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The clinical relevance of fractional curettage in the diagnostic management of primary endometrial cancer.

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Short Title: Clinical relevance of fractional curettage in endometrial cancer

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Abstract

Objective. Hysteroscopy and fractional curettage are commonly utilized techniques for the diagnosis of postmenopausal abnormal uterine bleeding (AUB) and histopathological verification of primary endometrial cancer (EC). This study delves into the clinical significance of procuring preoperative endocervical tissue in conjunction with corpus fractions through fractional curettage.

Design. This retrospective study encompassed a cohort of 84 patients diagnosed with T1-stage endometrial cancer (EC) and 55 patients diagnosed with T2-stage EC, who underwent primary treatment between the years 2011 and 2021 at the University Hospital Frankfurt or Jung-Stilling Hospital Siegen.

Materials, Setting, Methods. Among the postoperative T2-stage EC patients, a stratification was performed based on preoperative endocervical curettage (ECC) results obtained through fractional curettage. Categorical and continuous variables were compared utilizing the Pearson-Chi-square test, while for multivariate analyses and regression modeling, the Kaplan-Meier method and Cox regression models were respectively employed.

Results. The median age of patients with pT2-stage EC was 64 years (range: 38 to 85). A predominant majority of these patients exhibited the endometrioid subtype of EC (90.9%). Upon conducting comparative analysis between groups, a notably higher frequency of laparotomies was observed (p=0.002) among patients in whom preoperatively detected positive endocervical curettage (ECC) was evident. The detection performance of fractional curettage in identifying positive ECC yielded a sensitivity of 70.9% and a specificity of 73.8%. In multivariate analysis, age at diagnosis (p=0.022), positive ECC observed during fractional curettage (p=0.036), and the FIGO stage (p=0.036) emerged as prognostic determinant for progression-free survival (PFS). Independent prognostic factors for overall survival (OS) were age at diagnosis (p=0.003), positive ECC (p=0.008), histological grading (p=0.016), and the FIGO stage (p=0.022). A significant difference in OS was evident between patients characterized by preoperative negative ECC and those displaying positive ECC (81.8 vs. 59.5 months, p=0.019).

Limitations. The retrospective design of the study, as well as a small number of patients.

Conclusions. Preoperative determination of endocervical involvement of primary T2-stage EC could be a prognostic indicator in decision-making to treat EC. The conduct of prospective trials is necessary to definitively establish the routine application and associated benefits of fractional curettage in the context of primary endometrial cancer.

Introduction

Endometrial cancer (EC) stands as the foremost gynecological malignancy, demonstrating a noteworthy increase in global incidence rates over recent decades [1]. Abnormal uterine bleeding (AUB) emerges as an initial symptom, whereas an atypical sonographic portrayal of endometrial thickness exceeding 3mm in postmenopausal women offers an opportunity for early EC diagnosis, aligning with stages I and II according to the FIGO classification [2,3]. The prompt identification of this malignancy not only enhances patient prognosis but also alleviates the financial burden on healthcare infrastructures [4]. In most countries, hysteroscopy and fractional curettage constitute the predominant modalities for diagnosing AUB and histologically confirming primary EC [5]. In the recent past, evaluating endocervical involvement in fractional curettage was essential for deciding between radical hysterectomy and simple hysterectomy. For patients with positive endocervical curettage (ECC) results, *radical* hysterectomy was recommended [6,7]. However, the benefits of radical

hysterectomy concerning overall survival (OS) and progression-free survival (PFS) were not observed in patients with primary EC [8]. Consequently, this procedure is no longer recommended due to increased postoperative morbidity according to guidelines [9]. Moreover, preoperative corpus curettage offers the possibility of pre-therapeutically determining the treatment-relevant mismatch repair (MMR) and p53 proteins through immunohistochemical (IHC) staining [9]. The protein expression pattern in IHC and the mutational profile of POLE (polymerase-epsilon) in Next-Generation-Sequencing (NGS) have become increasingly pivotal for therapy management and disease prognosis [10] and are recommended for inclusion in preoperative diagnostics [9]. Their preoperative determination in curettage and their application in disease staging, as per the newly published FIGO classification of 2023 [11], enable precise risk-group stratification, allowing for up- and down-staging between FIGO stages I and II. With higher sensitivity and specificity, both exceeding 98%, in detecting and differentiating endometrial polyps, fibroids, and carcinoma, the combination of fractional curettage and hysteroscopy surpasses their individual applications as a diagnostic method [12]. In a meta-analysis by Visser et al., the concordance rate between preoperative imaging diagnostics and the final histological diagnosis of EC was 0.70 for dilatation and curettage and 0.89 for hysteroscopic biopsy [13]. Specimen collection using a pipelle or Tao-Brush as an alternative to fractional curettage could not be established in routine clinical use in Germany, given the high predictive value of fractional curettage and hysteroscopy, along with the lack of doctors' experience [5].
The aim of this study is to assess the predictive and prognostic value of a positive endocervical curettage (ECC) in fractional curettage and its practical relevance in clinical routine.

