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Original research

Surgical stage in the era of molecular profiling of endometrial cancer

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ABSTRACT

Introduction: Molecular classification has reshaped risk stratification in endometrial cancer (EC), yet the relevance of tumor spread within molecular subgroups has not been reported so far.
Material and methods: This multicenter retrospective study included 2056 EC patients treated between 1994 and 2018 across 11 European centers. All histopathological subtypes and FIGO stages were included. Tumors were classified into four molecular subgroups: *POLE*-mutated (*POLE*mut), mismatch repair deficient (MMRd), no specific molecular profile (NSMP), and *TP53*/p53 abnormal (p53abn). Clinical and pathological data were extracted from existing cohort databases.

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Results: Patients were diagnosed with FIGO stage I (69 %), II (9 %), III (16 %), and IV (6 %), and classified into: *POLE*mut (8 %), MMRd (28 %), NSMP (44 %), and p53abn (21 %). The overall 5-year cancer-specific death (CSD) and recurrence rates were 16.5 % (95 % CI, 14.9 %-18.2 %) and 23.8 % (95 % CI, 22.0 %-25.7 %), respectively. In multivariable analysis cancer-specific survival (CSS) was independently associated with molecular subtype, FIGO stage, age, histopathological type, grade, lymphovascular space invasion, adjuvant therapy, residual tumor, and lymphadenectomy. FIGO stage was significantly associated with CSD also in within each molecular subgroup ($p < 0.001$). Patients with tumors confined to the uterus had the most favourable prognosis. Lymph node metastases significantly decreased CSS in *POLE*mut, MMRd, and p53abn groups. Within FIGO stage IV, molecular subtype was not significantly related to outcome.
Discussion: Surgical stage remains a strong prognostic factor across molecular subtypes and should be considered alongside molecular classification when tailoring adjuvant treatment in EC.

1. Introduction

Historically, preoperative risk stratification of endometrial cancer (EC) has been based on histopathological factors, and tumor spread by clinical examination and imaging. Based on this risk assessment, hysterectomy with bilateral salpingo-oophorectomy may be extended by staging procedures such as sentinel node procedure or lymphadenectomy, peritoneum and omentum biopsies to detect metastases. In addition to other risk factors, including age or lympho-vascular space invasion (LVSI), the presence of tumor spread beyond the uterus including distant metastases, categorized by FIGO (International Federation of Gynecology and Obstetrics) stage, determines if adjuvant treatment is recommended [1,2].

Currently, the molecular classification of EC subdivides patients into four groups that are directly related to prognosis [3]. Polymerase epsilon ultra-mutated *(POLE*mut*)* tumors were found to have the best prognosis whereas *TP53*/p53 abnormal (p53abn) tumors the worst. The groups mismatch repair deficient (MMRd), and nonspecific molecular profile (NSMP) are associated with an intermediate prognosis. In the European Society of Gynecological Oncology, European Society for Radiotherapy and Oncology, and European Society of Pathology (ESGO-ESTRO-ESP) guideline, the molecular subgroups have been integrated to guide adjuvant treatment [4]. To some extent the guidelines are based on PORTEC studies, in which surgical staging was not mandatory [5]. This makes extrapolation to protocols, where surgical staging is routinely performed difficult. For patients with p53abn tumors adjuvant chemotherapy and radiation are recommended but suggested to be withheld in almost all *POLE*mut ECs. This raises questions about the relevance of surgical staging for each molecular group, and whether outcomes are driven more by tumor spread or by intrinsic tumor biology [6]. Recent papers have reported that patterns of spread, and recurrence differ within the molecular subgroups [7–10]. In addition, literature has shown that metastatic disease may be present in all four molecular groups [11]. Yet, it remains unclear if the tumor stage is relevant and should still be considered to guide surgical staging and adjuvant treatment. FIGO was updated, partially involving tumor aggressiveness (i.e. tumor grade and molecular subtypes) in upgrading patients from FIGO I to II [12]. The translation into treatment recommendations remains challenging as the extent of the disease is in some ways less clearly described within FIGO 2023 [13]. Patients with EC are often elderly with multiple comorbidities, which requires proper balancing of the benefits and treatment-related toxicity of adjuvant therapy. Consequently, more detailed information on prognosis integrating both FIGO stage and molecular subgroup may facilitate shared decision making and help weighing the risk of recurrence and the toxicity of adjuvant treatment.

Therefore, the aim of this study was to determine outcomes in relation to FIGO stage for each molecular group to define the relevance of tumor spread as an additional prognosticator.

2. Methods

2.1. Patients

This retrospective, multicenter study is based on data from merged patient cohorts (Supplementary Table 1). The study was approved by The Regional Committee for Medical and Health Research Ethics (REK) in Norway (2014/701), and data protection office for the Oslo University Hospital (OUS) and the Institutional Review Boards of all participating centers. The cohorts consisted of patients who were surgically treated for EC at OUS from 2006 to 2018, ENITEC/Radboudumc (European Network for Individualized Treatment and Radboud university medical center) from 1994 to 2018, Innsbruck Medical University (MUI) from 1999 to 2014 and Amsterdam University Medical Centers (Amsterdam UMC) from 2000 to 2015. Data used in this study were from previously published studies by our research groups [8,9,14,15] therefore, informed consent was waived for participants. This study followed the ESMO-Guidance for Reporting Oncology real-world evidence (GROW) guideline.

2.2. Disease classification

Patients were included independent of histopathological type, grade of differentiation and FIGO stage. Tumor samples were molecularly profiled according to the ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer) classification or by full next-generation sequencing (NGS) [16]. Medical data was collected from the databases of the existing cohorts. Patients were allocated into FIGO stage (I-IV) according to the FIGO 2009 classification, and grade (1−3) and histopathological type (endometrioid and non-endometrioid) according to the World Health Organization guideline 2020 [14,17]. Central histopathological revision was not performed, yet all diagnoses were made by expert gynecological pathologists. Presumed low- or intermediate-risk, early-stage patients were predominantly treated by hysterectomy and bilateral salpingo-oophorectomy [4]. High-risk EC patients generally underwent a staging procedure, including lymph node sampling, either by pelvic (and/or para-aortic) lymphadenectomy or sentinel lymph node sampling and possibly omentectomy and peritoneal biopsies. Adjuvant therapy was based on final risk classification including FIGO stage and was classified as: none, radiotherapy (external beam radiotherapy (EBRT), vaginal brachytherapy (VBT)), chemotherapy, chemotherapy and EBRT combined or chemotherapy and VBT combined. Both surgical- and adjuvant treatment was left to institutional and national guidelines.

