SENECA study: staging endometrial cancer based on molecular classification

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ABSTRACT

Objective Management of endometrial cancer is advancing, with accurate staging crucial for guiding treatment decisions. Understanding sentinel lymph node (SLN) involvement rates across molecular subgroups is essential. To evaluate SLN involvement in early-stage (International Federation of Gynecology and Obstetrics 2009 I–II) endometrial cancer, considering molecular subtypes and new European Society of Gynaecological Oncology (ESGO) risk classification.

Methods The SENECA study retrospectively reviewed data from 2139 women with stage I–II endometrial cancer across 66 centers in 16 countries. Patients underwent surgery with SLN assessment following ESGO guidelines between January 2021 and December 2022. Molecular analysis was performed on pre-operative biopsies or hysterectomy specimens.

Results Among the 2139 patients, the molecular subgroups were as follows: 272 (12.7%) p53 abnormal (p53abn, 1191 (55.7%) non-specific molecular profile (NSMP), 581 (27.2%) mismatch repair deficient (MMRd), 95 (4.4%) POLE mutated (POLE-mut). Tracer diffusion was detected in, at least one side, in 97.2% of the cases; with a bilateral diffusion observed in 82.7% of the cases. By ultrastaging (90.7% of the cases) or one-step nucleic acid amplification (198 (9.3%) of the cases), 205 patients were identified with affected sentinel lymph nodes, representing 9.6% of the sample. Of these, 139 (67.8%) had low-volume metastases (including micrometastases, 42.9%; and isolated tumor cells, 24.9%) while 66 (32.2%) had macrometastases. Significant differences in SLN involvement were observed between molecular subtypes, with p53abn and MMRd groups having the highest rates (12.50% and 12.40%, respectively) compared with NSMP (7.80%) and POLE-mut (6.30%), (p=0.004); (p53abn, OR=1.69 (95% CI 1.11 to 2.56), p=0.014; MMRd, OR=1.67 (95% CI 1.21 to 2.31), p=0.002). Differences were also noted among ESGO risk groups (2.84% for low-risk patients, 6.62% for intermediate-risk patients, 21.63% for high–intermediate risk patients, and 22.51% for high-risk patients; p<0.001).

Conclusions Our study reveals significant differences in SLN involvement among patients with early-stage endometrial cancer based on molecular subtypes. This underscores the importance of considering molecular characteristics for accurate staging and optimal management decisions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The molecular profile of endometrial cancer is a strong independent prognostic factor and predicts the response to adjuvant treatment. However, its influence on lymph node involvement in early endometrial cancer is unknown.

WHAT THIS STUDY ADDS

⇒ Molecular subgroups of endometrial cancer have distinctive sentinel node involvement patterns. The p53 abnormal and mismatch repair deficient molecular profile are the two groups with the highest tendency to present nodal involvement. The European Society of Gynaecological Oncology high–intermediate risk and high prognostic risk groups are groups with high lymph node involvement.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In this study, molecular profiling emerges as a predictor of nodal involvement. This suggests the potential of molecular classification in the personalization of surgical lymph node staging protocols for patients with endometrial cancer.

INTRODUCTION

Endometrial cancer is the most common gynecological cancer in Europe, encompassing a 5-year prevalence of 34.7%, amounting to 445 805 cases.[1] In recent years, sentinel lymph node biopsy (SLN) has emerged as a viable alternative to complete lymph node dissection in early-stage disease.[2 3] Prospective

clinical trials have confirmed the high sensitivity to detect lymph node metastasis and the high negative predictive value using a standardized SLN algorithm in high-risk/high-grade endometrial cancer.[4–7] In particular, when performed according to state-of-the-art principles, a negative SLN is acceptable to confirm pN0.[8 9]

The Cancer Genome Atlas Research Network identified in 2013 four molecular subgroups of endometrial cancer with different clinical and prognostic outcomes.[10–14] The significance of this development led the European Society of Gynecologic Oncology (ESGO) to the integration of the new molecular classification into the prognostic risk classification of endometrial cancer.[8] This transition involved shifting from a risk classification based purely on histopathologic factors to a new prognostic risk classification that incorporates the molecular subtype in addition to the different histologic features. However, there is a lack of evidence on the role of molecular classification in the sentinel node biopsy algorithm.[9]

Therefore, the primary objective of this study was to assess the rate of SLN involvement according to the different molecular subtypes in patients with stage I–II endometrial cancer (International Federation of Gynecology and Obstetrics (FIGO) 2009).[15] Second, we aimed to evaluate the accuracy of the new ESGO prognostic risk classification (including molecular profiling) for the prediction of SLN involvement with respect to the classic risk classification (based on histological factors).

