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Lymphovascular space invasion in endometrial carcinoma

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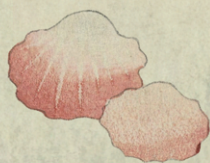
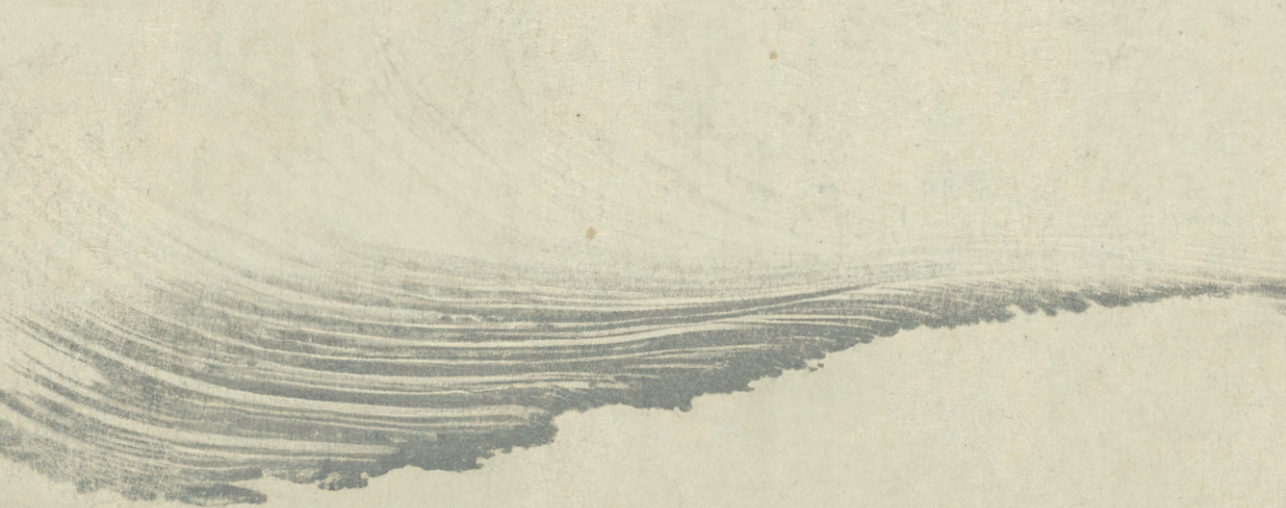
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CHAPTER 4

PROGNOSTIC IMPACT OF HISTOLOGICAL REVIEW OF HIGH-GRADE ENDOMETRIAL CARCINOMAS IN A LARGE DANISH COHORT

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Abstract

The aim of this study was to investigate the outcome of histological subtype review of high-grade EC and its prognostic impact in a large well-documented Danish nationwide cohort. From the Danish Gynecological Cancer Database (DGCD) 2005-2012 cohort we included 425 patients with an original diagnosis of high-grade EC, independent of histologic subtype. Of these, at least one haematoxylin and eosin (H&E) stained slide from 396 cases (93.2%) was available for review. The histologic subtype was reviewed by specialized gynecopathologists blinded to the original diagnosis and clinical outcome. Interobserver variability between original and revised histologic subtype was analysed using simple Kappa statistics. Hazard ratios (HR), recurrence free survival (RFS) and overall survival were calculated for original and revised subtypes, respectively.

Overall histologic subtype agreement was moderate ($\kappa=0.42$) with the highest agreement for endometrioid-type EC (EEC; 75.5%) and serous-type EC (SEC; 63.8%). For clear cell carcinoma and un-/dedifferentiated EC, agreement was significantly lower; 30.1% and 33.3% respectively. Of the 396 reviewed cases, only two (0.5%) were re-classified as low-grade EEC upon revision. Interestingly, GR3 EEC had better RFS than SEC with stronger significance after revision, HR 2.36 (95% CI 1.43-3.89), $p=0.001$, compared to original diagnosis, HR 1.74 (95% CI 1.07-2.81), $p=0.024$.

In conclusion, this study confirmed that pathology review results in substantial shift in histological subtype in high-grade EC. After review, a stronger prognostic benefit for GR3 EEC as compared to other histological subtypes was observed. This work supports maintaining a low threshold for pathology revision of high-grade EC in clinical practice.