2.3. Immunohistochemical staining and scoring

Detailed information about the immunohistochemical staining for p53 and mismatch repair (MMR) endonucleases PMS2 and MSH6 can be found in the Supplementary Methods and original published studies [8,14]. In brief, staining for p53 was considered outside reference range when more than 80 % of tumor cell nuclei showed strong expression

(overexpression), or if unequivocal cytoplasmic staining was present or when there was a complete absence of nuclear staining [18]. Mismatch repair deficiency was defined as loss of protein expression of MSH6, PMS2, MLH1 and MSH2 in tumor cells (with presence of positive internal control cells) and tumors with subclonal loss were considered MMRd (OUS, MUI, Amsterdam UMC), or as total loss of nuclear staining of MSH6 and/or PMS2 (with presence of positive internal control) (ENITEC/Radboudumc).

2.4. DNA analyses

DNA was extracted from 10 to 20 μm thick sections from representative areas of EC from the surgical specimen. Details are described in Supplementary Methods. In short, molecular profiling was performed by full NGS for the ENITEC/Radboudumc cohort. Samples were sequenced with single-molecule molecular inversion probes (smMIPs). The design (Integrated DNA Technologies), as well as the library preparation, were previously published [14]. For the detection of MSI, 55 MSI markers were tested according to the previously published design [19]. In case MMR status could not be determined by NGS, it was based on immunohistochemistry. Information on smMIP design, library preparation, and sequencing are provided in the Supplementary Methods. OUS, MUI and Amsterdam UMC samples were analyzed by allele-specific polymerase chain reaction (PCR) for the five most common pathogenic *POLE*-mutations (P286R, V411L, S297F, A456P and S459F), accounting for approximately 95 % of pathogenic variants in the *POLE* gene in endometrial cancer by Taqman® Genotyping Assays (Thermo Fisher Scientific).

2.5. Molecular profiling

The final molecular classification into the groups *POLE*mut, MMRd, NSMP and p53abn groups was performed as recommended by ESMO [1]. Samples that contained more than one molecular classifying feature, were classified into the group with the best prognosis [20].

2.6. Statistics

Counts and proportions were used to describe categorical variables, while median and interquartile range (IQR) were used to describe continuous variables. Pearson's χ^2 test was used to assess differences between categorical variables, while Kruskal-Wallis H test was used to assess differences between a categorical and a continuous variable. Two endpoints were applied for survival analyses, cancer-specific survival (CSS) and time to recurrence (TTR). Both were defined as proposed by Punt et al. [21]. The associated times were calculated from the date of diagnosis and limited to at most 5 years because of differences in follow-up time between the cohorts. Whether a variable associated with an endpoint was assessed using the Mantel-Cox log-rank test, and an associated hazard ratio (HR) with 95 % confidence interval (CI) was calculated using a Cox regression analysis. Survival curves were plotted with the Kaplan-Meier method. All event rates were estimated using the cumulative incidence function with death from other causes than EC as competing event. Multivariable survival analyses were performed with the following established prognostic variables, in addition to molecular classification or within a molecular subgroup: age at diagnosis, FIGO surgical stage (2009), histopathological type with grade for endometrioid adenocarcinomas, LVSI, adjuvant treatment, residual tumor, and lymphadenectomy. We assessed the proportional hazards assumption and multicollinearity and found them acceptable. As a sensitivity analysis, we performed multivariable analyses of the entire cohort with multiple imputation by chained equations (MICE) with 100 imputations. To investigate influence of institutional differences, we adjusted for center by including a frailty term in the Cox model. The interaction between FIGO stage and molecular classification was studied by including their interaction term in the multivariable model. Subgroup analysis excluding patients with presumed FIGO I and II EC without known nodal status was done to assess the effect of lymph node sampling on the study results as a sensitivity analysis. A two-sided $p < 0.05$ was considered statistically significant. The analyses were performed using Stata/SE 18.5 (StataCorp, TX).

3. Results

3.1. Study population

Of the entire cohort of 2083 patients, a total of 2056 patients with EC, of whom molecular classification and FIGO stage (2009) was known, were included in the analysis (1208 from OUS, 646 from ENITEC/Radboudumc, 130 from MUI and 72 from Amsterdam UMC). An

Table 1
Patient characteristics of the entire cohort.

Characteristic	All
Patients	2056
Age at diagnosis, years	67 (59–74)
Stage (FIGO 2009)	
IA	892 (43 %)
IB	531 (26 %)
II	182 (9 %)
III	8 (<1 %)
IIIA	51 (2 %)
IIIB	18 (1 %)
IIIC	30 (1 %)
IIIC1	135 (7 %)
IIIC2	88 (4 %)
IV	1 (<1 %)
IVA	3 (<1 %)
IVB	117 (6 %)
Histopathological type and grade	
Endometrioid carcinoma low-grade	653 (32 %)
Endometrioid carcinoma intermediate-grade	530 (26 %)
Endometrioid carcinoma high-grade	356 (17 %)
Serous carcinoma	205 (10 %)
Clear cell carcinoma	77 (4 %)
Mixed with clear cell/serous	93 (5 %)
Carcinosarcoma	107 (5 %)
Undifferentiated carcinoma	17 (1 %)
Unclassifiable carcinoma	9 (<1 %)
Squamous cell carcinoma	2 (<1 %)
Mucinous carcinoma	7 (<1 %)
Lymphovascular space invasion	
No	1460 (71 %)
Yes	591 (29 %)
Missing	5 (<1 %)
Adjuvant treatment	
No adjuvant treatment	974 (47 %)
Chemotherapy	533 (26 %)
External beam radiotherapy	205 (10 %)
Brachytherapy	226 (11 %)
Chemotherapy and external beam radiotherapy	43 (2 %)
Chemotherapy and brachytherapy	35 (2 %)
Missing	40 (2 %)
Residual tumor	
No	1916 (93 %)
Yes	72 (4 %)
Missing	68 (3 %)
Lymphadenectomy	
No	724 (35 %)
Yes	1329 (65 %)
Missing	3 (<1 %)
Molecular classification	
No specific molecular profile	895 (44 %)
p53 abnormal	424 (21 %)
Mismatch repair deficient	577 (28 %)
POLE mutated	160 (8 %)
Follow-up time from diagnosis, years	5.0 (3.7–5.0)

Data are median (IQR) or *n* (%). FIGO = International Federation of Gynecology and Obstetrics; IQR = interquartile range; MMRd = mismatch repair deficient; p53abn = *TP53/p53* abnormal; *POLE* = DNA polymerase epsilon.

overview of patient characteristics is shown in Table 1 and Supplementary Table 1. Patients had a median age at diagnosis of EC of 67 years (IQR 59–74). The median follow-up was 5 years (IQR 3.7–5.0). Figure 1B illustrates the subclassification into FIGO stage and molecular group, and Supplementary Table 2 shows the association between all patient characteristics and molecular group. We found 111 double, and 10 triple classifiers (n = 121/2056, 5.9 %).