Materials and methods

In this retrospective analysis, we consecutively enrolled 203 patients with T1 and T2 stage endometrial cancer (EC) who underwent primary surgical treatment from 2011 to 2021 at University Hospital Frankfurt and Jung-Stilling-Hospital Siegen. Patient data for each participant were retrieved from either the digital or analog archives of the University Center for Tumor Diseases Frankfurt (UCT) and the Cancer Center of Jung-Stilling-Hospital Siegen. All patient data had been prospectively documented in the comprehensive cancer center databases of both hospitals, both of which are certified gyneco-oncological centers by the German Cancer Society. All surgeries were performed by senior surgeons with subspecialization in gynecological oncology. Histopathological examinations and immunohistochemistry (IHC) assessments were conducted and reported separately by two certified gyneco-oncopathologists at each hospital. Positivity of endocervical curettage was determined by the presence of endometrial malignant cells in fractional curettage, and the pT2 stage of the disease was defined as cervical stromal involvement after histological examination of uterus according to the TNM-UICC classification in our study. The assessment of intrauterine tumor dissemination in numerous instances was conducted through expert ultrasound, while the comprehensive staging involved the utilization of a CT scan. In instances characterized by ambiguity or specificity pertaining to invasion of the uterus or cervix, recourse to an MRI scan was employed. Cases with missing or doubtful data regarding clinicopathological factors, histological subtypes other than endometrioid, serous, or clear cell EC were excluded from this analysis. Similarly, patients with EC diagnosed beyond hysteroscopy and fractional curettage were not included. The flowchart (Figure 1) illustrates the inclusion and exclusion criteria for the patients in this study. For comparative analysis, patients with pT2-stage EC were divided postoperatively into two groups based on their preoperative ECC (endocervical curettage) status (positive or negative) as revealed in fractional curettage. Differences in clinicopathological factors, such as age, performance and obesity status, comorbidities, histological features, clinical staging, and therapeutic aspects, were investigated. Survival rates and predictive factors influencing survival were analyzed for both groups. To calculate the sensitivity and specificity of fractional curettage, the clinicopathological factors of 84 pT1 patients were compared with those of 55 pT2 patients.

Following surgery, all patients were presented at an internal multidisciplinary tumor board in both hospitals to determine the need for adjuvant treatment. Based on disease stage and in accordance with European and German guidelines [14], adjuvant radiotherapy and/or chemotherapy was considered. According to previous guidelines [5], adjuvant chemotherapy could be considered for pT2-stage EC following a detailed discussion and clarification with the patient. After completing the primary therapy, patients were enrolled in a follow-up program in line with the guidelines, which included examinations every three months for the first three years after primary treatment or until symptoms occurred. Each follow-up appointment, conducted by experienced gynecologists during our specialized consulting hours, included gynecological clinical examinations along with transvaginal and abdominal sonography.

Most patients preferred alternating follow-up observations with their own referred experienced gynecologist's office. Further additional examinations, such as CT, MRI, or positron emission tomography scans, were conducted

when there were suspicions of disease recurrence, such as the presence of symptoms or abnormal findings during clinical examinations. The most recent follow-up data for each case included in our analysis were obtained either through direct contact with patients and their treating gynecologists or from their insurance records. The need for informed consent was waived due to the retrospective nature of this study. The study received approval from the Institutional Review Boards of the UCT and the Ethical Committee at the University Hospital Frankfurt (project numbers: UCT-19-2021, UCT-31-2020).

Statistical analysis

All statistical analyses were performed using SPSS Statistics (Version 29; IBM, NY, USA). A probability value of $p < 0.05$ was considered statistically significant for all tests conducted. Survival analyses were performed using the Kaplan-Meier method and Cox regression models. Odds ratios for predictive factors influencing the survival rate were estimated using stepwise Cox regression models. A Pearson chi-square test was conducted to compare categorical and continuous variables. To calculate the sensitivity and specificity of hysteroscopy and fractional curettage, a fourfold table and appropriate statistical formulas were used.

Results

The median age of the cohort was 64 years, with a range of 38 to 85 years, and two-thirds were postmenopausal (72.7%). Approximately half of the patients (50.9%) were suffering from obesity, and the majority (89.1%) had a good ECOG performance status. Solely, one-third (29.1%) of cases were over 65 years old at the initial diagnosis of the disease. Comorbidities such as arterial hypertension (40.0%) and diabetes mellitus (29.1%) were the most commonly observed. Most cases exhibited the endometrioid subtype (90.9%) of histology, while a minority presented with serous (5.4%), clear cell (1.8%), and mixed (1.8%) serous and endometrioid EC. High-grade differentiation of the tumor and invasion of lymphovascular space (LVSI) were observed in 34.5% and 32.7% of patients, respectively. Pelvic and para-aortic lymph node involvement was observed in 9 (16.4%) of pT2 cases, resulting in an upgrade of the stage to FIGO IIIC. Additionally, in 3 (5.5%) cases, distant metastasis of FIGO IVB was detected, with positive lymph nodes beyond the previously mentioned regions.

