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1 **IMPACT OF THE NEW MOLECULAR CLASSIFICATION OF ENDOMETRIAL**
2 **CANCER: A FRENCH COHORT STUDY**
3

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23 **Abstract**

24

25 **Objective:** To evaluate the potential impact of the latest ESGO guidelines for endometrial
26 cancer with molecular classification on the management strategy in a French cohort.

27 **Methods:** All patients treated between January 1st, 2014 and December 31, 2020 for an
28 endometrial cancer at the Centre Hospitalier Intercommunal de Créteil (CHIC, FRANCE)
29 were selected from our prospectively maintained database. All postoperative samples were
30 reviewed to confirm histological subtype, myometrial infiltration, cytonuclear grade and
31 presence of lymphovascular emboli. Analysis of p53, MLH1, MSH2, MSH6, PMS2 genes
32 was performed by immunohistochemistry first then a systematic POLE sequencing was
33 performed to identify gene mutation. The impact of the latest ESGO 2020 guidelines was
34 assessed regarding adjuvant therapy, surgical strategy, and survival.

35 **Results:** Eighty patients were analyzed, including 70% NSMP (n = 56), 13.75% MSI (n =
36 11), 10% p53 mutated (n = 8) and 6.25% POLEmut (n = 5). A total of 21 patients (26.3%)
37 were reclassified using the latest ESGO classification. Patients classified at low risk or with
38 advanced / metastatic disease were not reclassified using molecular analysis. Molecular
39 analysis and the latest ESGO classification had the most important impact on patients initially
40 classified at intermediate – high risk that were reclassified in intermediate (10/23) and in low
41 (4/23) risk. Nine patients (11.3%) were overtreated according to the 2020 ESGO
42 classification: six patients in the low – risk group (4 received vaginal brachytherapy and 2
43 external radiotherapy) and three in the intermediate risk group (3 received external irradiation
44 and 1 received chemotherapy). None of the patients in our cohort would have been
45 undertreated using the 2020 ESGO classification. Patients within the p53 mutated group were
46 the most likely to experience recurrence (37.5%, 3/8) and none of the patients POLE mutated
47 recurred.

48 **Conclusion:** Around one in 4 patients were reclassified in a more accurate prognostic group
49 using molecular diagnosis and the latest ESGO guidelines which could decrease the use of
50 adjuvant therapies to spare morbidity.

51 **Keywords:** endometrial cancer; molecular classification; ESGO guidelines; survival; risk
52 assessment; prognostic

53

54

55 **Introduction**

56 Endometrial carcinoma (EC) is currently the most common gynecological pelvic
57 malignancy in developed countries, accounting for 57.8% of new cases of gynecological
58 cancers in the US in 2020 (1). Preoperative assessment of the risk of lymph node invasion is
59 currently based on histotype and grade in patients that do not exhibit lymph node invasion on
60 preoperative MRI (2). These parameters have been shown to have poor reproducibility (3).
61 The generalization of the sentinel lymph node procedure even in patients classified
62 preoperatively at low risk has significantly reduced the complication risk and the morbidity
63 rates and reshuffled the cards (4,5). However, preoperative accurate assessment of lymph node
64 invasion risk still matters to both anticipate adjuvant therapies and inform patients accordingly
65 (6). Besides, lymphovascular space invasion, which could be very relevant to refine risk
66 group, is hardly assessed on preoperative biopsy (7,8). All of these factors result in partial
67 preoperative assessment potentially leading to inadequate surgical gestures. Moreover, the
68 postoperative risk of recurrence assessment has been shown to have a limited predictive value
69 as some patients at “low – risk” experience recurrences sometimes with a short delay
70 following treatment (9).

71 In 2013, the Cancer Genome Atlas (TCGA) research network group performed an
72 integrated genomic characterization of 373 endometrial carcinomas (EC) using sequencing
73 and array-based technologies (10). Based on these findings, the ProMisE classification has
74 identified four molecular groups of EC with different prognoses(11): the POLE-mut group
75 (POLEmut), the mismatch repair-deficient group (MMRd), the p53-abn group is classified as
76 "high copy number" and the p53-wild-type group (p53-wt) or "non-specific molecular profile"
77 (NSMP). More than individually, the ProMise classification appears to be a beneficial and
78 complementary contribution to the 2013 ESMO classification. Talhouk *et al* in 2017 reported
79 that regarding the main oncological outcomes (OS, DFS and PFS), ProMisE use alone seems
80 to perform as well as ESMO, or even better when postoperative parameters are

81 considered(12). The new ESTRO ESGO ESP 2020 guidelines have integrated the molecular
82 classification into the management algorithms, with a modification of the risk groups and
83 therefore of the medical and surgical management of endometrial cancers (13). The ultimate
84 goal of applying accurate prognostic classification using molecular subtypes is to eventually
85 reduce iatrogenic morbidity by decreasing indications of unindicated adjuvant therapies
86 according to ESGO 2020 guidelines while efficiently reserving these treatments for patients
87 truly at high risk.

