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Published in:
Gynecologic Oncology

DOI:
10.1016/j.ygyno.2008.11.023

Publication date:
2009

Gynecologic Oncology 112 (2009) 521–525

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

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ARTICLE INFO

Article history:
Received 2 September 2008
Available online 10 January 2009

Keywords:
Endometrial neoplasm
Neoplasm staging
Curettage

ABSTRACT

Objective. The presence of cervical involvement is important to establish a rational treatment for endometrial cancer patients. We investigated the value of preoperative endocervical curettage (ECC) in predicting cervical involvement.

Methods. Preoperative ECC of 290 patients with clinical stage I epithelial endometrial cancer was compared with histopathology of the uterus.

Results. Amongst all ECCs, 245 (84.5%) were negative and 45 (15.5%) were positive for endometrial cancer. In the uterine specimen, cervical involvement was found in 20% (58/290). PPV and NPV of ECC were 86.7% and 92.2%. False negative and false positive ECC occurred in 6.6% and 2.1%. Of all patients with positive ECC, 46.7% had FIGO stage II disease and 46.7% had extra uterine tumor spread (FIGO III, IV).

Conclusion. ECC is an acceptable diagnostic tool to predict the presence or absence of cervical involvement in early stage endometrial cancer patients.

Introduction

Endometrial cancer is the most common gynecological malignancy in developed countries and 90% of the patients are postmenopausal [1]. In most women endometrial cancer is detected at an early stage as postmenopausal vaginal bleeding is an early presenting symptom. Tumour stage, grade, histological type, depth of myometrial invasion [2–7], lymph vascular space invasion (LVSI) [8] and age [4,9] are known prognostic factors in endometrial cancer.

In 1988, the International Federation of Gynecology and Obstetrics (FIGO) redefined stage of disease on the basis of surgical pathological criteria. The main intent of the staging system was to establish a rational treatment program for each individual patient. Extension of endometrial carcinoma to the cervix, which was first described by Heyman in 1941, occurs in 10 to 15% of all cases of endometrial cancer. Since cervical invasion of endometrial cancer is recognized to increase the risk of pelvic lymph node metastases [10,11], a more extended surgical procedure is recommended including pelvic and para aortic lymph node dissection, performed by a gynecological oncologist in a specialized centre [3,10,12]. When cervical involvement is found after the operation and no lymphadenectomy has been performed, patients are treated with adjuvant radiotherapy. Morbidity of adjuvant radiotherapy is substantial. Especially mild, mainly gastrointestinal, side effect are common, of which 50% are transient[13].

Endocervical curettage (ECC) has been commonly used to assess cervical involvement, but the accuracy of this procedure remains controversial [7,10,11,14–19]. The aim of this study is to investigate the value of ECC as a diagnostic procedure in the preoperative staging of patients with adenocarcinoma of the endometrium prior to primary surgery.

Patients and methods

Patients

Since 1978, clinicopathological and follow-up data of all patients referred to the Department of Gynecological Oncology of the University Medical Centre Groningen are prospectively collected during treatment and follow-up and stored in a computerized registration database, which is managed in accordance with the hospital regulations.

For the current study, all consecutive endometrial cancer patients (n=771) treated between January 1978 and January 2006 were selected. Excluded were patients with a non-epithelial endometrial cancer (n=166). Secondly, patients with macroscopically cervical involvement (i.e. clinical stage IIB) were excluded (n=47). Finally, patients with extended disease who did not undergo surgical treatment and patients who received preoperative radiotherapy were excluded (n=21). Of the remaining patients, preoperative diagnostic procedures were not performed in 165 patients and in another 74 patients the histopathological reports could not be

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0090-8258/$ – see front matter
doi:10.1016/j.ygyno.2008.11.023

Table 1
Clinicopathological characteristics of 290 clinical early stage epithelial endometrial carcinoma patients