3.1.1. Cancer-specific, and recurrence-free survival

Within the entire study cohort (n = 2056), the 5-year cancer-specific death (CSD) and recurrence rates were 16.5 % (95 % CI, 14.9 %-18.2 %) and 23.8 % (95 % CI, 22.0 %-25.7 %), respectively. Patients in the *POLE*mut group had the most favorable outcome, the NSMP/MMRd groups had an intermediate outcome, and the p53abn group had the worst outcome (Figure 1, Table 2). Recurrence data was missing for two patients from the p53abn group, diagnosed with FIGO stage III and IV disease and alive at the end of follow-up.

3.1.2. Prognosis of molecular group for each FIGO stage

Overall, the prognosis of patients with FIGO stage I disease was favorable, in the *POLE*mut, MMRd, and NSMP groups with a 5-year CSD rate of 0.8 % (95 %CI, 0.1 %-3.8 %), 7.6 % (95 %CI, 5.2 %-10.6 %), and 5.8 % (95 %CI, 4.2 %-7.7 %), respectively (Figure 1, Table 2). The prognosis was substantially worse in the p53abn group (5-year CSD rate of 22.0 % (95 %CI, 16.4 %-28.0 %). The risk of recurrence increased gradually from the *POLE*mut, NSMP, MMRd to the p53abn group (Table 2, Supplementary Figure 1A).

Within FIGO stage II EC, the pattern was similar (Figure 1D), although the difference was not statistically significant in the analysis of TTR (Table 2, Supplementary Figure 1C).

The difference in survival rates between molecular groups was largest in patients diagnosed with FIGO stage III EC. The 5-year CSD rates varied from 11.8 % to 53.6 % (Figure 1E, Table 2).

Remarkably, molecular classification had no significant impact on prognosis in patients with FIGO stage IV disease (Figure 1F, Table 2, Supplementary Figure 1E).

3.2. Prognosis of FIGO stage for each molecular group

The 5-year CSD and recurrence rates of patients within the *POLE*mut group were 3.2 % (95 % CI, 1.2 %-6.9 %) and 5.1 % (95 % CI, 2.4 %-9.3 %), respectively. The prognosis was statistically significantly associated with FIGO stage, LVSI and residual tumor but not with age, histopathological type and grade, adjuvant treatment and lymphadenectomy (Figure 2A, Table 2, Supplementary Figure 2A and 3–4).

For patients within the MMRd group, the 5-year CSD and recurrence rates were 12.7 % (95 % CI, 10.0 %-15.6 %) and 23.0 % (95 % CI, 19.6 %-26.6 %), respectively. The prognosis of patients with locoregional tumor spread and lymph node metastases (FIGO stage II and III) was similar, but substantially worse than in patients with localized tumors (FIGO stage I) and otherwise substantially better than in patients with advanced disease (FIGO stage IV) (Figure 2b, Table 2, Supplementary Figure 2C).

The patients in the NSMP group had a 5-year CSD rate of 11.0 % (95 % CI, 9.0 %-13.2 %) and a recurrence rate of 17.1 % (95 % CI, 14.7 %-19.7 %). The risk of recurrence was rather similar between patients in the NSMP group diagnosed with FIGO stage II and III, but their CSD rates differed notably based on the difference in HR (Figure 2C, Table 2, Supplementary Figure 2C).

In p53abn patients, the prognosis was relatively poor but still markedly associated with the FIGO stage ($p < 0.0001$) (Figure 2D, Table 2).

3.3. Multivariable analysis

In multivariable analyses, all factors had a statistically significant effect on CSS and all except for the lymphadenectomy status had a statistically significant effect on TTR (Table 3). Variables associated with reduced CSS were older age, higher FIGO stage, higher grade or non-endometrioid histopathological type, LVSI, presence of residual tumor, performed lymphadenectomy and no adjuvant treatment, in particular no adjuvant chemotherapy. The outcomes were comparable for both the entire cohort and the subgroup of patients who underwent lymphadenectomy. The molecular classification was also statistically significant in the multivariable analyses, patients with p53abn tumors having a worse prognosis and patients with *POLE*mut tumors having a better prognosis compared to NSMP patients, while no statistically significant difference was observed between the NSMP and MMRd groups. These analyses included only the 94.6 % of patients with complete data, but similar results were observed when applying MICE to include all patients in the analyses (Supplementary Table 3). Moreover, including a frailty term in the Cox model further supported the reliability of the findings and a neglectable influence of institutional differences (Supplementary Table 4a-4b). By including an interaction term between FIGO stage and molecular classification in the multivariable model, we observed a statistically significant interaction (Supplementary Table 5).

Multivariable analyses were also performed for each molecular group separately, except for the *POLE*mut group where the number of events was too low. In all the other molecular groups, FIGO stage, histopathological type and grade, LVSI, residual tumor and performance of lymphadenectomy significantly affected CSS (Table 4). Whereas adjuvant treatment had effect on outcome in the MMRd group, but not in patients with NSMP and p53abn tumors. These variables influenced TTR too, except for residual tumor and lymphadenectomy in the MMRd and NSMP groups, as well as age in the MMRd group and adjuvant treatment in the NSMP group (Supplementary Table 6 and 7).

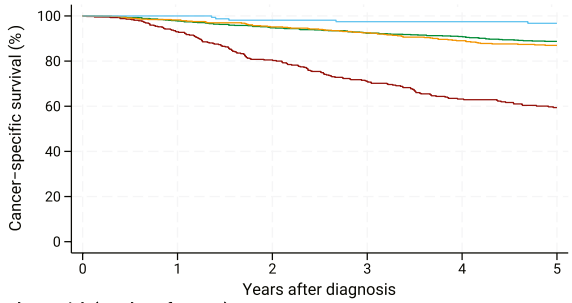
Multivariable analyses were also performed for each molecular group separately excluding patients with unknown lymph node status (Supplementary Table 6b, 7b and 8b). Within the entire MMRd group, CSS was worse in FIGO stage II and IIIA & B (HR, 6.52; 95 % CI 2.89–14.72 and 6.86; 95 %CI 2.61–18.04) than in FIGO stage IIIC (HR, 3.15; 95 % CI 1.34–7.43) compared to FIGO stage I (Supplementary Table 6a). However, in MMRd patients who had lymphadenectomy, CSS was statistically different between FIGO stage IIIC and FIGO stage I (HR, 3.22; 95 %CI 1.32–7.84). FIGO stage affected both CSS and TTR in the NSMP group (Supplementary Tables 7a and 7b), but only FIGO stage IV was significantly different from FIGO stage I in multivariable analysis of CSS independent of lymphadenectomy (HR, 9.53; 95 % CI 4.59–19.77 for all NSMP patients; HR, 8.64; 95 % CI 3.79–19.73 for NSMP patients who had lymphadenectomy). Finally, histopathological type and grade was not statistically associated with CSS in p53abn patients who had lymphadenectomy ($p = 0.084$) (Supplementary Table 8b).