METHODS

Study Design

The study was a retrospective multicentric international observational study reviewing data of patients diagnosed with early-stage (FIGO stage 2009 I–II)[15] endometrial cancer who underwent standard surgical protocol according to ESGO guidelines[8] including total hysterectomy and bilateral salpingo-opherectomy together with the SLN algorithm[9] between January 2021 and December 2022. Patients were considered eligible if all the following criteria were met: age 18 years or older; histological confirmation of endometrial cancer with endometrioid histology or high-risk histology (serous, clear cell, carcinosarcoma, and mixed histologies); pre-operative FIGO stage I or II by MRI or ultrasound; pre-operative CT scan or PET-CT without evidence of local or distant disease (could be omitted in low-risk and intermediate-risk endometrial carcinoma with low-grade histology according to the ESGO guidelines.[8] In addition, a detailed SLN study protocol had to be accredited, either by ultrastaging or one-step nucleic acid amplification.[16 17] Molecular analysis had to be performed on the pre-operative biopsy or hysterectomy specimen.

The definition of POLE was predicated on the identification of exonuclease domain mutations within the gene. The participating centers employed diverse DNA sequencing methodologies, encompassing next-generation sequencing and Sanger sequencing. Definition of mismatch repair deficient (MMRd): An MMRd tumor was discerned via the immunostaining of at least two (PMS2 and MSH6), or preferably four (PMS2, MLH1, MSH6, and MSH2) MMR proteins. The complete absence of expression in one or more of these MMR proteins constituted a diagnostic criterion for MMRd endometrial cancer. Analysis of p53: p53 immunostaining was regarded as a near-flawless surrogate marker for an underlying TP53 mutation in nearly all cases studied. In only a handful of instances, the determination of TP53 was additionally corroborated by extensive DNA sequencing techniques; both results were admitted for classification purposes.

According to ESGO guidelines, POLE mutation analysis could be omitted in low-risk and intermediate-risk endometrial carcinoma with low-grade histology (stage IA endometrioid+low-grade + lymphovascular space invasion (LVSI) negative or focal or stage IB endometrioid+low-grade + LVSI negative or focal) while information on MMRd and p53 abnormal (p53abn) status was available in all cases.[8] Patients were excluded if they were pregnant; if they had undergone previous hysterectomy and/or previous pelvic/para-aortic lymphadenectomy; if extra-uterine disease (peritoneal, visceral, or suspicious lymph node metastasis) was present; or they had a past medical history of any invasive tumor, previous abdominal or pelvic radiotherapy of any type (including brachytherapy), and history of pre-operative neoadjuvant chemotherapy.

Accrual and Data Source

Gynecological cancer centers/units/hospitals regularly performing elective surgeries for endometrial cancer internationally were invited to participate. Invitations were sent through international/national and informal networks. Participating sites registered with the central audit team at Clinica Universidad de Navarra and were provided with unique user access credentials for the database.

Each participating site identified a principal investigator who was responsible for coordinating data entry at their local site. After obtaining ethical consent from our central institutional review board, we required a certificate of approval from the local ethics committees from all the investigators. An anonymized complete case record form, including 140 items by Google Forms database was sent to all the principal investigators. Before completing the case collection, all researchers signed a final declaration affirming that all the submitted data matched the data in the patients' charts. The trial was registered in clinicaltrials.gov under the identification number NCT05707312.

Statistical Analysis

A sample size of 1032 patients may provide sufficient statistical power to evaluate the association between molecular subgroups and sentinel lymph node status. We assumed a 90% power for a two-sided p value of 0.05 and a minimum difference of 4.4 percentage points in prevalence rates of positive lymph nodes. We expected a potential dropout rate of 10%. Quantitative data will be presented as mean and SD and qualitative variables with absolute values and percentages. Additionally, qualitative variables among groups will be compared by X^2 test or Fisher exact test; and quantitative variables with t-test and analysis of variance test.