	Overall
Mean age in years (n=290)	63.4 (11.2)
Differentiation grade (n=275)[a]	
I (well differentiated)	139 (50.5%)
II (moderately differentiated)	88 (32.0%)
III (poorly differentiated)	46 (16.7%)
IV (undifferentiated)	2 (0.7%)
Histological subtype (n=290)	
Adenocarcinoma	248 (85.5%)
Adenosquamous carcinoma	11 (3.8%)
Clearcell carcinoma	14 (4.8%)
Papillary serous carcinoma	11 (3.8%)
Undifferentiated	3 (1.0%)
Other	3 (1.0%)
Depth of myometrial invasion (n=288)[b]	
Endometrium only	31 (10.8%)
<1/2 in myometrium	153 (53.1%)
≥1/2 in myometrium	104 (36.1%)
LVSI (n=271)[c]	
Negative	210 (77.5%)
Positive	61 (22.5%)
Year of diagnosis (n=290)	
First decade (1978–1987)	58 (20.0%)
Second decade (1988–1996)	110 (37.9%)
Third decade (1997–2006)	122 (42.1%)
Type of operation (n=290)	
Simple hysterectomy	173 (59.7%)
Radical hysterectomy	117 (40.3%)
Adjuvant radiotherapy (n=288)[d]	
Yes	162 (56.3%)
No	126 (43.8%)

Missing values in respectively 15 (5.1%)[a], 2 (0.7%)[b] ,19 (6.5%)[c] and 2 (0.7%)[d] patients.

retrieved. In total, preoperative assessment of cervical involvement was carried out by endocervical curettage (ECC) or endocervical biopsy (ECB) in 290 and 8 patients, respectively. There were no statistically significant differences on the main characteristics (tumour stage, differentiation grade, histological sub type, depth of myometrial invasion, age) between the women with an ECC performed (n=290) and the women without an ECC performed (n=165). Due to small sample size the ECB group was not considered in further analyses, resulting in 290 patients with clinical stage I disease.

After preoperative clinical staging, patients underwent primary surgical therapy within four to six weeks according to protocol [20], which is total abdominal hysterectomy and bilateral salpingo oophorectomy in case of a clinical stage I disease and total abdominal hysterectomy and bilateral salpingo oophorectomy, pelvic and para aortic lymphadenectomy in case of a clinical stage IIA (positive ECC) disease.

IRB approval

For the present study, all relevant data were retrieved from our computerized database into a separate, anonymous password protected database. Patients' identity was protected by study specific, unique patient numbers, which codes were only known to two dedicated data managers. In case of uncertainties with respect to clinicopathological and follow-up data, the larger databases could only be checked through the data managers, thereby ascertaining the protection of the patients' identity. Due to these procedures according to Dutch law, no further patient or International Review Board (IRB) approval was needed.

Methods

In all patients, the diagnosis of endometrial cancer was histopathologically established preoperatively by micro curettage (pipelle) or fractionated curettage. Subsequently, endocervical tissue was obtained by ECC. Histopathological results of the ECC slides were divided into two different groups, namely endometrial cancer in the ECC (i.e. positive) and no endometrial cancer in the ECC (i.e. negative). These criteria were based on the leading well known atlas of gynecologic surgical pathology [21] The criterion for preoperative diagnosis of a positive ECC was as follows: endocervical tissue present and tumour in relation with cervical tissue. Criteria for preoperative diagnosis of a negative ECC were as follows: 1) endocervical tissue without cancer; 2) obtained tissue was insufficient to establish a diagnosis; 3) loose tumour fragments without relation with endocervical tissue. Our expert gynecological pathologist (H.H.) judged the majority (~85%) of all slides during the initial presentation. Misclassified slides and slides allocated to the separate group were revised, without prior knowledge of the definitive outcome. The initially interpreted slides and revised slides by H.H. were used for further analysis. Of the original false negative, false positive and separate group slides, the review report differed from the initial diagnosis in 5% (1/20), 57.1% (8/14) and 0% (0/34), respectively. In total, about 23% (68/290) of the slides were reviewed by H.H of which 3.1% (9/290) differed from the original report.

