Predicting the Risk of nOdal disease with histological and Molecular features in Endometrial cancer: the prospective PROME trial

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ABSTRACT

Objective To assess the role of histopathological and molecular features in predicting the risk of nodal metastases in apparent early-stage endometrial cancer patients undergoing sentinel node mapping.

Methods This is a prospective trial. Consecutive patients with apparent early-stage endometrial cancer, undergoing laparoscopic hysterectomy, bilateral salpingo-oophorectomy, and sentinel node mapping, were enrolled. Histological and molecular features were used to predict the node positivity.

Results Charts of 223 apparent early-stage endometrial cancer patients were included in this study. Four (1.8%) patients were excluded from this study due to the lack of data about molecular features. Additionally, nine (4%) patients did not meet the inclusion criteria (due to the presence of peritoneal carcinomatosis or bulky nodes (the presence of p53 abnormality correlated with the presence of advanced stage disease (p<0.001)). The study population included 178 (84.8%) and 32 (15.2%) patients with endometrioid and non-endometrioid endometrial cancer, respectively. According to pathological uterine risk factors, 93 (44.3%), 45 (21.4%), 40 (19.1%), and 32 (15.2%) were classified as low, intermediate, intermediate-high, and high-risk, respectively. Using the surrogate molecular classification, 10 (4.8%), 42 (20%), 57 (27.1%), and 101 (48.1%) were included in the POLE mutated, p53 abnormal, MMRd/MSI-H, and NSMP, respectively. Overall, 41 (19.5%) patients were detected with positive nodes. Molecular features were not associated with the risk of having nodal metastases (OR 1.03, 95% CI 0.21 to 5.05, p=0.969 for *POLE* mutated; OR 0.788, 95% CI 0.32 to 1.98, p=0.602 for p53 abnormal; OR 1.14, 95% CI 0.53 to 2.42, p=0.733 for MMRd/MSI-H). At multivariable analysis, only deep myometrial invasion (OR 3.318, 95% CI 1.357 to 8.150, p=0.009) and lymphovascular space invasion (OR 6.584, 95% CI 2.663 to 16.279, p<0.001) correlated with the increased risk of positive nodes.

Conclusion Our data suggest that molecular classification does not seem useful to tailor the need of nodal dissection in apparent early-stage endometrial cancer. p53 abnormality predicts the risk of having advanced disease at presentation. Further external validation is needed.

Clinical trial registration NCT05793333.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Molecular classification overcomes the limitation of current histological risk assessment, being an accurate tool for prognostic assessment. Only limited data, evaluating the association between molecular classes of risk and nodal disease, are available. The present prospective study aims to test the role of histological and molecular features in predicting positive nodes in endometrial cancer patients undergoing sentinel node mapping.

WHAT THIS STUDY ADDS

⇒ This study highlighted that conventional histological features represent the most accurate tool for predicting disease harboring in non-bulky sentinel lymph nodes. However, p53 abnormality correlates with a high risk of having an advanced disease at presentation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In apparent early stage endometrial cancer, the integration between histological and molecular features seems the most appropriate approach for assessing patient risk.

INTRODUCTION

Endometrial cancer is one of the most common gynecological malignancies. Over the last decade, the incidence of endometrial cancer (49 560 in 2013 vs 66 200 in 2023) and endometrial cancer-associated deaths (8190 in 2013 vs 13 030 in 2023) has increased by more than one-third in the USA.[1] Similar trends have been observed in European countries.[2] The increase in life expectancy and the prevalence of risk factors, including obesity, are the main causes explaining this trend.[2]

Surgery, including hysterectomy (with or without salpingo-oophorectomy), represents the mainstay of treatment of apparent early-stage disease.[3 4] However, the role of retroperitoneal staging is still controversial.[3 4] Cumulative results of two large randomized trials showed that lymphadenectomy increases

morbidity but does not improve oncologic outcomes compared with the execution of hysterectomy alone.[5] Nevertheless, several retrospective studies highlighted the potential role of lymphadenectomy in tailoring appropriate adjuvant treatments.[6] The growing adoption of sentinel node mapping overcomes surgery-related issues, providing reliable data on nodal status.[7 8] The adoption of ultrastaging sentinel node mapping allows the identification of low-volume diseases, including isolated tumor cells and micrometastases, which are not detectable with conventional histopathological evaluation.[9]