88 To date, potential impact of these new guidelines on prognostic assessment and
89 management of patients with endometrial cancers has not been evaluated in a French cohort to
90 assess its external validity.

91

92

93 **Materials and methods**

94 The protocol was validated by the Research Organization Committee of the Centre
95 Hospitalier Intercommunal de Créteil on September 26, 2019. Written consent was obtained
96 for all patients as part of the PELVIMASS protocol (CPP No. 2016-A01381-42)

97

98 Population

99 All patients treated between January 1st, 2014 and December 31, 2020 for an
100 endometrial cancer at the Centre Hospitalier Intercommunal de Créteil (CHIC, FRANCE)
101 were selected from our prospectively maintained database. Patients for whom the tissue was
102 not usable due to alterations during preservation or due to poor quality of DNA's extractions
103 were excluded. Young patients < 18 years, those with rare histological forms, and those with
104 numerous missing data were not included.

105 Data of interest were abstracted from patients' chart, including socio demographic
106 characteristics, preoperative imaging and pathological analysis, prospective management
107 including surgery and adjuvant therapies as well as survival data.

108

109 Prospective management

110 Patients were treated in accordance with European recommendations at the time of
111 prospective management(14,15). Preoperative management included clinical examination,
112 pelvic ultrasonography and abdomino-pelvic MRI to determine loco-regional extension,
113 lymph node involvement and distant metastases. Tumors' markers such as cancer antigen 125
114 (CA125) were measured in patients with type II tumors. The 2009 - FIGO classification was
115 used to classify tumors (16).

116 Follow-up consisted of a clinical examination every 4 months for 3 years, then every 6
117 months for 2 years and then annually. Depending on the clinical findings, the histological
118 type of the tumor and the initial extension of the tumor, a thoraco-abdomino-pelvic CT scan

119 could be requested as well as a biological evaluation including tumor markers CA125 for
120 non-endometrioid tumors.

121

122 Pathological et molecular analysis

123 All postoperative samples were reviewed to confirm histological subtype, myometrial
124 infiltration, cytonuclear grade and presence of lymphovascular emboli. A systematic analysis
125 of p53, MLH1, MSH2, MSH6, PMS2 genes was performed first by immunohistochemistry.
126 Immunohistochemical staining was performed on a Ventana BenchMark Ultra© machine,
127 according to the protocols of the various antibody suppliers. The Thermo Fisher© monoclonal
128 antibody (DO-7 clone) was used for p53 testing. Results were characterized in 2 categories: a
129 heterogeneous positivity classified the sample as wild type. A strong and diffuse positivity (
130 over-expression) or a complete absence of marking (negative) classified the sample as
131 abnormal. A systematic POLE sequencing was performed to identify gene mutation. This was
132 first screened by HRM (High Resolution Matching) PCR to select samples with suspected
133 POLE gene mutation. In order to precisely characterize the type of mutation, a gene
134 sequencing technique (Next-Generation Sequencing or NGS) was performed on the samples
135 previously selected by HRM.

136 In cases of loss of expression of immunophenotypic markers or ambiguity of the
137 immunostaining, a molecular technique was used using Idylla© (Biocartis, Mechelen,
138 Belgium). Eight cases had microsatellite instability searched using PCR prior the initiation of
139 this study.

140

141 Assessment of the new ESGO 2020 classification impact

142 All patients were reclassified according to the new ESGO 2020 classification, using
143 molecular analysis. The new risk group was then compared with the initial risk assessed

144 during prospective management. The impact of the new ESGO 2020 guidelines was assessed
145 by comparing adjuvant therapy and surgical strategy.

146 Survival of patients according to histological characteristics, prognostic risk group, and by
147 molecular group were analyzed.