Surgical pathological information was gathered from the pathology reports, which included histological tumour type, grade, FIGO stage, myometrial invasion and tumour features such as lymph vascular space involvement. Cervical involvement in the uterine specimen was defined as endocervical glandular involvement only (i.e. FIGO stage IIA) or cervical stromal invasion (i.e. FIGO stage IIB).

Statistical analysis

Preoperative histopathological results of ECC were compared with definitive histopathological results of cervical involvement obtained

Table 2
Clinicopathological risk factors of patients with cervical involvement present in uterine specimen

	Cervical involvement present (n=58)	Odds ratio	
		Univariate	Multivariate
Mean age in years (n=58)	63.9 (11.1)		
Age ≤63 years		1	n.i.
Age > 64 years		0.9 (0.5–1.6)	
Differentiation grade (n=51)[a]			
Well differentiated	19 (37.3%)	1	n.i.
Moderately differentiated	19 (37.3%)	1.7 (0.9–3.5)	
Poorly-undifferentiated	13 (25.5%)	2.3 (1.1–5.2)*	
Histological subtype (n=58)			
Adenocarcinoma,-squamous	50 (86.2%)	1	n.i.
Clearcell/serous/undiff/other	8 (13.8%)	1.5 (0.6–3.4)	
Depth of myometrial invasion (n=57)[b]			
Endometrium only	2 (3.5%)	1	1
<1/2 in myometrium	21 (36.8%)	2.3 (0.5–10.4)	2.3 (0.5–10.4)
≥1/2 in myometrium	34 (59.6%)	7.0 (1.6–31.3)*	7.0 (1.6–31.3)
LVSI (n=53)[c]			
Negative	33 (62.3%)	1	n.i
Positive	20 (37.7%)	2.6 (1.4–5.0)*	
Year of diagnosis (n=58)			
First decade (1978–1987)	14 (24.1%)	1	n.i.
Second decade (1988–1996)	20 (34.5%)	0.70 (0.3–1.5)	
Third decade (1997–2006)	24 (41.4%)	0.77 (0.4–1.6)	

Missing values in respectively 7(12.1%)[a], 1(1.7%)[b] and 5(8.6%)[c] patients.
*p<0.05; n.i.=not included.

Table 3
Predictive values of ECC for cervical involvement found in final uterine specimen ($n=290$)

ECC	Cervical involvement found in final uterine specimen		Total
	Present	Absent	
Positive	39	6	45
Negative	19	226	245
	58	232	290

PPV=86.7%; NPV=92.2%; Misclassification=8.6%.

from the uterine specimen (gold standard). Clinicopathological features of the patients were described in total and for the patient group in which cervical involvement was found (Tables 1 and 2). Univariate logistic regression analyses were performed with cervical involvement as dependent variable and the histopathological characteristics as described in Table 2 as independent variables. Odds ratios (OR's) and 95% confidence intervals (95%-CI's) were calculated. Multivariate logistic analysis was performed by using a backward step model with cervical involvement as dependent variable and the statistically significant related variables, as assessed in the univariate logistic regression analysis, as independent variables. Variables were excluded from the model if $p \geq 0.05$.

With cervical involvement in the hysterectomy specimen as gold standard, positive predictive value (PPV), negative predictive value (NPV) and misclassification (1-accuracy) were calculated for the ECC procedure. Logistic regression analyses were performed using age, differentiation grade and histological subtype as potential predictors for misclassification.

In Table 4, histopathological features of early and advanced stage patients were characterized. Logistic regression analyses were performed with advanced stage disease as dependent variable and known prognostic factors (cervical involvement, differentiation grade, histological subtype, depth of myometrial invasion and LVSI) as independent variables. All statistical analyses were performed using SPSS software version 14.01. A p-value<0.05 was considered as significant (tested 2-sided).