The primary objective was to evaluate the lymph node involvement rate (sentinel) for each molecular subtype in patients with stage I–II endometrial cancer. The sentinel lymph node involvement rate included isolated tumor cells (isolated tumor cells <0.2 mm or less than 200 tumorous cells in a single histologic section), micrometastases (0.2–2 mm or more than 200 tumorous cells in a single histologic section) and macrometastases (metastases >2 mm). The SLN involvement was compared among molecular subtype groups (POLE-mutated (POLE-mut); MMRd; non-specific molecular profile (NSMP); and p53abn. Patients harboring more

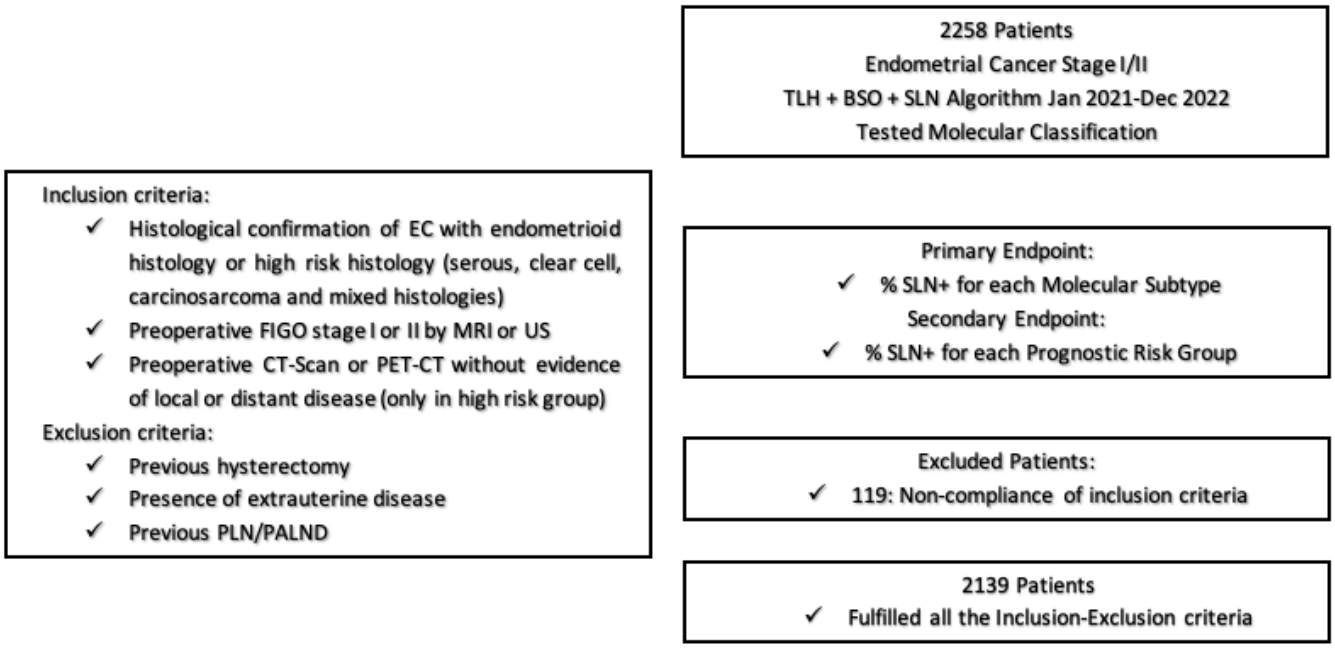

Figure 1 Flowchart of study population. BSO, bilateral salpingo-opherectomy; EC, endometrial cancer; FIGO, International Federation of Gynecology and Obstetrics; PALND, para-aortic lymph node dissection; PLN, pelvic lymph node; SLN, sentinel lymph node; TLH, total hysterectomy.

than one molecular feature were classified according to the guideline's recommendations.[8] The rate of sentinel lymph node involvement was studied including isolated tumor cells; however, for staging purposes, isolated tumor cells were considered as pN0i+.

The hypothesis is that there will be differences in the lymph node involvement rate among molecular subtype groups. The z-test for independent proportions and the logistic regression will be used to test this hypothesis.

The secondary objectives include evaluation of the lymph node involvement rate (sentinel) for each ESGO prognostic risk group (new risk classification including molecular profile versus classic risk classification without including molecular profile). The patients were categorized according to the ESGO classification criteria into: low-risk, intermediate-risk, high–intermediate and high-risk groups.[8] Nodal status was not taken into account to establish the groups since it was the target variable. For the multivariate analysis, a logistic regression model will be used. All analyses were performed with the IBM SPSS 26.0 and the Stata 14 packages.