One of the most impacting innovations in the field of endometrial cancer is the adoption of molecular and genomic profiling. Starting from the data published by The Cancer Genomic Atlas (TCGA) in 2013, the European Society for Medical Oncology (ESMO) and European Society of Gynaecological Oncology/European SocieTy for Radiotherapy and Oncology/European Society of Pathology (ESGO/ESTRO/ESP) guidelines, as well as the updated 2023 International Federation of Gynecology and Obstetrics (FIGO) staging system, promoted the use of surrogate classification to capture the heterogeneity of this complex disease.[3 4 10–12] Endometrial cancer patients are classified into four subgroups: (1) *POLE* mutated (*POLE*mut), (2) mismatch repair deficiency/microsatellite-instable (dMMR/MSI-H), (3) *TP53*-mutant or p53 abnormal (p53abn), and (4) no specific mutational profile (NSMP). Accumulating data support the prognostic value of this classification.[10–14] However, to date, no prospective data support the adoption of this surrogate classification to tailor surgical and adjuvant treatments. The aim of this prospective study was to define the value of conventional histopathological and molecular features in predicting the risk of positive nodal disease in endometrial cancer.

METHODS

Patients were prospectively enrolled in this trial between January 2022 and June 2023. The protocol was approved by the Institutional Review Board (IRB) of the Fondazione IRCCS Istituto Nazionale dei Tumori di Milano (IRB#140.20). The trial was registered in clinicaltrials.gov under the identification number NCT05793333. This a prospective study designed to test the role of molecular features (not only limited to four molecular classes) in predicting node positivity and long-term survival outcomes. All patients included signed informed consent for research purpose.

Inclusion criteria were: (1) histologically confirmed endometrial cancer; (2) clinical stage I disease; (3) having retroperitoneal staging via sentinel node mapping. Exclusion criteria were: (1) age <18 years; (2) consent withdrawal; (3) having sentinel node mapping plus backup lymphadenectomy; (4) clinical stage II–IV disease; (5) presence of bulky nodes detected at pre-operative workup or at the time of surgery. In the present analysis, we aimed to identify factors predicting positive nodes. Patients were staged according to the 2009 FIGO staging system, since the trial started before 2023.[15] Histological classification and degree of glandular differentiation were classified according to the WHO and FIGO classification systems, respectively.[13–15]

Patients included had pre-operative workup including transvaginal ultrasound, radiomics analysis (data will be reported in a dedicated paper when mature for being correlated with survival outcomes), and CT scan. All patients included had total laparoscopic hysterectomy with or without bilateral salpingo-oophorectomy and sentinel node mapping. Details about the execution of sentinel node mapping and ultrastaging have been reported in a previous investigation by our study group.[16 17] Side-specific lymphadenectomy was performed in cases of failure of mapping into the hemipelvis. Looking at the pathological evaluation, all lymph nodes were placed in formalin and subsequently embedded in paraffin. The sentinel nodes were sectioned parallel to their major axis, forming slices 2–3 mm thick, which were then stained (hematoxylin and eosin). Finally, in case of negative results, two sections were subjected to immunohistochemical examination with cytokeratins (AE1 and AE3) to identify low-volume disease (ie, micrometastasis or isolated tumor cells) with ultrastaging. When nodal metastasis was identified, the lymph node was fixed in formaldehyde and included in paraffin for further control sections. The non-sentinel lymph nodes were dissected along the major axis, stained (hematoxylin and eosin), and subsequently examined traditionally. According to the American Joint Committee on Cancer classification, macrometastasis, micrometastasis, and isolated tumor cells were defined by the presence of clusters of neoplastic cells >2 mm, 0.2 to 2 mm, and <0.2 mm, respectively.[9] Frozen section was not routinely performed on nodes removed.