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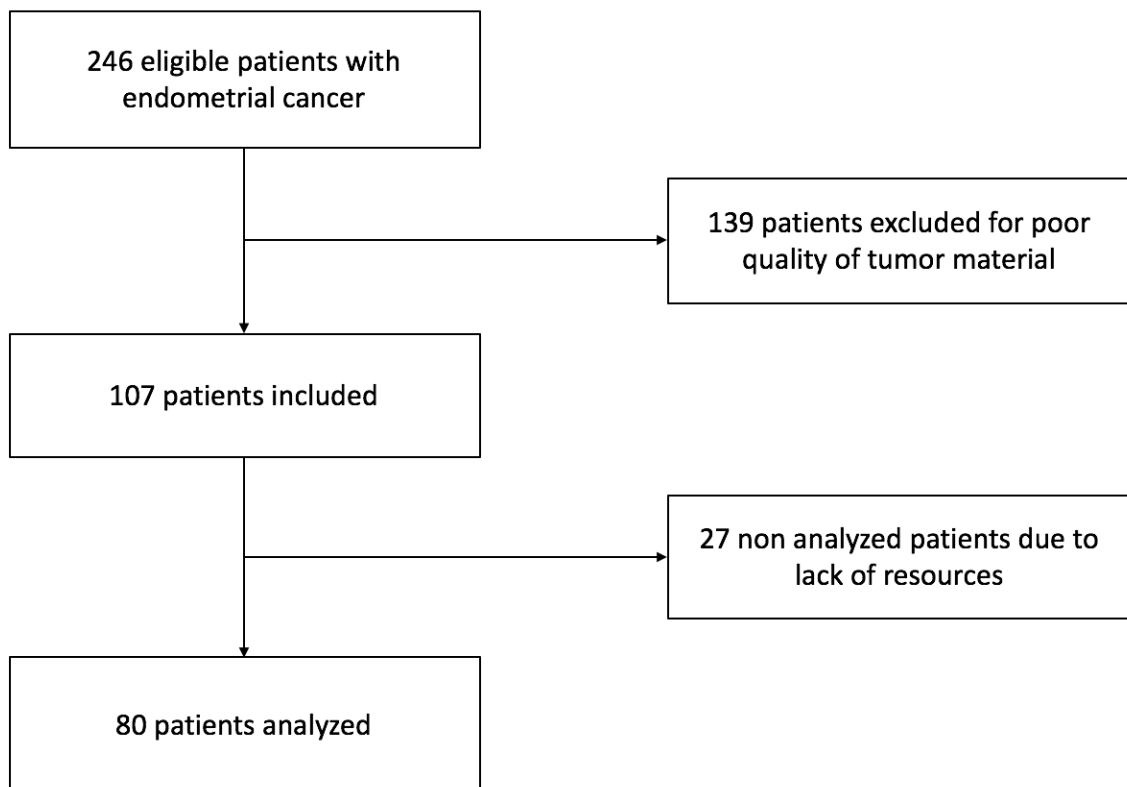
149 Statistical analysis

150 The data used were collected on a secure Excel sheet (Microsoft Corporation, Redmond, WA,
151 USA) and all statistical analyses were performed using the freely available online R software
152 (version 1.3.1093). For all analyses performed, a p-value < 0.05 was considered to indicate a
153 statistically significant difference. Categorical variables were compared using a Chi2 or
154 Fisher test according to the number of participants, and quantitative variables were compared
155 using a Student's t test. Kaplan-Meier survival curves were generated to assess recurrence-free
156 survival and overall survival according to the groups determined. The log-rank test was used
157 to compare survivals.

1 **Results**

2 Among the 246 eligible patients, 107 patients were included and 139 patients were
3 excluded due to poor quality of tumor material. Eventually, 27 unselected patients did not
4 undergo molecular analysis due to lack of resources during the COVID 19 pandemic and thus
5 were excluded leading to a total of 80 patients analyzed (Figure 1).

6



7

8 Figure 1: Flow chart of the study

9

10 Characteristics of the population

11 The main characteristics of the patients included are displayed in Table 1. The mean age was
12 66 years old (range 34-87 years old) with an average BMI of 31kg/m² (range 20-51kg/m²).
13 Diagnosis was obtained through endometrial biopsies in 76% (61/80) cases and operative
14 hysteroscopy in 24% (19/80) cases. Patients that could not undergo molecular analysis due to
15 COVID 19 pandemic were similar to those that did (Supplementary Table 1 and 2).

16 On preoperative MRI, 13.8% of patients (11/80) had pelvic lymph node involvement and
 17 6.3% (5/80) had para-aortic lymph node involvement (Table 1). Most patients had stage I
 18 endometrial cancer 72.5% (58/80).

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Characteristics	Final population N = 80 (%)
Age in years (mean \pm sd)	66 \pm 11.6
Body mass index (kg/m ²) mean (\pm sd)	31 (\pm 7.1)
Nulliparity	18 (26.5)
High blood pressure	43 (54)
Diabetes	14(18)
Menopausal	70 (87.5)
Bleeding	70 (87.5)
FIGO MRI stage	
IA	25 (31.25)
IB	33 (41.25)
II	5 (6.25)
III	7 (8.75)
IV	6 (7.5)

Surgery	78 (97.5)
HBSO	2 (2.5)
Total Hysterectomy and ovarian sparing	11 (13.8)
Omentectomy	6 (7.5)
Appendectomy	3 (3.8)
Pelvic sentinel node	30 (37.5)
Pelvic lymphadenectomy	26 (32.5)
Para-aortic lymphadenectomy	3 (3.8)
Inguinal lymphadenectomy	32 (40)
External beam radiotherapy	1 (1.3)
Neoadjuvant chemotherapy	21 (26.3)
Adjuvant chemotherapy	56 (70)
Brachytherapy	
Preoperative ESMO	
Low	22 (27)
Intermediate	29 (39)
High	26 (32,5)
NA	3

29 Table 1: Characteristics of the study population, treatments received by patients and
30 ESMO/ESGO 2013 preoperative classification. HBSO:
31 Total hysterectomy with bilateral salpingo-oophorectomy
32 NA: Not assessed

33 Patients' management

34 Lymph node staging was performed by sentinel node procedure in 3.8% cases, by pelvic
35 lymphadenectomy in 37.5% and para-aortic lymphadenectomy in 32.5% of the cases. No
36 lymph node staging was performed in 56% (45/80) and 17.5% of the patients (14/80)
37 underwent secondary surgery for lymph node staging.

