Molecular endometrial carcinoma classification: facing up to the challenges of clinical implementation

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Chapter 6

Prognostic relevance of the molecular classification in high-grade endometrial cancer for patients staged by lymphadenectomy and without adjuvant treatment

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Abstract

Introduction

The clinical role of the molecular endometrial cancer (EC) classification has not been fully explored in patients staged with lymphadenectomy or without adjuvant treatment, conditions that could potentially moderate the prognostic value of the classification. We aimed to evaluate the clinical outcome of the molecular subgroups in patients with high-grade EC staged by lymphadenectomy and those without adjuvant treatment.

Methods

DNA-sequencing for the detection of pathogenic *POLE*-exonuclease domain mutations and immunohistochemistry for mismatch repair (MMR) proteins and p53 expression were performed on 412 high-grade ECs from the Danish Gynaecological Cancer Database (2005-2012) to classify them as *POLE*-ultramutated (*POLE*mut), MMR-deficient (MMRd), p53-mutant (p53abn), or no specific molecular profile (NSMP). Patients with stage IV or residual disease after surgery were excluded. Kaplan-Meier method, log-rank test and Cox proportional hazard models were used for analysis.

Results

Molecular analysis was successful in 367 ECs; 251 patients had undergone lymphadenectomy. Five-year recurrence rates in this subgroup of patients was 36.7% for women with p53abn EC, 0.0% for *POLE*mut EC, 13.4% for MMRd EC and 42.9% for NSMP EC (p<0.001). Similar results were observed among stage IA-IB patients. Among patients without adjuvant treatment (n=264), none with *POLE*mut EC (n=26) had a recurrence.

Conclusion

The molecular EC classification has strong prognostic value, independent of clinicopathological factors, also among high-grade EC patients staged by lymphadenectomy and those without adjuvant treatment. The unfavourable prognosis of early-stage p53abn EC is not due to undetected lymph node metastasis, and the indolent behaviour of *POLE*mut EC is independent of adjuvant treatment.

Introduction

The molecular endometrial cancer (EC) classification first described by The Cancer Genome Atlas (TCGA) has prompted a paradigm shift from a morphology-based classification towards an integrated model based on molecular and histologic features.[1] In the years after the publication of TCGA's results, several studies were able to identify four subgroups analogous to those originally described by the use of surrogate markers :[2-6] *POLE*-ultramutated (*POLE*mut), mismatch repair deficient (MMRd), p53-abnormal (p53abn) and No Specific Molecular Subgroup (NSMP). Using this approach, the molecular EC classification has proven to have a strong prognostic value in clinical trials and unselected cohorts.[2-6] Furthermore, molecular profiling of the ECs of PORTEC-3 trial participants highlighted the value of the molecular subgroups in predicting benefit from adjuvant chemoradiotherapy. These results have led to the integration of the molecular subgroups in current classification systems and treatment guidelines.[7,8]

The different studies performed have consistently shown that patients with p53abn EC have a poor clinical outcome. Although p53abn ECs present more frequently at advanced stage disease compared to the other molecular subgroups, multivariable cox regression analysis has shown that the prognostic value of the molecular EC classification is independent of stage. Nevertheless, not all patients included in these studies were staged with systematic lymphadenectomy and previous studies have not focussed on patients staged with lymphadenectomy.[2-6] It could therefore be hypothesized that undetected lymph node metastases, especially in the p53abn subgroup, may explain the differences in clinical outcome observed among the four molecular subgroups.

Most patients in previous studies received adjuvant treatment, raising the possibility that the differences observed in clinical outcome are (partly) the result of differences in benefit from adjuvant treatment between the molecular subgroups. This hypothesis is particularly relevant in the context of *POLE*mut EC, where de-escalation of adjuvant treatment is considered.[8-10] A recent meta-analysis, as well as survival analyses from small groups of patients with *POLE*mut EC who had not received adjuvant treatment, suggest that the clinical outcome of these patients is independent of adjuvant treatment.[9,11,12] However, most of the patients in these studies had low or intermediate-risk disease by ESMO guidelines.[13] It is therefore, still unclear what the natural behaviour of high-grade and/or high-risk *POLE*mut EC is in the absence of adjuvant treatment.

The addition of the molecular classification to established histological features further refines prognosis in high-grade EC. In intermediate(-high)-risk EC, the integration of extent of lymphovascular space invasion (LVSI), a strong prognostic factor associated with risk of lymph node metastases, recurrence and poor survival, and molecular features has proven

to improve risk assessment.[3] However, the prognostic value of LVSI in molecularly profiled high-grade EC has not been explored yet.

In order to investigate these aspects of the natural behaviour of the EC molecular subgroups, we analysed the clinical outcome of a cohort of patients with high-grade EC in which the majority were staged by lymphadenectomy and had no adjuvant treatment.

Methods

Patient selection

The Danish Gynaecological Cancer Database (DGCD) is a nationwide clinical database including 4706 prospectively registered ECs (excluding carcinosarcomas) diagnosed between January 1st 2005 to December 31st 2012,[14] and contains information on surgical and adjuvant treatment, pathology diagnosis and follow-up data. Any missing data was retrieved from the patient's medical records, the national patients file registry and pathology reports using the Danish pathology database. Deaths were retrieved from the Danish Central Person Register and cause of death was checked from the patient's medical records.[15] Histologically-verified recurrences were retrieved from the Danish pathology database, while those not histologically verified were identified from the medical records collected for patients who had died from EC. Medical records were reviewed to collect time and site of recurrence.[15] As previously described, patients underwent abdominal hysterectomy, bilateral salpingo-oophorectomy and intra-abdominal assessment.[15] Routine systematic pelvic lymphadenectomy (removal of external iliac, obturator, and common iliac nodes) was recommended for high-risk patients according to national Danish guidelines (http://dgcg.dk/index.php/guidelines/corpuscancer), with some institutions also performing para-aortic lymphadenectomy (removal of precaval, laterocaval, interaortocal, preaortic and lateroaortic nodes). Adjuvant treatment regimens were decided upon according to the national Danish guidelines (http://dgcg.dk/index.php/guidelines/corpuscancer).

There were 713 patients with high-grade EC registered in the DGDC, of which 460 had haematoxylin and eosin-stained slides available for pathology review regarding assessment and quantification of LVSI, by four pathologists, as described in detail by Peters et al (Supplementary methods),[16] and selection of tumour tissue for molecular profiling. Formalin-fixed paraffin-embedded tumour tissue was collected from 426 ECs. Patients with high-grade EC stage IA-b and IIIc from all Danish hospitals, while those stage II and IIIa-b were collected only from one institution. Finally, patients with stage IV or residual disease after surgery were excluded from the study (n=45) (Supplementary figure S1).

Molecular profiling

Immunohistochemical stains for PMS2, MSH6 and p53 were performed on unstained slides from all included cases and scored as previously described (see also Supplementary methods).[6 17] Cases with loss of expression or with doubtful staining pattern of PMS2 and/or MSH6 were additionally stained for MLH1 and MSH2. Only on cases with unevaluable MMR immunohistochemistry, microsatellite instability (MSI) analysis was performed using the MSI analysis system version 1.2 (Promega, Madison, WI) (n=2). If p53 immunohistochemistry was not evaluable, *TP53* mutational status was used (n= 11).

DNA isolation was performed as previously described.[6] Next-generation sequencing was used to assess the mutational status of the exonuclease domain of *POLE*, using the AmpliSeq Cancer Hotspot Panel, version 6 (Thermo Fisher Scientific, Waltham, MA). This panel included *POLE* exonuclease domain and *TP53* exons 2-11. If sequencing with the NGS panel failed, KASPar competitive allele-specific polymerase chain reaction (LGC Genomics, Berlin, Germany) assays were used to screen for the presence of *POLE* hotspot variants at codons 286, 297, 411, 456, and 459 (n=41). *POLE* exonuclease domain mutations (EDM) were considered causative of ultra-mutated phenotype following criteria by Leon-Castillo et al.[18]

Sequencing and immunohistochemistry stain results were evaluated blinded for patient outcome and histopathological features. EC were molecularly classified according to the algorithm provided by Vermij et al (Supplementary figure S1).19

Statistical analysis

Median follow-up time was calculated using the reverse Kaplan-Meier method. Recurrence rate was calculated from the date of surgery to date of first relapse, censoring patients dying from other causes than EC. Overall survival (OS) was defined as time from the date of surgery to the date of death due to any cause. Disease specific survival (DSS) was calculated from the date of surgery to date of death due to EC, censoring patients dying from other causes. Analyses were consecutively performed on all included patients and on subgroups of those staged by lymphadenectomy and on those without adjuvant therapy.