The entire cohort of pT2 stage EC was divided into two groups: thirty-nine patients (70.9%) with positive ECC and 16 patients (29.1%) with negative ECC before hysterectomy. No statistically significant differences between both groups were found regarding clinicopathological factors such as age at diagnosis (p=0.351), ECOG status (p=0.282), BMI (p=0.556), arterial hypertension (p=0.716), diabetes mellitus (p=0.279), obesity (p=0.274), hormonal status (p=0.509), subtype of histology (p=0.639), grading (p=0.635), FIGO stage (p=0.430), node status (p=0.223), distant metastasis (p=0.868), and LVSI (p=0.157). The baseline characteristics of patients are illustrated in Table 1.

All patients underwent hysterectomy and bilateral salpingo-oophorectomy (BSO), either via laparotomy (49.1%) or minimally invasive techniques (50.9%). Laparotomy was significantly more common in the positive ECC group than in the negative ECC group (64.1% vs. 18.7%, p=0.002). This difference is likely due to the indication for radical hysterectomy in cases of endocervical involvement. However, in the later years of the study, minimally invasive approaches were increasingly used in 35.9% of patients, even though the duration of surgery did not significantly differ between both groups (242 min. vs. 225 min, p=0.395).

In four (7.3%) patients, BSO was performed for benign indications prior to cancer surgery. Approximately one-fifth of patients (18.2%) did not undergo lymphadenectomy due to a high risk of perioperative complications related to cardiovascular diseases, coagulopathy, or patient refusal. Omentectomy was indicated in 4 (7.3%) cases based on non-endometrioid histology. Microscopic residue was identified at the resection margin in one patient; however, the patient declined re-resection. Adjuvant radiotherapy was administered to 72.7% of the cases, while 27.3% refused this treatment despite being adequately informed. Adjuvant chemotherapy, following guideline recommendations at the time, was offered as an optional treatment. Consequently, 20.0% of the patients received adjuvant chemotherapy for enhanced oncological safety. No significant differences in surgical procedures and adjuvant therapies were observed between the two groups, as shown in Table 2.

The median follow-up time was 56 months, ranging from 5 to 122 months. Seven patients (12.7%) experienced a recurrence after primary therapy. Most recurrences, in 6 patients, occurred within 0-36 months after diagnosis, with only one patient experiencing a recurrence after 36 months. Sixteen deaths (29.1%) were observed.

Sensitivity and specificity of fractional curettage.

Eighty-four patients with T1-stage EC and 55 patients with T2-stage EC were included in this analysis. Nearly all patients (99.3%) underwent fractional curettage to obtain an endometrial sample for histological confirmation. Only one patient (0.7%) had fractional curettage without hysteroscopy due to vulnerable cervical tissue. Comparison of the results of the tissue sample obtained by fractional curettage with the results of uterine

examination after hysterectomy revealed two significant findings. Firstly, twenty-two patients (15.8%) with preoperative positive ECC were negative after hysterectomy in the cervix, indicating false positives. Secondly, 16 patients (11.5%) with preoperative negative ECC were found to be positive in the uterus after hysterectomy, indicating false negatives. The sensitivity of fractional curettage in detecting ECC was 70.9%, with a specificity of 73.8%, as shown in Table 3. In summary, the main results include a sensitivity and specificity of 70.9% and 73.8%, respectively, for fractional curettage in detecting ECC. Additionally, there was a significant difference in OS (p=0.019) between preoperative endocervical negative and positive patients. Furthermore, preoperative detection of ECC influenced both OS and PFS as an independent factor.

Regression analysis of pT2-stage patients.

PFS was clinically better in patients with negative ECC compared to those with positive ECC (77.6 months vs. 59.5 months, p=0.054, Figure 2). However, statistical significance was not achieved. Independent prognostic factors for PFS included age at diagnosis (OR 1.05; 95% CI 1.00-1.10; p=0.022), positive ECC in fractional curettage (OR 6.20; 95% CI 1.13-34.03; p=0.036), and FIGO stage (OR 2.69; 95% CI 1.06-6.82; p=0.036) (Table 4). The comparative analysis of the groups revealed a statistically significant benefit in OS rates. OS rates were 81.8 months for patients with negative ECC compared to 59.5 months for patients with positive ECC (p=0.019, Figure 3). In the stepwise multivariate Cox regression analysis, age (OR 1.09; 95% CI 1.02-1.15; p=0.003), positive ECC in fractional curettage (OR 29.18; 95% CI 2.36 – 359.53; p=0.008), grading (OR 3.45; 95% CI 1.25-9.50; p=0.016), and FIGO stage (OR 3.44; 95% CI 1.19-9.94; p=0.022) were found to be statistically significant prognostic factors for OS (Table 5).