38 Discrepancy between pre and postoperative histology occurred in 11.6% (7/60) and 10.5%
39 (2/19) of patients diagnosed by endometrial biopsy and operative hysteroscopy, respectively.

40 Regarding adjuvant therapies, brachytherapy, external radiotherapy and chemotherapy were
41 used in 70% (56/80), 40% (32/80), and 26.3% (21/80), respectively (Table 1).

42

43 **Comparison of ESGO 2020 and ESMO 2016**

44 The NSMP group was the most represented (70%, 56/80), followed by the MSI (13.75%;
 45 11/80), the mutated P53 (10%, 8/80) and the POLEmut (6.25%, 5/80) groups (Table 2).

46 Morphological characteristics of tumors according to molecular group are described in
 47 Supplementary Table 3.

48

	N = 80 (%)
Histological type	
Endometrioid	70 (87.5)
Serous	7 (8.75)
Serous + Endometrioid	1 (1.25)
Clear cell	2 (2.5)
Grade	
Low grade	62 (77.5)
High grade	18(22.5)
LVSI	
0	37 (46)
<5	13 (16)
>5	30 (38)
Molecular group	
POLE	5(6.25)
MSI	11(13.75)
NSMP	56 (70)
P53	8 (10)

49

50 Table 2: Histological and molecular characteristics of the study population

51

52 A total of 21 patients (26.3%) were reclassified following application of the new
 53 ESGO 2020 classification (table 3). Concordance between the two classifications regarding
 54 postoperative risk was observed in 73.7% (59/80). Patients classified at low risk or with
 55 advanced / metastatic disease were not reclassified using molecular analysis. Molecular
 56 analysis and the latest ESGO classification had the most important impact on patients initially
 57 classified at intermediate – high risk that were reclassified in intermediate (10/23) and in low
 58 (4/23) risk.

59 Two patients with clear cell adenocarcinoma classified NSMP were considered at high – risk.

60

ESMO 2016 \ ESGO 2020	Low	Intermediate	Intermediate high	High	Advanced/metastatic
Low	18 (75%)	2 (8%)	4 (17%)	0	0
Intermediate	0	10 (50%)	10 (50%)	0	0
Intermediate high	0	0	9 (64%)	5 (36%)	0
High	0	0	0	15 (100%)	0
Advanced metastatic	0	0	0	0	7 (100%)

61

62 Table 3: Number of patients classified into risk groups according to ESMO 2016 and ESGO
 63 2020 recommendations. Proportions are calculated based on the ESGO 2020 group size.

64

65 **Impact of the molecular classification**

66 Twelve patients (15%) had lymph node involvement on final analysis. Of these patients, 50%
 67 were p53 mutated and 33% had no specific molecular profile. All of these patients were
 68 classified as high risk (58%) or advanced/metastatic (42%). Patients in the p53mutated group
 69 had lymph node involvement in 75% cases (6/8). The distribution of patients with lymph node
 70 involvement by molecular group and prognostic classification is presented in Table 4.

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	Pelvic lymph node involvement (N=7)	Para-aortic lymph node involvement (N=9)	Lymph node involvement (N=12)
Molecular group			
● POLE mutated (N=5; 6.25%)	0	0	0
● MSI (N=11; 13.75%)	0	2 (18%)	2 (18%)
● NSMP (N=56; 70%)	3 (5.4%)	2 (3.6%)	4 (7.1%)
● P53 mutated (N=8; 10%)	4 (50%)	5 (62.5%)	6 (75%)
ESGO Risk Group 2020			
● Low (N=24; 30%)	0	0	0
● Intermediate (N=20; 25%)	0	0	0
● Intermediate-high (N=14; 17%)	0	0	0
● High (N=15; 19%)	4 (27%)	4 (27%)	7 (47%)
● Advanced/metastatic (N=7; 9%)	3 (43%)	5 (71%)	5 (71%)

76

77 Table 4: Node involvement by molecular group and ESGO 2020 risk group. The proportions
78 of lymph node involvement were calculated according to the size of the molecular groups or
79 the 2020 risk groups

80

81

82 **Impact of the ESGO 2020 classification**

83 The 2020 ESGO classification could have spared secondary surgery for staging in 21.4%
84 (3/14) of patients classified at low or intermediate risk. According to the latest ESGO 2020
85 guidelines, 86% (69/80) of our patients could have benefited from the sentinel lymph node
86 procedure (only intermediate-high risk or high - risk patients with FIGO stage >2 are not
87 eligible).

88 A total of 9 patients (11.3%) were overtreated according the 2020 ESGO classification: Six
89 patients in the low – risk group (4 received vaginal brachytherapy and 2 external
90 radiotherapy) and three in the intermediate risk group (3 received external irradiation and 1
91 received chemotherapy).