Clinicopathological characteristics of patients were compared between molecular subgroups using the chi-square test for categorical variables and the Mann-Whitney U test for ordinal variables and non-normally distributed continuous variables. Differences in recurrence, OS and DSS between groups were tested using the log-rank test. Multivariate regression analyses with prespecified covariates were performed including the molecular subgroups, age (<70 year versus 70 years or older), stage (I-II versus stage III), LVSI (absent or focal versus substantial) and American Society of Anesthesiologist Physical Status Classification System (ASA) score (1-2 versus 3-5) and received adjuvant treatment (none versus any). Since patients were not randomly allocated to adjuvant treatment, a propensity score was

used to correct for potential confounding by indication bias. Factors significantly related to the allocation of adjuvant treatment were identified using logistic regression. A propensity score was calculated using the resulting multivariable logistic regression model including age (<70 versus 70 or older), ASA score (1-2 versus 3-5), stage (IA versus IB versus II versus III) and histology (endometrioid versus non-endometrioid). Finally, the propensity score was included as a covariate in the multivariable cox regression models. A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed using Stata 11 (StataCorp LLC, Collage Station, TX, USA).

Results

A total of 381 high-grade EC samples were collected from patients with stage I-III disease and molecular testing was successful in 367 (96.3%; Supplementary figure S2). Median follow-up was 8.1 years (range 0.01-15.44). Clinicopathological features of all included patients are shown in table 1. The ECs of these 367 patients were classified into one of the molecular subgroups: 38 *POLE*mut EC (10.4%), 161 p53abn (43.9%), 107 MMRd (29.2%) and 61 NSMP EC (16.6%). Stage III disease and substantial LVSI were similarly present in p53abn, MMRd and NSMP EC (16.8%, 14.0% and 13.1%, respectively). Lymphadenectomy was performed on 251 of 367 patients (68.4%) and 264 of 367 patients (71.9%) did not receive adjuvant therapy (see supplementary tables S2 and S3 for clinicopathological features of these groups).

Clinical outcome

Across all 367 included patients, those with *POLE*mut and MMRd EC had a favourable prognosis with a 5-year recurrence rate of 5.4% (95%CI 1.4-30%) and 12.0% (95%CI 7.0-20.2%), a 5-year OS of 86.8% (95%CI 71.2-94.3%) and 75.7% (95%CI 66.4-82.8%), and 5-year DSS of 97.4% (95%CI 82.8-99.6%) and 90.0% (95%CI 82.2-94.5%), respectively. Patients with p53abn and NSMP ECs had poor prognoses: 5-year recurrence rate 41.5% (95%CI 34.0-49.9%) for p53abn and 37.9% (95%CI 26.7-51.8%) for NSMP EC, 5-year OS 54.0% (95%CI 46.0-61.4%) for p53abn EC and 55.7% (95%CI 42.5-67.1%) for NSMP EC, and 5-year DSS 65.9% (95%CI 57.5-72.9%) and 68.7% (95%CI 54.8-79.0%) respectively (supplementary figure S3). Histological subtype (endometrioid grade 3 EC versus non-endometrioid EC), was not a predictor of recurrence, OS and DSS (univariable analysis: recurrence HR 1.37, 95%CI 0.91-2.07, p=0.130; OS HR 1.20, 95%CI 0.84-1.70, p=0.315; DSS HR 1.41, 95%CI 0.89-2.24, p=0.145). Substantial LVSI and the EC molecular subgroup were an independent predictor of recurrence, OS and DSS in multivariable analyses (supplementary table S1).

Table 1. Clinicopathological features by molecular subgroups (n=367).

	Total	p53abn	*POLE*mut	MMRd	NSMP	p-value
	n=367 (100%)	n=161 (43.9%)	n=38 (10.4%)	n=107 (29.2%)	n=61 (16.6%)	
Age, years						0.005
<70	193 (52.6)	73 (45.3)	30 (78.9)	63 (58.9)	27 (44.3)	
≥70	174 (47.4)	88 (54.7)	8 (21.1)	44 (41.1)	34 (55.7)	
Histotype						<0.001
Endometrioid grade 3	159 (43.3)	42 (26.1)	21 (55.3)	65 (60.7)	31 (50.8)	
Serous	125 (34.1)	89 (55.3)	11 (28.9)	15 (14.0)	10 (16.4)	
Clear cell	76 (20.7)	26 (16.1)	6 (15.8)	24 (22.4)	20 (32.8)	
Undifferentiated	7 (1.9)	4 (2.5)	0 (0)	3 (2.8)	0 (0)	
Stage						0.212
IA	172 (46.9)	77 (47.8)	23 (60.5)	46 (43.0)	26 (42.6)	
IB	99 (27.0)	40 (24.8)	11 (28.9)	32 (29.9)	16 (26.2)	
II	28 (7.6)	13 (8.1)	2 (5.3)	8 (7.5)	5 (8.2)	
IIIA	6 (1.6)	2 (1.2)	1 (2.6)	1 (0.9)	2 (3.3)	
IIIB	11 (3.0)	2 (1.2)	0 (0)	5 (4.7)	4 (6.6)	
IIIC	51 (13.9)	27 (16.8)	1 (2.6)	15 (14.0)	8 (13.1)	
Lymphovascular space invasion						0.456
Absent	286 (77.9)	129 (80.1)	33 (86.8)	77 (72.0)	47 (77.0)	
Focal	37 (10.1)	14 (8.7)	3 (7.9)	13 (12.1)	7 (11.5)	
Substantial	42 (11.4)	18 (11.2)	2 (5.3)	15 (14.0)	7 (11.5)	
Unknown	2 (0.5)	0 (0)	0 (0)	2 (1.9)	0 (0)	
Lymphadenectomy						0.602
No	116 (31.6)	53 (32.9)	11 (28.9)	29 (27.1)	23 (37.7)	
Pelvic	208 (56.7)	86 (53.4)	25 (65.8)	63 (58.9)	34 (55.7)	
Para-aortic	1 (0.3)	1 (0.6)	0 (0)	0 (0)	0 (0)	
Pelvic and para-aortic	42 (11.4)	21 (13.0)	2 (5.3)	15 (14.0)	4 (6.6)	
Adnexectomy						0.491
Yes	338 (92.1)	148 (91.1)	35 (92.1)	98 (91.6)	57 (93.4)	
No*	21 (5.7)	10 (6.2)	2 (5.3)	8 (7.5)	1 (1.6)	
Missing	8 (2.2)	3 (1.9)	1 (2.6)	1 (0.9)	3 (4.9)	
Peritoneal staging biopsies						0.174
Yes	36 (9.8)	18 (11.2)	5 (13.2)	8 (7.5)	5 (8.2)	
No	314 (85.6)	140 (87.0)	30 (78.9)	94 (87.9)	50 (82.0)	
Missing	17 (4.6)	3 (1.9)	3 (7.9)	5 (4.7)	6 (9.8)	
Omentectomy						0.003
Yes	152 (41.4)	86 (53.4)	15 (39.5)	32 (29.9)	19 (31.1)	
No**	200 (54.5)	69 (42.9)	21 (55.3)	72 (67.3)	38 (62.3)	
Missing	15 (4.1)	6 (3.7)	2 (5.3)	3 (2.8)	4 (6.6)	

Table 1. Continued

Adjuvant treatment received						0.714
None	264 (71.9)	119 (73.9)	26 (68.4)	73 (68.2)	46 (75.4)	
Radiotherapy	34 (9.3)	13 (8.1)	6 (15.8)	11 (10.3)	4 (6.6)	
Combined chemo- and radiotherapy	6 (1.6)	2 (1.2)	1 (2.6)	1 (0.9)	2 (3.3)	
Chemotherapy	63 (17.2)	27 (16.8)	5 (13.2)	22 (20.6)	9 (14.8)	
ASA score						0.302
1	95 (25.9)	36 (22.4)	15 (39.5)	28 (26.2)	16 (26.2)	
2	232 (63.2)	101 (62.7)	18 (47.4)	72 (67.3)	41 (67.2)	
3	40 (10.9)	24 (14.9)	5 (13.2)	7 (6.5)	4 (6.6)	
4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
ESGO-ESTRO-ESP 2020 prognostic risk groups (without known molecular classification)						0.219
Low	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Intermediate	103 (28.1)	48 (29.8)	13 (34.2)	28 (26.2)	14 (23.0)	
High-intermediate	64 (17.4)	11 (6.8)	9 (23.7)	31 (30.0)	13 (31.3)	
High	200 (54.5)	102 (63.4)	16 (42.1)	48 (44.9)	34 (55.7)	

ASA, American Society of Anesthesiologist Physical Status

*Additionally, 19 (5,2%) patients had previously removed adnexa.