In case of the presence of either macrometastasis or micrometastasis in the evaluated nodes, patients were classified with positive nodes (FIGO stage IIIC). The findings of isolated tumor cells did not change the FIGO staging, but where considered having positive node in the present study. Positive nodes were considered in a hierarchical fashion (macrometastasis > micrometastasis > isolated tumor cells). Stratification by molecular classification followed the surrogates of the TCGA classification,[11] and the patients were grouped as follows: *POLE*-mut (polymerase-epsilon mutated), dMMR/MSI-H (mismatch repair deficient/microsatellite instability high), p53-abn (p53 abnormal), and NSMP (non-specific mutational profile). In case of multiple molecular classifications, the so called 'multiple classifier', the current guidelines were followed.[12 13]

Evaluating peri-operative outcomes, we used the Clavien-Dindo severity system to classify the severe complications and the Martin criteria to improve the quality of reporting of complications.[16 17] Criteria for adjuvant therapy administration and detailed descriptions of follow-up protocols are reported elsewhere.[16 17] Adjuvant therapy was chosen by radiation oncologists and medical oncologists. The choice of delivering adjuvant therapy depended on the ESGO/ESTRO/ESP class of risk evaluated using conventional histopathological data and molecular features.[3] In low-risk disease, adjuvant therapy was not performed. In the case of intermediate-risk disease, vaginal brachytherapy or external beam radiotherapy was considered the standard of care.[16 17] The high-risk patients underwent radiotherapy with or without chemotherapy, or chemotherapy alone, as adjuvant treatment. External beam radiotherapy was administered using three-dimensional conformal or intensity-modulated radiotherapy to deliver standard pelvic doses of 45–50.4 Gy and para-aortic doses of 45 Gy. Immune checkpoint inhibitors were not administered during the study period. Systematic therapy included the use of a platinum-based combination plus paclitaxel. When chemotherapy was the only adjuvant modality, four to six cycles (more commonly, six cycles) were delivered in standard

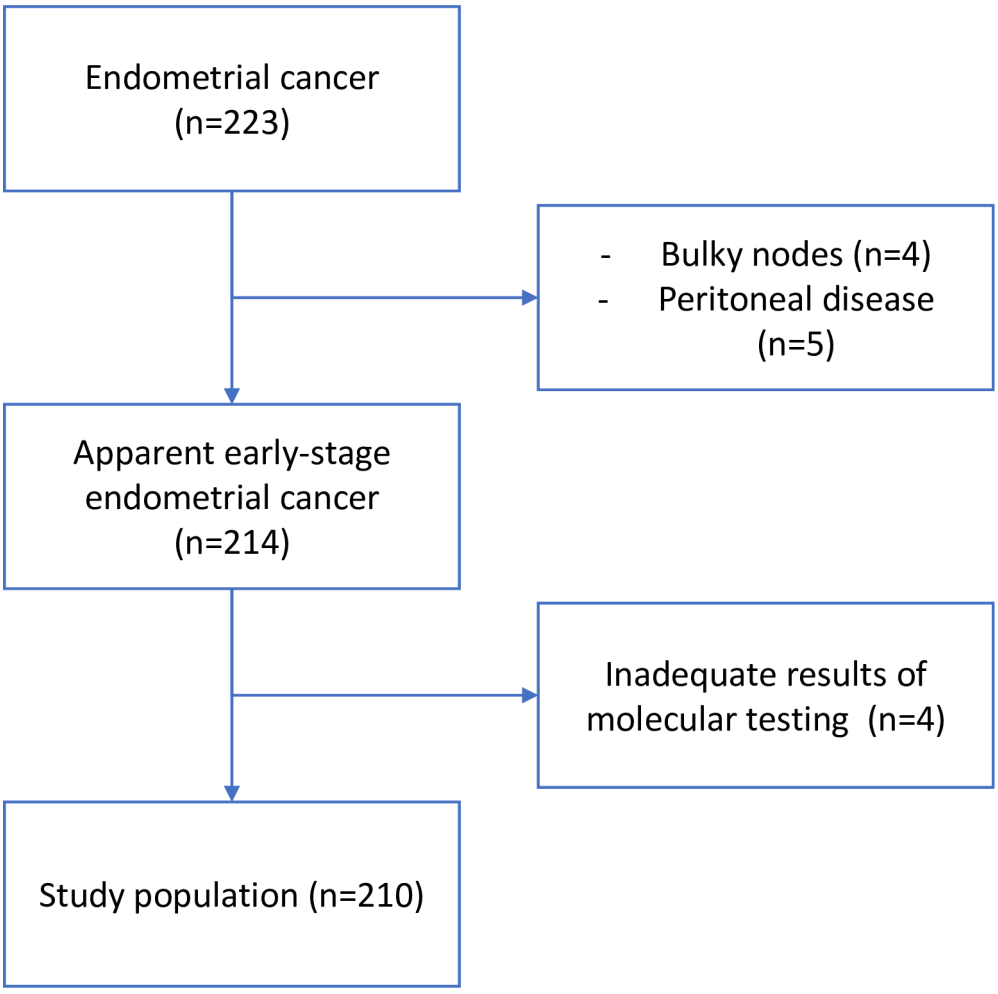

Figure 1 Study design.

doses. Owing to the short-term follow-up data, we did not perform survival analysis.