RESULTS

From January 1, 2023, to September 1, 2023, we collected data from 2258 patients across 66 institutions spanning 16 different countries. A total of 119 patients did not meet the inclusion–exclusion criteria or had missing information and were excluded (Figure 1). Tables 1 and 2 show the patient characteristics. Mean age was 64.5 years (SD 10.80). Mean body mass index was 30.2 kg/m^2 (SD 6.65). The diagnostic method used in most patients was hysteroscopy (998 (46.7%)) followed by blind biopsy (630 (29.5%)) and curettage (476 (22.3%)). Regarding the surgical approach, a total of 2026 patients (94.7%) underwent minimally invasive procedures and 113 were operated by laparotomy (5.3%). Among patients who underwent minimally invasive surgery, 594 patients (27.8%) were operated on robotically.

Focusing on the SLN approach, the majority of the cases, 2059 (96.2%), were performed with indocyanine green as a tracer (alone or in combination), injected at a volume of 4 cc (1544 (72.2%) patients). In 1686 (78.8%) patients lymph node staging was performed exclusively by sentinel lymph node biopsy. The median number of sentinel nodes was two per patient (range 0–6). Tracer diffusion was detected in, at least one side, in 97.2% of the cases; with a bilateral diffusion observed in 82.7% of the cases. By ultrastaging (1941 (90.7%) of the cases)) or one-step nucleic acid amplification (198 (9.3%) of the cases), 205 patients were identified with affected sentinel lymph nodes, representing 9.6% of the sample. Of these, 139 (67.8%) patients had low-volume metastases (including micrometastases, 42.9%; and isolated tumor cells, 24.9%) while 66 (32.2%) patients had macrometastases. The most common final pathology was low-grade (1655 (77.4%) cases, including G1 and G2 tumors) endometrioid tumors (1866 (87.2%) cases) without lymphovascular space invasion (1649 (76.7%) cases). FIGO 2009 stages I and II were recorded in 1946 (90.9%) of the cases.

Molecular profiling was predominantly tested in the final postoperative specimen (64.5% of the cases vs 35.5% tested preoperatively). A complete molecular profile was obtained in 1217 (56.8%) cases, while in 922 (43.2%) patients, POLE-mut analysis was omitted due to low-risk or intermediate-risk endometrial cancer with low-grade histologies. Concerning the distribution of the groups, the most prevalent groups were NSMP in 1191 (55.7%) cases and MMRd in 581 (27.2%), followed by p53abn in 272

Table 1 Baseline characteristics

Baseline characteristics	n=2139
Age (years), mean (SD)	64.55 (10.80)
Body mass index (kg/m^2),mean (SD)	30.24 (6.65)
Diagnostic method, N (%)	
Hysteroscopy	998 (46.7)
Blind biopsy	630 (29.5)
Gynecologic curettage	476 (22.3)
Not reported	35 (1.6)
Surgical approach, N (%)	
Laparoscopic	1432 (66.9)
Robotic	594 (27.8)
Open	113 (5.3)
Nodes approach, N (%)	
SLNB	1686 (78.8)
SLNB+PLND (only one pelvic side)	131 (6.1)
SLNB+PLND (both pelvic sides)	188 (8.8)
SLNB+PLND (one side) + PALND	7 (0.3)
SLNB+PLND (both sides) + PALND	115 (5.4)
SLNB+PALND	12 (0.6)
Tracer, N (%)	
Indocyanine green	1865 (87.2)
Radiocolloid and indocyanine green	189 (8.8)
Blue dye	74 (3.5)
Blue dye and indocyanine green	5 (0.2)
Radiocolloid and blue dye	2 (0.1)
Not reported	4 (0.2)
Tracer volume, N (%)	
4 cc	1544 (72.2)
2 cc	371 (17.3)
1 cc	90 (4.2)
Not reported	134 (6.3)
SLN median, number (range)	2 (0–6)
SLN distribution, N (%)	
Both pelvic sides	1729 (80.8)
Right pelvic side	152 (7.1)
Left pelvic side	150 (7.0)
Both pelvic sides+aortic area	41 (1.9)
Left pelvic side+aortic area	8 (0.4)
Right pelvic side+aortic area	1 (0.05)
Aortic area	1 (0.05)
No SLN identified	57 (2.7)
SLN diagnostic method, N (%)	
Ultrastaging	1941 (90.7)
OSNA	198 (9.3)
SLN involvement, N (%)	205 (9.6)
Isolated tumor cells	51 (24.9)
Micrometastases	88 (42.9)
Macrometastases	66 (32.2)

OSNA, one-step nucleic acid amplification; PALND, para-aortic lymph node dissection; PLND, pelvic lymph node dissection; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy.