Results

Study group

Clinicopathological characteristics of 290 clinical early stage epithelial endometrial carcinoma patients are given in Table 1. The majority of the patients had well to moderately differentiated carcinomas of the uterus (82.5%). About 11% of the patients had no myometrial invasion, but endometrial carcinoma limited to the endometrium only (FIGO stage IA). LVSI was present in 22.5% of all patients. The contribution of included patients over decades was equally distributed for the last two decades (about 40% per decade). The lowest number of patients was included in the first decade (20%). Nearly 60% of all patients did undergo a simple hysterectomy (without lymphadenectomy). A substantial part of the patients (56.3%) received radiotherapy after surgery. The clinicopathological characteristics of the patients were related to the presence of cervical involvement in the uterine specimen (Table 2). On multivariate analysis, only depth of invasion≥of the myometrium (OR: 7.0; 95%-CI: 1.6–31.3) was statistically significantly associated with presence of cervical involvement.

Diagnostic value of ECC in predicting cervical involvement in the uterine specimen

Cervical involvement in the final uterine specimen was found in 58 (20%) of 290 patients (Table 3). Among all ECC procedures, 245 (84.5%) were negative and 45 (15.5%) were positive for cervical involvement. The PPV and NPV of ECC were 86.7% and 92.2%, respectively. Misclassification (1-accuracy) occurred in 8.6% (25/290) samples, consisting of 6.6% (19/290) false negative samples and 2.1% (6/290) false positive samples. As a potential predictor of misclassification, age>63 years (OR: 4.0; 95%-CI: 1.3–12.4) was independently related to the presence of false negative samples (data not shown).

Relation between ECC and FIGO stage

Based on the final FIGO stage, 66.2% (192/290) of all included patients had early stage (FIGO stage I) endometrial cancer and 33.8% (98/290) had FIGO stage≥II disease (Table 4). Of all patients with negative ECC samples, 77.1% (189/245) were classified as FIGO stage I and 22.9% (56/245) as FIGO≥II stage. Of all positive ECC samples, 6.7% (3/45) were classified as FIGO stage I disease and 93.3% as FIGO stage≥II ,of which 46.7% (21/45) with FIGO stage II disease and 46.7% (21/45) with extra uterine tumour spread (i.e. FIGO III, IV). On univariate analysis, a significant effect of a positive ECC (OR: 47.3; 95%-CI: 14.1–158.2), a poorly or undifferentiated grade (OR: 4.5; 95%-CI: 2.2–9.0), a non-endometrioid tumour type (OR: 2.3; 95%-CI: 1.1–4.9),≥1/2 myometrial invasion (OR: 6.1; 95%-CI: 2.2–17.0) and a positive LVSI (OR: 2.8; 95%-CI: 1.5–5.0) was found for the presence of FIGO stage≥II disease. On multivariate analysis, a positive ECC result (OR: 41.0; 95%-CI: 11.4–146.8), poorly or undifferentiated tumour cells (OR: 3.2; 95%-CI: 1.4–7.4) and depth of invasion≥1/2 of myometrium (OR: 7.3; 95%-CI: 1.6–33.4) were independently associated with FIGO≥II stage disease. If we correlated ECC with extra uterine spread (i.e. FIGO III, IV) the effect remained significant (OR: 2.77; 95%-CI: 1.2–6.3) on multivariate analysis.

Discussion

This is a large study analyzing the role of ECC as a preoperative staging procedure, in predicting cervical involvement in clinical early

Table 4
Histopathological features of FIGO stage I ($n=192$) and FIGO stage≥II ($n=98$)

