Gynecologic Oncology 167 (2022) 196–204

Contents lists available at ScienceDirect

Gynecologic Oncology

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

The amount of preoperative endometrial tissue surface in relation to final endometrial cancer classification

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HIGHLIGHTS

- Obtaining higher amount of preoperative endometrial tissue does not increase correct final EC classification.
- No significant difference was found between the diagnostic sampling methods and the correct final EC classification.
- Patients with concordant low-grade EC had a significant superior DSS compared to patients that were downgraded.
- Patients with concordant high-grade EC had a significant impaired DSS compared to patients that were upgraded.

ARTICLE INFO

Article history:
Received 28 March 2022
Received in revised form 19 August 2022
Accepted 22 August 2022
Available online 10 September 2022

Keywords:
Endometrial carcinoma
Diagnosis
Concordant
Discordant
Pathology
Endometrial sampling

ABSTRACT

Objective. To evaluate whether the amount of preoperative endometrial tissue surface is related to the degree of concordance with final low- and high-grade endometrial cancer (EC). In addition, to determine whether discordance is influenced by sampling method and impacts outcome.

Methods. A retrospective cohort study within the European Network for Individualized Treatment of Endometrial Cancer (ENITEC). Surface of preoperative endometrial tissue samples was digitally calculated using ImageJ. Tumor samples were classified into low-grade (grade 1–2 endometrioid EC (EEC)) and high-grade (grade 3 EEC + non-endometroid EC).

Results. The study cohort included 573 tumor samples. Overall concordance between pre- and postoperative diagnosis was 60.0%, and 88.8% when classified into low- and high-grade EC. Upgrading (preoperative low-grade, postoperative high-grade EC) was found in 7.8% and downgrading (preoperative high-grade, postoperative low-grade EC) in 26.7%. The median endometrial tissue surface was significantly lower in concordant diagnoses when compared to discordant diagnoses, respectively 18.7 mm^2 and 23.5 mm^2 ($P = 0.022$). Sampling method did not influence the concordance in tumor classification. Patients with preoperative high-grade and postoperative low-grade showed significant lower DSS compared to patients with concordant low-grade EC ($P = 0.039$).

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https://doi.org/10.1016/j.ygyno.2022.08.016

Conclusion. The amount of preoperative endometrial tissue surface was inversely related to the degree of concordance with final tumor low- and high-grade. Obtaining higher amount of preoperative endometrial tissue surface does not increase the concordance between pre- and postoperative low- and high-grade diagnosis in EC. Awareness of clinically relevant down- and upgrading is crucial to reduce subsequent over- or undertreatment with impact on outcome.

1. Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in industrialized developed countries with an increasing incidence [1–3]. These carcinomas are histopathological classified as either endometrioid endometrial cancer (EEC) or non-endometrioid endometrial cancer (NEEC) [4]. Primary surgical treatment for EC consist of hysterectomy and bilateral salpingo-oophorectomy [5,6]. Additional lymph node surgery, i.e. sentinel lymph node mapping, lymph node dissection or algorithm-based approach for staging, is recommended in patients with increased risk of lymph node metastasis (LNM) [7,8]. The recent ESGO-ESTRO-ESP guideline recommended a modified binary FIGO grading considering both grade 1 and 2 EC together as low-grade EC and grade 3 EC and NEEC as high-grade EC [9]. Most patients are diagnosed with low-grade EC, and generally have a favorable prognosis with a 5-year survival rate of 85.6% [5]. About 20.0% of the patients are diagnosed with high-grade EC, have an overall poor prognosis with a 5-year survival rate of 58.8% and are associated with increased risk of regional or distant metastases [5,3].

A meta-analysis has shown only moderate concordance of 67.0% between pre- and postoperative tumor grading [11]. The lowest concordance was found for grade 2 EC (61.0%), and as these are generally classified as low-grade, disagreement in grading might impact treatment and outcome since performance of lymph node surgery is generally performed in high-grade EC only [9,12,13]. Explanations for discordance on grade include 1) sampling errors leading to missed tumor components, 2) interobserver disagreement due to subjective interpretation of the defined criteria and 3) limited amount of tissue obtained by preoperative endometrial sampling, that might impair assessment of tumor characteristics. In 13–30% of the pipelle endometrial samples, insufficient material requires repeated biopsy for a reliable diagnosis, as in 7.3% of the failed samples women are subsequently diagnosed with EC [14–17]. Interestingly, Visser et al. showed that hysteroscopic biopsies had a higher concordance (89%) compared to samples obtained by dilatation and curettage (D&C) (70%), questioning whether in addition to the amount of tissue, the sampling method may also be relevant [11].