**One additional patient had omentum previously removed.

Prognostic value of the molecular subgroups in patients staged by lymphadenectomy

The clinicopathological characteristics of the 251 patients who underwent lymphadenectomy are presented in supplementary table S2. Also, in these surgically staged patients, the EC molecular subgroups had marked differences in 5-year recurrence rates: p53abn 36.7% (95%CI 28.2-46.7%), *POLE*mut EC 0.0%, MMRd 13.4% (95%CI 7.4-23.4%) and NSMP EC 42.9% (95%CI 28.8-60.2%) (figure 1). Significant differences were also observed for 5-year OS and DSS (figure 1). Notably, multivariable analysis showed that, even among patients staged with lymphadenectomy, the molecular EC classification was a strong prognostic factor for recurrence, OS and DSS, independent of stage (table 2).

Among patients who were staged by lymphadenectomy as stage I disease, the risk of recurrence was significantly different between the molecular subgroups (figure 2). Patients with p53abn (n=74) and NSMP ECs (n=23) had the poorest prognosis, with a 5-year recurrence rate of 28.1% (95%CI 19.2-40.16%) and 35.3% (95%CI 19.5-58.5%), respectively. No recurrences were recorded among patients with *POLE*mut EC (n=25). MMRd ECs (n=50) had a 5-year recurrence rate of 6.4% (95%CI 2.1-18.7%). 5-year OS and DSS are presented in figure 2.

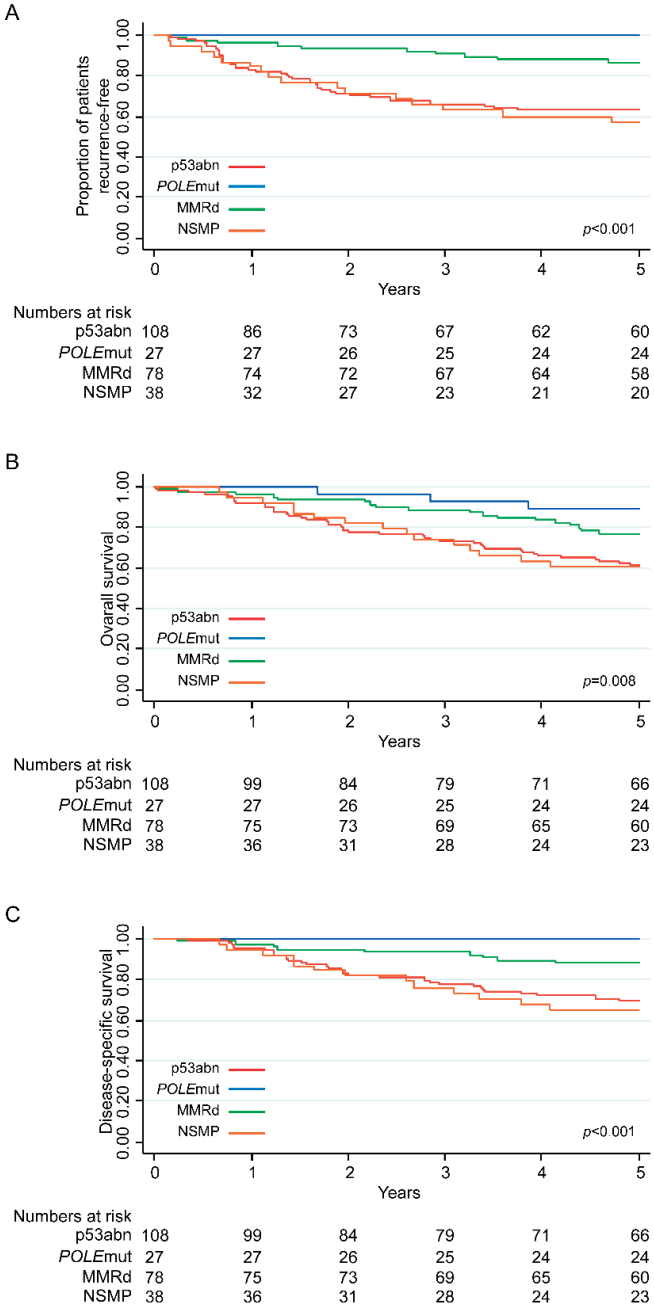

Figure 1. Recurrence, overall survival and disease specific survival for patients staged by lymphadenectomy (n=251). Kaplan-Meier survival curves of patients staged by lymphadenectomy for (A) recurrence rate for patients with p53abn endometrial cancer (EC) (at 5 years: 36.7%, 95%CI 28.2-46.7%), *POLE*mut EC (0%), MMRd EC (13.4%, 95%CI 7.4-23.4%) and NSMP EC (42.9%, 95%CI 28.8-60.2%), (B) overall survival for with p53abn EC (at 5 years: 61.1%, 95%CI 51.3-69.6%), *POLE*mut EC (88.9%, 95%CI 69.4-96.3%), MMRd EC (76.9%, 95%CI 65.9-84.8%) and NSMP EC (60.5%, 95%CI 43.3-74.0%), and (C) disease specific survival for patients with p53abn EC (at 5 years: 69.7%, 95%CI 59.8-77.7%), *POLE*mut EC (100%), MMRd EC (88.1%, 95%CI 78.3-93.6%), and NSMP EC (65.0%, 95%CI 47.3-78.0%).