	(FIGO I)	(FIGO ≥II)	Odds ratio	
			Univariate	Multivariate
ECC (n=290)				
Negative	189 (77.1%)	56 (22.9%)	1	1
Positive	3 (6.7%)	42 (93.3%)	47.3 (14.1–158.2)**	41.0 (11.4–146.8)**
Differentiation grade (n=275)[a]				
Well differentiated	108 (77.7%)	31 (22.3%)	1	1
Moderately differentiated	56 (63.6%)	32 (36.4%)	2.0 (1.1–3.6)	1.6 (0.8–3.2)
Poorly-undifferentiated	21 (43.7%)	27 (56.3%)	4.5 (2.2–9.0)*	3.2 (1.4–7.4)*
Histological subtype (n=290)				
Adenocarcinoma, -squamous	177 (68.3%)	82 (31.7%)	1	n.i.
Clearcell/serous/ undiff/other	15 (48.4%)	16 (51.6%)	2.3 (1.1–4.9)*	
Depth of invasion (n=288)[b]				
Endometrium only	26 (83.9%)	5 (16.1%)	1	1
< 1/2 in myometrium	117 (76.5%)	36 (23.5%)	1.6 (0.6–4.5)	2.6 (0.6–11.6)
≥ 1/2 in myometrium	48 (46.2%)	56 (53.8%)	6.1 (2.2–17.0)*	7.3 (1.6–33.4)*
LVSI (n=271)[c]				
Negative	153 (72.9%)	57 (27.1%)	1	n.i
Positive	30 (49.2%)	31 (50.8%)	2.8 (1.5–5.0)*	

Missing values in respectively 15 (5.1%)[a], 2 (0.7%)[b] and 19 (6.5%)[c] patients.
*$p<0.05$.
**$p<0.001$ n.i.=not included.

stage endometrial cancer patients. In these patients, ECC has a PPV of 86.7% and a NPV of 92.2% for cervical involvement in the uterine specimen. Misclassification (i.e. FN and FP samples) occurred in 8.6% of all cases and false negative samples were only related to age. As can be seen in Table 1, our patient group is representative for clinical early stage endometrial cancer patients despite the high amount of missing patient data.

A broad scope of diagnostic tools is used preoperatively to predict the presence and extent of uterine disease in endometrial cancer patients. Numerous studies reported the value of other preoperative staging procedures in diagnosing cervical involvement, such as cervical cytology [7,10,12,22], CT scan [23], transvaginal ultrasonography [12,23] and MRI [23,24]. Cervical cytology, CT and transvaginal ultrasonography showed poor results and are not suitable for detecting cervical involvement [7,10,12,22,23]. MR imaging is the only modality that has been shown to accurately (*Q*-value 0.92; 95% CI: 0.87–0.95) depict cervical invasion [24] but due to its high costs and time consuming factor is not recommended as a routine procedure in the Dutch guidelines.

In this series, 2.1% of all cases were false positive. The reason for the amount of changed FP cases after reviewing by H.H. was due to a wrong interpretation by other pathologists (referral patients, not revised by H.H) of the ECC samples with free floating tumour fragments without cervical tissue (i.e. separate group). These samples were interpreted as being positive, but according to our study protocol considered as being negative. Several hypotheses are argued to explain the occurrence of false positive ECC results. In our study, in three cases the curetting might have had a therapeutic value by removing all tumour from the endocervix. In one case a tumour protruded from the endometrial cavity into the endocervix. From the pathological report it can be concluded that in the other two cases the tumour arose in the lower segment of the uterus. Oppositely, during pathological examination tumour might be missed in a particular section slide, because of limited number of section slides.