RESULTS

Overall, 223 apparent early-stage endometrial cancer patients were included in this study. Nine (4%) patients did not meet the inclusion criteria and were excluded. Additionally, four (1.8%) patients were excluded by this study due to the lack of data about molecular features (inadequate results). The study population included 210 (94.2%) patients: 178 (84.8%) and 32 (15.2%) with endometrioid and non-endometrioid endometrial cancer, respectively. Figure 1 shows the study design.

Table 1 reports baseline characteristics of patients included. According to pathological uterine risk factors (using conventional pathological characteristics according to the ESGO/ESTRO/ESP guidelines), 93 (44.3%), 45 (21.4%), 40 (19.1%), and 32 (15.2%) were classified as low, intermediate, intermediate-high, and high-risk, respectively. Using the surrogate molecular classification, 10 (4.8%), 42 (20%), 57 (27.1%), and 101 (48.1%) were included in the *POLE* mutated, p53 abnormal, MMRd/MSI-H, and NSMP, respectively. Table 2 shows the correlation between histological uterine risk factors (assessed per the ESGO/ESTRO/ESP guidelines) and molecular classes of risk. Online Supplemental Material 1 shows details about the prevalence of different molecular features in various classes of risk.

Overall, 41 (19.5%) patients were detected with positive nodes. Macrometastases and low volume disease (micrometastases and isolated tumor cells) were observed in 21 (10%) and 20 (9.5%) patients, respectively. Online Supplemental Material 2 shows details regarding patients with positive nodes. Molecular features were not associated with the risk of having nodal metastases (OR 1.03, 95% CI 0.21 to 5.05, p=0.97 for *POLE* mutated; OR 0.788, 95% CI 0.32 to 1.98, p=0.602 for p53 abnormal; OR 1.14, 95% CI 0.53 to 2.42, p=0.73 for MMRd/MSI-H); even patients with NSMP did not have an increased risk having positive nodes (OR 1.03, 95% CI 0.52 to 2.04, p=0.99). At univariate analysis, only conventional pathological factors influenced the risk of nodal metastases (histology, FIGO grade, myometrial invasion, and lymphovascular space invasion (LVSI)).

At multivariable analysis, only deep myometrial invasion (OR 3.318, 95% CI 1.357 to 8.150, p=0.009) and the presence of LVSI (OR 6.584, 95% CI 2.663 to 16.279, p<0.001) correlated with the risk of having positive nodes. Table 3 reports data regarding factors predicting the presence of positive nodes. Online Supplemental Material 3 shows the distribution of patients with positive nodes, according to histological and molecular features. Restricting the analysis on macrometastases only, we observed that molecular

Table 1 Baseline characteristics of the study population

	N=210
Age, years	64 (56–73)
BMI, kg/m^2	27 (23–30)
Histology	
Endometrioid	178 (84.8%)
Non-endometrioid	32 (15.2%)
FIGO grade	
Grade 1	33 (15.7%)
Grade 2	113 (53.8%)
Grade 3	64 (30.5%)
Myometrial invasion	
<50%	132 (62.9%)
≥50%	78 (37.1%)
LVSI	
No	147 (70.0%)
Focal	14 (6.7%)
Substantial	49 (23.3%)
Positive nodes	
No	169 (80.5%)
Yes	41 (19.5%)
Molecular classification	
dMMR/MSI-H	57 (27.1%)
POLE mutated	10 (4.8%)
p53 abnormal	42 (20%)
NSMP	101 (48.1%)

Data are reported as median (range, 25% and 75% percentile); number (%).
BMI, body mass index; dMMR/MSI-H, mismatch repair deficient/microsatellite instability high; FIGO, International Federation of Obstetrics and Gynecology; LVSI, lymphovascular space invasion; NSMP, non-specific mutational profile; POLE, polymerase-epsilon.

classification was not able to predict the risk of having positive nodes (p=0.13). Similarly, no association was observed when we tested the association between molecular features with macrometastases+micrometastases (p=0.57). However, looking at the presence of isolated tumor cells only, we observed that patients with POLE (10%) and MMRd/MSI-H (12.3%) were more likely to be detected with this occurrence than patients with p53 abnormal (0%) and NSMP (3.9%) endometrial cancers (p=0.045).