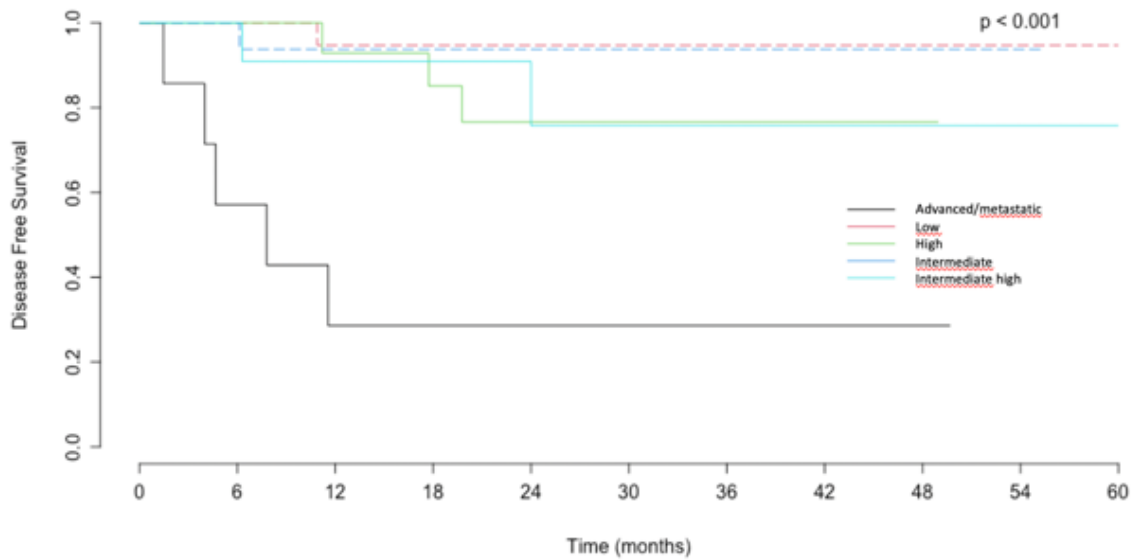
92 None of the patients in our cohort would have been undertreated.

93

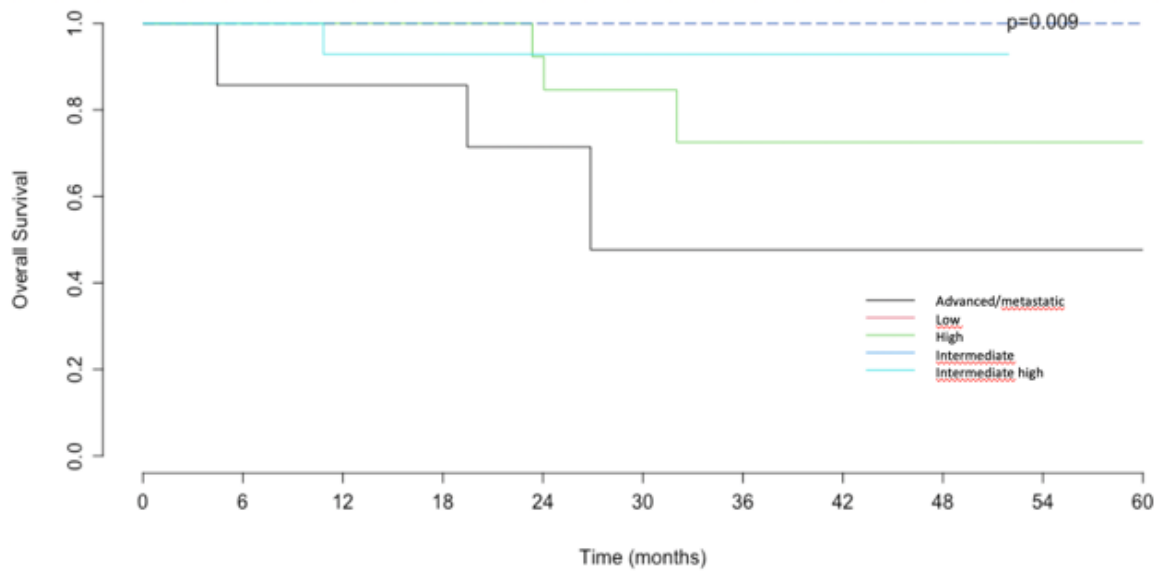
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95 Survival analysis

96 The median follow-up time was 25 months (0-64). During follow-up, 12 patients relapsed
97 (15%) and 7 patients died (9%). The 2020 ESGO postoperative risk groups but not molecular
98 subtypes were significantly associated with disease free survival ($p < 0.001$) and overall
99 survival ($p = 0.005$) (Figure 2 and 3). Survival curves according to the histological type, the
100 FIGO stage, the cytonuclear grades, the presence of lymphovascular emboli and the ESMO
101 2016 classification are available in the Supplementary Figure 1



