Impact of the new molecular classification of endometrial cancer: A French cohort study

Jeremie Benichou, Corentin Schwall, Xavier Sastre-Garau, Julie Méreaux, Grégoire Miailhe, Sofiane Bendifallah, Bassam Haddad, Cyril Touboul, Rana Mitri-Frangieh, Yohann Dabi

IMPACT OF THE NEW MOLECULAR CLASSIFICATION OF ENDOMETRIAL CANCER: A FRENCH COHORT STUDY

Jeremie Benichou[1]*, Corentin Schwall[2]*, Xavier Sastre-Garau[2], Julie Méreaux[1], Grégoire Miailhe[1], Sofiane Bendifallah[3], Bassam Haddad[1], Cyril Touboul[3], Rana Mitri – Frangieh[2], Yohann Dabi[3]

* These two authors contributed equally to this work and should be considered as joint first authors.

1. Unversity of Medicine Paris XII, Department of Obstetrics and Gynecology, Centre Hospitalier Intercommunal, Créteil, France
2. University of Medicine Paris XII, Department of Pathology, Centre Hospitalier Intercommunal de Créteil, Créteil, France
3. Sorbonne University - Department of Obstetrics and Gynecology, Tenon Hospital, AP-HP, Paris, France

Corresponding author:
Yohann DABI, M.D
Sorbonne University, Department of obstetrics and Gynecology, Tenon Hospital AP-HP
4 rue de la Chine, 75020 Paris, France
E- mail: yohann.dabi@gmail.com
Tel : 01.56.01.70.00