Introduction

The prognostic relevance of histologic subtype within high-grade endometrial carcinomas (EC) is poorly defined. It is however generally accepted that high-grade endometrioid-type (EEC, GR3) have a slightly better prognosis than the high-grade non-endometrioid ECs. For adjuvant treatment decisions, a risk stratification (e.g., low/intermediate/high-intermediate/high risk) is made, which relies on a combination of clinicopathological risk factors including The International Federation of Gynecology and Obstetrics (FIGO) stage, grade, age, lymphovascular space invasion (LVSI) and histologic subtype. FIGO stage III/IV disease is considered high-risk per definition, independent of any of the other factors. In stage I/II disease the risk assignment is stratified depending, among other factors, on grade and histotype [1]. For risk-assignment of a patient with stage I/II disease with a high-grade EC, histologic subtype is considered relevant: patients with FIGO stage IA myoinvasive grade 3 endometrioid-type EC (GR3 EEC) without substantial LVSI are considered intermediate risk, whereas myoinvasive stage IA non-endometrioid-type (non-EEC) are considered high risk. Similarly, FIGO stage IB GR3 EEC are high-intermediate risk, whereas FIGO stage IB non-EEC would be considered high-risk [1]. Therefore, in the context of stage I/II disease, distinguishing histologic subtype of a high-grade EC may have consequences for clinical management.

High-grade EC is an heterogenous group of tumours consisting of GR3 EEC and non-EECs including serous carcinoma (SEC), clear cell carcinoma (CCC), mixed epithelial carcinomas, de-/undifferentiated endometrial carcinomas (DEC) and uterine carcinosarcoma (UCS). Despite the apparently clear histological description of high-grade histologic subtypes in the WHO classification [2], it has now been well documented that significant interobserver variability exists, even among experts [3–7]. This is likely due of the morphologic heterogeneity of this disease, in which a significant number of cases are difficult to classify. Although in these ambiguous high-grade EC immunohistochemical markers may help (e.g., Napsin A for the diagnosis of CCC), these markers are frequently not conclusive [8, 9]. This is causing a problem for the clinical management of those stage I/II patients for which the risk assignment relies on histologic subtype.

Research groups aware of this problem invest significant amounts of time reviewing retrospective cohorts by specialized gynecopathologists to ensure uniformity in the research setting [7, 10–12]. In addition, this interobserver variability issue has resulted in the recommendation to apply a low threshold for pathology revision of high-grade EC in clinical practice, suggesting that experienced and specialized pathologists maybe in a better position to assign histologic subtype. The obvious downside of this practice is the time and costs involved, both in clinical and research setting. The consequences of this general practice are only poorly studied; hence it is worth to clarify the impact of possible changes on clinical outcome in relation to the revised diagnosis. Therefore, the aim of this study was to investigate

the effects of histological review of high-grade EC and its prognostic impact in a large national Danish cohort.

Materials and methods

The Danish Gynecological Cancer Database (DGCD) includes 4707 EC patients diagnosed between January 1, 2005 to December 31, 2012 [13]. The DGCD holds prospectively registered information about initial surgical and adjuvant treatment, pathology diagnosis and follow-up data [14]. From the DGCD 2005-2012 cohort we included 425 patients with an original diagnosis of high-grade EC (all histologic subtypes except uterine carcinosarcomas). Of these, at least one haematoxylin and eosin (H&E) stained slide from 396 cases (93.2%) could be retrieved for review (Figure 1).

These cases were originally diagnosed at 19 different pathology institutes distributed throughout Denmark. Distribution in age, original histologic subtype, stage, lymphovascular space invasion (LVSI) status and risk group according to ESMO-ESGO-ESTRO 2016 [15] are shown in Table 1. Follow-up data for Cox analyses and Kaplan-Meier curves were retrieved from the database, from the national patients file registry and patient's medical records. Missing data regarding recurrences were retrieved from the pathology reports in the Danish pathology database. Deaths were retrieved from the Danish Person Register and Cause of Death Register.