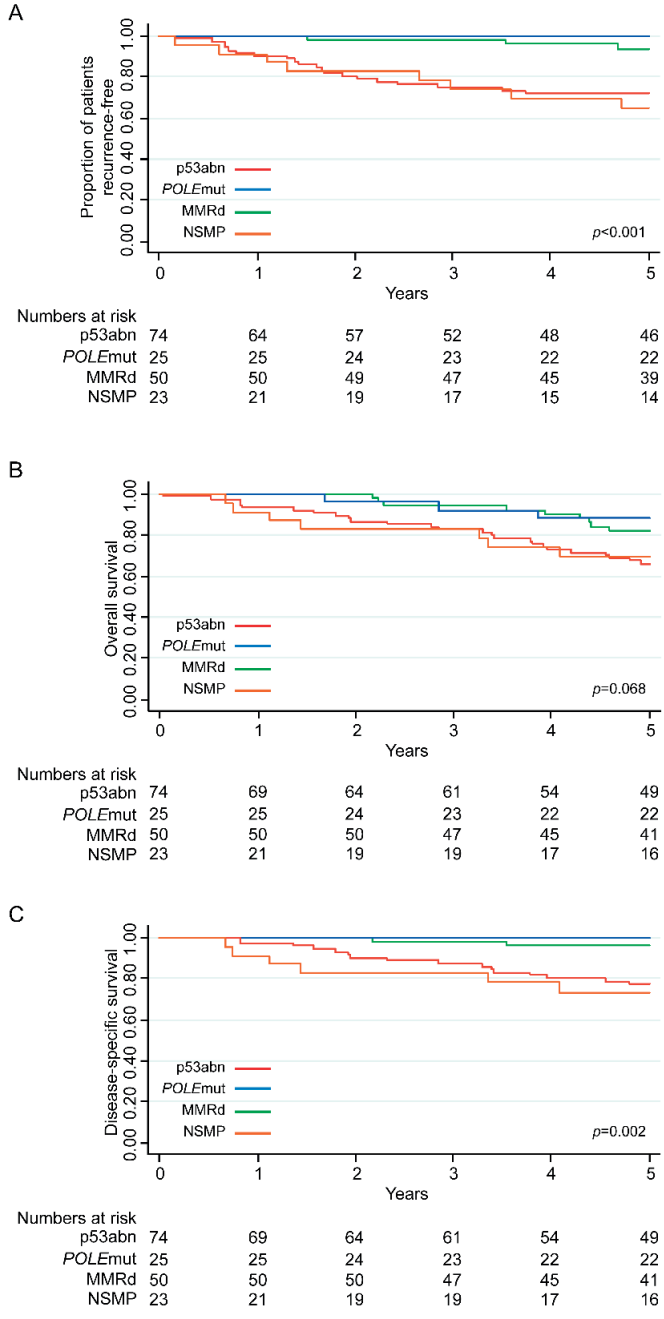

Figure 2. Recurrence, overall survival and disease specific survival for patients staged by lymphadenectomy as stage I (n=172). Kaplan-Meier survival curves of patients staged by lymphadenectomy as stage I for (A) recurrence rate for patients with p53abn endometrial cancer (EC) (at 5 years: 28.1%, 95%CI 19.2-40.16%), *POLE*mut EC (0%), MMRd EC (6.4%, 95%CI 2.1-18.7%) and NSMP EC (35.3%, 95%CI 19.5-58.5%), (B) overall survival for patients with p53abn EC (at 5 years: 66.2%, 95%CI 54.2-75.8%), *POLE*mut EC (88.0%, 95%CI 67.3-96.0%), MMRd EC (82.0%, 95%CI 68.3-90.2%) and NSMP EC (69.6%, 95%CI 46.6-84.2%) and (C) disease specific survival for patients with p53abn EC (at 5 years: 77.1%, 95%CI 65.3-85.3%), *POLE*mut EC (100%), MMRd EC (95.9%, 95%CI 84.6-99.0%), NSMP EC (73.4%, 95%CI 50.1-87.1%).

Table 2. Multivariable analysis of molecular subgroups and clinicopathological features in high-grade endometrial cancer patients staged with lymphadenectomy (n=251). Results are corrected for confounding by indication by a propensity score.

	Recurrence			Overall survival			Disease specific survival		
	n events=64			n events=78			n events=53		
Parameter	**HR**	**95%CI**	***p*-value**	**HR**	**95%CI**	***p*-value**	**HR**	**95%CI**	***p*-value**
Age									
<70	1			1			1		
≥70	0.896	0.516-1.553	0.695	1.779	1.081-2.926	0.023	1.073	0.581-1.984	0.821
Molecular subgroups									
MMRd	1			1			1		
p53abn	3.938	1.924-8.058	<0.001	1.875	1.064-3.304	0.030	3.244	1.510-6.969	0.003
*POLE*mut	-	-	-	0.622	0.180-2.156	0.454	-	-	-
NSMP	4.685	2.083-10.537	<0.001	2.031	1.007-4.096	0.048	3.954	1.648-9.486	0.002
Stage									
I-II	1			1			1		
III	0.379	0.122-1.176	0.093	0.498	0.167-1.485	0.395	0.448	0.123-1.625	0.222
LVSI									
Absent or focal	1			1			1		
Substantial	2.495	1.336-4.658	0.004	2.377	1.366-4.133	0.002	2.93	1.508-5.692	0.002
Adjuvant treatment									
No	1			1			1		
Yes	0.671	0.351-1.281	0.226	0.684	0.362-1.293	0.243	0.654	0.323-1.325	0.238
ASA score									
1-2	1			1			1		
3-5	1.440	0.466-4.455	0.526	2.248	0.980-5.158	0.056	1.314	0.362-4.770	0.678

LVSI, lymphovascular-space invasion; ASA, American Society of Anesthesiologist Physical Status Classification System

Results are corrected for confounding by indication by a propensity score.

Prognostic value of the molecular subgroups in patients without adjuvant treatment

Among the 264 patients that did not receive any adjuvant treatment (clinicopathological features presented in supplementary table S3), survival analysis revealed that none of the patients with *POLE*mut EC (n=26) had a recurrence. Patients with MMRd EC had 5-year recurrence rate of 8.9% (95%CI 4.1-18.8%), while those with p53abn or NSMP EC had the poorest clinical outcomes with 5-year recurrence rates of 39.1% (95%CI 30.7-48.9%) and 34.6% (95%CI 22.4-50.9%) respectively (Figure 3). In multivariable analysis these differences in recurrence were independent from well-known prognostic clinicopathological features, including stage (table 3). The only other feature in the analysis with strong independent prognostic value for recurrence was substantial LVSI.

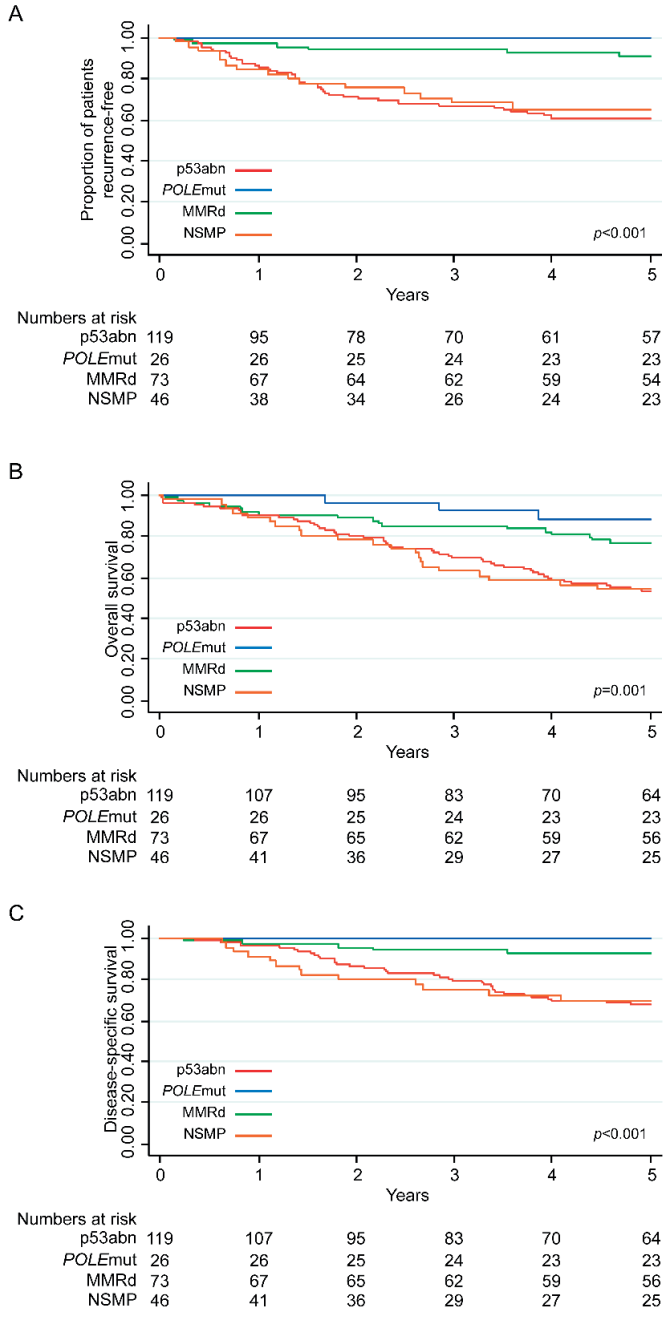

Figure 3. **Recurrence, overall survival and disease specific survival for patients not receiving adjuvant treatment (n=264).** Kaplan-Meier survival curves of patients not receiving adjuvant treatment for (A) recurrence rate for patients with p53abn endometrial cancer (EC) (at 5 years: 39.1%, 95%CI 30.7-48.9%), *POLE*mut EC (0%), MMRd EC (8.9% (95%CI 4.1-18.8%) and NSMP EC (34.6%, 95%CI 22.4-50.9%) , (B) overall survival for patients with p53abn EC (at 5 years: 53.8%, 95%CI 44.4-62.2%), *POLE*mut EC (88.5%, 95%CI 68.4-96.1%), MMRd EC (76.7%, 95%CI 65.2-84.8%) and NSMP EC (54.4%, 95%CI 39.0-67.4%) and (C) disease specific survival for patients with p53abn EC (at 5 years: 67.4%, 95%CI 57.6-75.4%), *POLE*mut EC (100%), MMRd EC (92.7%, 95%CI 83.3-96.9%) and NSMP EC (69.8%, 95%CI 53.5-81.3%).