Finally, we performed multivariable analyses for each FIGO stage separately (Figure 1C-F, Supplementary Tables 9–12). Molecular classification was significantly associated with CSS in the FIGO stage groups with most patients, FIGO stage I ($p = 0.0010$; Supplementary Table 9) and III ($p = 0.026$; Supplementary Table 11). Molecular classification was not statistically significant in our analyses of FIGO stage II ($p = 0.36$; Supplementary Table 10) and IV ($p = 0.49$; Supplementary Table 12). Similar findings were observed for multivariable analysis of TTR (Supplementary Tables 9–12).

4. Discussion

This large multicenter retrospective cohort study is the first to offer a comprehensive overview of survival data, stratified by molecular group and combined with FIGO stage. Advanced and particularly metastatic EC patients had poor prognosis irrespective of molecular classification and patients with p53abn tumors had relatively poor prognosis

A Analysis of CSS in all patients



Number at risk (number of events)

NSMP	895	(19)	860	(27)	811	(20)	772	(12)	700	(16)	615
p53abn	424	(29)	378	(50)	316	(37)	267	(28)	215	(12)	178
MMRd	577	(10)	548	(17)	518	(14)	487	(18)	439	(10)	400
*POLE*mut	160	(0)	159	(3)	154	(1)	146	(0)	140	(1)	130

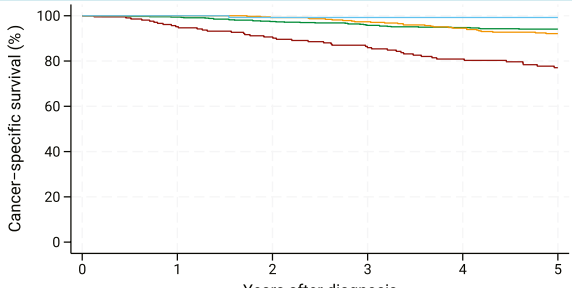
NSMP, ref.	**Univariable analysis** p<0.0001	**Multivariable analysis** p<0.0001
p53abn	HR=4.38 (95% CI 3.39-5.66)	HR=1.48 (95% CI 1.08-2.04)
MMRd	HR=1.15 (95% CI 0.85-1.58)	HR=0.90 (95% CI 0.65-1.25)
*POLE*mut	HR=0.28 (95% CI 0.11-0.69)	HR=0.24 (95% CI 0.10-0.59)

B Distribution between FIGO stage and molecular classification of the entire cohort

	Molecular classification (N (%))				
Stage (FIGO 2009)	*POLE*mut	MMRd	NSMP	p53abn	Total
I	132 (82%)	401 (69%)	680 (76%)	210 (50%)	1423
II	8 (5%)	58 (10%)	79 (9%)	37 (9%)	182
III	17 (11%)	96 (17%)	97 (11%)	120 (28%)	330
IV	3 (2%)	22 (4%)	39 (4%)	57 (13%)	121
Total	160 (100%)	577 (100%)	895 (100%)	424 (100%)	2056*

FIGO = International Federation of Gynecology and Obstetrics;
p53abn = TP53 abnormal; *POLE*mut = polymerase epsilon mutated;
MMRd = Mismatch repair deficient; NSMP = No specific molecular profile.
* The 2056 patients included in univariable analyses.

C Analysis of CSS in patients in FIGO stage I

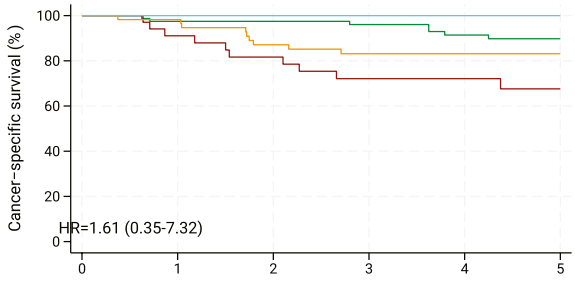


Number at risk (number of events)

NSMP	680	(4)	664	(13)	639	(11)	613	(6)	561	(4)	506
p53abn	210	(10)	195	(9)	175	(9)	160	(9)	136	(6)	113
MMRd	401	(0)	387	(3)	376	(7)	356	(10)	322	(8)	295
*POLE*mut	132	(0)	131	(1)	129	(0)	123	(0)	118	(0)	109

NSMP, ref.	**Univariable analysis** p<0.0001	**Multivariable analysis** p=0.0010
p53abn	HR=4.24 (95% CI 2.74-6.57)	HR=1.95 (95% CI 1.15-3.30)
MMRd	HR=1.27 (95% CI 0.78-2.06)	HR=0.79 (95% CI 0.47-1.32)
*POLE*mut	HR=0.13 (95% CI 0.02-0.95)	HR=0.11 (95% CI 0.02-0.84)

D Analysis of CSS in patients in FIGO stage II

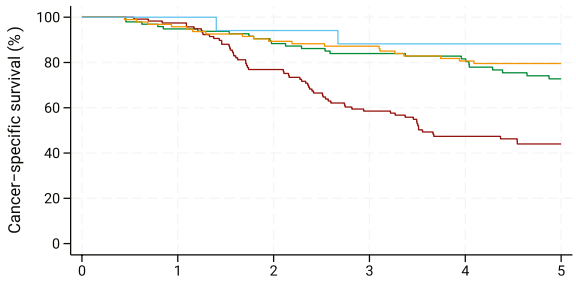


Number at risk (number of events)

NSMP	79	(2)	77	(0)	71	(1)	68	(3)	58	(1)	49
p53abn	37	(3)	29	(3)	26	(3)	21	(0)	19	(1)	15
MMRd	58	(1)	55	(6)	45	(2)	39	(0)	36	(0)	30
*POLE*mut	8	(0)	8	(0)	7	(0)	6	(0)	6	(0)	6

NSMP, ref.	**Univariable analysis** p=0.015	**Multivariable analysis** p=0.36
p53abn	HR=3.92 (95% CI 1.49-10.31)	HR=1.61 (95% CI 0.35-7.32)
MMRd	HR=1.94 (95% CI 0.72-5.22)	HR=2.92 (95% CI 0.90-9.47)
*POLE*mut	HR=0.00 (95% CI 0.00-∞)	HR=0.00 (95% CI 0.00-∞)

E Analysis of CSS in patients in FIGO stage III

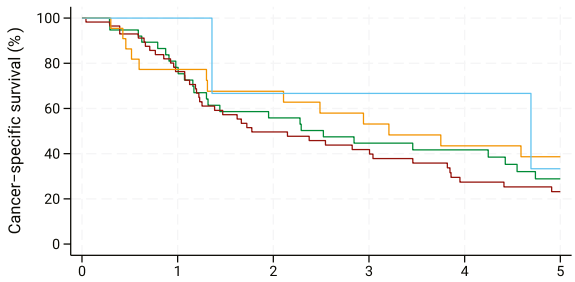


Number at risk (number of events)