Pathology revision

The review was performed by four gynecopathologists (EEMP, ALC, VTHBMS and TB). Even though in some instances immunohistochemistry was used for the original diagnosis, the histology review for this study was performed with H&E slides only. The vast majority of cases included H&E slides from the hysterectomy specimen (394/396; 99.5%), but in two cases it was limited to an H&E of the endometrial biopsy (2/396; 0.5%). The average and median number of slides reviewed per case was 10.9 (range 1-70, median 10), and cases were equally and randomly distributed among the members of the reviewing group. Prior to final histologic subtype assignment, all cases with ambiguous morphology (68/396; 17.2%) were discussed by the review group together to reach consensus diagnosis. The review group was blinded to the original diagnosis and any of the other clinicopathological variables listed in Table 1. The pathology review focused on histologic subtype and did not include re-assessment of grade or FIGO stage. The review group also assessed LVSI extent in this study cohort, results of which will be published separately.

The cases included were originally diagnosed as high-grade carcinomas including GR3 EEC, SEC, CCC or un-/dedifferentiated carcinoma (DEC). For histologic subtype assignment the review group used the terminology of the WHO 2014 [2]. In a minority of cases, histology could not be assessed due to poor tissue fixation, too small tumour, or no remaining tumour in the available slides from the hysterectomy.

Table 1. Distribution in age, original histological type, FIGO stage, lymphovascular space invasion (LVSI) status and risk group according to ESMO-ESGO-ESTRO 2016 [15]

All patients	n	396
	Median	Range
Age at diagnosis (years)	69	43-94
Lower quartile (years)	63	
Upper quartile (years)	76	
	Median	Range
Follow-up time	8.5	5.1-13.0
<i>Histological type</i>	n	%
GR3 EEC	163	41.2
SEC	141	35.6
CCC	83	21.0
DEC	9	2.3
<i>FIGO stage</i>	n	%
Stage I	292	73.7
Stage II	31	7.8
Stage IIIc1	46	11.6
Stage IIIc2	19	4.8
Stage IV	8	2.0
<i>Risk group</i>	n	%
High risk	324	81.8
High-intermediate risk	72	18.2
<i>LVSI</i>	n	%
No	210	53.0
Yes	98	24.7
Unknown	88	22.2

SEC: Serous EC; CCC: Clear cell carcinoma; DEC: De-/undifferentiated EC; GR3 EEC: Grade 3 endometrioid-type EC

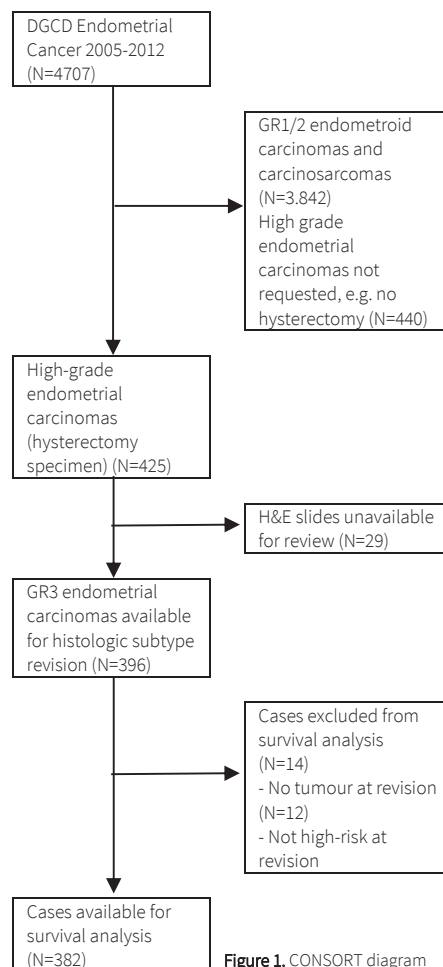


Figure 1. CONSORT diagram

Statistics

For statistical analysis regarding interobserver variability between original diagnosis and reviewed diagnosis we used eight categories as shown in Table 2, similar to a categorization made in two other studies, that were based on histological cell type or major/minor disagreement, respectively [3, 5]. Mixed cell carcinomas were categorized according to their high-grade component or to the major component in case of two high-grade components. Interobserver variability was analysed using simple Kappa statistics and calculated with 95% confidence limits. Furthermore, interobserver variability was stratified by original diagnosis from subspecialized or general institute and stage, respectively, and tested for differences with hypothesis of equal means. Calculations were done using SAS v.9.4 (SAS Institute, Cary, NC, USA).