Discussion

The current surgical treatment for pT2 stage EC consists of simple hysterectomy, bilateral salpingo-oophorectomy (BSO), and sentinel lymphadenectomy. Until recently, the preoperative assessment of cervical stromal involvement played a crucial role in deciding whether to perform radical hysterectomy in primary EC [15]. However, radical hysterectomy was associated with various perioperative complications, including prolonged surgery duration, extended hospital stays, and severe postoperative urinary tract dysfunction. Importantly, it did not significantly improve local recurrence-free survival, progression-free survival (PFS), or overall survival (OS) [6, 16]. Despite the retrospective nature of these studies, clinical analysis results prompted a shift from radical to simple hysterectomy as the preferred surgical approach for pT2 stage EC.

The predictive role of preoperative positive endocervical curettage (ECC) in pT2 stage primary EC remains unclear. Despite advances in molecular and genetic markers, conventional histology remains a crucial component of EC pathology assessment. Further exploration and integration of ECC into clinical protocols harbor the potential to predict intraoperative staging for patients classified as T2. Consequently, in instances such as FIGO IA, where preoperative imaging does not reveal evidence of cervical stromal invasion, a positive ECC could serve as a predictive tool, warranting consideration for intraoperative frozen section analysis of the uterus. In the event of the identification of cervical stromal invasion during intraoperative frozen pathology, resulting in a disease upstaging from FIGO IA to II, the indication for and execution of sentinel lymph node biopsy could be advocated within the context of the same primary surgical treatment. In our multivariate analysis, preoperative positive ECC in pT2 stage carcinoma, compared to negative ECC, was associated with worse OS rates and established as an independent prognostic factor for survival (p=0.019).

The prognostic value of cervical stromal invasion remains controversial in the literature and is often associated with poor prognostic factors such as lymphovascular invasion (LVSI) and depth of myometrial infiltration [17,18]. Pitson et al. conducted a retrospective analysis of prognostic factors in pT2 stage EC following adjuvant radiotherapy. They found that cervical involvement is a significant unfavorable factor for OS, along with other factors such as LVSI and patient age [17]. In contrast, Zaino et al. reported that endocervical involvement does not significantly affect survival when compared to pT1 stage disease in multivariate analysis. Therefore, the authors did not recommend using endocervical involvement as a determinant of pT2 stage. Additionally, the reproducibility rate for determining the pattern of endocervical involvement by different pathologists was not high [17,19].

Interestingly, a retrospective multivariate analysis by Solmaz et al. [20] revealed a correlation between cervical stromal invasion and lymph node metastasis (OR 4.04, 95% CI 2.02–8.07) in primary EC. In contrast, our study did not identify significant differences between positive and negative ECC cohorts concerning lymph node metastasis (p=0.223). Additionally, positive ECC patients underwent significantly more laparotomies than minimal invasive surgery (p=0.002) in our analysis. This was because, in the early period of the study, surgeons opted for radical

hysterectomy via laparotomy for cT2 tumors based on preoperatively positive ECC, as the evidence for the oncologic safety of minimally invasive procedures was lacking. In all histologically diagnosed primary EC cases, guidelines recommend determining the expression of p53 and MMR proteins through IHC staining or assessing the POLE mutational status via NGS-assay. This is preferably done pre-treatment on tissue obtained by fractional curettage or endometrial biopsy [9]. These markers (MMRP, p53abn, and POLEmut) are already part of the risk stratification in addition to conventional histology and are crucial for determining adjuvant therapy [9].
The newly published FIGO classification for endometrial carcinoma includes these new molecular markers, making risk stratification in stages I and II precise and helping to avoid overtreatment in adjuvant therapy. This marks the first clinical staging system in gyneco-oncology in which such molecular markers are implemented [11].
Our results demonstrated a sensitivity of 70.9% and a specificity of 73.8% for the detection of endocervical invasion in fractional curettage. NCCN guidelines recommend primary office endometrial biopsy for the diagnostic evaluation of patients with metrorrhagia [21,22]. These examinations aim to minimize healthcare costs and reduce the low false-negative rate. A study by Leitao et al. showed that the upstaging from stage I to stage II/III in primary EC cases in a diagnostic setting was significantly lower when tissue was obtained using dilation and curettage compared to other diagnostic methods (8.7% vs. 17.4%) [23]. The combination of hysteroscopy and fractional curettage has a high sensitivity of 98.2% and specificity of 100% in detecting corpus mucosa polyps, endometrial carcinomas, and endometrial myomas [12]. Therefore, hysteroscopy with fractional curettage is often applied for diagnosing alterations of the endometrium [5,9]. Additionally, the assessment of endocervical involvement could be complemented using transvaginal ultrasound (TVUS) or magnetic resonance imaging (MRI). In a meta-analysis comprising 17 studies, Juan Luis Alcazar et al. [24] reported a pooled sensitivity of 63% (95% confidence interval [CI], 51%–74%) and a specificity of 91% (95% CI, 87%–94%) for detecting cervical invasion in EC with TVUS. MRI showed a low pooled sensitivity of 0.58 (95% confidence interval [CI] 0.55-0.62) but a high specificity of 0.95 (95% CI 0.94-0.95) in detecting cervical invasion with EC in a meta-analysis by Qiu Bi et al. [25]. Limitations of this study include its retrospective and unicenter design, as well as a small number of patients, which could influence the accuracy of these results. Nevertheless, precise patient selection, inclusion of only well-documented cases, surgeries performed, and pathological slide reviews by the same experienced team at our institution may enhance the validity of our analysis.
In conclusion, the preoperative detection of endocervical involvement could be evaluated as a prognostic factor in primary EC and may be implemented for therapeutic decision-making. Its determination in fractional curettage showed high sensitivity and specificity in preoperative diagnostics. Further prospective studies with a larger cohort are needed to establish the final role of positive ECC and fractional curettage in the diagnostic and therapeutic management of primary EC, as well as their role in combination with new molecular and immunohistochemical markers.