In a previous study of our research group, we showed that the amount of endometrial tissue surface to classify an endometrial sample as conclusive with high diagnostic accuracy as malignant or non-malignant, was defined by a minimum cut-off level of 35 mm^2 [11,14]. However, this study was not designed to further specify the diagnosis on tumor grade and/or histological subtype. Therefore, in the present study, we aim to evaluate the amount of preoperative endometrial tissue surface in relation to the degree of concordance with final low- and high-grade EC. Furthermore, we investigate whether discordancy in pre- and postoperative grading is influenced by the sampling method and whether discordancy impacts outcome.

2. Methods

2.1. Patients

The samples of patients were retrospectively collected within the European Network for Individualized Treatment of Endometrial Cancer (ENITEC) from a previous study including 1199 EC patients [15]. Patients were only included when they were diagnosed by an expert gynecological pathologist of the participating hospitals, with complete data on treatment and histopathology. Clinical and pathological data were recorded from the patient files into a database; including patient age, date of diagnosis, preoperative sampling method, surgical treatment, original pre- and postoperative tumor grade and histological subtype, myometrial invasion (MI), cervical invasion (CI), lymphovascular space invasion (LVSI), FIGO (International Federation of Gynaecology and Obstetrics) stage, adjuvant treatment, recurrent disease and death [15]. The sole additional inclusion criterion used for this study was the availability of preoperative EC tissue samples, resulting in 644 patients.

2.2. Tumor classification

In addition to the FIGO three-tiered tumor grade, EC tissue samples were classified into low- and high-grade EC as recommended by the recent ESGO-ESTRO-ESP guideline and the World health organization (WHO) classification of tumors [9,18]. Low-grade EC was defined as grade 1 and 2 EEC, and included samples with mucinous histology as well since prognosis and molecular characterization are similar to low-grade EECs [15]. High-grade EC included grade 3 EEC and NEEC, i.e. serous, clear cell carcinoma, carcinosarcoma and mixed carcinomas [9,18]. Endometrial tissue samples were defined as upgraded if the preoperative sample was low-grade and postoperative high-grade EC. Downgraded was defined as preoperative high-grade and postoperative low-grade EC. Biopsies initially diagnosed as premalignant, but EC on final hysterectomy specimen were included in this study.

2.3. Scoring

All the preoperative endometrial sampling slides were digitalized using Pannoramic Scanner 250 Flash III (3DHISTECH, Budapest, Hungary). As described previously by Reijnen et al., images were saved as a JPEG-compressed file and the area of endometrial tissue was digitally calculated using ImageJ software, selecting only benign, premalignant and malignant endometrial epithelium (*Supplementary Fig. S1)* [14]. Thresholds 24-bit RGB images based on Hue Saturation and Brightness (HSB) were used to select the endometrial tissue surface, by adjusting the different threshold values to segment the image into the area of interest and the background. The Pannoramic Viewer software was used to examine the original-size digital slide in order to ensure ImageJ correctly selected the proper tissue. Subsequently, analysis was performed on the area selection to count and measure pixels in the threshold images and calculate the total area of endometrial tissue. A set of 50 slides were scored independently by two investigators (AH, CR) to assess the degree of inter-rater variability and intraclass correlation coefficient (ICC). A set of 90 slides were double-checked by a third investigator (SV) to ensure ImageJ selected the proper tissue.

2.4. Statistical analysis

All statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) statistics for Windows, version 25.0 (released 2017, Armonk, NY, United States) and $P < 0.05$ was

considered statistically significant. For observing within the low- and high-grade classification, the pre- and postoperative tumor diagnosis was specified in individual FIGO tumor grade and histological subtype. These included the original diagnosis (including premalignant tissue); grade 1, grade 2, grade 3 EEC or NEEC. For continuous data that were not normally distributed, the Mann-Whitney U and Kruskal Wallis test were used to compare the differences in median endometrial tissue surface and patient characteristics. Clinicopathological characteristics between dichotomous subgroups were compared using the χ^2 or Fisher's exact test for categorical data. Survival analyses were performed using the Kaplan Meier curves (first 10 years after diagnosis). Disease-specific survival (DSS) was defined as time from date of diagnosis to date of death from EC, all censored by date of last contact.

2.5. Ethics approval

Ethical approval was obtained from the Institutional Review Board (IRB) CMO Radboudumc (number: 2018–4955).