Table 3. Multivariable analysis of molecular subgroups and clinicopathological features in high-grade endometrial cancer patients with no adjuvant treatment (n=262). Two patients with unknown LVSI status were excluded from the analysis.

	Recurrence			Overall survival			Disease specific survival		
	n events=64			n events=95			n events=52		
Parameter	**HR**	**95%CI**	***p*-value**	**HR**	**95%CI**	***p*-value**	**HR**	**95%CI**	***p*-value**
Age									
<70	1			1			1		
≥70	0.787	0.477-1.299	0.349	1.981	1.259-3.119	0.003	0.885	0.508-1.542	0.667
Molecular subgroups									
MMRd	1			1			1		
p53abn	5.703	2.376-13.689	<0.001	1.961	1.112-3.458	0.020	5.069	1.940-13.248	0.001
*POLE*mut	-	-	-	0.500	0.144-1.743	0.277	-	-	-
NSMP	4.645	1.716-12.569	0.002	2.046	1.047-3.995	0.036	4.879	1.661-14.330	0.004
Stage									
I-II	1			1			1		
III	1.484	0.652-3.377	0.347	1.225	0.593-2.530	0.584	1.296	0.521-3.228	0.577
LVSI									
Absent or focal	1			1			1		
Substantial	2.941	1.416-6.107	0.004	1.871	1.016-3.447	0.044	3.174	1.456-6.909	0.004
ASA score									
1-2	1			1			1		
3-5	1.410	0.722-2.755	0.315	2.614	1.613-4.236	<0.001	1.666	0.816-3.401	0.161

LVSI, lymphovascular-space invasion; ASA, American Society of Anesthesiologist Physical Status Classification System

Clinical value of substantial lymphovascular-space invasion and lymphadenectomy in the context of the molecular classification

Substantial LVSI was an important prognostic factor for recurrence, OS and DSS, independent of molecular subgroups and other clinicopathological features in the complete cohort (supplementary table S1). Within the subgroup of 251 patients who had lymphadenectomy, multivariable analysis confirmed substantial LVSI as a strong independent prognostic feature (recurrence HR 2.50, 95%CI 1.34-4.66, *p*=0.004; OS HR 2.38, 95%CI 1.37-4.13, *p*=0.002), whereas stage did not carry prognostic value (recurrence HR 0.38, 95%CI 0.12-1.18, *p*=0.093; OS HR 0.50, 95%CI 0.17-1.49, *p*=0.395).

Among the 251 patients staged by lymphadenectomy, 35 patients had substantial LVSI. Of these 35 patients, 20 did not have lymph node metastasis. Of the remaining 15 patients who had lymph node metastasis, five were upstaged from stage I or II to stage IIIc.

Additionally, among these 251 patients that were staged by lymphadenectomy, 35 were upstaged (13.9%): 27 from preoperative stage I to IIIc (10.8%) and eight from preoperative stage II to IIIc (3.2%). Most of the upstaged patients had a p53abn EC (n=21, 60.0%), followed by MMRd EC (n=7, 20.0%) and NSMP EC (n=5, 14.3%). Only one patient with *POLE*mut EC was upstaged.

Discussion

In this study, we provide evidence of the strong and independent prognostic value of the molecular classification among patients with high-grade EC, both in those staged with lymphadenectomy and those who did not receive adjuvant therapy. Patients with p53abn EC had a poor clinical outcome, even if lymph node negative and stage I. Women with *POLE*mut EC had an excellent survival, also without adjuvant therapy. Finally, substantial LVSI was a strong prognostic factor, independent of molecular subgroups.

Patients with p53abn EC have consistently shown to have a poor clinical outcome in the different published cohorts.[1-6,20] Additionally, multivariable analysis has shown that the prognostic role of the molecular subgroups was independent of clinicopathological features, such as stage and histotype.[6,20] Despite this, it has been hypothesized that the poor outcome of patients with p53abn EC may (partly) be explained by undetected stage IIIC disease due to the lack of systematic lymphadenectomy, as not all patients in earlier studies were staged with lymphadenectomy (54.4% to 85.5% of patients),[2,4-6] and no analysis was performed specifically on those having undergone lymphadenectomy. This notion is supported by the higher prevalence of stage IIIc within p53abn EC. In contrast to this reasoning, our analysis on patients staged with lymphadenectomy show that the poor outcomes of patients with p53abn EC is independent of stage and likely the result of an intrinsic aggressive biology. Additionally, even among patients staged by lymphadenectomy and with stage I disease, p53abn EC patients had high recurrence rates and poor OS and DSS. This implies that the unfavourable prognosis of stage I p53abn EC cannot be explained by undetected lymph node metastasis.

The present study confirmed that patients with *POLE*mut EC (also among those with otherwise high-risk features) have an excellent survival, even among women not receiving adjuvant treatment. These results are consistent with previous studies, including the translational analysis on PORTEC-3 trial patients, where women with high-risk *POLE*mut EC had a 5-year OS and recurrence-free survival of 98%, and had no benefit from the addition of chemotherapy to adjuvant radiotherapy.[6] A recent meta-analysis based on individual patient data assessing treatment effect in patients with *POLE*mut EC did not show benefit from adjuvant treatment either. However, 87% of the patients had a low- or intermediate-risk EC by ESMO 2013 criteria.[9] Similarly, previous studies analysing small cohorts of mainly

low or intermediate (-high) risk patients with *POLE*mut EC (the majority of them having low-grade EC) and no adjuvant treatment (n=16) have reported no recurrences.[11,12] These data align with the current hypothesis that the indolent behaviour of *POLE*mut EC is the result of an effective anti-tumour immune response provoked by neoantigens produced due to the ultra-high mutational burden.[21-23] Accordingly, in our study none of the patients with *POLE*mut EC who had no adjuvant treatment (n=26) recurred. In contrast to the previous studies mentioned, our cohort was composed of patients with high-grade EC only, supporting prospective investigation on the de-escalation of adjuvant treatment in patients with *POLE*mut EC, even when of high grade, non-endometrioid histology or in the presence of substantial LVSI. The ongoing PORTEC-4a clinical trial for patients with intermediate-high risk EC will compare standard adjuvant brachytherapy to individualized treatment based on the tumour's molecular profile, including observation after surgery for women with *POLE*mut EC.[24] The POLE-BLUE trial within the RAINBO program (Refining Adjuvant Treatment in Endometrial Cancer Based on Molecular Profile) is a prospective trial investigating the de-escalation of adjuvant treatment for *POLE*mut EC, with no adjuvant treatment for early stages and de-escalated treatment for stage III.[10] Results from these trials will provide prospective data on whether adjuvant treatment can be safely omitted in *POLE*mut EC.

The implementation of the molecular classification typically results in the stratification of patients into three prognostic groups: favourable (*POLE*mut), intermediate (MMRd and NSMP) and poor (p53abn).[1,3-5] However, patients in our cohort with NSMP EC (high-grade EC, with a high proportion of non-endometrioid cancers) had a poor clinical outcome compared to previous studies,[3,4,6] shifting from an intermediate to an unfavourable prognosis. A similarly poor prognosis of NSMP EC was observed in the TransPORTEC high risk EC pilot study and other cohorts addressing non-endometrioid EC.[20,25,26] A few hypotheses could explain these results. NSMP ECs are a molecularly heterogeneous subgroup, classified based on the absence of diagnostic molecular features (i.e. *POLE* wild-type, MMR proficient, wild-type expression of p53), without a unifying molecular feature. It is therefore likely that yet undiscovered subgroups with distinct clinical outcome exist within what is now referred to as NSMP EC. Our study is based only on high-grade EC, and is strongly enriched for non-endometrioid histologies, in contrast to previous studies where in general the majority of NSMP EC were low-grade endometrioid cancers.[3,4,6] It could therefore be theorized that high-grade endometrioid and non-endometroid NSMP EC may represent a distinct subset of NSMP ECs with a poorer clinical outcome than the, more common, low-grade endometrioid NSMP EC. This is supported by previous studies enriched for or only consisting of high-grade EC.[20,25,26] Furthermore, high-grade NSMP EC could have a higher expression of biomarkers associated with a poor clinical outcome as compared to low-grade endometrioid NSMP EC. Several works have referred to the potential refining prognostic role of L1CAM overexpression (IHC stain) within NSMP EC.[3,27,28] Notably, the percentage of non-endometrioid cancers with L1CAM positivity, and particularly in clear cell carcinomas,

is higher than that seen in (low-grade) endometrioid histology.[3,27,29] Finally, in our cohort, only a minority of patients with NSMP EC received adjuvant radiotherapy (9.9%), whereas in previous studies this percentage ranged between 70.5% and 100%,[3,6] suggesting that NSMP EC may benefit from this specific adjuvant treatment modality.