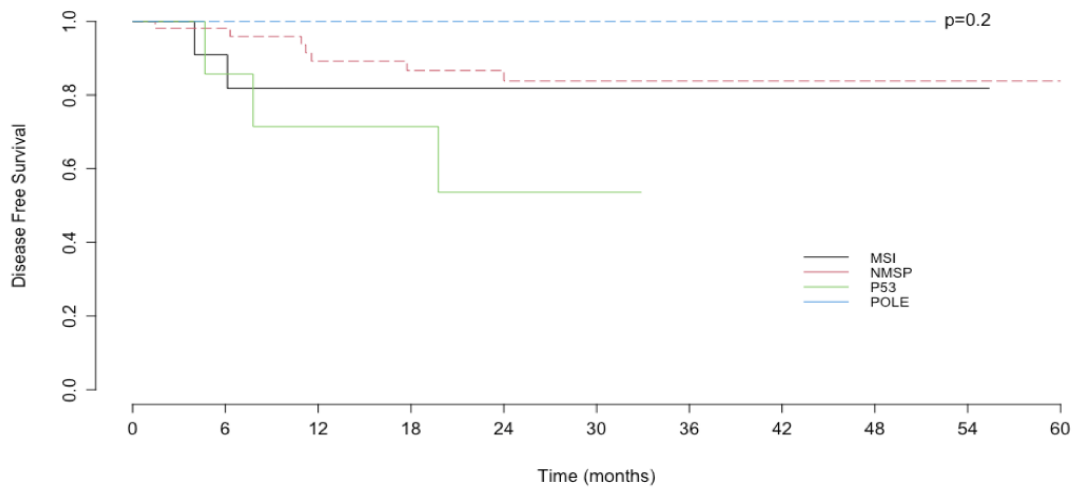
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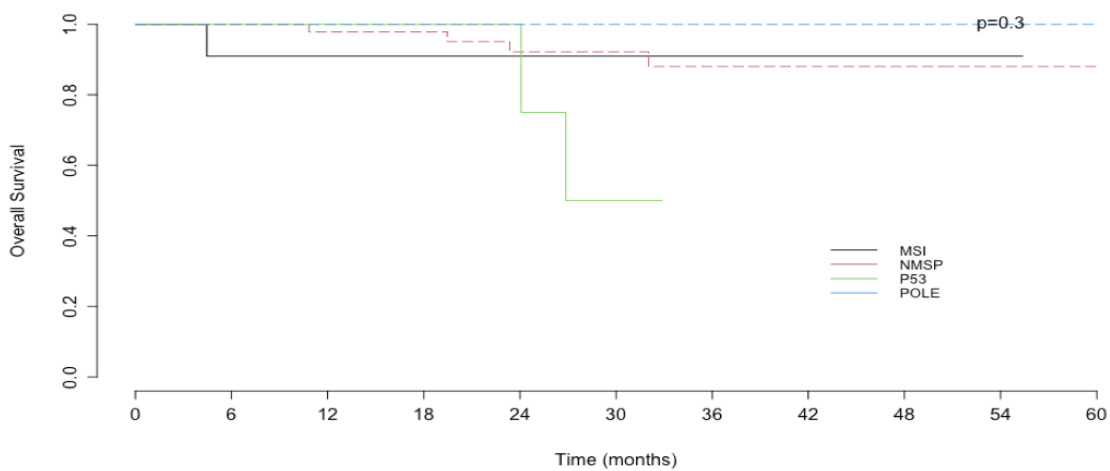
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105 Figure 2: Recurrence-free survival (left) and overall survival (right) stratified by risk groups
 106 according to ESGO/ESTRO/ESP 2020 (in months). There were a significant difference
 107 between groups (p-value 0.001 and 0.009 respectively).
 108



109



110

111 Figure 3: Recurrence-free survival (left) and overall survival (right) stratified by molecular
 112 groups according to ESGO/ESTRO/ESP 2020 (in months). There was not a significant
 113 difference between groups neither for recurrence – free nor overall survival (p-value =
 114 0.2 and 0.3, respectively)
 115

116 Relapses occurred on average at 9 months (1 - 23) and were localized as follow: locoregional
 117 (vagina = 1, rectum = 3, parametrium = 2, pelvic non - specified = 6), lymph node (para-
 118 aortic, n = 6) and distant (peritoneum = 5, lung = 5, liver = 5 and bone = 1). Patients within
 119 the p53 mutated group were the most likely to experience recurrence (37.5%, 3/8), followed
 120 by those MSI (18%, 2/11) and NSMP (12.5%, 7/56). None of the patients with a POLE
 121 mutation recurred. Location of recurrence varied with the molecular subtype. In patients with
 122 NSMP, 86% (6/7) had distant recurrence. All p53 patients had a distant relapse and one
 123 patient also had locoregional recurrence. Patients in the MSI group had pelvic recurrences
 124 without distant lesions.