Abstract

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

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

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

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

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

Introduction

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

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

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

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

Materials and methods

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

Population

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

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

Prospective management

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

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

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

Pathological et molecular analysis

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

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

Assessment of the new ESGO 2020 classification impact

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

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

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

Statistical analysis

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

Results

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

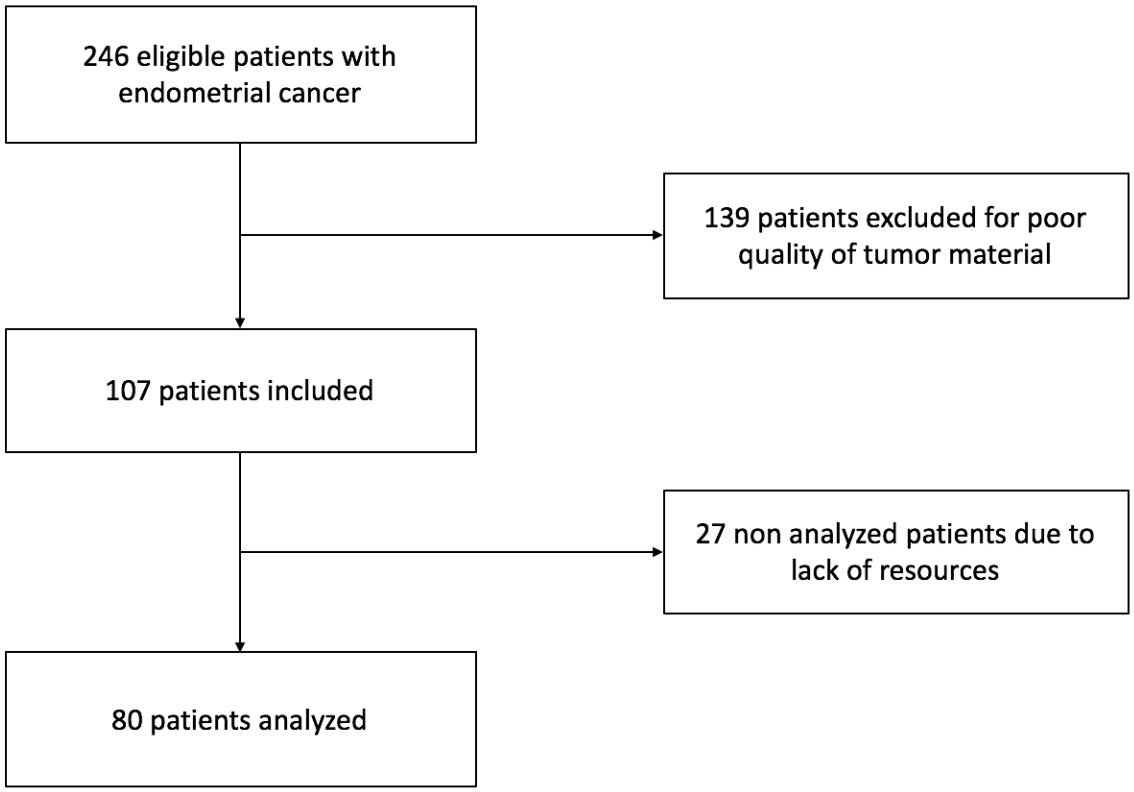

Figure 1: Flow chart of the study

Characteristics of the population

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

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

Characteristics	**Final population** **N = 80 (%)**
Age in years (mean ± sd)	66 ± 11.6
Body mass index (kg/m^2) mean (± sd)	31 (± 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 IB II III IV	 25 (31.25) 33 (41.25) 5 (6.25) 7 (8.75) 6 (7.5)

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

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

Patients' management

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

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

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

Comparison of ESGO 2020 and ESMO 2016

The NSMP group was the most represented (70%, 56/80), followed by the MSI (13.75%; 11/80), the mutated P53 (10%, 8/80) and the POLEmut (6.25%, 5/80) groups (Table 2). Morphological characteristics of tumors according to molecular group are described in Supplementary Table 3.

	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)

Table 2: Histological and molecular characteristics of the study population

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

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

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%)

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

Impact of the molecular classification

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

	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%)