The aim of this study was to focus on early-stage endometrial cancer. Looking at the study design of the trial, nine patients were excluded due to peritoneal disease and bulky nodes. All the five patients with peritoneal carcinomatosis were characterized by p53 abnormalities, while two and two patients with bulky nodes were characterized by p53 abnormality and NSMP, respectively. Those data highlighted that the presence of p53 abnormality might predict the presence of having an advanced stage of disease at presentation (0% in *POLE* mutated and MMRd/MSI-H, 1.9% in NSMP, and 14% in p53 abnormal; p<0.001).

DISCUSSION

Summary of Main Results

This is a prospective study evaluating predictors for nodal disease in apparent early-stage endometrial cancer undergoing sentinel node mapping. The present study reported a number of noteworthy findings. First, the surrogate molecular classification is not useful to tailor the need of sentinel node mapping. Second, deep myometrial invasion and LVSI are the only variables predicting the risk of nodal involvement. Third, patients with NSMP are more likely to be detected with low-volume disease in comparison to patients with p53 abnormal cancers.

Results in Context of Published Literature

The introduction of sentinel node mapping and molecular classification represent two of the main advantages in endometrial cancer management. Accumulating data supported the safety and effectiveness of adopting sentinel node mapping instead of lymphadenectomy. Sentinel node mapping enables reduction in morbidity related to lymphadenectomy, improving the diagnostic accuracy (detecting patients harboring low volume nodal disease (through ultrastaging)). The data reported by the TCGA and by the experiences of surrogate molecular classification highlighted the prognostic role of this classification in identifying patients at risk of recurrence.

In comparison to conventional histopathological data, molecular features provide more precise and reliable information for prognostication and for tailoring the most appropriate (adjuvant) treatments.[10–14] Since molecular data can be acquired at the time of pre-operative biopsy, several authors have speculated

Table 2 Correlation between histological and molecular risk factors

Class of risk*	POLE mutated	dMMR/MSI-H	p53 abnormal	NSMP
Low risk (n=93)	2 (2.1%)	23 (24.7%)	6 (6.5%)	62 (66.6%)
Intermediate risk (n=45)	4 (8.9%)	15 (33.3%)	12 (26.7%)	14 (31.1%)
Intermediate-high risk (n=40)	4 (10%)	14 (35%)	6 (15%)	16 (40%)
High risk (n=32)	0	5 (15.6%)	18 (56.3%)	9 (28.1%)

Data are reported as number (%).
*Classes of risk based on uterine risk factors according to the ESGO/ESTRO/ESP guidelines.
dMMR/MSI-H, mismatch repair deficient/microsatellite instability high; ESGO/ESTRO/ESP, European Society of Gynaecological Oncology/European SocieTy for Radiotherapy and Oncology/European Society of Pathology; NSMP, non-specific mutational profile; p53 abn, p53 abnormal; POLE, polymerase-epsilon.

Table 3 Predictors of positive nodes

	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, years*	0.978 (0.739 to 1.288)	0.862	–	–
BMI, kg/m^2†	0.95 (0.695 to 1.256)	0.653	–	–
Histology		0.074		0.38
Endometrioid	Reference		Reference	
Non-endometrioid	2.155 (0.929 to 5.002)		0.571 (0.164 to 1.998)	
FIGO grade		0.005		0.48
Grade 1 and 2	Reference		Reference	
Grade 3	2.706 (0.1.341 to 5.460)		1.461 (0.504 to 4.238)	
Depth of myometrial invasion		<0.001		0.009
<50%	Reference		Reference	
>50%	6.875 (3.191 to 14.811)		3.318 (1.357 to 8.150)	
Cervical stromal involvement		0.650		–
No	Reference		–	
Yes	0.57 (0.240 to 2.412)		–	
Adnexal/serosal involvement		0.311		–
No	Reference		–	
Yes	0.05 (0.001 to 65.560)		–	
LVSI		<0.001		<0.001
No	Reference		Reference	
Yes	11.24 (5.108 to 24.731)		6.584 (2.663 to 16.279)	
Positive peritoneal washing		0.690		–
No	References		–	
Yes	0.06 (0.001 to 50.801)		–	
POLE mutation		0.969		–
No	Reference		–	
Yes	1.032 (0.211 to 5.053)		–	
dMMR/MSI-H		0.733		–
No	Reference		–	
Yes	1.140 (0.536 to 2.424)		–	
p53 abnormal		0.602		–
No	Reference		–	
Yes	0.788 (0.322 to 1.928)		–	
NSMP		0.992		–
No	Reference		–	
Yes	1.035 (0.523 to 2.048)		–	