3. Results

3.1. Patients

From the original cohort of 1199 patients, 644 preoperative biopsies were available, of those 46 patients were excluded because absence of tumor tissue due to insufficient amount of tissue and benign endometrium and 25 because of an unspecified grade on preoperative biopsy, resulting in a total of 573 patients included in this study with a median follow-up of 5.7 years (Supplementary Fig. S2). Excluded patients did not significantly differ from included patients with respect to tumor histology (*data not shown*). Baseline characteristics for all included patients, classified into postoperative low- and high-grade, are summarized in Table 1. Among these 573 patients, 462 patients (80.6%) were postoperative low-grade and 111 (19.4%) high-grade EC. The mean age at diagnosis was 64.8 years, most patients were preoperative diagnosed with grade 1 EEC (53.8%) and postoperative FIGO stage I (82.9%). The most used preoperative sampling method was the pipelle (45.2%). Patients diagnosed with postoperative high-grade EC were significantly older, had lower Body Mass Index (BMI), more often LNM, subsequently resulting in more applied adjuvant chemotherapy and chemoradiotherapy compared to patients with low-grade EC.

In Supplementary Table S1 detailed baseline information about patients diagnosed with postoperative NEEC ($n = 34$) is shown. Most patients with NEEC had serous histology ($n = 14$, 41.2%).

3.2. Concordance pre- and postoperative tumor grade and histology

Fig. 1 shows the number and percentages of the pre- vs. postoperative individual tumor grade and histological subtype. *Dark green* shows the exact concordance between grading and histology, *light green* the concordance for the clinically relevant low- and high-grade classification and in *red* the clinically relevant discordancy. Overall, of the 573 EC tissue samples, 60.0% ($n = 345$) showed concordant pre- and postoperative tumor grade and histological subtype (*dark green*). The lowest concordance was found for preoperative grade 3 EC (51.4%).

Concordance between pre-and postoperative low- and high-grade EC was found in 88.8% ($n = 509$) patients (*light green + dark green*). Patients with preoperative low-grade EC showed concordant diagnoses in 92.2% ($n = 435$) and were upgraded to high-grade EC in 7.8% ($n = 37$). Patients with preoperative high-grade EC showed concordant diagnoses in 73.3% ($n = 74$) and were downgraded in 26.7% ($n = 27$).

3.3. Median endometrial tissue surface and degree of concordance

An overview of the median endometrial tissue surface related to pre- vs. postoperative tumor grade and histological subtype is shown in

Table 1
Baseline characteristics.

	Total ($n = 573$)	Postoperative Low-grade ($n = 462$)	Postoperative High-grade ($n = 111$)	*P*
Age (years)	64.8 ± 9.8	64.1 ± 9.6	66.6 ± 10.0	0.014*
BMI (kg/m^2)	30.2 ± 6.7	30.4 ± 6.5	28.7 ± 5.5	0.013*
Preoperative grade				
Premalignant†	8 (1.4)	8 (1.7)	0 (0.0)	<0.001*
1 EEC	308 (53.8)	295 (63.9)	13 (11.7)	
2 EEC	156 (27.2)	132 (28.6)	24 (21.6)	
3 EEC	74 (12.9)	22 (4.8)	52 (46.8)	
NEEC	27 (4.7)	5 (1.1)	22 (19.8)	
Preoperative sampling method				
Pipelle	259 (45.2)	199 (43.1)	60 (54.1)	0.002*
D&C	77 (13.4)	63 (13.6)	14 (12.6)	
Hysteroscopic biopsy	213 (37.2)	189 (40.9)	24 (21.6)	
Not specified	24 (4.2)	11 (2.4)	13 (11.7)	
FIGO stage				
I	475 (82.9)	413 (89.4)	62 (55.9)	<0.001*
II	36 (6.3)	24 (5.2)	12 (10.8)	
III	45 (7.9)	22 (4.8)	23 (20.7)	
IV	17 (2.9)	3 (0.6)	14 (12.6)	
Positive nodes				
No	299 (52.2)	240 (52.0)	59 (53.2)	<0.001*
Pelvic	17 (3.0)	7 (1.5)	10 (9.0)	
Para-aortic	11 (1.9)	2 (0.4)	9 (8.1)	
Both	5 (0.9)	1 (0.2)	4 (3.6)	
Not specified	241 (42.0)	212 (45.9)	29 (26.1)	
Adjuvant treatment				
No	267 (46.7)	238 (51.5)	29 (26.1)	<0.001*
Radiotherapy	263 (46.0)	204 (44.2)	59 (53.2)	
Chemotherapy	17 (3.0)	5 (1.1)	12 (10.8)	
Chemoradiotherapy	25 (4.4)	14 (3.0)	11 (9.9)	
Missing	1 (0.2)	1 (0.2)		

Data is presented in number (%), mean ± standard deviation (SD).
Abbreviations: EEC, endometrioid endometrial cancer; NEEC, non-endometroid endometrial cancer; BMI, Body Mass Index; FIGO, International Federation of Gynaecology and Obstetrics
* $P < 0.05$.
† Including simple or complex hyperplasia, with or without atypia.