125 Patients were most likely to die during follow – up when p53 mutated (25%; 2/8) than when
 126 part of the NSMP (7%, 4/56) or MSI (9%, 1/11) groups (p=0,3)
 127 The distribution and characteristics of patients who recurred or died according to their risk
 128 group or molecular status are presented in Tables 5 and Supplementary Table 4.
 129

	Patients that had recurrence during follow - up (N=12)	Patients that died during follow - up (N=7)
Molecular group		
• POLE mutated (N=5)	0	0
• MSI (N=11)	2 (18%)	1 (9%)
• NSMP (N=56)	7 (12.5%)	4 (7%)
• P53 mutated (N=8)	3 (37.5%)	2 (25%)
ESGO Risk Group 2020		
• Low (N=24; 30%)	1 (8.3%)	0
• Intermediate (N=20; 25%)	1 (8.3%)	0
• Intermediate-high (N=14; 17%)	2 (16.7%)	2 (28.6%)
• High (N=15; 19%)	3 (25%)	2 (28.6%)
• Advanced/metastatic (N=7; 9%)	5 (41.7%)	3 (42.8%)
ESGO Risk Group 2016		
• Low (N=18; 23%)	1 (8.3%)	0
• Intermediate (N=12; 15%)	0	0
• Intermediate-high (N=23; 28%)	2 (16.7%)	1 (14.3%)
• High (N=20; 25%)	4 (33.3%)	3(42.8%)

<ul style="list-style-type: none"> Advanced/metastatic (N=7; 9%) 	5 (41.7%)	3 (42.8%)
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130 Table 5: Distribution in molecular groups and prognosis of recurrence and death

131

132

133 **Discussion**

134 In this first report of a French cohort following the latest issue of ESGO guidelines for
135 endometrial cancer, around ¼ of the patients were reclassified into a more accurate group of
136 prognosis. Molecular analysis and the latest ESGO classification had the most important
137 impact on patients initially classified at intermediate – high risk that were reclassified in
138 intermediate (10/23) and in low (4/23) risk. The 2020 ESGO classification could have spared
139 secondary surgery for staging in 21.4% of patients classified at low or intermediate risk. A
140 total of 9 patients (11.3%) were over-treated according to the 2020 ESGO classification: six
141 patients in the low – risk group (4 received vaginal brachytherapy and 2 external
142 radiotherapy) and three in the intermediate risk group (3 received external irradiation and 1
143 received chemotherapy). None of the patients in our cohort were undertreated. The 2020
144 ESGO postoperative risk groups but not molecular subtypes were significantly associated
145 with disease free survival ($p < 0.001$) and overall survival ($p = 0.005$).

146 In our cohort, the molecular group distribution included a higher proportion of NSMP tumors
147 than the study of Kommos et al.(17) and the meta-analysis of Raffone et al. (18) that
148 included 2818 patients, but with an equivalent proportion of POLEmut and p53 mutated.
149 Patients diagnosed either in the POLEmut group or in the p53 mutated group were little
150 represented (16.75%). These two groups are associated with extreme prognoses with very low
151 and high risk of recurrence / death, respectively. Such discrepancy in the repartition of the
152 molecular groups could be explained by the limited number of patients included, leading to an
153 over-representation of patients classified NMSP that have mild benefit of the molecular
154 subtype assessment. Regarding pathological characteristics, our findings were consistent with
155 previous study(12,19). In the studies by Talhouk et al, the POLEmut group was composed of
156 92% of endometrioid tumors including 58% of low-grade tumors and 58% with LVSI. Of
157 note, a significant proportion of POLEmut patients in our cohort had a myometrium
158 infiltration > 50% (80%) with 40% LVSI which are poor prognostic factors for recurrence

159 and survival. Our findings highlight the limited value of these parameters to assess the risk of
160 recurrence and advocate for molecular diagnosis use to decrease adjuvant therapies in patients
161 with excellent prognosis. On the other side, patients with p53 mutation usually have
162 numerous factors associated with bad prognosis with 75% serous tumors with 88% of LVSI
163 and infiltration of myometrium > 50%. In our cohort, significant survival differences existed
164 by ESGO 2020 groups but not by the different molecular groups. These results are conflicting
165 with those reported by Talhouk et al. (12,20,21) that found that compared to the "non -
166 specific molecular profile" group, the risk was reduced by 77% in overall survival rates and
167 84% in recurrence-free survival rates for the POLE group, whereas the risk of death or
168 recurrence was multiplied by 3.29 and 2.19 times respectively for the p53 mutated group. The
169 main issue with molecular analyses remain the availability of the technic, limited by both the
170 cost and the time – consuming procedure. In the case of the POLE mutation research, High
171 Resolution Melting (HRM) screening of candidates for gene sequencing by NGS allows to
172 limit the final cost of the analysis, with a unit cost of 10 € for HRM against 120 € for Next
173 Generation sequencing (NGS). The time required for molecular biology analysis of POLE
174 mutations or microsatellites can be long when confirming cases in NGS or for microsatellite
175 analysis. McConechy et al. reported a concordance rate of more than 93% for the diagnostic
176 performance of immunohistochemistry and molecular biology (22). This problematic is
177 relative for p53 analysis as IHC has a high performance (Se: 90-100%, Sp: 94%, PPV: 98%,
178 NPV: 74%)(3). When adjuvant therapy decision relies on molecular analysis, the delay to
179 obtain results is crucial. This is all the more important since these patients could exhibit bad
180 prognostic factors that could encourage clinicians to prescribe unindicated adjuvant therapies.
181 In our cohort, 9 patients had unindicated adjuvant treatment according to ESGO 2020
182 guidelines. In the PORTEC 3 study, side effects (neuropathy, alopecia, hematological,
183 gastrointestinal, auditory side-effects, pain etc.) were significantly more important in the
184 group treated by chemotherapy in combination with radiotherapy (23). In the study by De