*OR per 10-year increase in age.
†OR per 5-unit increase in BMI.
BMI, body mass index; dMMR/MSI-H, mismatch repair deficient/microsatellite instability high; FIGO, International Federation of Obstetrics and Gynecology; LVSI, lymphovascular space invasion; NSMP, non-specific mutational profile; p53 abn, p53 abnormal; POLE, polymerase-epsilon.

about the potential role of molecular classification in tailoring the surgical approach. Molecular classification has ushered in a new era in the management of endometrial cancer, offering unprecedented insights into tumor biology. The integration of molecular data into the decision-making process for nodal dissection holds immense potential for refining surgical strategies, optimizing patient outcomes, and paving the way toward a more personalized approach to endometrial cancer care. Ideally, molecular classification could be useful in identifying patients who should undergo nodal dissection.

To our knowledge, this is the only study correlating molecular features with the risk of having positive nodes in apparent early-stage endometrial cancer undergoing sentinel node mapping. Jamieson et al[18] reported retrospective data of 172 patients undergoing sentinel node mapping plus lymphadenectomy. The authors showed that molecular classification correlated with the probability of nodal involvement (p53 abnormal 44.8%; MMRd 14.9%; POLE mutated 14.2%; NSMP 10.8%). However, this research had different inclusion criteria, in comparison to our study. Our study failed to demonstrate an association between the surrogate molecular classification and the risk of having positive nodes in apparent early-stage endometrial cancers undergoing sentinel node mapping.

The results of this study supported mature evidence correlating deep myometrial invasion and LVSI with the presence of lymphatic disease.[15 19 20] The present study was designed to test the role of molecular and histological features in predicting the presence of positive nodes (including macrometastasis, micrometastasis, and isolated tumor cells). However, macrometastasis and low-volume disease (ie, micrometastasis and isolated tumor cells) have different prognostic roles and has an impact on the patient's journey.[16 21] This study does not have enough power to test the ability of adopting molecular classification in predicting the presence of low-volume disease.[9] The study will continue to enroll patients to test this association.

Strengths and Weaknesses

The main strengths of this study are its prospective nature and the innovative topic. The main weakness of the present research is related to the small sample size. Additionally, some variables (including tumor size and pattern of myometrial infiltration) are missing, thus limiting the generalization of our results. Six other points deserve to be addressed. First, the molecular classification was evaluated on the uterine specimen after surgery, while it would be more interesting to test the role of molecular data achieved on pre-operative endometrial samples. Evidence supporting the reliability of pre-operative and uterine samples is still lacking. Second, certain molecular features (beyond TP53, MMRd/MSI-H, and POLE) might play a role in predicting node positivity. A step forward in our protocol is to test molecular features (not limited to the four classes) in relation to nodal disease and survival outcomes. Third, external validation is needed to confirm the reproducibility of these results. Hence, our results should be considered preliminary. Fourth, patients with POLE and MMRd/MSI-H were more likely to be diagnosed with isolated tumor cells than patients with p53 abnormalities and NSMP. However, due to the limited number of patients with isolated tumor cells, it was not possible to conduct any exploratory analysis. Fifth, the prevalence of positive nodes reported in our study might be considered low, especially considering that high-risk patients represent 15.2% of our series. Although in high-risk patients the prevalence of positive nodes is higher than 30%,[22] the majority of our patients are at low and intermediate risk (84.8%). Sixth, due to the short-term follow-up, we decided not to evaluate survival outcomes. Further analysis will be carried out.

Implications for Practice and Future Research

Our data showed that integrating histological and molecular features might be the most appropriate approach for the identification of endometrial cancer at risk of nodal metastases. Developing an algorithm implementing both those variables would be useful to identify patients at risk.