Statement of Ethics

The study received approval from the Institutional Review Boards of the UCT and the Ethical Committee at the University Hospital Frankfurt (project numbers: UCT-19-2021, UCT-31-2020). Written informed consent was not required due to the retrospective nature of this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Maria Laura Dokara-Friedrich: Drafting the word and manuscript, design, data collection
Marius Loeffler: data collection
Inna Shehaj: data collection
Morva Tahmasbi-Rad: revising the manuscript
Bahar Gasimli: revising the manuscript and data collection
Thomas Karn: statistical analysis
Mourad Sanhaji: data analysis
Sven Becker: interpretation, supervision
Khayal Gasimli: conception, supervision, design, interpretation

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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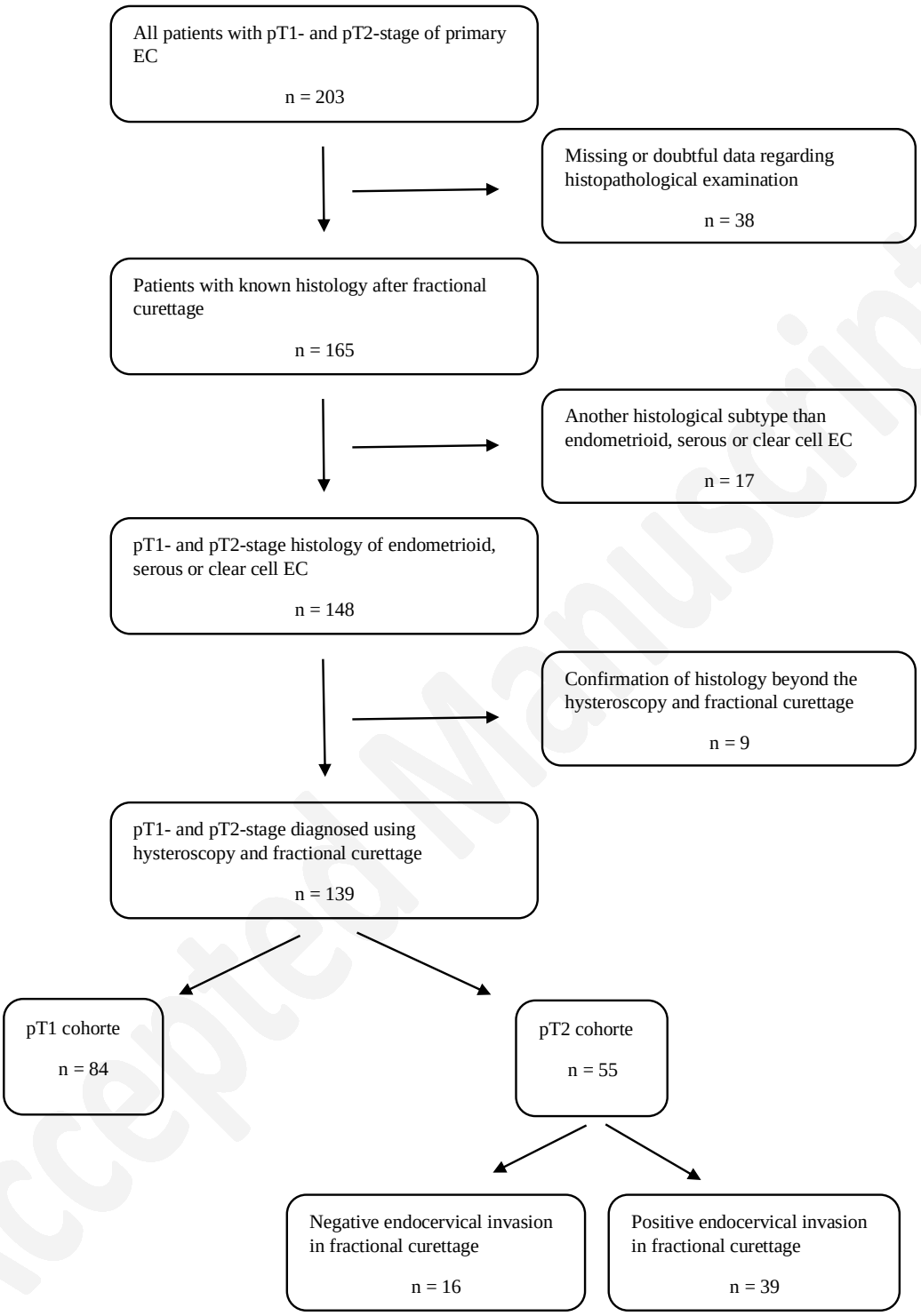
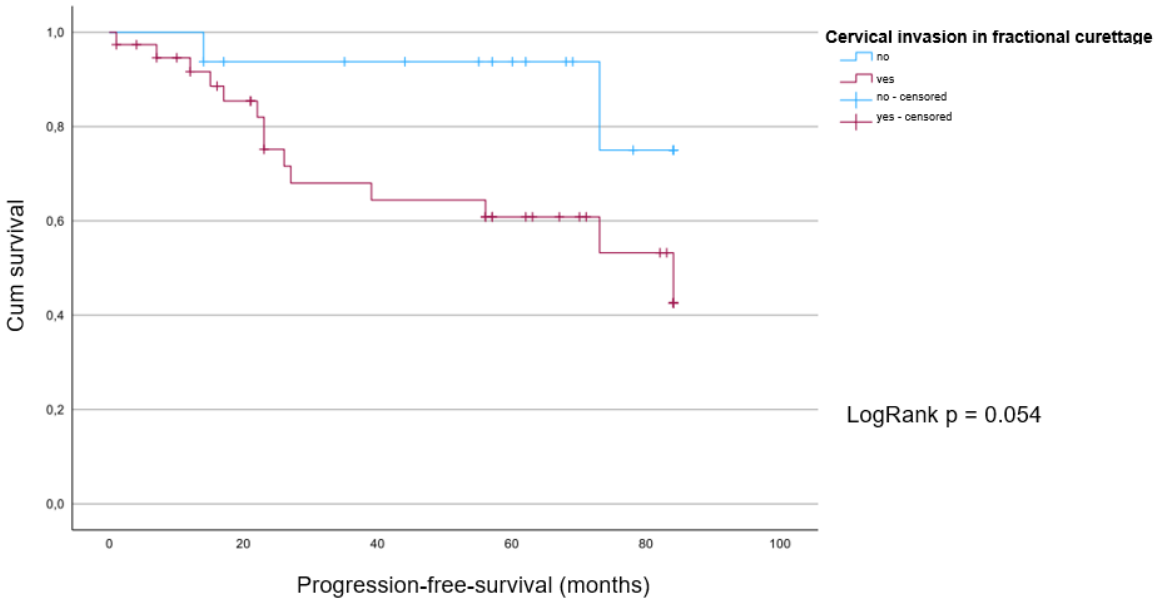
Figure Legends