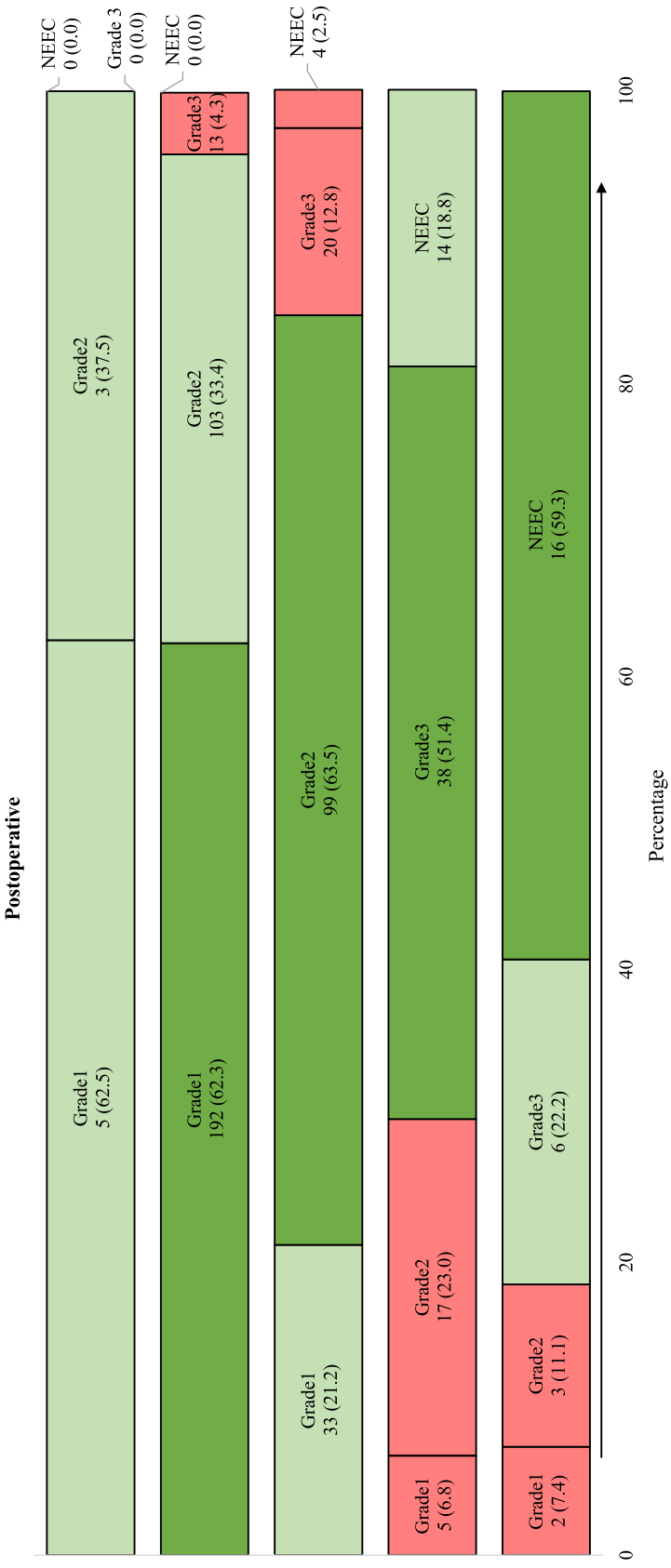

Fig. 1. Number and percentages (*n* (%)) of the pre- vs. postoperative individual tumor grade and histological subtype.
Abbreviations: EEC, endometroid endometrial cancer; NEEC, non-endometroid endometrial cancer.

Table 2
Overview of pre- vs. postoperative tumor grade and histological subtype. Median endometrial tissue surface (mm^2) of endometrial cancer patients are shown. Displayed in dark green are the concordant diagnoses. *Dark green* shows the exact concordance between grading and histology, *light green* the concordance for the clinically relevant low- and high-grade classification and in *red* the clinically relevant discordancy.