(12.7%) patients. The lowest prevalence group was POLE ultramutated in 4.4% of cases (95 patients).

Among the 205 patients with sentinel node involvement, we observed significant differences between molecular subtypes, with the p53abn and MMRd subgroups being the two groups with the highest rate of sentinel node involvement, 12.5% and 12.4%,

Table 2 Histopathological and molecular characteristics

Histology, N (%)	
Endometrioid	1866 (87.2)
Serous	129 (6.0)
Mixed histology	63 (2.9)
Carcinosarcoma	42 (2.0)
Clear cell	30 (1.4)
Not reported	9 (0.4)
Grade, N (%)	
Low grade	1655 (77.4)
High grade	432 (20.2)
Not reported	52 (2.4)
LVSI, N (%)	
No	1649 (76.7)
Yes	479 (22.4)
Not reported	20 (0.9)
FIGO stage 2009, N (%)	
IA	1278 (59.7)
IB	518 (24.2)
II	150 (7.0)
IIIA	28 (1.3)
IIIB	5 (0.3)
IIIC1	154 (7.2)
IIIC2	4 (0.2)
IV	2 (0.1)
Molecular profile, N (%)	
POLE-mut	95 (4.4)
MMRd	581 (27.2)
NSMP	1191 (55.7)
p53abn	272 (12.7)

FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; MMRd, mismatch repair deficient; NSMP, non-specific molecular profile; p53abn, p53 abnormal ; POLE-mut, POLE-mutated.

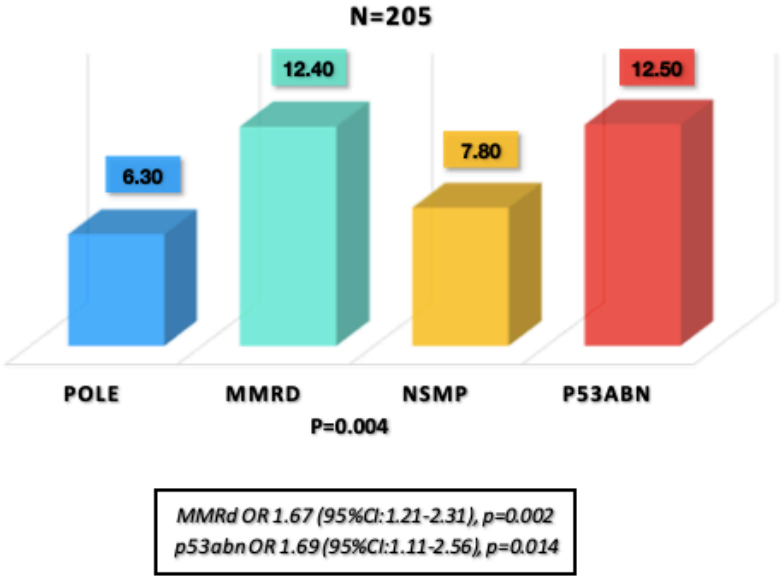

Figure 2 Rate of sentinel lymph node involvement according to the molecular profile. MMRD, mismatch repair deficient; NSMP, non-specific molecular profile; p53ABN, p53 abnormal; POLE, polymerase epsilon.

respectively, compared with 7.8% in NSMP and 6.3% in POLE ultramutated (p=0.004) (Figure 2). Patients with MMRd and p53abn had a 1.6 times higher chance of having sentinel lymph node involvement (OR=1.67 (95% CI 1.21 to 2.31), p=0.002 and OR=1.69 (95% CI 1.11 to 2.56), p=0.014, respectively). In this context, a higher rate of deep myometrial invasion (40.1%) was observed in the MMRd group, as well as a higher prevalence of high-grade (62.1%) non-endometrioid tumors (61.4%) with positive LVSI (31.6%) in the p53abn group (p<0.001).