Stage is currently an important factor for risk stratification of EC patients.[8] In order to assess extent of the disease, lymphadenectomy is recommended for patients with high-intermediate or high-risk EC to subsequently tailor adjuvant treatment.[8,30,31] In our multivariable analysis on patients staged with lymphadenectomy, stage was not a significant predictor for recurrence or survival after correcting for the molecular subgroups. These results could have been influenced by the study design where adjuvant treatment was not assigned randomly but was rather based on risk of recurrence which led to patients with advanced disease to receive more intensive treatment. Although the effect of confounding by indication was reduced by including a propensity score in the multivariable analysis, it could still have influenced the results presented. Additionally, not all stage I-III patients were included in the study what could have furthered influenced our results. Nevertheless, it is also possible that the clinical value of stage within this specific population of patients (grade 3 EC, stage I-III) is limited when including strong prognostic factors such as the molecular subgroups. This is especially relevant considering the intra-and postoperative complications and morbidity associated with lymphadenectomy.[32] Alternatively, sentinel lymph node biopsy is a procedure with a high accuracy in detecting lymph node metastasis and a low risk of complications and morbidity.[33-35] This data supports the implementation of the sentinel lymph node procedure over full lymphadenectomy in patients with molecularly profiled EC.

LVSI is a known risk factor for lymph node metastasis, recurrence and shorter survival in EC.[8,36-39] Studies have now reported on the clinical relevance of assessing the extent of LVSI, independent of other clinicopathological features.[16,39,40] The prognostic role of substantial LVSI has previously been explored in the context of the molecular subgroups in intermediate (-high) risk EC patients,[3,40] where substantial LVSI was an independent prognostic factor. Our study also supports the assessment of extent of LVSI, even among molecularly profiled high-grade ECs. Importantly, the long-term results of the PORTEC-2 clinical trial revealed a decreased rate of nodal recurrence in patients with substantial LVSI having received adjuvant external beam radiation therapy versus vaginal brachytherapy alone.[40] Together with our results, these data support the integration of substantial LVSI with the molecular EC classification for risk assessment and adjuvant treatment decision-making even among high-grade ECs, as introduced in the 2021 ESGO-ESTRO-ESP guidelines.[8] Future studies should address the clinical value of substantial LVSI within the different molecular subgroups.

Our study is retrospective with limitations intrinsic to this design. Firstly, not all high-grade EC patients with stage I-III were available for pathology review and inclusion in the study, especially stages II and IIIA-B. Furthermore, materials from patients with stage II

and III disease were only collected from one hospital. Secondly, as previously mentioned, treatment was not randomized, resulting in confounding by indication. This may have reduced the prognostic impact of all risk factors for recurrence that were known at the time of treatment, including stage and histotype. We aimed to correct for this bias by using a propensity score in the multivariable analysis. Registration bias is inherent to retrospective studies, but we expect this to be minimal thanks to the high-quality prospective registrations in Denmark. Nonetheless, residual confounding cannot be excluded. Finally, since only the medical records of patients who died from EC were reviewed to retrieve recurrences not confirmed histologically, it is possible that a small number of these events were omitted. However, considering the long follow-up period of the cohort and the fact that treatment for recurrence is seldom administered without histological confirmation in Denmark, we estimate this number to be very low. Despite these limitations, this study is valuable as it is one of the largest cohorts of molecularly profiled high-grade EC patients who were often staged by lymphadenectomy and did not receive adjuvant treatment, enabling answering important clinical questions.

In conclusion, our study shows the strong prognostic value of the molecular EC classification also in the context of patients staged with lymphadenectomy or not having received adjuvant therapy. Patients with p53abn EC have an inherently poor clinical outcome, independent of stage, even when staged by lymphadenectomy as stage I. *POLE*mut ECs have an excellent prognosis, also when not having received adjuvant therapy, supporting prospective studies on de-escalation of adjuvant therapy in both high-intermediate and high-risk *POLE*mut EC.

Disclosure

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Dr. Nout reports grants from Dutch Cancer Society, Dutch Research Council, Elekta, Varian, and Accuray outside the submitted work. He also reports an advisory board honorarium for his institution from Merck outside the submitted work.

Dr. Bosse report grants from Dutch Cancer Society, during the conduct of the study.

Dr. Creutzberg reports grants from Dutch Cancer Society during the conduct of the study. She also reports grants from Varian, non-financial support from Elekta, and compensation paid to her institution for time spent on independent data monitoring committee from Merck outside the submitted work.

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Supplementary material

Supplementary Methods

Lymphovascular-space invasion assessment

The presence and extent of LVSI was scored as absent, focal or substantial. For cases where myometrium was not present on the slides available (n=7), original pathology reports was used if LVSI was recorded as “absent”; if LVSI was not stated in the original pathology report or only stated as “presence”, the case was annotated as “missing LVSI data”.

Immunohistochemical stains

Immunohistochemical stains for PMS2 (clone EP51, 1:50, DAKO), MSH6 (clone EPR3945, 1:800, GENE TEX) and p53 (clone DO-7, 1:2000, DAKO). ECs were considered MMR deficient if more than 10% of the tumour showed loss of expression of at least one MMR protein. Cases with loss of expression or with doubtful staining pattern of PMS2 and/or MSH6 were additionally stained for MLH1 (clone ES05, 1:100, DAKO) and MSH2 (clone FE11, 1:100, DAKO).

Cancers were assigned to have an abnormal p53 expression if over 10% of tumoral surface presented strong positive nuclear staining in 80-100% of tumour cell nuclei (overexpression), complete absence of staining with positive internal control or cytoplasmic staining.[1]

DNA isolation was performed as previously described. Next-generation sequencing was used to assess the mutational status of the exonuclease domain of *POLE*, using the AmpliSeq Cancer Hotspot Panel, version 6 (Thermo Fisher Scientific, Waltham, MA). This panel included *POLE* exonuclease domain and *TP53* exons 2-11. If sequencing with the NGS panel failed, KASPar competitive allele-specific polymerase chain reaction (LGC Genomics, Berlin, Germany) assays were used to screen for *POLE* hotspot variants at codons 286, 297, 411, 456, and 459. *POLE* exonuclease domain mutations (EDM) were considered causative of ultramutated phenotype following criteria by Leon-Castillo et al.[2]

Sequencing and immunohistochemistry stain results were evaluated blinded for patient outcome. ECs were molecularly classified according to the algorithm provided by Vermij at al.[3]

Supplementary Tables

Supplementary table S1. Multivariable analysis of molecular subgroups and clinicopathological features in high-grade endometrial cancer patients (n=367).

	Recurrence n events=98			Overall survival n events=129			Disease specific survival n events=79		
	HR	**95%CI**	***p*-value**	**HR**	**95%CI**	***p*-value**	**HR**	**95%CI**	***p*-value**
Age									
<70	1			1			1		
≥70	0.982	0.637-1.514	0.934	2.084	1.405-3.092	<0.001	1.118	0.684-1.830	0.656
Molecular subgroups									
MMRd	1			1			1		
p53abn	4.352	2.217-8.175	<0.001	1.922	1.204-3.068	0.006	3.877	1.933-7.776	<0.001
*POLE*mut	0.520	0.115-2.346	0.395	0.579	0.218-1.533	0.271	0.328	0.042-2.585	0.290
NSMP	4.227	2.066-8.645	<0.001	1.971	1.132-3.434	0.017	3.807	1.728-8.387	0.001
Stage									
I-II	1			1			1		
III	0.655	0.271-1.587	0.349	0.492	0.223-1.088	0.080	0.613	0.225-1.670	0.339
LVSI									
Absent or focal	1			1			1		
Substantial	1.840	1.072-3.159	0.027	2.094	1.316-3.332	0.002	2.365	1.332-4.200	0.004
Adjuvant treatment									
No	1			1			1		
Yes	0.858	0.502-1.466	0.575	0.793	0.485-1.296	0.355	0.717	0.397-1.296	0.271
ASA score									
1-2	1			1			1		
3-5	2.088	1.083-4.028	0.028	2.891	1.756-4.758	<0.001	2.179	1.063-4.467	0.033

LVSI, lymphovascular-space invasion; ASA, American Society of Anesthesiologist Physical Status Classification System. Results are corrected for confounding by indication by a propensity score.