Fig. 1. Flowchart of patients with primary EC underwent surgical treatment from 2011 to 2021.
Fig. 2. Progression free survival (PFS) according to endocervical invasion in fractional curettage.
Fig. 3. Overall survival (OAS) of T2-stage patients according to endocervical invasion in fractional curettage.





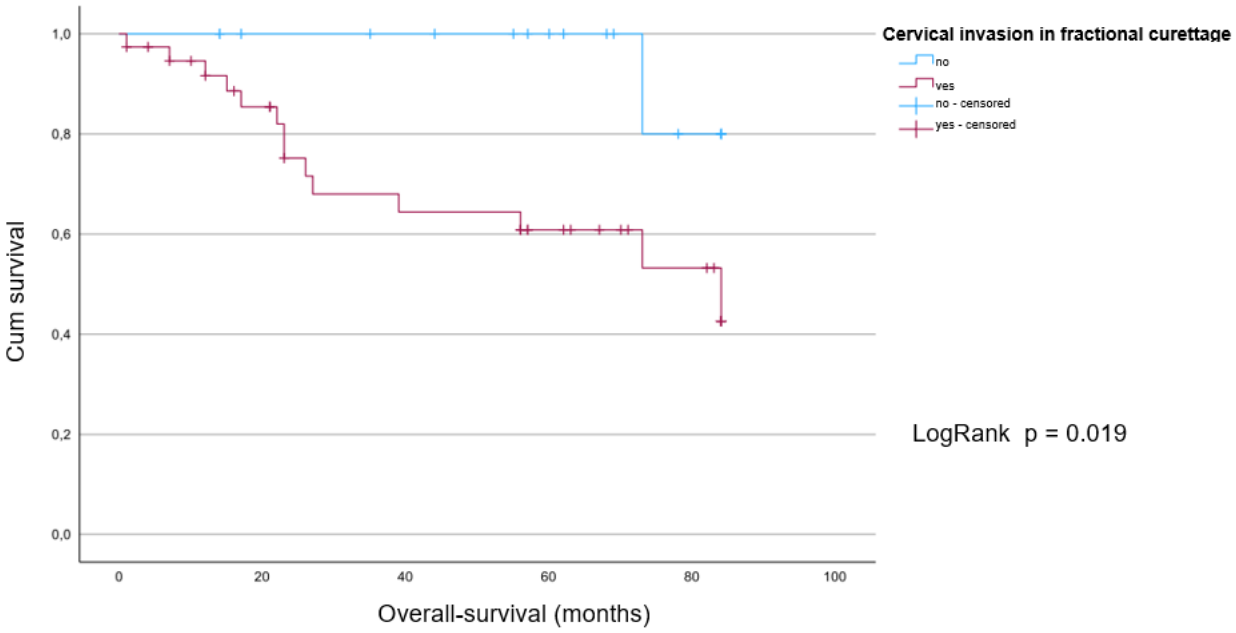


Table 1. Baseline-characteristics of pT2-stage primary endometrial cancer patients.