For statistical analyses regarding clinical outcome, a predefined categorisation into four groups was used. This allowed for a comparison between GR3 EEC, SEC, CCC and other high-grade EC. The other group contained all other histological subtypes of high-grade EC, such as DEC and UCS. Recurrence free survival (RFS) was calculated from time of surgery to first recurrence, omitting patients dying from other causes than EC. Overall survival (OS) was calculated from time of surgery to death. The Kaplan-Meier method was used to calculate survival rates, p-values for Kaplan-Meier curves being based on log rank test. Hazard ratios were calculated with Cox regression analyses, where adjustments were made for age, comorbidity using ASA score, FIGO stage, lymph node resection and/or adjuvant treatment. GR3 EEC was used as reference. Cases that were not high-grade carcinoma at revision were omitted from calculations of RFS and OS. P-values for RFS and OS were calculated using adjusted Cox proportional hazards model. Calculations were done using STATA 11 (StataCorp, College Station, TX, USA).

Table 2. Categories for histological types

Histological type categories for interobserver variability	Original histological type	Revised histological type
SEC	SEC	SEC; Mixed SEC/EEC; Mixed SEC/CCC
CCC	CCC	CCC; Mixed CCC/EEC; Mixed CCC/SEC
DEC	DEC	DEC
GR3 EEC	GR3 EEC	GR3 EEC
EIN	N.A.	EIN
UCS	N.A.	UCS
MC	N.A.	MC
Cannot assess	N.A.	Poor tissue fixation; tumour too small or no tumour in available slides

SEC: serous EC; CCC: clear cell carcinoma; EEC: endometrioid type EC; DEC: de-/undifferentiated EC; GR3 EEC: grade 3 EEC; EIN: endometrioid intraepithelial neoplasia; UCS: uterine carcinosarcoma; MC: mucinous carcinoma

Results

The distribution of the original histologic subtypes and the revised histologic subtypes are shown in Table 3. Of a total of 396 high-grade EC, histology review could be performed on 384 (97%). These 384 cases were originally diagnosed as GR3 EEC (n=163; 41.2%), SEC (n=141;

35.6%), CCC (n=83; 21.0%) and un-/dedifferentiated carcinomas (n=9; 2.3%). This distribution changed substantially after review, including one additional category: GR3 EEC (n=181; 45.7%), SEC (n=133; 33.6%), CCC (n=38; 9.6%), DEC (n=17; 4.3%) and UCS (n=13; 3.3%). Only two cases were not considered to be high-grade EC on review (0.5%), but EIN (0.25%, n=1) and mucinous carcinoma (0.25%, n=1), respectively. In both these outlier cases, the available H&E slides were from representative tumour from the hysterectomy specimen. The original diagnosis of these two cases were GR3 EEC and CCC, respectively. Furthermore, 12 cases (3.0%) could not be revised; 10 due to lack of tumour in the available H&E slides and 2 due to insufficient fixation quality for assessment. The distribution of these cases is presented in Table 4.

Overall kappa value was 0.42. The highest concordance was obtained for GR3 EEC and SEC with 75.5% and 63.8%, respectively. For CCC and undifferentiated carcinoma, the concordance was considerably lower with 30.1% and 33.3%, respectively. The main histologic subtype shift was from SEC to GR3 EEC (26/43; 60.5%), followed by GR3 EEC to SEC (19/39; 48.7%). Interestingly, review of the 83 original CCC resulted in 29 GR3 EEC and 23 SEC, while only 25 remained CCC. Examples of CCC that were reclassified are shown in Figure 2.