Supplementary table S2. Clinicopathological features by molecular subgroups of patients staged with lymphadenectomy (n=251).

	Total	p53abn	POLEmut	MMRd	NSMP	*p*-value
	n=251 (100%)	n=108 (43.0%)	n=27 (10.8%)	n=78 (31.1%)	n=38 (15.1%)	
Age. years						0.054
<70	152 (60.6)	56 (51.9)	23 (85.2)	50 (64.1)	23 (60.5)	
≥70	99 (39.4)	52 (48.1)	4 (14.8)	28 (35.9)	15 (39.5)	
Histotype						<0.001
Endometrioid grade 3	107 (42.6)	25 (23.1)	16 (59.3)	48 (61.5)	18 (47.4)	
Serous	87 (34.7)	61 (56.5)	9 (33.3)	9 (11.5)	8 (21.1)	
Clear cell	51 (21.3)	18 (16.7)	2 (7.4)	19 (24.4)	12 (31.6)	
Undifferentiated	6 (2.4)	4 (3.7)	0 (0)	2 (2.6)	0 (0)	
Stage						0.206
IA	115 (45.8)	53 (49.1)	15 (55.6)	34 (43.6)	13 (34.2)	
IB	57 (22.7)	21 (19.4)	10 (37.0)	16 (20.5)	10 (26.3)	
II	19 (7.6)	6 (5.6)	1 (3.7)	7 (9.0)	5 (13.2)	
IIIA	1 (0.4)	0 (0)	0 (0)	1 (1.3)	0 (0)	
IIIB	8 (3.2)	1 (0.9)	0 (0)	5 (6.4)	2 (5.3)	
IIC	51 (20.3)	27 (25.0)	1 (3.7)	15 (19.2)	8 (21.1)	
Lymphovascular space invasion						0.720
Absent	190 (75.7)	83 (76.9)	23 (85.2)	54 (69.2)	30 (78.9)	
Focal	26 (10.4)	10 (9.3)	2 (7.4)	10 (12.8)	4 (10.5)	
Substantial	35 (13.9)	15 (13.9)	2 (7.4)	14 (17.9)	4 (10.5)	
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Lymphadenectomy						0.537
No	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Pelvic	208 (82.9)	86 (76.6)	25 (92.6)	63 (80.8)	34 (89.5)	
Para-aortic	1 (0.4)	1 (0.9)	0 (0)	0 (0)	0 (0)	
Pelvic and para-aortic	42 (16.7)	21 (19.4)	2 (7.4)	15 (19.2)	4 (10.5)	

Adjuvant treatment received						
None	178 (70.9)	77 (71.3)	22 (81.5)	53 (67.9)	26 (68.4)	0.608
RT	18 (7.2)	9 (8.3)	2 (7.4)	6 (7.7)	1 (2.6)	
CTRT	6 (2.4)	2 (1.9)	1 (3.7)	1 (1.3)	2 (5.3)	
CT	49 (19.5)	20 (18.5)	2 (7.4)	18 (23.1)	9 (23.7)	
ASA score						0.701
1	70 (27.9)	26 (24.1)	11 (40.7)	22 (28.2)	11 (28.9)	
2	163 (64.9)	73 (67.6)	13 (48.1)	52 (66.7)	25 (65.8)	
3	18 (7.2)	9 (8.3)	3 (11.1)	4 (5.1)	2 (5.3)	
4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	

ASA, American Society of Anesthesiologist Physical Status Classification System

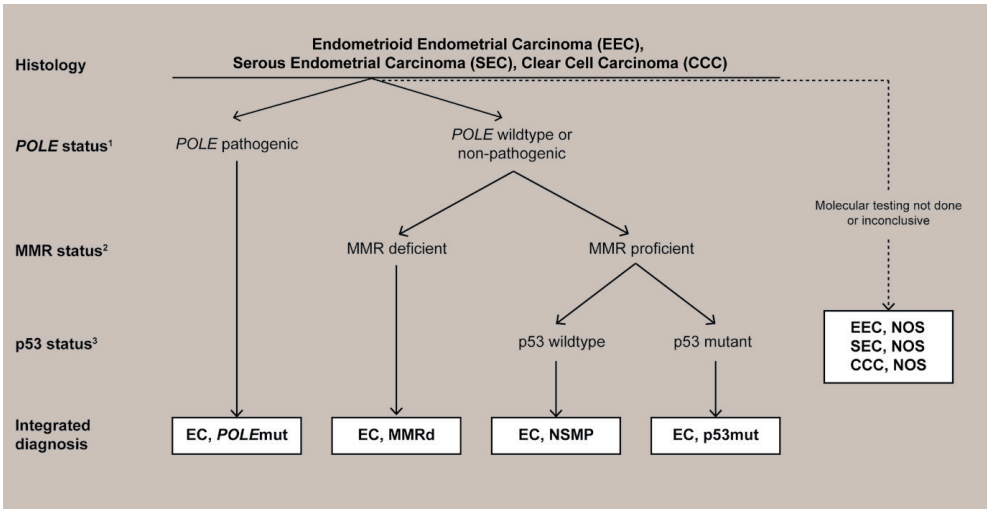
Supplementary table S3. Clinicopathological features by molecular subgroups of patients without adjuvant treatment (n=264).

	Total n=264 (100%)	p53abn n=119 (45.1%)	POLEmut n=26 (9.9%)	MMRd n=73 (27.7%)	NSMP n=46 (17.4%)	*p*-value
Age. years						0.001
<70	125 (47.3)	47 (39.5)	22 (84.6)	40 (54.8)	16 (34.8)	
≥70	139 (52.7)	72 (60.5)	4 (15.4)	33 (45.2)	30 (65.2)	
Histotype						<0.001
Endometrioid grade 3	126 (47.7)	34 (28.6)	15 (57.7)	52 (71.2)	25 (54.3)	
Serous	85 (32.2)	62 (52.1)	7 (26.9)	8 (11.0)	8 (17.4)	
Clear cell	48 (18.2)	21 (17.6)	4 (15.4)	10 (13.7)	13 (28.3)	
Undifferentiated	5 (1.9)	2 (1.7)	0 (0)	3 (4.1)	0 (0)	
Stage						0.276
IA	158 (59.8)	75 (63.0)	18 (69.2)	41 (56.2)	24 (52.2)	
IB	69 (26.1)	30 (25.2)	7 (26.9)	22 (30.1)	10 (21.7)	
II	20 (7.6)	9 (25.2)	1 (3.8)	6 (8.2)	4 (8.7)	
IIIA	3 (1.1)	1 (0.8)	0 (0)	0 (0)	2 (4.3)	
IIIB	5 (1.9)	0 (0)	0 (0)	2 (2.7)	3 (6.5)	
IIIC	9 (3.4)	4 (3.4)	0 (0)	2 (2.7)	3 (6.5)	
Lymphovascular space invasion						0.458
Absent	211 (79.9)	100 (84.0)	22 (84.6)	53 (72.6)	36 (78.3)	
Focal	29 (11.0)	10 (8.4)	3 (11.5)	10 (13.7)	6 (13.4)	
Substantial	22 (8.3)	9 (7.6)	1 (3.8)	8 (11.0)	4 (8.7)	
Unknown	2 (0.8)	0 (0)	0 (0)	2 (2.7)	0 (0)	
Lymphadenectomy						0.106
No	86 (32.6)	42 (35.3)	4 (15.4)	20 (27.4)	20 (43.5)	
Pelvic	155 (58.7)	66 (55.5)	21 (80.8)	44 (60.3)	24 (52.2)	
Para-aortic	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Pelvic and para-aortic	23 (8.7)	11 (9.2)	1 (3.8)	9 (12.3)	2 (4.3)	