Variables	All patients (n=55)	Positive ECC cohort (n=39)	Negative ECC cohort (n=16)	*p*-value
Age at initial diagnosis [years; median (range)]	64 (38-85)	66 (38-85)	59.5 (43-72)	0.351
Age at diagnosis (years)				
<65	39 (70.9%)	21 (53.8%)	11 (68.8%)	0.127
≥65	16 (29.1%)	18 (46.2%)	5 (31.3%)	
ECOG performance status				
0	32 (58.2%)	20 (51.3%)	12 (75%)	0.282
I	17 (30.9%)	13 (33.3%)	4 (25%)	
II	4 (7.3%)	4 (10.3%)	0 (0%)	
III	2 (3.6%)	2 (5.1%)	0 (0%)	
BMI [kg/m ²; median (range)]	30.5 (18-51)	30 (18-51)	32 (22-46)	0.556
Metabolic syndrome				
Arterial Hypertension	22 (40.0%)	15 (38.5%)	7 (43.8%)	0.716
Diabetes Mellitus	16 (29.1%)	13 (33.3%)	3 (18.8%)	0.279
Obesity	28 (50.9%)	18 (46.2%)	10 (62.5%)	0.274
grade I	13 (23.6%)	7 (17.9%)	6 (37.5%)	
grade II	7 (12.7%)	4 (10.3%)	3 (18.75%)	
grade III	8 (14.5%)	7 (17.9%)	1 (6.3%)	
Hormonal status				
Premenopausal	12 (21.8%)	8 (20.5%)	4 (25.0%)	0.509
Perimenopausal	3 (5.5%)	3 (7.7%)	0 (0%)	
Postmenopausal	40 (72.7%)	28 (71.8%)	12 (75.0%)	
Histology				
endometrioid	50 (90.9%)	35 (89.7%)	15 (93.8%)	0.639
non-endometrioid[1]	5 (9.1%)	4 (10.3%)	1 (6.3%)	
Grading				
G1	15 (27.3%)	10 (25.6%)	5 (31.3%)	0.635
G2	21 (38.2%)	14 (35.9%)	7 (43.8%)	
G3	19 (34.5%)	15 (38.5%)	4 (25.0%)	
FIGO stage				
II	43 (78.2%)	29 (74.4%)	14 (87.5%)	0.430
IIIC	9 (16.4%)	8 (20.5%)	1 (6.3%)	
IVB	3 (5.4%)	2 (5.1%)	1(6.3%)	
Node status (pN)				
pNx[2]	10 (18.2%)	7 (18.0%)	3 (18.8%)	0.223
pN0	33 (60.0%)	21 (53.8%)	12 (75.0%)	
pN1	12 (21.8%)	11 (28.2%)	1 (6.2%)	
Distant metastasis				
M0	52 (94.5%)	37 (94.9%)	15 (93.8%)	0.868
M1	3 (5.4%)	2 (5.1%)	1 (6.3%)	
Lymphovascular space invasion (pLVSI)				
negative	37 (67.3%)	24 (61.5%)	13 (92.2%)	0.157
positive	18 (32.7%)	15 (38.5%)	3 (18.8%)	
Recurrences				
0-36 Months	6 (10.1%)	4 (10.3%)	2 (12.5%)	

>36 Months	1 (1.8%)	1 (2.6%)	0 (0%)	
Death	16 (29.1%)	14 (35.9%)	1 (6.3%)	
Follow-up [months; median (range)]	56 (5-122)	57 (1-122)	60 (14-94)	0.273

ECC – endocervical curettage; Obesity grade – ranks according to the WHO BMI classification; *BMI* – Body-mass index; *ECOG* performance status – Eastern Cooperative Oncology Group; *FIGO* – International Federation of Gynecology and Obstetrics (2009); Bold values indicate statistical significance ($p<0.05$)

[1] three serous EC, one clear cell EC, one mixed endometrioid and serous EC

[2] patients had no lymphadenectomy due to high risk for perioperative complications or refusal

Table 4. Cox regression analysis for prognostic factors influencing progression free survival (PFS).

Parameter	B	SE	Wald	OR	95% CI		*p*-value
					Lower Bound	Upper Bound	
Age at diagnosis	0.053	0.023	5.275	1.055	1.008	1.104	**0.022**
Endocervical invasion in fractional curettage (positive/negative)	1.825	0.869	4.414	6.202	1.130	34.037	**0.036**
FIGO stage	0.991	0.474	4.378	2.695	1.065	6.822	**0.036**
Grading	0.561	0.331	2.875	1.753	0.916	3.355	0,090
Histology	-0.228	0.179	1.623	0.796	0.561	1.131	0.203
Hormonal status	-0.429	0.630	0.463	0.651	0.190	2.239	0.496
ECOG	0.048	0.362	0.018	1.049	0.516	2.134	0.895
BMI	-0.001	0.041	0.001	0.999	0.922	1.082	0.980

Table 5. Cox regression analysis for prognostic factors influencing overall survival.