NSMP	97	(5)	91	(6)	81	(4)	76	(2)	67	(7)	51
p53abn	120	(3)	114	(24)	89	(21)	65	(12)	47	(3)	39
MMRd	96	(4)	90	(6)	83	(2)	81	(6)	72	(1)	67
*POLE*mut	17	(0)	17	(1)	16	(1)	15	(0)	14	(0)	14

NSMP, ref.	**Univariable analysis** p<0.0001	**Multivariable analysis** p=0.026
p53abn	HR=2.64 (95% CI 1.65-4.23)	HR=2.26 (95% CI 1.18-4.30)
MMRd	HR=0.76 (95% CI 0.42-1.39)	HR=1.01 (95% CI 0.54-1.92)
*POLE*mut	HR=0.42 (95% CI 0.10-1.76)	HR=0.50 (95% CI 0.11-2.25)

F Analysis of CSS in patients in FIGO stage IV



Number at risk (number of events)

NSMP	39	(8)	28	(8)	20	(4)	15	(1)	14	(4)	9
p53abn	57	(13)	40	(14)	26	(4)	21	(7)	13	(2)	11
MMRd	22	(5)	16	(2)	14	(3)	11	(2)	9	(1)	8
*POLE*mut	3	(0)	3	(1)	2	(0)	2	(0)	2	(1)	1

NSMP, ref.	**Univariable analysis** p=0.63	**Multivariable analysis** p=0.49
p53abn	HR=1.17 (95% CI 0.71-1.93)	HR=0.66 (95% CI 0.36-1.24)
MMRd	HR=0.81 (95% CI 0.41-1.58)	HR=0.65 (95% CI 0.29-1.47)
*POLE*mut	HR=0.70 (95% CI 0.17-2.97)	HR=0.46 (95% CI 0.09-2.37)

Fig. 1. Distribution between stage and molecular classification of the entire cohort and cancer-specific survival data of the entire cohort subdivided by molecular classification and specified for each FIGO stage. CSS = cancer-specific survival; FIGO = Federation of Gynecology and Obstetrics; p53abn= *TP53*/p53 abnormal; *POLE*mut = DNA polymerase epsilon mutated; MMRd = mismatch repair deficient; NSMP = no specific molecular profile, HR = Hazard ratio; CI = confidence interval.

Table 2
Five-year specific recurrence rate and cancer specific death rate subdivided by molecular classification and specified for each FIGO (2009) stage.

RR	FIGO I	FIGO II	FIGO III	FIGO IV	All
POLEmut	3.1 % (1.0 %-7.3 %)	0 % (0 %-0 %)	11.8 % (2.0 %-31.2 %)	66.7 % (5.4 %-94.5 %)	5.1 % (2.4 %-9.3 %)
MMRd	16.0 % (12.5 %-19.8 %)	34.9 % (22.4 %-47.6 %)	36.5 % (27.0 %-46.1 %)	59.1 % (36.1 %-76.2 %)	23.0 % (19.6 %-26.6 %)
NSMP	10.7 % (8.5 %-13.2 %)	25.5 % (16.2 %-35.9 %)	33.5 % (24.1 %-43.2 %)	73.7 % (56.6 %-84.9 %)	17.1 % (14.7 %-19.7 %)
p53abn	29.3 % (23.2 %-35.6 %)	39.0 % (23.3 %-54.3 %)	63.8 % (54.4 %-71.9 %)	78.3 % (64.8 %-87.1 %)	46.5 % (41.6 %-51.2 %)
All	8.1 % (6.8 %-9.7 %)	15.6 % (10.5 %-21.5 %)	33.6 % (28.4 %-38.8 %)	68.0 % (58.6 %-75.6 %)	23.8 % (22.0 %-25.7 %)
CSD rate	**FIGO I**	**FIGO II**	**FIGO III**	**FIGO IV**	**All**
***POLE*mut**	0.8 % (0.1 %-3.8 %)	0 % (0 %-0 %)	11.8 % (2.0 %-31.2 %)	66.7 % (5.4 %-94.5 %)	3.2 % (1.2 %-6.9 %)
MMRd	7.6 % (5.2 %-10.6 %)	16.4 % (8.1 %-27.3 %)	19.9 % (12.6 %-28.4 %)	59.1 % (36.1 %-76.2 %)	12.7 % (10.0 %-15.6 %)
NSMP	5.8 % (4.2 %-7.7 %)	10.1 % (4.4 %-18.6 %)	26.3 % (17.7 %-35.7 %)	67.5 % (49.7 %-80.2 %)	11.0 % (9.0 %-13.2 %)
p53abn	22.0 % (16.4 %-28.0 %)	29.7 % (15.3 %-45.5 %)	53.6 % (44.1 %-62.2 %)	72.0 % (58.1 %-82.0 %)	38.7 % (33.9 %-43.4 %)
All	8.1 % (6.8 %-9.7 %)	15.6 % (10.5 %-21.5 %)	33.6 % (28.4 %-38.8 %)	68.0 % (58.6 %-75.6 %)	16.5 % (14.9 %-18.2 %)

Data are in % (95 % confidence interval), CSD = Cancer specific death, FIGO = International Federation of Gynecology and Obstetrics, NSMP = no specific molecular profile, MMRd = mismatch repair deficient, p53abn = *TP53*/p53 abnormal; *POLE* = DNA polymerase epsilon; mut = mutated; RR = recurrence rate.

irrespective of stage. Our results underline the relevance of adequate surgical staging in EC in determining the prognosis and adjuvant treatment.

The distribution of molecular groups and prognostic outcomes in our cohort aligns with data from the Cancer Genome Atlas (TCGA) Research Network and the initial validation cohort [3,16]. Since then, the impact of different adjuvant treatment regimens across molecular group has been widely studied [22–24], while research on the relevance of staging is still limited [25]. Although the current study included all FIGO (2009) stages, previous research has primarily focused on the role of lymphadenectomy and the impact of lymph node metastases. The SENECA, PROME trials and other studies have reported metastasis in the sentinel lymph node in up to 19.7 % of EC patients and among all molecular groups, yet with varying prevalence [10,26–29]. In a retrospective, Danish cohort of 251 patients who underwent lymphadenectomy, stage did not significantly affect the recurrence rate [30]. However, in a cohort of 756 surgically staged patients, Praiss et al. reported poorer survival when lymph node metastases were detected in all molecular groups [27]. In the large number of cases included in our cohort, 1326 out of 2056 patients (65 %) underwent nodal staging. In the multivariate analyses lymphadenectomy had a significant negative effect on CSS (HR 0.55 (95 % CI 0.41–0.74, $p < 0.0001$). This is a consequence of upstaging of patients with positive lymph nodes following lymphadenectomy, as we observed that FIGO stage III was associated with worse prognosis than FIGO stage I in all molecular groups, except for the NSMP group. Independent of lymphadenectomy, CSS in the NSMP group did not differ significantly between FIGO stage I, II, IIIA & B and IIIC disease, though TTR did. In addition, our data confirm the earlier findings that molecular classification was of no prognostic significance in stage IV EC [15,31]. In summary, the prognostic impact of stage remains even when molecular profiling is incorporated.

