D&C and operative hysteroscopy with D&C were performed

Table 2 Diagnostic performance for final tumor grading

Grade	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)
G1	51	89	78	70	71
G2	65	85	67	84	79
G3	76	93	80	92	89
Mean	64	89	75	82	80

G1, grade 1; G2, grade 2; G3, grade 3; NPV, negative predictive value; PPV, positive predictive value.

Table 3 Concordant and discordant cases of tumor grading

Final tumor grading	Pre-operative tumor grading (%)				Total	k	P value
	AH	G1	G2	G3			
G1	27 (41.5)	31 (47.5)	7 (11.0)	–	65 (44.0)	0.39	<0.00
G2	1 (2.2)	8 (17.4)	30 (65.2)	7 (15.2)	46 (31.0)	0.52	<0.00
G3	–	1 (2.7)	8 (21.6)	28 (75.7)	37 (25.0)	0.71	<0.00
Total	28 (19.0)	40 (27.0)	45 (30.4)	35 (23.6)	148 (100.0)	0.46	<0.00

AH, atypical hyperplasia; G1, grade 1; G2, grade 2; G3, grade 3; k, Coehn's Kappa.

respectively in 11.4% (n=17) and 13.5% (n=20) of cases (*Table 1*). We finally diagnosed 131 (88.5%) endometrioid and 17 (11.5%) non-endometrioid carcinomas; the accuracy for endometrioid histotype is 77% (sensitivity 78%; specificity 63%; PPV 94%; NPV 30%). Subgroup analysis for each tumor grade (G1, G2 and G3) revealed a low sensitivity for well-differentiated tumor, with a mean accuracy of 80% (*Table 2*), regardless of the type of EST.

Overall concordance for histotype, regardless EST, was fair (k=0.36; SE 0.08; 95% CI: 0.08–0.41; P<0.00), given 27 patients (17.6%) with a preoperative finding of atypical hyperplasia (AH) that finally revealed an endometrioid carcinoma. On the contrary, adoption of operative hysteroscopy with or without D&C showed moderate histotype concordance (k=0.41; SE 0.096; 95% CI: 0.17–0.55; P<0.00).

Overall concordance for tumor grading (*Table 3*) was moderate (k=0.46; SE 0.05; 95% CI: 0.36–0.56; P<0.00). Subgroup analysis of grading concordance, regardless EST adopted, showed good concordance for G3 (k=0.71; SE 0.07; 95% CI: 0.57–0.84; P<0.00), moderate for G2 (k=0.52; SE 0.07; 95% CI: 0.38–0.67; P<0.00) and only fair for G1 (k=0.39; SE 0.07; 95% CI: 0.24–0.53; P<0.00). Subsequent analysis, clustered for ESTs, demonstrated a moderate tumor grading concordance for operative hysteroscopy (k=0.54; SE 0.08; 95% CI: 0.37–0.70; P<0.00) and for operative hysteroscopy with D&C (k=0.53; SE 0.14; 95% CI: 0.26–0.79; P<0.00), without any statistical difference between the groups (P=0.87). Notably, patients underwent endometrial biopsy with operative hysteroscopy (both with and without D&C) showed a moderate concordance for G1 (k=0.418; SE 0.082; 95% CI: 0.26–0.57; P<0.00) and good for G2 (k=0.62; SE 0.081; 95% CI: 0.41–0.73; P<0.00) and for G3 (k=0.721; SE 0.075; 95% CI: 0.57–0.86; P<0.00). Multivariate logistic regression analysis (*Table 4*) identified two factors influencing tumor grading concordance: time from diagnosis to treatment in G1 tumors (HR 1.06; 95% CI: 1.02–1.52; P=0.04) can slightly increase the risk of discordance, while the use of operative hysteroscopy in G3 tumors (HR 0.17; 95% CI: 0.03–0.94; P=0.04) instead reduces the chance of discordance. Interestingly, preoperative biopsy volume did not affect the chance to increase concordance for tumor grading (*Table 4*).