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

Impact of the ESGO 2020 classification

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

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

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

Survival analysis

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

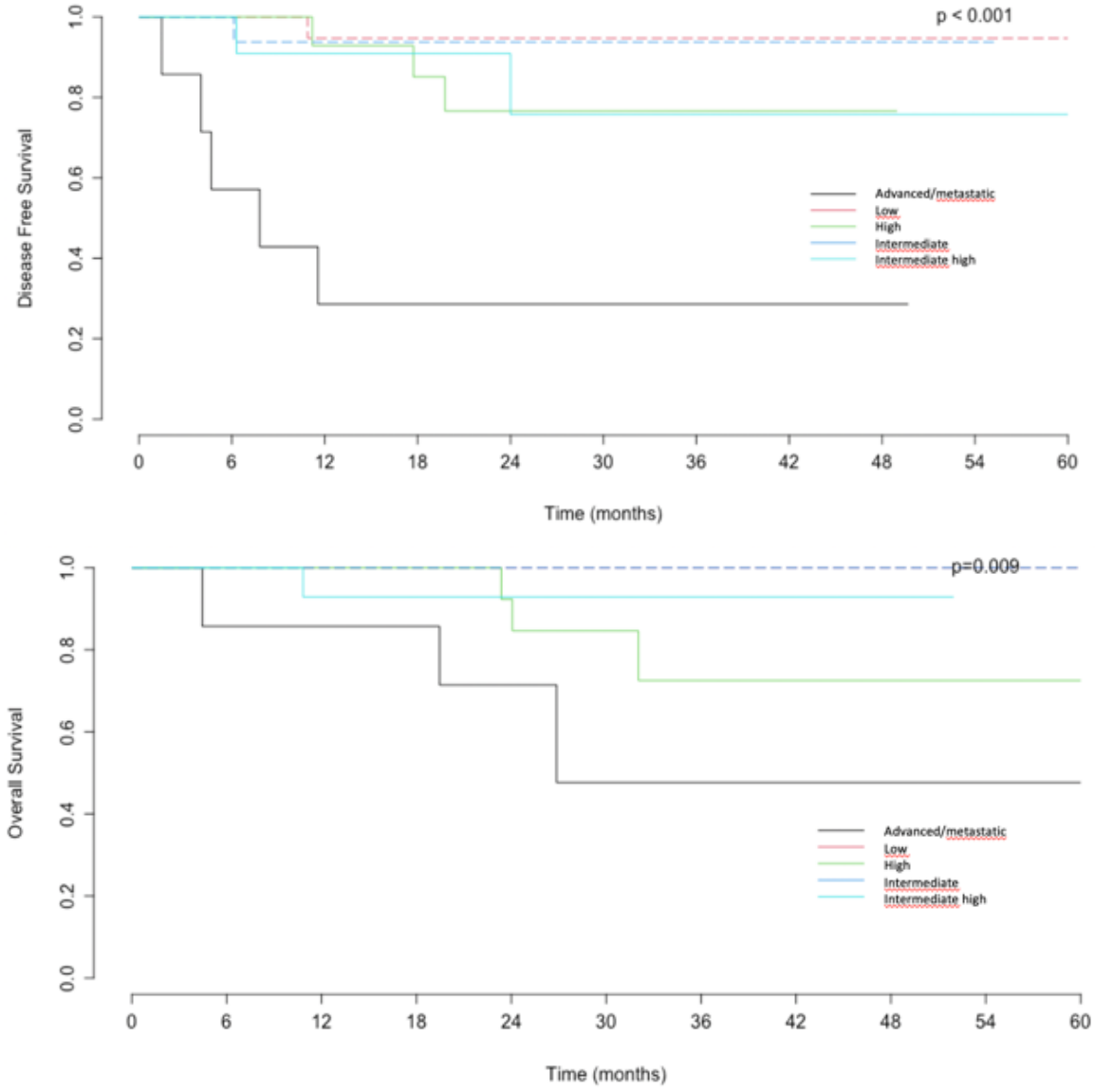

Figure 2: Recurrence-free survival (left) and overall survival (right) stratified by risk groups according to ESGO/ESTRO/ESP 2020 (in months). There were a significative difference between groups (p-value 0.001 and 0.009 respectively).