Finally, significant differences in the SLN involvement rate were observed between the different groups of the new (molecular profile known) ESGO prognostic risk classification (2.84% for low-risk patients, 6.62% for intermediate-risk patients, 21.63% for high–intermediate risk patients and 22.51% for high-risk patients; p<0.001) (Figure 3A). This rate of nodal involvement remained very similar compared to the old (molecular profile unknown) ESGO prognostic risk classification (2.6% in low risk, 7.0% in intermediate risk, 20.6% in high–intermediate risk and 23.4% for high-risk patients) with no significant differences in the area under the curve between the two models (AUC 0.74 vs 0.75; p=0.73) (Figure 3B).

DISCUSSION

Summary of Main Results

In this retrospective study we showed that there are significant differences in sentinel node involvement for patients with early-stage endometrial cancer according to their molecular subtypes (p53abn: 12.50%; MMRd 12.40%; NSMP: 7.80%; POLE ultramutated: 6.30%). Second, we have defined the rate of SLN involvement for each of the new ESGO prognostic risk groups including molecular profiling (2.8% for low-risk patients, 6.6% for intermediate-risk patients, 21.6% for high–intermediate risk patients, and 22.5% for high-risk patients; p<0.001). This rate of nodal involvement remained very similar to that of the old ESGO prognostic risk classification (without including molecular profiling), with no significant differences in the area under the curve between the two models.

Results in the Context of Published Literature

This is a real-life study, in which a tracer distribution rate of 97.2% was revealed, with a bilateral mapping rate of 82.7%. These figures are in line with previous prospective studies.[4–7] However, this bilateral tracer distribution rate highlights a lack of standardization of the sentinel node dissection technique. A competency assessment tool for performing SLN biopsy in surgical quality assurance is now available from Moloney et al.[18] This might help to reduce the morbidity associated with lymphadenectomy in cases of tracer non-diffusion and to increase the rate of bilateral mapping.

Our study shows that 205 patients with stage I–II (FIGO 2009) endometrial cancer had sentinel lymph node involvement (9.6%), of which 24.9% had isolated tumor cells. With the introduction of ultrastaging and the one-step nucleic acid amplification protocol,[16 17 19] isolated tumor cells are increasingly identified in routine practice. Isolated tumor cells are not considered as pTN+, although they seem to have prognostic implications. Recently, Cucinella et al[20] conducted a multicenter retrospective study comparing the prognosis of patients with negative nodes versus those with isolated tumor cells in sentinel lymph nodes who are considered low risk—namely, FIGO 2009 IA cases with endometrioid grade 1 or 2. From 15 centers worldwide, 494 patients (42 isolated tumor cells and 452 node negative) were included. Twenty-one recurrences (4.3%) were identified, including in five patients with isolated tumor cells and 16 patients with negative lymph nodes. The study