		Postoperative				
		Grade 1 EEC	Grade 2 EEC	Grade 3 EEC	NEEC	Total**
Preoperative	Premalignant	7.3 (0.8-8.4)	2.9 (1.0-3.5)	NA	NA	4.4 (0.8-8.4)
	Grade 1 EEC	17.2 (0.2-298.7)	15.6 (0.0-354.0)	16.1 (0.5-145.0)	NA	16.6 (0.0-354.0)
	Grade 2 EEC	35.1 (1.0-251.4)	21.9 (0.6-278.7)	30.0 (1.9-110.9)	18.2 (10.1-30.6)	24.6 (0.6-278.7)
	Grade 3 EEC	42.4 (12.5-94.2)	38.6 (0.4-274.9)	29.7 (0.2-210.2)	16.1 (1.4-81.7)	24.4 (0.2-274.9)
	NEEC	26.7 (9.8-43.6)	16.6 (0.1-44.7)	11.5 (0.9-18.1)	21.1 (0.7-49.4)	14.7 (0.1-49.3)
	Total*	18.7 (0.2-298.7)	19.9 (0.0-354.0)	23.3 (0.2-210.2)	17.6 (0.7-81.7)	

Data is presented in median (range).
Abbreviations: EEC, endometroid endometrial cancer; NEEC, non-endometroid endometrial cancer.
*$P = 0.888$ between the total median postoperative endometrial tissue surface.
**$P = 0.063$ between the total median preoperative endometrial tissue surface.

Table 2. There was no significant difference between the median endometrial tissue surface of the individual tumor grade and histological subtype preoperatively, nor postoperatively, ($P = 0.063$ and $P = 0.888$, respectively).

The median endometrial tissue surface between concordant (*dark green*) and discordant (*light green + red*) individual tumor grade and histological subtype showed no significant difference (19.6 mm^2 vs. 18.6mm^2, respectively, $P = 0.468$). For the clinically relevant low- and high-grade classification, the median endometrial tissue surface for concordant diagnoses (*dark green + light green*) was significant lower compared to the discordant diagnoses (*red*) (18.7 mm^2 vs. 23.5 mm^2, respectively, $P = 0.022$) (Table 2). In Supplementary Table S2 the correlation between median endometrial tissue and concordant and discordant diagnoses is shown per included center.

Patients with concordant pre- and postoperative low-grade EC showed lower median endometrial tissue surface compared to preoperative low-grade and postoperative high-grade EC (upgraded), but not significantly (18.4 vs 20.1 mm^2, $P = 0.335$). Patients with concordant pre- and postoperative high-grade EC had significant lower endometrial tissue surface compared to patients with preoperative high-grade and postoperative low-grade EC (downgraded) (20.3 vs 38.6 mm^2, $P = 0.044$) (Fig. 2).

3.4. Sampling method

For 549 (95.8%) patients preoperative sampling method was available. Pipelle endometrial sampling was performed in 47.2%, D&C in 14.0% and hysteroscopic biopsy in 38.8% of the patients with available sampling method (Supplementary Table S3). No significant difference was found between the diagnostic sampling methods and the concordance between pre- and postoperative low- and high-grade EC ($P = 0.364$), nor for the individual tumor grade and histological subtype ($P = 0.097$).

Median endometrial tissue surface for the preoperative sampling method pipelle was 18.6 mm^2, D&C 67.8 mm^2 and hysteroscopic biopsy 15.4 mm^2 ($P < 0.001$). All preoperative sampling methods (pipelle, D&C, hysteroscopic biopsy) showed higher median endometrial tissue surface in discordant low- and high-grade diagnoses, compared to concordant low- and high-grade diagnoses. Similar was shown for individual tumor grade and histological subtype diagnoses (Supplementary Fig. S3).

3.5. Concordance, discordance and survival outcome

The DSS of the concordant and discordant diagnoses are shown in Fig. 3A-C. Fig. 3A showed the DSS of the patients with concordant high-grade EC, concordant low-grade EC, and clinically relevant downgraded and upgraded diagnoses ($P < 0.001$). Patients with concordant low-grade EC had a significant superior DSS compared to patients that were downgraded (96.5% and 88.9% respectively, $P = 0.039$) (Fig. 3B). Patients with concordant high-grade EC had a significant impaired DSS compared to patients that were upgraded (71.4% and 88.6% respectively, $P = 0.046$) (Fig. 3C).