The therapeutic consequences of surgical stage in each molecular group needs further assessment. *POLE*mut EC is known to be associated with a favorable prognosis, although due to its low incidence, survival data on stages III and IV is limited, and the role of adjuvant treatment remains unclear [4]. While subgroup analyses of the PORTEC-3 data indicated that adjuvant chemotherapy is least effective in MMRd tumors [5], analyses of our cohort indicated fewer recurrences and improved survival with adjuvant chemotherapy. The promising data on outcomes with immunotherapy in MMRd EC have prompted new studies exploring its effect in the neoadjuvant setting [23,32-35]. However, further research is needed to determine which combinations of treatment—radiotherapy, chemotherapy, or immune checkpoint therapy—is best suited for each patient. Patients with NSMP tumors represent a heterogenous group, constituting nearly half of all EC patients. Further subclassifications warranted to allow more refined prognostication and therapy strategies [14,35–39]. An essential first step was taken by adding hormonal status to the prognostic subgroup as published in the new ESGO-ESTRO-ESP guideline [4]. Unfortunately, estrogen receptor status was only available for a minority of the cases in our cohort and was therefore not included in the analyses. Finally, subgroup analysis of PORTEC3 data suggests that patients with p53abn tumors benefit from chemotherapy combined with radiotherapy compared to radiotherapy alone, regardless of stage [5]. Our data indicates that stage I p53abn tumors, even when more than half received no adjuvant treatment, still have a relatively good survival (5-year CSD rate of 22.0 %). Combining molecular classification with other prognostic factors, such as stage, enhances the accuracy of survival predictions. This refined risk stratification is essential for personalizing treatment, particularly in deciding whether to extend or omit adjuvant therapy in young or frail patients.

5. Strengths and limitations

Despite difference in patient characteristics between the study cohorts (Supplementary Table 1), the distribution of molecular subgroups was generally consistent with previous studies. Based on the representative distribution of both tumor types and stages, and large cohort size we expect limited bias. Due to the retrospective study design, information on some prognostic markers was missing, such as body mass index, smoking or myometrial invasion in those with advanced stage. The diagnostic work-up, including histopathological assessment, and molecular classification, was not uniformly performed and surgical and adjuvant treatments varied across institutions.

Lymphadenectomy was performed in 65 % of the study population, leading to possible understaging and heterogeneity in the accuracy of FIGO classification across molecular groups. Additional sensitivity analyses, also including subgroup analysis of the patients who had lymphadenectomy, supported the reliability of our findings. Although differences in diagnostic testing and therapeutic options reflect real-world clinical practice, they might introduce some heterogeneity. The ongoing discussion on how to classify LVSI challenges the interpretation in retrospective study cohorts [27,40,41]. Nevertheless, the benefits of studying this large cohort outweigh the limitations associated with the retrospective design.

In 2023, the FIGO classification was updated and incorporated specific prognostic factors in addition to the anatomic location of EC. Since our study focused on the impact of the anatomical disease location on prognosis within the molecular groups and patients were mostly treated before 2023, we decided to use the FIGO 2009 classification. The results of the current study align well with the FIGO 2023 framework, reinforcing the importance of a more integrated approach that combines both anatomical stage and molecular profile. The association between stage and molecular group is now incorporated within stages IA1-IIC, and this may evolve for stage III in the future. This combined classification enhances personalized prognosis and treatment decision-making,