In addition, 6.6% of all cases were false negative. This can be due to an inadequate technique of curetting or the curette did not reach the upper segment of the endocervical canal. The latter explanation occurred in 8 patients, in which a tumour in the upper segment of the endocervical canal was found in the uterine specimen. As a result, areas of cervical tumour involvement might escape histological identification. In 8 false negative samples, massive tumour growth of the cervical canal was found. Therefore, besides loose tumour fragments, no pre-existent cervical tissue was seen in the ECC. Actually, these cases might have been missed during speculoscopy. Furthermore, it has been suggested in some reports that involvement of the cervical stroma by extension of the tumour can occur under intact endocervical mucosa, which could explain 3 false negative samples in our study [25,26]. Moreover, due to curetting, endometrial tumour cells can be implanted in the endocervical glandular tissue called cervical implantation metastasis [27]. Another phenomenon called atypical reactive proliferation involving the endocervical surface is commonly seen in association with endometrial cancer and has the potential to be misinterpreted as endocervical involvement by tumour in the uterine specimen. Scott and colleagues hypothesized that the proliferation is most likely a reactive response to recent curettage [28]. According to this theory, the true number of false negative samples might be smaller. Overall, in our study only a significant relation was found between false negative samples and older age (>63 years) (OR: 4.0; 1.3–12.4). Misclassification was not related to differentiation grade and histological subtype. We hypothesized that atrophy of the cervical canal in older postmenopausal women (i.e.>63 years) might hamper endocervical curetting.

Negative and positive predictive values of the ECC procedure varied between (87.5%–98.3%) and (15.1%–62.5%) in previous studies [7,10,12,23,25]. These differences can partly be explained by heterogeneity in patient selection and differences in assessment of the curettage. The strict criteria for selecting patients and the systematic way of classifying the ECC samples are the strength of our study; only clinical early stage patients were included. Hence, the prevalence of cervical involvement in our patient population is much lower, which exert influence on the predictive value. Importantly, we excluded clinically stage IIB patients, as cervical involvement has already been observed macroscopically during speculoscopy. In general, ECC has no value in clinical advanced staged patients. Furthermore, solely speculoscopy to exclude cervical involvement appears to be insufficient as all included patients did have a macroscopically normal aspect of the cervix. Secondly, one gynecopathologist (HH) (re)viewed all slides and was able to accurately discriminate between positive and negative ECC samples. Free floating tumour fragments in the ECC sample were considered as contamination of tumour tissue from the corpus. These tumour fragments of the corpus were dragged along the endocervical canal during curettage or hysteroscopy. Therefore, without co-existing endocervical tissue this histological result was interpreted as being a negative ECC [21].

Even though predicting advanced stage disease is not the goal of ECC, it strikes that in nearly 95% of all positive ECC samples, the patients had FIGO stage≥II (Table 4). Consequently, these patients need a more extended hysterectomy by a gynecological oncologist in a specialized centre. Despite the high negative predictive value of ECC (92.2%), only 77.1% of all patients with a negative ECC sample truly did have FIGO stage I. Amongst the patients with extra uterine tumour spread (i.e. FIGO stage III or IV), 57.1% (36/63) did not have cervical involvement in the uterine specimen.

According to Table 4, a positive ECC sample is strongly related to the presence of FIGO stage≥II disease. Other important factors related to FIGO stage≥II disease were poorly or undifferentiated grade and depth of invasion≥1/2 of the myometrium. However, these parameters can only be assessed accurately postoperative. The risk of FIGO stage≥II disease in case of a positive ECC sample is substantial and might be guidance for the choice of surgical treatment and hence the centre of treatment.

The main objective is to get the best treatment results with the least morbidity for each patient. In patients with cervical invasion of endometrial cancer (i.e. clinical FIGO stage II), a more extended surgical procedure is recommended including lymphadenectomy, performed by a gynecological oncologist in a specialized centre [3,10,12]. As becomes clear from out data, ECC plays an important role in discriminating patients with clinical stage I or clinical stage IIA disease and therefore establishing a rational surgical treatment program for each patient, being either a simple or radical hysterectomy. The main intent of a preoperative ECC is to prevent surgical “over treatment” or “under treatment”. The chance of “over treatment” (i.e. lymphadenectomy in case of false positive ECC samples) and “under treatment” (i.e. no lymphadenectomy in case of false negative ECC) is low (2.1% and 6.6%).

In conclusion ECC is an acceptable diagnostic tool to predict the presence or absence of cervical involvement in early stage endometrial cancer, allowing selection of patients for either a simple hysterectomy or a more extended hysterectomy with lymphadenectomy, performed by a gynecological oncologist in a specialized centre.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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