4. Discussion

This study assessed whether the amount of preoperative endometrial tissue surface is related to the degree of concordance with final classification of low- and high-grade EC, and whether discordance is influenced by the diagnostic sampling method and impacts outcome. Overall, 60% showed concordant pre- and postoperative tumor grade and histological subtype and there was 88.8% concordance in pre- and postoperative classification into low- and high-grade EC, with 92.2% concordant low-grade, and 73.3% concordant high-grade EC. The median endometrial tissue surface between concordant and discordant individual tumor grade and histological subtype showed no significant difference. Interestingly, concordant diagnoses revealed a significant lower median endometrial tissue surface compared to discordant diagnoses. Furthermore, the sampling method did not influence the degree of concordance. Finally, patients with preoperative low-grade and postoperative high-grade EC had significant improved DSS compared to patients with concordant high-grade EC.

Numerous studies stated that preoperative endometrial sampling is poorly correlated with final tumor grade and histological subtype [19–21]. On the contrary, Sany et al. mentioned good agreement between preoperative and final pathology with sensitivities of 96.5% for EECs and 86.5% for NEECs [22]. Our study findings are in line with Visser et al. who reported an overall moderate concordance of 67% on tumor grade [11]. Clinically relevant downgrading was reported in 26% of the included patient samples and upgrading in 8% [11]. Our results show similar clinically relevant downgrading of 26.7% and upgrading in 7.8%. Several studies note that the diagnostic consensuses of tumor grade and histological subtype based on morphology alone are overall moderate. Performing immunohistochemical (IHC) markers on preoperative tissue could help to improve the degree of concordance between pre- and postoperative diagnosis, especially for preoperative grade 2 and grade 3 EC with the lowest concordance [11,23–26]. For preoperative grade 2, a panel of progesterone (PR) and p53 biomarkers has been recommended, and, for grade 3/high-grade EC additional PR, IMP3 and L1CAM [26]. Whether combined pathologic and molecular

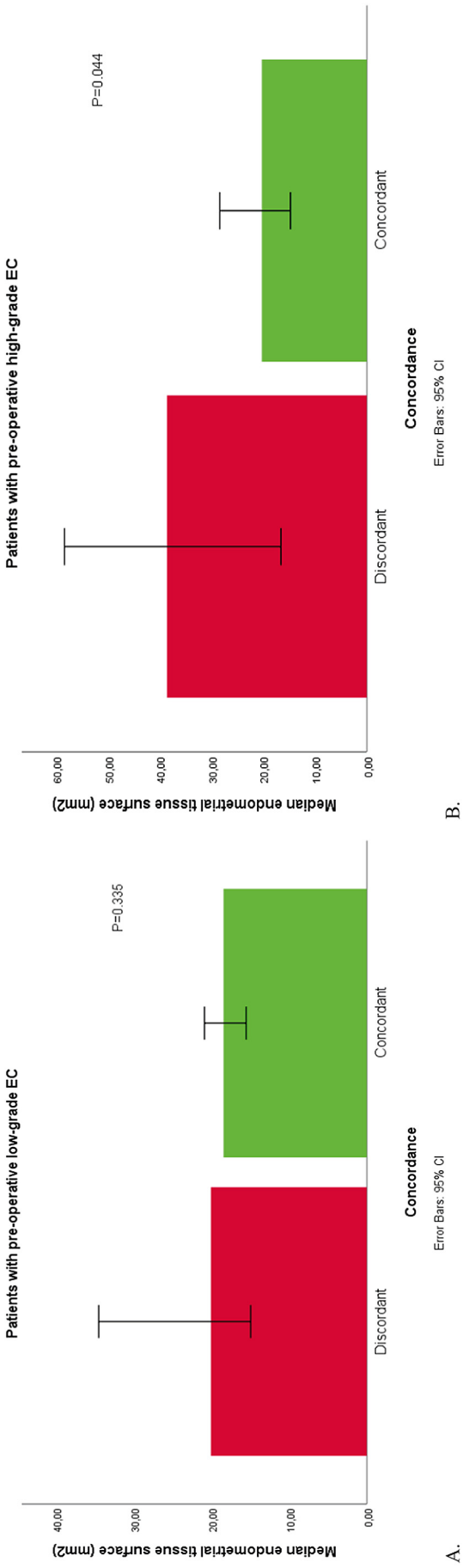

Fig. 2. A-B: A. Patients with preoperative low-grade endometrial cancer (EC) and the median endometrial tissue surface for postoperative discordant or concordant diagnoses. B. Patients with preoperative high-grade EC and the median endometrial tissue surface for postoperative discordant or concordant diagnoses.

classification might further improve preoperative classification for high-grade EC needs to be determined [27].