Discussion

Operative hysteroscopy with resectoscopic biopsy is the most reliable technique for endometrial sampling in case of suspected endometrial cancer, owing to a moderate concordance for both histotype and tumor grading. Endometrioid well-differentiated carcinoma suffer misdiagnosis, mainly due to AH at preoperative endometrial

Table 4 Multivariate logistic regression analysis of factors influencing final tumor grading concordance

Variables	Final tumor grading								
	G1			G2			G3		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age	1.05	0.98–1.11	0.132	1.01	0.96–1.07	0.693	1.03	0.96–1.10	0.46
Menopause	0.172	0.03–1.02	0.06	0.43	0.08–2.44	0.341	0.62	0.08–4.57	0.64
BMI	0.99	0.91–1.08	0.83	0.97	0.89–1.06	0.52	0.95	0.85–1.07	0.46
Ultrasound endometrial thickness (mm)	0.95	0.90–1.02	0.11	0.98	0.93–1.04	0.48	1.00	0.94–1.07	0.89
Ultrasound MI ≥50%	0.82	0.27–2.56	0.74	1.5	0.45–4.96	0.50	0.53	0.12–2.40	0.41
Operative hysteroscopy	0.78	0.28–2.28	0.65	0.42	0.14–1.25	0.12	*0.17*	*0.03–0.94*	*0.04*
Preoperative biopsy volume (cc)	0.98	0.85–1.14	0.83	1.00	0.89–1.13	0.95	1.02	0.87–1.18	0.85
Time to treatment (days)	*1.06*	*1.02–1.52*	*0.04*	0.97	0.95–1.02	0.07	0.98	0.95–1.02	0.24

In italic the statistically significant results. G1, grade 1; G2, grade 2; G3, grade 3; HR, hazard ratio; CI, confidence interval; BMI, body mass index; mm, millimeters; MI, myometrial invasion; cc, cubic centimeters.

biopsy and to carcinoma progression during the time from diagnosis to treatment.

In a meta-analysis on 1,106 patients, hysteroscopic resection presented the lower recurrence rate of unexpected endometrial cancer after hysterectomy for atypical endometrial hyperplasia (5.8%) compared with D&C and hysteroscopically guided biopsy , respectively 32.7% and 45.3% (28). However, a retrospective Polish study showed a higher level of concordance with D&C, especially for endometrioid carcinomas and a moderate strength of association between initial and final diagnosis for all histotype of endometrial cancer. Interestingly, the lowest concordance in tumor grading definition between D&C and final histology was detected for well-differentiated cancers, while in moderate- and poor-differentiated tumors, concordance levels were more elevated, 75.8% and 73.3% respectively (29). On the contrary, in 2017, the research group of the National Cancer Institute of Milan published a retrospective analysis of patients underwent preoperative hysteroscopy reporting an overall level of agreement between preoperative and postoperative tumor grading that was moderate and good respectively for G2 and G3 tumors (k=0.531; 95% CI: 0.286–0.777; P<0.001 and k=0.774; 94% CI: 0.534–1; P<0.001 respectively) while it was moderate in well differentiated tumors (k=0.679; 95% CI: 0.432–0.926; P<0.001); of note, they further reported an overall accuracy in detecting endometrial cancer of 80.2% (30). Similarly, in a more recent systematic review and meta-analysis on 12,459 patients, hysteroscopic endometrial biopsy demonstrated a greater level of accuracy in well and poor differentiated tumors but with a lower agreement rate for G2 tumors (31). Lago *et al.* confirmed the limitations in the assessment of tumor grading for various preoperative biopsy procedures (D&C, Pipelle and hysteroscopy procedures) and particularly in G1, G2 and big tumors, while G3 tumors showed better correlation with final histology. Hysteroscopy presented the highest tumor grading agreement, but no difference between the three analyzed methods was found (hysteroscopy, D&C and Pipelle with respectively k=0.55, k=0.39 and k=0.43). Interestingly, the authors hypothesize that the low volume of tissue available at biopsy had an influence in the tumor grade discrepancies in the final pathological assessment (15).