ASA score						0.455
1	65 (24.6)	25 (21.0)	9 (34.6)	18 (24.7)	13 (28.3)	
2	163 (61.7)	73 (61.3)	13 (50.0)	48 (65.7)	29 (63.0)	
3	36 (13.6)	21 (17.6)	4 (15.4)	7 (9.6)	4 (8.7)	
4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	

ASA, American Society of Anesthesiologist Physical Status Classification System

Supplementary Figures

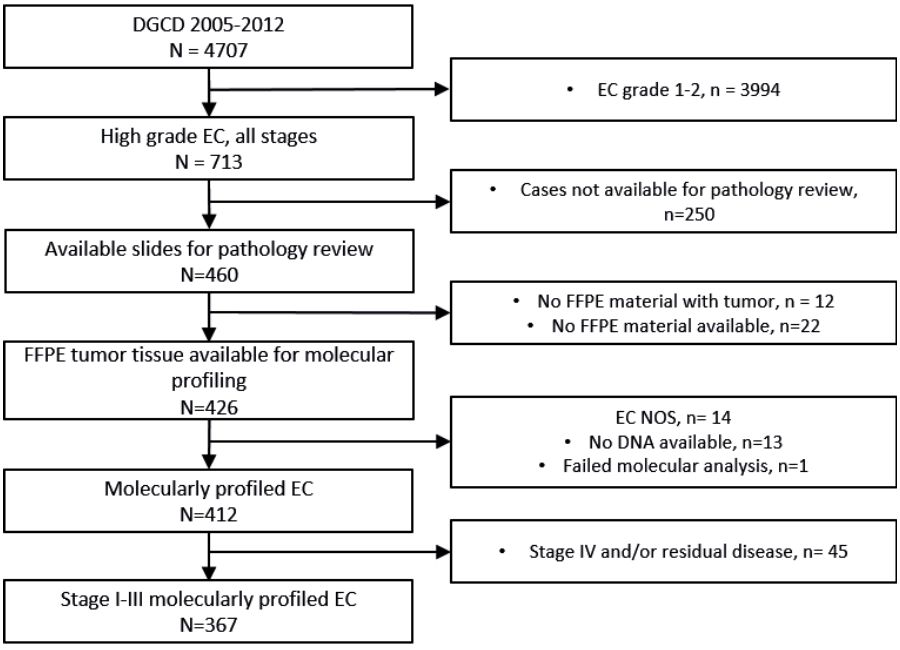


Supplementary figure S1. Diagnostic algorithm for the molecular classification of endometrial cancer, from Vermij et al, Histopathology 2020.[3] First, *POLE* exonuclease domain mutations were assessed, followed by mismatch repair (MMR) status and, lastly, p53 expression. If one or more of these features could not be assessed, the cancer was classified as endometrial cancer "not otherwise specified" (NOS). NSMP: No specific molecular profile.

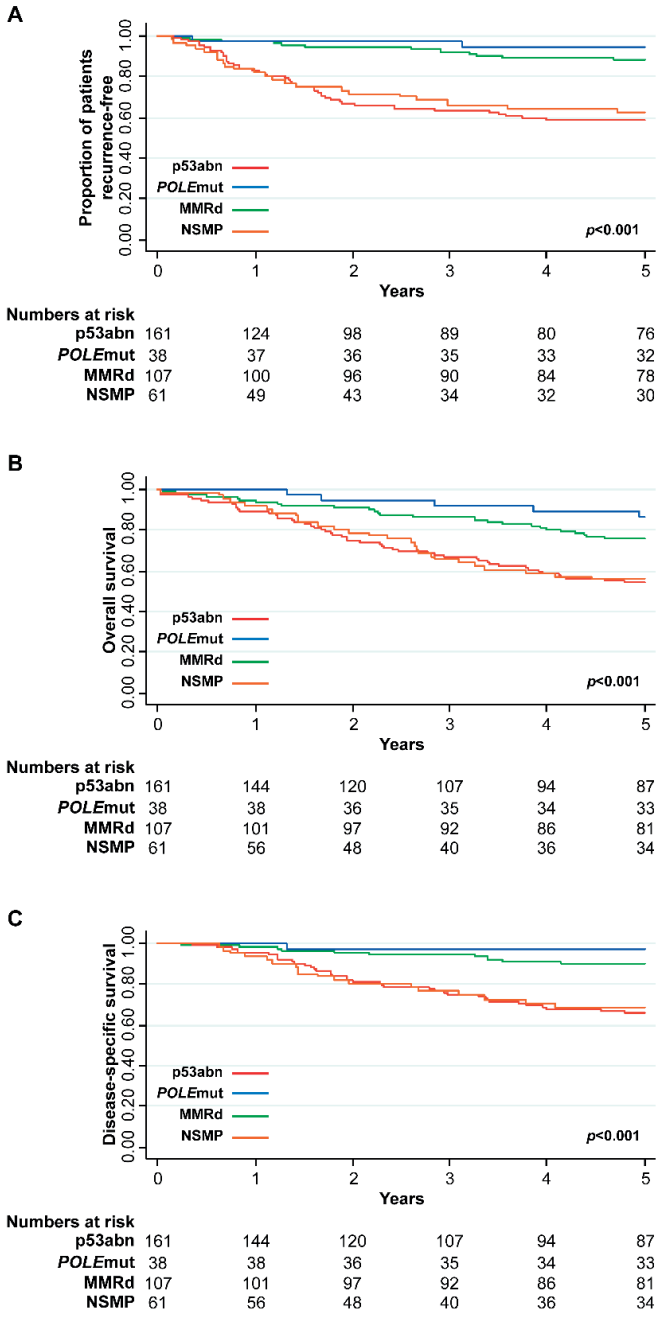
1 *POLE* exonuclease domain mutations were considered pathogenic (causative of ultra-mutated phenotype) according to the criteria described by Leon-Castillo et al.[2]

2 MMR deficiency is defined by the loss of one or more MMR-proteins. In cases with unevaluable MMR immunohistochemistry, microsatellite instability analysis was performed

3 p53 status was based on immunohistochemistry, and evaluated according to Singh et al.[1] In cases with unevaluable p53 immunohistochemistry, *TP53* mutational status was used.



Supplementary figure S2. Flowchart of sample analysis. DGCD, Danish Gynaecological Cancer Database; EC, endometrial cancer; FFPE, formalin fixed, paraffin-embedded; NOS, not otherwise specified.



Supplementary figure S3. Recurrence, overall survival and disease specific survival of patients with high-grade endometrial cancer (n=367). Kaplan-Meier survival curves for (A) recurrence rate for patients with p53abn endometrial cancer (at 5 years: EC; 41.5%, 95%CI 34.0-49.9%) , *POLE*mut EC (5.4% (95%CI 1.4-30%), MMRd EC (12.0%, 95%CI 7.0-20.2%) and NSMP EC (37.9%, 95%CI 26.7-51.8%), (B) overall survival for patients with p53abn EC (at 5 years: 54.0%, 95%CI 46.0-61.4%), *POLE*mut EC (86.8%, 95%CI 71.2-94.3%), MMRd EC (75.7%, 95%CI 66.4-82.8%) and NSMP EC (55.7%, 95%CI 42.5-67.1%), and (C) disease specific survival for patients with p53abn EC (at 5 years: 65.9%, 95%CI 57.5-72.9%), *POLE*mut EC (97.4%, 95%CI 82.8-99.6%), MMRd EC (90.0%, 95%CI 82.2-94.5%) and NSMP EC (68.7%, 95%CI 54.8-79.0%).

References

1. Singh N, Piskorz AM, Bosse T, et al. p53 immunohistochemistry is an accurate surrogate for TP53 mutational analysis in endometrial carcinoma biopsies. J Pathol 250(3):336-45,2020.
2. León-Castillo A, Britton H, McConechy MK, et al. Interpretation of somatic POLE mutations in endometrial carcinoma. J Pathol 250(3):323-35,2020.
3. Vermij L, Smit V, Nout R, et al. Incorporation of molecular characteristics into endometrial cancer management. Histopathology 76(1):52-63,2020.