Our study design is comparable to Reijnen et al. in which the diagnostic accuracy of pipelle endometrial sampling and the amount of endometrial tissue surface for benign, premalignant and malignant tissue was quantified [14]. Reijnen et al. found a positive correlation between the amount of endometrial tissue surface and concordance of diagnosis for premalignant and malignant tissue, furthermore he defined a minimum cut-off of 35 mm^2 to classify an endometrial sample as conclusive. Interestingly, whereas the amount of tissue seems to be important for classifying tissue as premalignant or malignant, in our study, no positive correlation was found when malignant tissue was classified into tumor grade and histology and we did not found a minimum cut-off for concordant grading (*data not shown*). An explanation for this contra-intuitive finding could be interobserver agreement, yet, both studies show a high intraclass correlation coefficient (ICC) (0.98 vs. 0.92 in our study) [14]. Another explanation could be sampling bias or a missed tumor component by the pathologist. In our study, three experienced expert gynecological pathologists (JB, HK, KV) performed an explorative analysis in 30 (46.9%) cases with low- vs. high-grade discrepancy. Sampling bias based on heterogeneous and mixed tumors, or only superficial tumor tissue sampling was present in a third of the cases. In two third of the cases the discrepancy was caused by the pathologist, by miscalculation of the percentage solid growth or missed tumor component (*data not shown*). So, incorrect classification by the pathologist seems to be present, and will remain in the current diagnostic context. This might partially be resolved by molecular profiling in high-grade EEC as demonstrated by Bosse et al., but will not solve the sampling bias [28].

The concordance between pre- and postoperative low- and high-grade EC did not significantly differ between the three sampling methods, which is quite comparable to other studies [11,29]. Illustrating, that more tissue provided with D&C or accurate sampling by hysteroscopic biopsy will not automatically result in more concordant diagnoses.

Accurate preoperative classification of tumor grade and histological subtype is crucial in EC, as this may be directive to the extent of the surgical approach. Consequently, postoperative upgrading will lead to omitted lymph node surgery and/or staging procedure and altered adjuvant therapy, whereas downgrading may result in unnecessarily surgical related complications both impacting clinical outcome [11]. A significant increase of DSS has been found in patients that were postoperatively upgraded, compared to patients with concordant high-grade EC. Furthermore, patients that were downgraded had significant decreased DSS compared to concordant low-grade EC. Both of our findings are in line with Werner et al. [13], and may be explained by the presence of tumor heterogeneity and/or minor mixed morphologic characteristics [30,31].

To our knowledge, this is the first study that quantified the amount of endometrial tissue surface by computerized measurement, and related this to the degree of concordance with final tumor grade and histological subtype in EC. The computerized assessment of the endometrial tissue surface was performed in a structured and reproducible fashion with a good interobserver agreement (ICC 0.92, 95% CI 0.80–0.97).

As this was a retrospective study, one limitation could be that there has been no study protocol for the assessment of endometrial tissue. In addition, there might be a selection bias as the original diagnosis and classification of both pre- and postoperative histology was used without centralized pathology review. However, slides were from large referral hospitals and diagnoses were made by expert gynecological-pathologists. The results of this study are therefore applicable to daily practice and, as agreement is in line with previous findings, bias may be therefore considered to be limited. Finally, the small number of patients with serous EC ($n = 14$, 2.4%) could limit the generalizability for this type of EC. Yet, serous carcinoma represents <10% of all ECs [32]. Also, it is known that there is poor interobserver agreement in