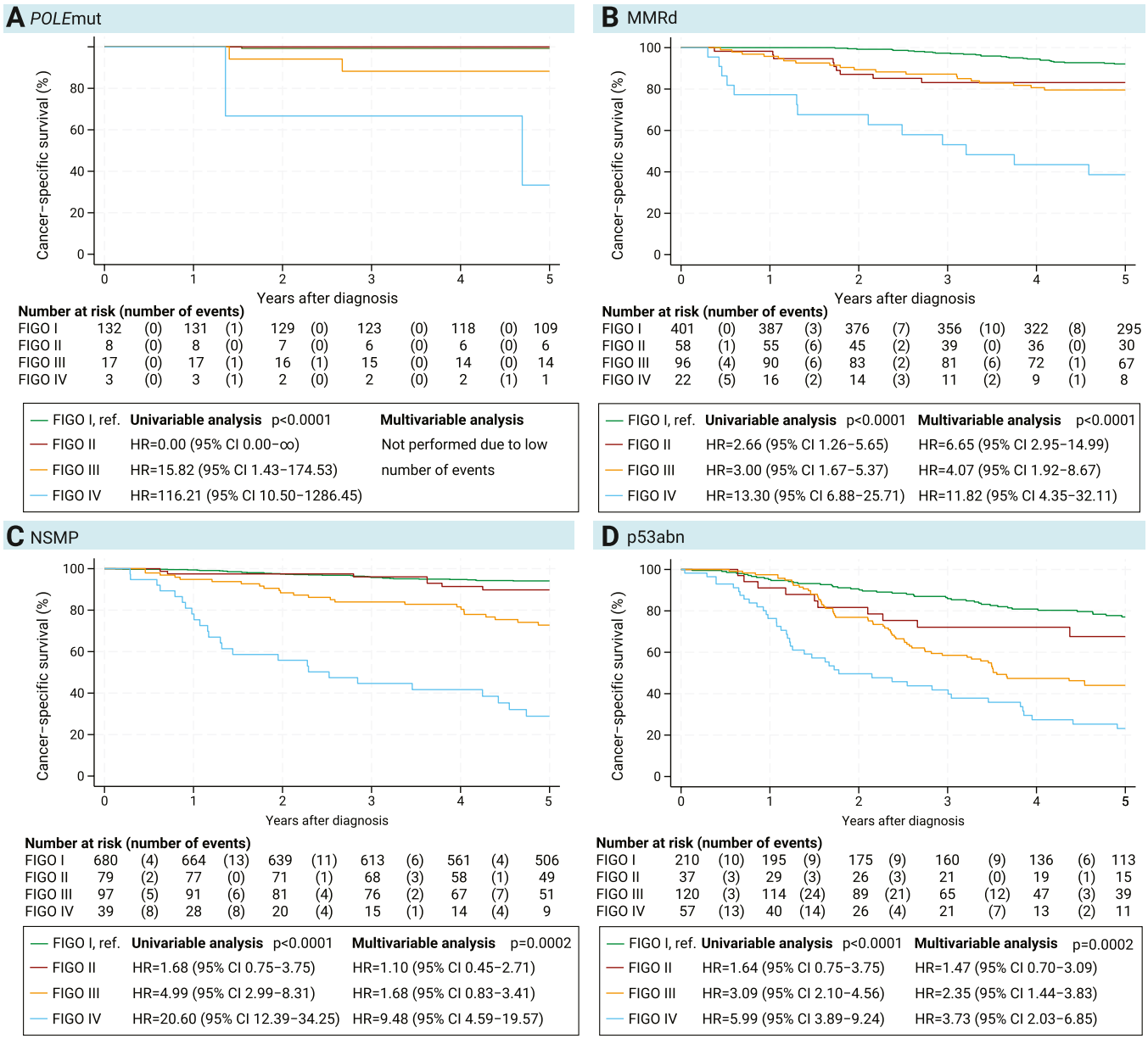


Fig. 2. Cancer-specific-survival of patients with a specific molecular classification for each FIGO stage. CSS = cancer-specific survival; FIGO = Federation of Gynecology and Obstetrics; p53abn= *TP53*/p53 abnormal; *POLE*mut = DNA polymerase epsilon mutated; MMRd = mismatch repair deficient; NSMP = no specific molecular profile, HR = Hazard ratio; CI = confidence interval.

improving the effectiveness of therapies and ultimately leading to better patient outcomes.

This publication provides important hypotheses for future research. Prospective trials are needed to identify key prognostic factors within each molecular group. Currently, the EUGENIE study investigates prospectively the clinical importance of surgical staging [42]. By analyzing metastatic patterns in each molecular subtype, more tailored surgical approaches may be developed. Moreover, the ENDORISK trial aims to combine multiple risk factors to calculate the individual risk of lymph node metastases in EC patients [43]. These studies are essential for developing patient-specific treatment strategies.

6. Conclusion

This study highlights that stage distribution significantly impacts the prognosis within the molecular groups. Given the heterogeneity of EC, it is crucial to account for all relevant risk factors when making treatment decisions. This surely includes tumor spread. Further prospective studies are needed to refine risk stratification and tailor precise treatment strategies for each patient.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Kristina Lindemann declares the following financial interests:

Table 3
Multivariable analysis time to recurrence and cancer-specific survival of the entire cohort.

Variable	Group	Entire cohort (n = 2056)				Subgroup of patients who had lymphadenectomy (n = 1329)			
		TTR		CSS		TTR		CSS	
		Multivariable analysis*		Multivariable analysis**		Multivariable analysis***		Multivariable analysis****	
		HR (95 % CI)	p	HR (95 % CI)	p	HR (95 % CI)	p	HR (95 % CI)	p
Molecular classification			< 0.0001		0.0002		0.0002		0.0003
	No specific molecular profile	ref.		ref.		ref.		ref.	
	p53 abnormal	1.60 (1.23–2.09)		1.48 (1.08–2.04)		1.44 (1.07–1.92)		1.57 (1.09–2.28)	
	Mismatch repair deficient	1.23 (0.96–1.57)		0.90 (0.65–1.25)		1.00 (0.75–1.34)		0.74 (0.49–1.12)	
	POLE mutated	0.28 (0.14–0.58)		0.24 (0.10–0.59)		0.27 (0.13–0.60)		0.32 (0.13–0.82)	
Age at diagnosis	≥ 60 years vs. < 60 years	1.62 (1.24–2.12)	0.0004	1.44 (1.03–2.00)	0.031	1.61 (1.20–2.17)	0.0015	1.59 (1.07–2.36)	0.021
Stage (FIGO 2009)			< 0.0001		< 0.0001		< 0.0001		< 0.0001
	I	ref.		ref.		ref.		ref.	
	II	2.60 (1.88–3.60)		1.78 (1.13–2.81)		2.19 (1.50–3.20)		1.31 (0.73–2.36)	
	III	2.75 (2.07–3.65)		2.83 (2.01–3.98)		2.82 (2.07–3.84)		2.86 (1.93–4.24)	
	IV	6.29 (4.42–8.94)		7.00 (4.67–10.51)		6.47 (4.30–9.74)		7.04 (4.32–11.48)	
Histopathological type & grade			< 0.0001		< 0.0001		< 0.0001		< 0.0001
	Endometrioid carcinoma low-grade	ref.		ref.		ref.		ref.	
	Endometrioid carcinoma intermediate-grade	1.81 (1.31–2.49)		2.54 (1.57–4.11)		1.46 (0.99–2.14)		1.86 (0.96–3.60)	
	Endometrioid carcinoma high-grade	3.66 (2.62–5.11)		7.44 (4.62–12.01)		2.49 (1.69–3.68)		5.23 (2.80–9.77)	
	Serous carcinoma	2.48 (1.66–3.70)		4.68 (2.70–8.09)		1.86 (1.19–2.88)		2.80 (1.42–5.52)	
	Clear cell carcinoma	2.04 (1.21–3.44)		5.33 (2.80–10.15)		1.37 (0.78–2.41)		3.39 (1.58–7.29)	
	Mixed with clear cell/ serous	2.00 (1.21–3.31)		3.95 (2.07–7.56)		1.38 (0.79–2.43)		2.16 (0.98–4.79)	
	Carcinosarcoma	4.80 (3.16–7.31)		11.93 (6.81–20.91)		3.34 (2.09–5.33)		6.64 (3.32–13.25)	
	Undifferentiated carcinoma	1.85 (0.72–4.76)		3.91 (1.31–11.65)		2.40 (0.92–6.22)		4.13 (1.31–13.01)	
	Unclassifiable carcinoma	1.91 (0.46–7.96)		6.42 (1.48–27.89)		0.78 (0.11–5.74)		2.62 (0.34–20.52)	
	Squamous cell carcinoma	13.49 (2.75–66.17)		103.83 (17.47–617.14)		12.71 (2.45–66.06)		95.26 (13.99–648.45)	
	Mucinous carcinoma	1.79 (0.43–7.34)		2.46 (0.33–18.28)		1.66 (0.39–6.97)		2.30 (0.29–17.95)	
LVSI	Yes vs. No	1.74 (1.41–2.14)	< 0.0001	2.16 (1.67–2.79)	< 0.0001	1.40 (1.10–1.78)	0.0064	1.86 (1.37–2.53)	< 0.0001
Adjuvant treatment			< 0.0001		0.038		< 0.0001		0.043
	No adjuvant treatment	ref.		ref.		ref.		ref.	
	Chemotherapy	0.51 (0.39–0.67)		0.62 (0.44–0.88)		0.47 (0.35–0.64)		0.59 (0.40–0.88)	
	External beam radiotherapy	0.57 (0.40–0.83)		0.72 (0.46–1.13)		0.57 (0.38–0.86)		0.66 (0.38–1.14)	
	Brachytherapy	0.80 (0.54–1.19)		0.87 (0.50–1.50)		0.73 (0.47–1.13)		0.87 (0.46–1.66)	
	Chemotherapy and external beam radiotherapy	0.40 (0.20–0.80)		0.29 (0.10–0.81)		0.30 (0.14–0.67)		0.22 (0.07–0.74)	
	Chemotherapy and brachytherapy	0.38 (0.20–0.75)		0.42 (0.18–1.01)		0.45 (0.24–0.86)		0.41 (0.17–1.00)	
Residual tumor	Yes vs. No	2.14 (1.49–3.06)	< 0.0001	2.36 (1.60–3.48)	< 0.0001	2.59 (1.72–3.90)	< 0.0001	2.49 (1.56–3.95)	< 0.0001
Lymphadenectomy	Yes vs. No	0.86 (0.68–1.10)	0.23	0.55 (0.41–0.74)	< 0.0001	na	na	na	na