Table 3. Original and revised histological types

Original histologic al type	Revised histological type										Total discrepant cases
		SEC	CCC	DEC	GR3 EEC	EIN	Cannot assess	UCS	MC	Total	
SEC	n	90	11	2	26	0	8	4	0	141	43
	%	63.8	7.8	1.4	18.4	0.0	5.7	2.8	0.0	100	
CCC	n	23	25	1	29	0	3	1	1	83	55
	%	27.7	30.1	1.2	34.9	0.0	3.6	1.2	1.2	100	
DEC	n	1	0	3	3	0	0	2	0	9	6
	%	11.1	0.0	33.3	33.3	0.0	0.0	22.2	0.0	100	
GR3 EEC	n	19	2	11	123	1	1	6	0	163	39
	%	11.7	1.2	6.8	75.5	0.6	0.6	3.7	0.0	100	
Total		133	38	17	181	1	12	13	1	396	

SEC: serous EC; CCC: clear cell carcinoma; EEC: endometrioid type EC; DEC: de-/undifferentiated EC; GR3 EEC: grade 3 EEC; EIN: endometrioid intraepithelial neoplasia; UCS: uterine carcinosarcoma; MC: mucinous carcinoma

Table 4. Distribution of cases that could not be revised

Original histological type	Reason not revised		
	No tumour (n)	Cannot assess (n)	Total (n)
SEC	7	1	8
CCC	3	0	3
DEC	0	0	0
GR3 EEC	0	1	1
Total	1	2	12

SEC: serous EC; CCC: clear cell carcinoma; EEC: endometrioid type EC; DEC: de-/undifferentiated EC; GR3 EEC: grade 3 EEC

Looking at concordance per stage, there were no statistically significant differences. Most of the patients were stage I (n = 292), and the distribution and type of discrepancies of stage I were completely in line with the overall results. For stage II–IV, numbers of patients were too small to

draw any conclusions, but we saw no obviously different tendencies. Also, there were no significant differences in concordance whether the original diagnosis was made at a general or subspecialized institute.

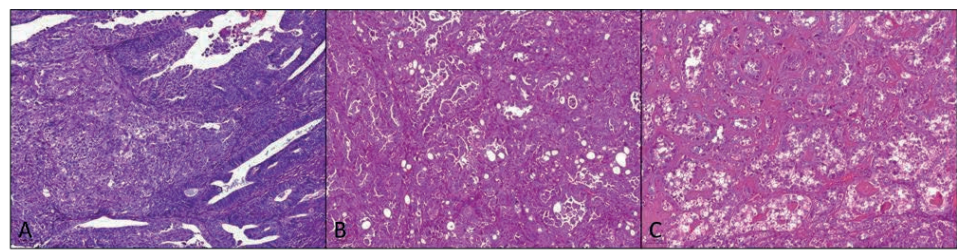


Figure 2. Original CCC that were re-classified as either GR3 EEC (A), SEC (B) or remained CCC (C)

Table 5. Five year overall survival and recurrence free survival, HR with 95% CI and *p*-values based on Cox proportional hazards model. GR3 EEC serves as reference

Overall five-year survival								
	Original				Revision			
	%	<i>p</i>	HR	95% CI	%	<i>p</i>	HR	95% CI
GR3 EEC	66		1		71		1	
SEC	59	0,676	1,09	0,74 – 1,61	56	0,138	1,34	0,91 – 1,98
CCC	65	0,452	0,83	0,52 – 1,32	61	0,759	1,10	0,60 – 1,20
Other	22	0,078	2,10	0,92 – 4,78	40	0,002	2,41	1,39 – 4,16

Recurrence free five-year survival								
	Original				Revision			
	%	<i>p</i>	HR	95% CI	%	<i>p</i>	HR	95% CI
GR3 EEC	79		1		83		1	
SEC	65	0,024	1,74	1,07 – 2,81	63	0,001	2,36	1,43 – 3,89
CCC	76	0,625	1,16	0,64 – 2,12	72	0,134	1,79	0,84 – 3,82
Other	60	0,174	2,35	0,69 – 8,06	55	<0,001	3,65	1,81 – 7,35

GR3 EEC serves as reference. SEC: Serous EC; CCC: Clear cell carcinoma; DEC: De-/undifferentiated EC; GR3 EEC: Grade 3 endometrioid-type EC; Other: Other types of high-grade EC.