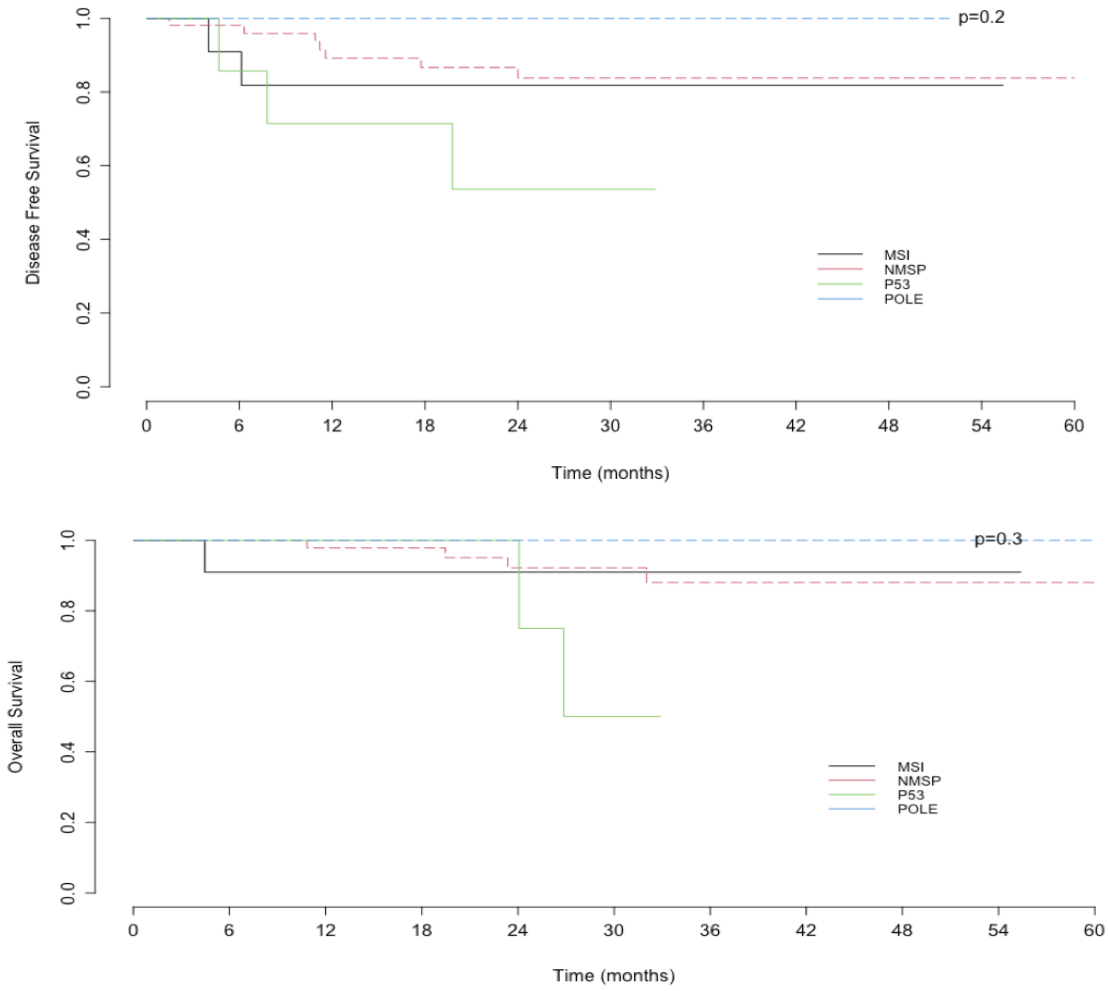

Figure 3: Recurrence-free survival (left) and overall survival (right) stratified by molecular groups according to ESGO/ESTRO/ESP 2020 (in months). There was not a significant difference between groups neither for recurrence – free nor overall survival (p-value = 0.2 and 0.3, respectively)

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

Patients were most likely to die during follow – up when p53 mutated (25%; 2/8) than when part of the NSMP (7%, 4/56) or MSI (9%, 1/11) groups (p=0,3)

The distribution and characteristics of patients who recurred or died according to their risk group or molecular status are presented in Tables 5 and Supplementary Table 4.

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

• Advanced/metastatic (N=7; 9%)	5 (41.7%)	3 (42.8%)

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

Discussion

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

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

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

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

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

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

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

Conclusion

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

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7‑30.
2. Patel S, Liyanage SH, Sahdev A, Rockall AG, Reznek RH. Imaging of endometrial and cervical cancer. Insights Imaging. nov 2010;1(5‑6):309‑28.
3. Peters EEM, Bartosch C, McCluggage WG, Genestie C, Lax SF, Nout R, et al. Reproducibility of lymphovascular space invasion (LVSI) assessment in endometrial cancer. Histopathology. juill 2019;75(1):128‑36.
4. Benedetti Panici P, Basile S, Maneschi F, Alberto Lissoni A, Signorelli M, Scambia G, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst. 3 déc 2008;100(23):1707‑16.
5. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. The Lancet. 10 janv 2009;373(9658):125‑36.
6. Soliman PT, Westin SN, Dioun S, Sun CC, Euscher E, Munsell MF, et al. A prospective validation study of sentinel lymph node mapping for high-risk endometrial cancer. Gynecol Oncol. août 2017;146(2):234‑9.
7. Talhouk A, Hoang LN, McConechy MK, Nakonechny Q, Leo J, Cheng A, et al. Molecular classification of endometrial carcinoma on diagnostic specimens is highly concordant with final hysterectomy: Earlier prognostic information to guide treatment. Gynecol Oncol. oct 2016;143(1):46‑53.
8. Stelloo E, Nout RA, Naves LCLM, Ter Haar NT, Creutzberg CL, Smit VTHBM, et al. High concordance of molecular tumor alterations between pre-operative curettage and hysterectomy specimens in patients with endometrial carcinoma. Gynecol Oncol. mai 2014;133(2):197‑204.
9. Fung-Kee-Fung M, Dodge J, Elit L, Lukka H, Chambers A, Oliver T, et al. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol. juin 2006;101(3):520‑9.
10. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2 mai 2013;497(7447):67‑73.
11. Raffone A, Travaglino A, Mascolo M, Carotenuto C, Guida M, Mollo A, et al. Histopathological characterization of ProMisE molecular groups of endometrial cancer. Gynecol Oncol. avr 2020;157(1):252‑9.
12. Talhouk A, McConechy MK, Leung S, Yang W, Lum A, Senz J, et al. Confirmation of ProMisE: A simple, genomics-based clinical classifier for endometrial cancer. Cancer. 1 mars 2017;123(5):802‑13.
13. Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer. 18 déc 2020;ijgc‑2020‑002230.
14. Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, Marini C, et al. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol. sept 2011;22 Suppl 6:vi35-39.
15. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol. janv 2016;27(1):16‑41.
16. Creasman W. Revised FIGO staging for carcinoma of the endometrium. Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet. mai 2009;105(2):109.
17. Kommoss S, McConechy MK, Kommoss F, Leung S, Bunz A, Magrill J, et al. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. Ann Oncol Off J Eur Soc Med Oncol. 1 mai