In our study, we included most of the known and widespread adopted ESTs, and we specifically differentiated among the various hysteroscopic procedures with subgroup analysis. Operative hysteroscopy with resectoscopic biopsy resulted to be the most reliable procedure that can predict histotype and tumor grading, showing for both a moderate concordance with the final diagnosis (respectively with k=0.41 and k=0.54). The addition of subsequent D&C after operative hysteroscopy, generally aimed to increase the sample volume and hence improve accuracy, did not improve the strength of concordance for tumor grading (k=0.53). These data seem to suggest that the visual examination of suspicious endometrial area under hysteroscopic view lead to a higher diagnostic accuracy, especially if biopsy is performed with

a subsequent resectoscopic biopsy. In fact, outpatient hysteroscopy as well as diagnostic hysteroscopy and D&C lead to lower levels of concordance for tumor grading (respectively k=0.31 and k=0.33). Nonetheless, we failed to identify a role in the volume biopsy as a predictor of tumor grading concordance, supporting hence the impact of direct visualization of a suspicious endometrial area. Finally, a greater time elapsed from diagnosis to treatment resulted to be a risk for carcinoma progression in well-differentiated tumor, even though this result can be due to the diagnosis of preoperative AH.

In accordance with the results from Lago (15) and the National Cancer Institute of Milan research group (30), the best diagnostic accuracy in our series was found for poor differentiated tumors, while our concordance was moderate for G2 tumors and only fair in G1 tumors. These results were confirmed including all preoperative ESTs, while in a separated analysis, we noticed a moderate concordance also for well-differentiated tumors in case of operative hysteroscopy (with or without D&C). The analysis of literature and of our series show that the major discrepancies in the definition of tumor grade were seen in well- and moderate-differentiated tumors that fall within the low and intermediate risk subgroups of endometrial cancer (7) for which lymph nodal staging is debated. In the next future to overcome this issue, molecular classification (32) and new methods of genetic analysis (33) will be hopefully able to predict genomic sub types through a preoperative biopsy that would more accurately guide the definition of surgical treatment. The recent PROMISE characterization is able to classify endometrial cancer in four prognostic groups based on molecular findings (34), even though there is a not negligible quote of unclassifiable cases (35). Ideally, a preoperative framing of these molecular groups can be of extreme usefulness to tailor the lymph nodal staging to avoid late complications such as the legs' lymphedema or avoid radiotherapy with its related side effects. So far, this classification can be used also in the post-operative setting to establish the need for adjuvant treatment in those cases with apparent low risk endometrial cancer. To ensure the success of the genomic testing it's recommendable to perform endometrial sampling with the most reliable technique, such as operative hysteroscopy with resectoscopic biopsy to obtain the most representative sample of tissue for diagnosis and genomic testing (36). Nonetheless, future endometrial biopsy techniques with miniaturization and consensual optimization of the biopsy instruments should be implemented (37), given the importance of the direct view of the target area for biopsy (38). Further studies on the prognostic definition of genomic sub types, both for endometrioid and non-endometrioid carcinomas found at preoperative biopsy, are required and given the small numbers of non-endometrioid carcinomas, multicentric studies are warranted with standardized methods of endometrial sampling and central pathological review.

Actually, the adequacy of the EST is a fundamental step for the tailoring of surgical extension, in particularly regarding the type of lymph nodal staging (39). In fact, while for ovarian cancer the open debate regards the different therapeutic surgical strategies to predict and to achieve a complete resection (40-44), instead, for endometrial, and similarly for vulvar (45) and cervical cancer (46), the current research topic is the validity of sentinel lymph node technique (47-49).

Our study has strengths and limitations. Among strengths, we included only consecutive patients with apparent early stage endometrial cancer diagnosed and treated in a single institution to decrease inter-observer agreement, and we conducted subgroup analysis of the different ESTs, with particular emphasis regarding the different type of hysteroscopic procedures and detailed framework for the selection of the EST. Among limitations, our study is a retrospective analysis, with a relatively small sample size, and it may not be exempt by potential selection bias.

Conclusions

According to our findings, we recommend a resectoscopic biopsy during hysteroscopy to minimize misdiagnosis of endometrial cancer and erroneous tumor grading classification. In case of suspect of endometrial cancer, surgeons should be aware that using other methods of endometrial sampling, in view of limiting factors for operative hysteroscopy, increases the risk of discordant tumor grading. Nonetheless, the volume of the endometrial biopsy does not affect the accuracy of tumor grading concordance. Lastly, a promptly treatment should be delivered to decrease the chance of cancer progression in well-differentiated tumors.

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