Five-year survival, hazard rates and *p*-values based on Cox proportional hazards model for OS and RFS are shown in Table 5 and Kaplan-Meier curves for OS and RFS in Figure 3. The OS of patients originally diagnosed with GR3 EEC, SEC and CCC were not significantly different, and despite the shift in histologic subtypes after revision, there were no significant differences. However, patients with SEC had a poorer RFS than GR3 EEC with stronger significance after revision, HR 2.36 (95% CI 1.43-3.89), *p*=0.001, compared to original diagnosis, HR 1.74 (95% CI 1.07-2.81), *p*=0.024. Finally, patients with an EC falling under the “other” category, consisting of un-/dedifferentiated carcinoma and UCS after review, had significantly worse OS and RFS than those with GR3 EEC for revised diagnoses with HR 2.41 (95% CI 1.39-4.16; *p*=0.002) and HR 3.65 (95% CI 1.81-7.35; *p*<0.001), respectively, while there was no statistically significant difference for original diagnoses with HR 2.10 (95% CI 0.92-4.78; *p*=0.078) and HR 2.35 (95% CI 0.69-8.06; *p*=0.174), respectively.

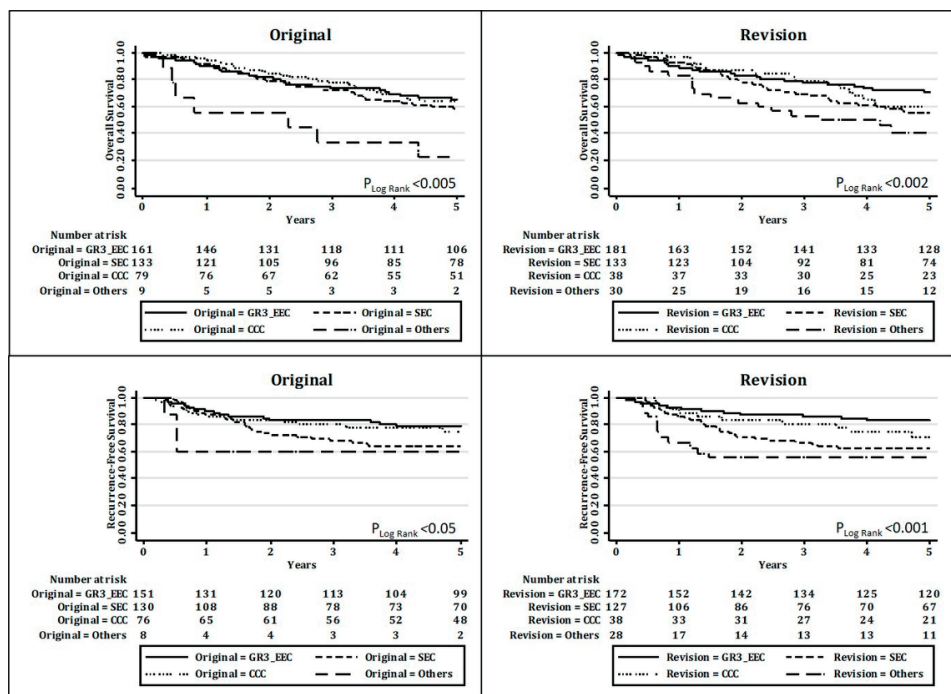


Figure 3. Kaplan-Meier curves for five-year overall and survival recurrence-free survival, original and revised diagnosis. SEC: Serous EC; CCC: Clear cell carcinoma; DEC: De-/undifferentiated EC; GR3 EEC: Grade 3 endometrioid-type EC; Other: Other types of high-grade EC.

Discussion

We present an interobserver pathology study of a large nationwide high-grade EC cohort including well documented clinical outcome data. We were able to retrieve 90% of all high-grade EC cases and thereby the data presented are a good reflection of the true distribution of high-grade EC in Denmark.

It was re-assuring to find that after revision as much as 99.5% of cases were consistently diagnosed high-grade EC by specialized gynecopathologists, despite the fact that the original diagnosis was made by 19 different pathology institutes, subspecialized as well as general. However, this study showed once again that histological subtyping of high-grade EC is poorly reproducible. From a clinical management perspective, one may argue that this inconsistency in histological type assignment has limited consequences, as adjuvant treatment recommendations according to international guidelines [1] would be altered for a minority of patients. This mainly involves reallocation from GR3 EEC to non-EEC and vice versa in FIGO stage I/II. In Denmark, currently the only exception would be the indication for omentectomy in SEC and DEC, which is not considered to be relevant for patients with GR3 EEC. In other countries, other choices are made, why the impact of the observed diagnostic shift may vary per country.