2018;29(5):1180‑8.
18. Raffone A, Travaglino A, Mascolo M, Carbone L, Guida M, Insabato L, et al. TCGA molecular groups of endometrial cancer: Pooled data about prognosis. Gynecol Oncol. nov 2019;155(2):374‑83.
19. Stelloo E, Bosse T, Nout RA, MacKay HJ, Church DN, Nijman HW, et al. Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative. Mod Pathol. juin 2015;28(6):836‑44.
20. Talhouk A, McAlpine JN. New classification of endometrial cancers: the development and potential applications of genomic-based classification in research and clinical care. Gynecol Oncol Res Pract. déc 2016;3(1):14.
21. Talhouk A, McConechy MK, Leung S, Li-Chang HH, Kwon JS, Melnyk N, et al. A clinically applicable molecular-based classification for endometrial cancers. Br J Cancer. juill 2015;113(2):299‑310.
22. McConechy MK, Talhouk A, Li-Chang HH, Leung S, Huntsman DG, Gilks CB, et al. Detection of DNA mismatch repair (MMR) deficiencies by immunohistochemistry can effectively diagnose the microsatellite instability (MSI) phenotype in endometrial carcinomas. Gynecol Oncol. mai 2015;137(2):306‑10.
23. de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. sept 2019;20(9):1273‑85.
24. de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. août 2016;17(8):1114‑26.
25. De Kerdaniel O, Body N, Davoine E, Foucher F, Henno S, Tavenard A, et al. [How were used recommendations for endometrial carcinoma? Britain retrospective study]. J Gynecol Obstet Biol Reprod (Paris). nov 2016;45(9):1045‑53.
26. He Y, Wang T, Li N, Yang B, Hu Y. Clinicopathological characteristics and prognostic value of POLE mutations in endometrial cancer: A systematic review and meta-analysis. Medicine (Baltimore). févr 2020;99(8):e19281.
27. Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol Off J Am Soc Clin Oncol. 01 2020;38(1):1‑10.
28. Sears JD, Greven KM, Hoen HM, Randall ME. Prognostic factors and treatment outcome for patients with locally recurrent endometrial cancer. Cancer. 15 août 1994;74(4):1303‑8.
29. Fujimoto T, Nanjyo H, Fukuda J, Nakamura A, Mizunuma H, Yaegashi N, et al. Endometrioid uterine cancer: histopathological risk factors of local and distant recurrence. Gynecol Oncol. févr 2009;112(2):342‑7.

Figures and table captions

Figure 1: Flow chart of the study.
Figure 2: Recurrence-free survival (left) and overall survival (right) of relapse risk groups according to ESGO/ESTRO/ESP 2020 (in months)
Figure 3: Recurrence-free survival (left) and overall survival (right) of molecular groups by ESGO/ESTRO/ESP 2020 (in months).
Table 1: Characteristics of the study population, treatments received by patients and ESMO/ESGO 2013 preoperative classification
Table 2: Histological and molecular characteristics of the study population
Table 3: Number of patients classified into risk groups according to ESMO 2016 and ESGO 2020 recommendations. Proportions are calculated based on the ESGO 2020 group size.
Table 4: Node involvement by molecular group and ESGO 2020 risk group. Pelvic lymph node involvement may be associated with para-aortic lymph node involvement. Para-aortic involvement may be associated with pelvic involvement. A total of 12 patients were classified as N+. Here are calculated the proportions of lymph node involvement according to the size of the molecular groups or the 2020 risk groups
Table 5: Distribution in molecular groups and prognosis of recurrence and death

365

366

367