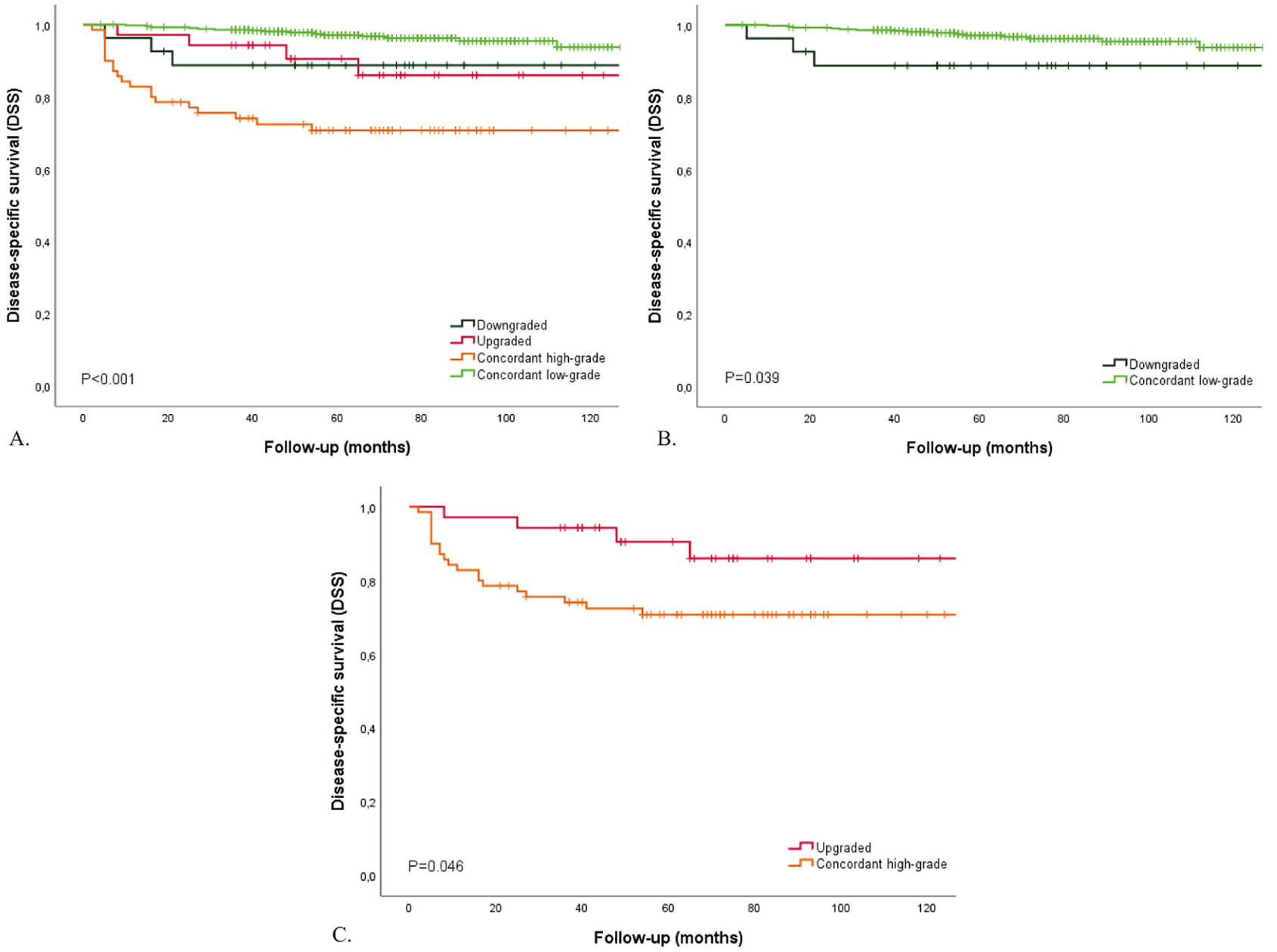

Fig. 3. A-C: Kaplan-Meier survival curves of disease-specific survival A. Disease-specific survival of concodant low-grade endometrial cancer (EC), concordant high-grade EC, downgraded and upgraded patients. B. Disease-specific survival of concordant low-grade EC and downgraded patients. C. Disease-specific survival of concordant high-grade EC and upgraded patients.

high-grade EEC based on preoperative histology [23,24,33–36].

Although several studies support the use of a binary grading system (low- vs. high-grade) over the FIGO grading system with respect to reproducibility, awareness of clinically relevant down- and upgrading remains crucial [9,18,35,37,38]. Instead of providing more endometrial tissue, the use of a simple and relatively cheap set of IHC markers, such as p53 (reflecting the most aggressive molecular subgroup of the TCGA), ER/PR and L1CAM, could improve the concordance between pre- and postoperative low- and high-grade EC, and pre- and postoperative individual tumor grade and histological subtype [26,39]. According to the recent recommendations of the Society of Gynecologic Oncology (SGO), current clinicopathological prognostic parameters (e.g. histology and grade) should guide initial clinical management in EC. Molecular classification, especially TP53 mutations, may help guide future treatment decisions [8].

In conclusion, obtaining a higher amount of preoperative endometrial tissue surface does not increase the concordance between pre- and postoperative low- and high-grade classification in EC. Awareness of clinically relevant down- and upgrading is crucial to reduce subsequent over- or undertreatment with impact on outcome.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2022.08.016.

Funding

This work was not funded.

CRediT author statement

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Declaration of Competing Interest

The authors report no conflict of interest.

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