The overall agreement of histologic subtype assignment in our high-grade EC cohort was just moderate with a kappa value of 0.42. This is in agreement with other studies with kappa values of 0.30-0.68 for high-grade EC [4, 5, 7, 10], illustrating the limited reproducibility of histological subtyping of high-grade EC. The highest reproducibility was obtained for GR3 EEC (75.5%) and serous EC (63.8%), respectively. In addition, 13 cases were reclassified as uterine carcinosarcomas upon revision. The higher number of revised histological types is likely a reflection of the lack of reproducible histologic subtype specific features. This appeared particularly problematic for the diagnosis of CCC, as CCC was the subtype with the worst reproducibility.

CCC often includes a mixture of architectural patterns and can be difficult to distinguish from variants of EEC and SEC. In the new WHO classification published in 2020 [16] it was stressed that strict adherence to architectural and cytological diagnostic criteria is required to optimize the diagnostic reproducibility of CCC. Adding an immunohistochemical panel of ER/PR, p53, NapsinA and HNF1Beta likely improves the correct diagnosis of CCC, but is not always helpful [8, 9]. Consequently, the WHO 2014 histology-based classification of EC is an insufficient basis for histotype-directed clinical treatment decisions and forms a poor basis for clinical trial inclusion. The WHO 2020 [16] introduced the molecular classification, which relies on the analysis of surrogate markers in order to identify the four subgroups analogous to the ones described by The Cancer Genome Atlas (TCGA) [17]. This novel classification has a strong prognostic value and higher reproducibility than the histology based classification [17–20] and therefore may be a better basis for future clinical trials [19]. Most of the data on the molecular EC classification is derived from analysis of EEC and SEC, however small series of CCC indicate that the molecular classification may also be applicable to CCC [21, 22].

Although the interobserver variability of high-grade EC diagnosis has been addressed in previous works, this is the first study to include an assessment of the impact of revision on RFS or OS. This is of obvious importance, as histologic classification systems are meant to serve as an important prognostic variable and guide treatment. The shift between the high-grade subtypes GR3 EEC, SEC and CCC at revision had no significant impact on overall survival. However, the group of GR3 EEC had better RFS with much stronger significance after revision compared to the original diagnosis. Furthermore, there were significantly poorer RFS and OS of the revised DEC and UCS. These findings support the most recent European guidelines which differentiates between GR3 EEC and non-endometrioid subtypes to assign risk groups and consequently different adjuvant treatment recommendations [1]. Therefore, our study builds on previous work and argues in favour of central pathology review for all high-grade EC in routine clinical practice.

This study is not without limitations. Due to the study design (selection of high-grade EC), there is an over-representation of serous carcinomas compared to the general EC population in Denmark where 70-80% are EEC and 10% are SEC according to the Danish national guideline

group [23], and therefore we cannot generalise our findings to low-grade EC. We note that previous studies analysing the interobserver reproducibility of histological diagnosis had a lower proportion of SEC [3, 4, 11, 12], however, their results did not differ substantially from the present work. Furthermore, due to our approach we did not adjust for stage in COX regression analysis, and therefore the role of stage in this context could not be addressed. Finally, for some cases only selected slides were available for review, possibly omitting the part of the tumour with the most representative morphology. This limitation is counterbalanced by our ability to retrospectively review cases with an average number of 10.9 H&E slides/case. Additionally, review diagnoses were solely based on H&E without any immunohistochemistry (IHC), although this would likely improve agreement, particularly in cases with ambiguous morphology [8, 9]. Therefore, an interesting future study would be to look at the value of a standard IHC marker panel on the interobserver variability of high-grade EC.

In conclusion, we confirmed the substantial interobserver variability in histologic subtyping high-grade EC in a large Danish population cohort. All but two cases remained high-grade, however a major shift in histologic subtype was observed, most significant for CCC. After revision, endometrioid-type high-grade carcinomas had strongly significant better RFS than SEC, and better RFS and OS than the group of DEC and UCS, but otherwise the shift between the different subtypes of high-grade EC did not change the outcome in terms of RFS or OS. We suggest keeping a low threshold for pathology revision of high-grade EC in clinical practice and foresee that molecular classification of high-grade EC will be a better fundament for future clinical management as it is built upon more objective parameters.

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