185 Boer et al., toxicities and quality of life scores were higher (with more severe symptoms) in
186 the radiochemotherapy group than in the radiotherapy alone group ($p<0.001$) and seemed to
187 improve over time (non-significant results at 12 months from the end of treatment) (24).
188 While survival has improved over the years, recent research has focused on quality of life
189 after treatment. It seems essential to adapt adjuvant therapies to the molecular profile by
190 limiting indications to selected subtypes

191 Molecular diagnosis also impacts surgical staging strategy. De kerdaniel et al. (25)
192 found surgical under-staging occurred in 26% of the cases according to the 2010 guidelines.
193 Older patients (>70 years) were more often under-staged than younger patients (<70 years)
194 ($p=0.037$). In a recent meta-analysis, He et al. reported a 6% rate of positive lymph nodes (7 /
195 118) in POLE mutated patients and no significant association between the POLE mutated
196 status and the risk of lymph node involvement (OR 0.41; $p=0.47$) (26). These results are in
197 line with our findings that no POLEmut patients had lymph node involvement that could
198 benefit from less morbid procedure such as sentinel lymph node. Similarly, patients p53
199 mutated are at high risk of lymph node involvement and could benefit from per-operative
200 lymph node analysis to decide immediate complete lymphadenectomy, avoiding secondary
201 surgery. The search for MSI status by immunohistochemistry (more accessible and faster)
202 and the efficacy of antiPD-1 (27) treatments on these tumors in case of treatment failure
203 reinforces the necessity for MSI systematic testing. The RAINBO (Refining Adjuvant
204 treatment IN endometrial cancer Based On molecular profile) program, led by the
205 TransPORTEC study group, will bring interesting insight on the value on molecular subtype-
206 based strategy.

207 Some limitations of our work deserve to be mentioned. This is a retrospective,
208 observational, single-center study with a limited number of patients included. Our follow up
209 could have been too short to diagnose some recurrences or death which might have bias the
210 results. However, it has been demonstrated that the higher rate of recurrence is within the first

211 two years of follow up (28,29). The proportions of patients with POLE, p53 and MSI were
212 insufficient which have limited the full exploration of their prognostic impact. Eventually, a
213 significant number of patients did not undergo lymph node staging at all which clearly limit
214 the extent of our conclusions, especially as many cancer centers now perform sentinel lymph
215 node procedures even in high-risk patients. This also underline the benefit of molecular
216 subtype assessment was more likely underestimated in this cohort. One issue with molecular
217 diagnosis is that it depends of the quality of the DNA used, which is directly impacted by cold
218 ischemia duration, transport duration, delay prior fixation and the quality of the latter (29).
219 The retrospective inclusion of the cases limited the control of the conditions of conservation
220 of the slides.

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225 **Conclusion**

226 Around one in 4 patients were reclassified in a more accurate prognostic group using
227 molecular diagnosis and the latest ESGO guidelines. which would significantly impact the use
228 of adjuvant therapies and help plan surgical strategy. Systematic molecular subtype
229 assessment will require easier and faster access to genetic platforms to enable short circuits
230 useful to impact endometrial cancer strategy. Eventually, it will help plan therapeutic strategy
231 and decrease the use of adjuvant therapies to spare morbidity.

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339 **Figures and table captions**

340 Figure 1: Flow chart of the study.

341 Figure 2: Recurrence-free survival (left) and overall survival (right) of relapse risk groups
342 according to ESGO/ESTRO/ESP 2020 (in months)

343 Figure 3: Recurrence-free survival (left) and overall survival (right) of molecular groups by
344 ESGO/ESTRO/ESP 2020 (in months).

345 Table 1: Characteristics of the study population, treatments received by patients and
346 ESMO/ESGO 2013 preoperative classification

347 Table 2: Histological and molecular characteristics of the study population

348 Table 3: Number of patients classified into risk groups according to ESMO 2016 and ESGO
349 2020 recommendations. Proportions are calculated based on the ESGO 2020 group size.

350 Table 4: Node involvement by molecular group and ESGO 2020 risk group. Pelvic lymph
351 node involvement may be associated with para-aortic lymph node involvement. Para-
352 aortic involvement may be associated with pelvic involvement. A total of 12 patients
353 were classified as N+. Here are calculated the proportions of lymph node involvement
354 according to the size of the molecular groups or the 2020 risk groups

355 Table 5: Distribution in molecular groups and prognosis of recurrence and death

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