CI = confidence interval; CSS = and cancer-specific survival; FIGO = International Federation of Gynecology and Obstetrics; HR = hazard ratio; LVSI = lymphovascular space invasion, na = not applicable; TTR = time to recurrence; *POLE* = DNA polymerase epsilon; Ref = reference. *Of the 2054 patients included in univariable analyses (478 with event and 1576 without event), 1943 (462 with event and 1481 without event) had complete data and were included in the multivariable analysis.; **Of the 2056 patients included in univariable analyses (324 with event and 1732 without event), 1945 (309 with event and 1636 without event) had complete data and were included in the multivariable analysis; ***Of the 1327 patients included in univariable analyses (375 with event and 952 without event), 1269 (363 with event and 906 without event) had complete data and were included in the multivariable analysis; ****Of the 1329 patients included in univariable analyses (234 with event and 1095 without event), 1271 (224 with event and 1047 without event) had complete data and were included in the multivariable analysis.

Table 4
Analyses of cancer-specific survival in patients with MMRd, NSMP or p53abn tumors.

Variable	Group	CSS MMRd		CSS NSMP		CSS p53abn	
		Multivariable analysis*		Multivariable analysis**		Multivariable analysis***	
		HR (95 % CI)	p	HR (95 % CI)	p	HR (95 % CI)	p
Age at diagnosis	≥ 60 years vs. < 60 years	1.98 (0.99–3.99)	0.055	1.53 (0.83–2.82)	0.17	1.24 (0.69–2.21)	0.47
Surgical stage (FIGO 2009)			< 0.0001		< 0.0001		0.0002
	I	ref.		ref.		ref.	
	II	6.65 (2.95–14.99)		1.10 (0.45–2.71)		1.47 (0.70–3.09)	
	III	4.07 (1.92–8.67)		1.68 (0.83–3.41)		2.35 (1.44–3.83)	
	IV	11.82 (4.35–32.11)		9.48 (4.59–19.57)		3.73 (2.03–6.85)	
Histopathological type and grade			0.0003		< 0.0001		0.0012
	Endometrioid carcinoma low-grade	ref.		ref.		ref.	
	Endometrioid carcinoma intermediate-grade	2.10 (0.99–4.47)		3.36 (1.58–7.15)		1.91 (0.50–7.27)	
	Endometrioid carcinoma high-grade	6.14 (2.84–13.29)		10.81 (4.90–23.82)		4.41 (1.28–15.28)	
	Serous carcinoma	4.94 (1.63–15.03)		5.64 (1.97–16.14)		2.81 (0.83–9.50)	
	Clear cell carcinoma	4.21 (0.52–33.96)		4.48 (1.40–14.29)		3.29 (0.89–12.17)	
	Mixed with clear cell/serous	5.77 (1.19–27.95)		2.91 (0.81–10.42)		2.61 (0.71–9.56)	
	Carcinosarcoma	6.15 (1.14–33.23)		17.22 (6.77–43.78)		6.48 (1.89–22.18)	
	Undifferentiated carcinoma	6.27 (1.57–24.97)		38.55 (4.01–370.75)		0.00 (0.00-∞)	
	Unclassifiable carcinoma	na		0.00 (0.00-∞)		3.03 (0.49–18.53)	
	Squamous cell carcinoma	93.69 (4.68–1876.95)		191.89 (13.65–2696.66)		na	
	Mucinous carcinoma	0 (0-∞)		2.63 (0.29–23.41)		0 (0-∞)	
LVSI	Yes vs. No	2.81 (1.59–4.94)	0.0004	1.96 (1.18–3.27)	0.0093	2.15 (1.46–3.15)	< 0.0001
Adjuvant treatment			0.0021		0.59		0.4
	No adjuvant treatment	ref.		ref.		ref.	
	Chemotherapy	0.29 (0.14–0.60)		1.43 (0.70–2.92)		0.63 (0.39–1.02)	
	External beam radiotherapy	0.16 (0.05–0.49)		1.27 (0.59–2.75)		0.83 (0.39–1.77)	
	Brachytherapy	1.10 (0.47–2.57)		0.86 (0.34–2.21)		0.59 (0.14–2.57)	
	Chemotherapy and external beam radiotherapy	0.10 (0.01–0.96)		0.45 (0.09–2.25)		0.25 (0.03–1.92)	
	Chemotherapy and brachytherapy	0.00 (0.00-∞)		0.73 (0.15–3.53)		0.58 (0.19–1.75)	
Residual tumor	Yes vs. No	6.95 (1.91–25.35)	0.0033	2.88 (1.33–6.24)	0.0073	2.23 (1.23–4.03)	0.0082
Lymphadenectomy	Yes vs. No	0.45 (0.24–0.83)	0.011	0.56 (0.33–0.95)	0.031	0.51 (0.31–0.82)	0.0057

CSS = cancer-specific survival; CI = confidence interval; FIGO = International Federation of Gynecology and Obstetrics; HR = hazard ratio; LVSI = lympho-vascular space invasion; MMRd = mismatch repair deficient; NSMP = no specific molecular profile; p53abn = *TP53*/p53 abnormal; *Of the 577 patients included in univariable analyses (69 with event and 508 without event), 529 (69 with event and 460 without event) had complete data and were included in the multivariable analysis; **Of the 895 patients included in univariable analyses (94 with event and 801 without event), 863 (88 with event and 775 without event) had complete data and were included in the multivariable analysis; ***Of the 424 patients included in univariable analyses (156 with event and 268 without event), 401 (147 with event and 254 without event) had complete data and were included in the multivariable analysis.

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All other authors declare that they have no known competing interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data sharing

The data that support the findings of this study can be made available to other researchers upon reasonable request by contacting the corresponding author, subject to approval by the relevant people or review board at the institutions that provided the original data.

Manuscript social media information

None

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.116164.

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