Parameter	B	SE	Wald	OR	95% CI		p-value
					Lower Bound	Upper Bound	
Age at diagnosis	0.086	0.029	8.581	1.090	1.029	1.155	**0.003**
Endocervical invasion in fractional curettage (positive/negative)	3.374	1.281	6.933	29.184	2.369	359.538	**0.008**
Grading	1.239	0.517	5.753	3.453	1.254	9.505	**0.016**
FIGO stage	1.238	0.540	5.254	3.449	1.197	9.941	**0.022**
Histology	-0.301	0.191	2.473	0.740	0.508	1.077	0.116
ECOG	0.224	0.369	0.368	1.251	0.607	2.580	0.544
Hormonal status	0.236	0.789	0.089	1.266	0.270	5.946	0.765
BMI	-0.002	0.043	0.002	0.998	0.918	1.086	0.967

Bold values indicate statistical significance (p<0.05)
B beta coefficient, *SE* standard error, *Wald* Wald-test *OR* Odds ratio, *CI* confidence interval, *FIGO* International Federation of Gynecology and Obstetrics (2009), *ECOG* performance status – Eastern Cooperative Oncology Group, BMI – Body-mass index

Table 2. Surgical procedures and adjuvant treatment of T2-stage patients.

Variables	All patients (n= 55)	Positive ECC cohort (n=39)	Negative ECC cohort (n=16)	*p*-value
Surgical entry				
Laparotomy	27 (49.1%)	25 (64.1%)	3 (18.7%)	**0.002**
Minimal invasive techniques	28 (50.9%)	14 (35.9%)	13 (81.3%)	
Duration of surgery [min; median (range)]	233.5 (112-435)	242 (171-435)	225 (112-321)	0.395
Surgical procedures				
Hysterectomy	55 (100%)	39 (100%)	16 (100%)	
Bilateral salpingo-oophorectomy				
yes	51 (92.7%)	37 (94.9%)	14 (87.5%)	0.339
no[1]	4 (7.3%)	2 (5.1%)	2 (12.5%)	
Pelvic lymphadenectomy				
primary	44 (80.0%)	31 (79.5%)	13 (81.3%)	0.289
secondary	1 (1.8%)	0 (0%)	1 (6.3%)	
no[2]	10 (18.2%)	8 (20.5%)	2 (12.4%)	
Para-aortic lymphadenectomy				
primary	30 (54.5%)	22 (56.4%)	8 (50%)	0.283
secondary	1 (1.8%)	0 (0%)	1 (6.3%)	
no	24 (43.6%)	17 (43.6%)	7 (43.8%)	
Omentectomy				
yes[3]	4 (7.3%)	2 (5.1%)	2 (12.5%)	0.339
no	51 (92.7%)	37 (94.9%)	14 (87.5%)	
Residual tumor				
pR0	54 (98.2%)	38 (97.4%)	16 (100%)	0.518
pR1	1 (1.8%)	1 (2.6%)	0 (0%)	
Adjuvant Therapy				
Radiotherapy[4]				
yes	40 (72.7%)	27 (69.2%)	13 (81.3%)	0.363
Brachytherapy	36 (65.5%)	24 (61.5%)	12 (75.0%)	0.340
External beam radiation therapy	15 (27.3%)	10 (25.6%)	5 (31.3%)	0.671
no[5]	15 (27.3%)	12 (30.8%)	3 (18.8%)	
Chemotherapy[6]				
yes	11 (20%)	9 (23.1%)	2 (12.5%)	0.373
no	44 (80%)	30 (76.9%)	14 (87.5%)	

Bold values indicate statistical significance (p<0.05); *ECC* – endocervical curettage
[1] it was already performed previously; [2] patients had no lymphadenectomy due to high risk for perioperative complications or refusal; [3] it performed by non-endometrioid EC; [4] eleven (20%) patients had both brachytherapy and external beam radiation therapy according to previous European and German guidelines; [5] procedure was refused by patients
[6] Chemotherapy *may be* applied for T2-patients according to previous European and German guidelines.

Table 3. Determination of the predictive value of fractional curettage.

		Fractional curettage		
		positive ECC	negative ECC	Total
Hysterectomy	positive ECC	39	16	55
	negative ECC	22	62	84
	Total	61	78	139

Accuracy	(39+62) / 139	72,7%
Sensitivity	39 / (39+16)	70,9%
Specificity	62 / (22+62)	73,8%
PPV	39 / (39+22)	63,9%
NPV	16 / (16+62)	79,5%

PPV – positive predictive value, *NPV* – negative predictive value,
ECC – endocervical curettage