CONCLUSIONS

This study showed that molecular features, per se, were not useful in predicting nodal disease, while conventional histopathological features (deep myometrial invasion and LVSI) predicted the presence of nodal disease in patients with apparent early-stage endometrial cancer. Knowing the presence of p53 abnormality before surgery might be useful to tailor the appropriate pre-operative workup for identifying patients with advanced stage disease. Further studies are warranted to confirm our results.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Fondazione IRCCS Istituto Nazionale dei Tumori di MIlano. Participants gave informed consent to participate in the study before taking part.

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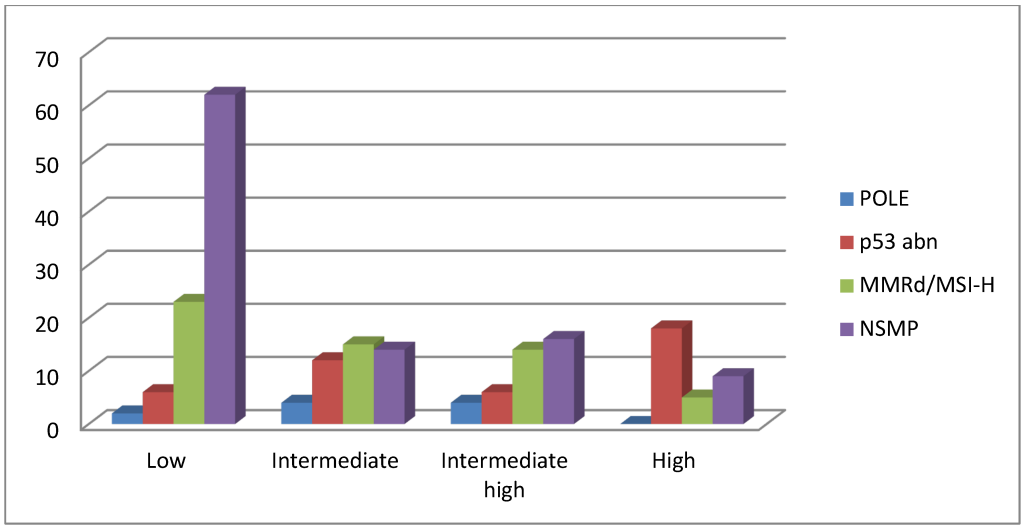
Supplemental material 1: Correlation between molecular and pathological uterine risk factors*



Abbreviation: dMMR/MSI-H, mismatch repair deficient/microsatellite instability high; p53 abn; p53 abnormal; *POLE*, Polymerase-epsilon; NSMP, non-specific mutational profile. * Classes of risk based on uterine risk factors according to the ESGO/ESTRO/ESP guidelines.

Supplemental material 2: Details about nodal disease according to histological uterine risk factors and molecular features

	Nodal disease (n=41)	Macrometastases (n=21)	Micrometastases (n=8)	Isolate tumor cells (n=12)
Histological classes*				
Low risk (n=93)	2 (2.2%)	0	1 (1.1%)	1 (1.1%)
Intermediate risk (n=45)	7 (15.6%)	1 (2.2%)	4 (8.9%)	2 (4.4%)
Intermediate-high risk (n=40)	22 (55%)	10 (25%)	3 (7.5%)	9 (22.5%)
High risk (n=32)	10 (31.3%)	10 (31.3%)	0	0
Molecular classes				
POLE mutated (n=10)	2 (20%)	0	1 (10%)	1 (10%)
dMMR/MSI-H (n=57)	12 (21%)	2 (3.5%)	3 (5.3%)	7 (12.3%)
p53 abnormal (n=42)	7 (16.6%)	5 (11.9%)	2 (4.8%)	0
NSMP (n=101)	20 (19.8%)	14 (13.9%)	2 (1.9%)	4 (3.9%)

Data are reported as number (%); Abbreviation: dMMR/MSI-H, mismatch repair deficient/microsatellite instability high; p53 abn; p53 abnormal; *POLE*, Polymerase-epsilon; NSMP, non-specific mutational profile. * Classes of risk based on uterine risk factors according to the ESGO/ESTRO/ESP guidelines.

Supplemental material 3: Patients with positive nodes according to histological and molecular features

	POLE mutated (n=2)	dMMR/MSI-H (n=12)	p53 abnormal (n=7)	NSMP (n=20)
Low risk (n=2)	0	1	0	1
Intermediate risk (n=7)	2	3	2	0
Intermediate-high risk (n=22)	0	8	3	11
High risk (n=10)	0	0	2	8