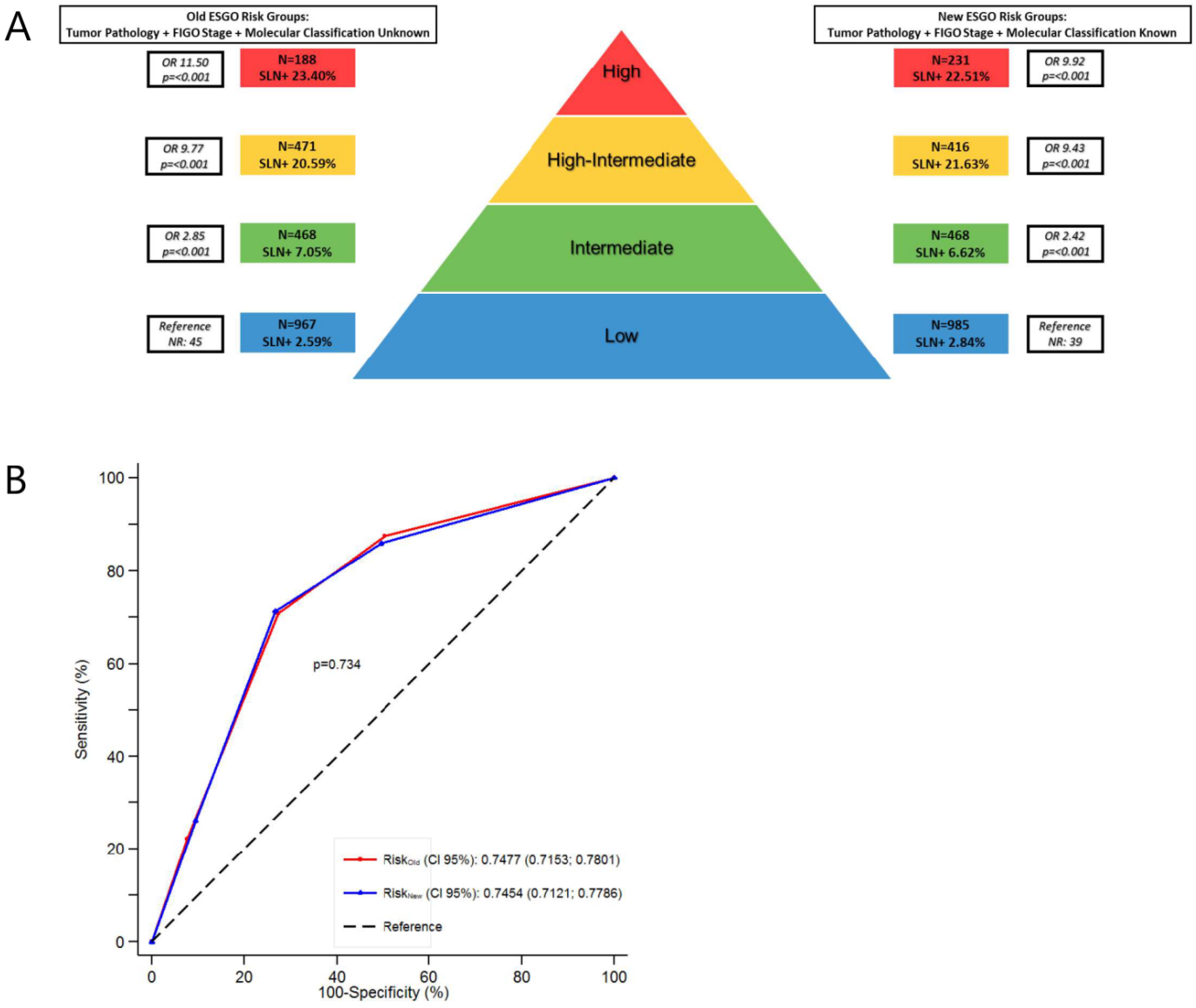

Figure 3 Rate of sentinel lymph node (SLN) involvement according to the European Society of Gynaecological Oncology (ESGO) prognostic risk classification (A). Area under the curve for the risk of sentinel lymph node involvement for the two models (B).

found that isolated tumor cells, grade 2, and lymphovascular space invasion were all associated with worse recurrence-free survival in the univariate analysis. Even when considering patients with negative lymphovascular space invasion, the presence of isolated tumor cells was still associated with higher non-vaginal recurrence (HR=4.47, 95% CI 1.21 to 16.6, p=0.03). Currently the author's group are conducting prospective studies to decide what is best when making recommendations in low-grade endometrioid endometrial cancer with isolated tumor cells. Until then, we should focus on uterine factors and molecular profiling of endometrial tumors to make the most educated decision for our patients.[21]

Regarding the molecular profile, a similar distribution was observed to that described by Kommoss et al[13] in the final validation of the ProMisE study where 452 patients with endometrial carcinoma and molecular profile were identified. Of these, 55.7% belonged to the NSMP group, 28.1% to MMRd followed by 12.2% belonging to the p53abn group, with ultramutated POLE being the least prevalent group with 9.3% of patients. In our study we obtained information from 2139 patients with a molecular profile; of these, the percentage of patients identified with ultramutated POLE was slightly lower (4.4% vs 9.3%) probably because their analysis was omitted in 43.2% of the sample due to low risk or intermediate risk endometrial cancer with low-grade histologies. As in the study by Kommoss et al, p53abn and MMRd remained the two molecular groups with the greatest lymph node involvement (34.5% p53abn and 9.4% MMRd vs 12.50% and 12.40%, respectively, in our study). This association was also observed by Jamieson et al[22] who reported retrospective data of 172 patients undergoing sentinel node mapping plus lymphadenectomy. The authors showed that molecular classification was correlated with the probability of nodal involvement (p53abn 44.8%; MMRd 14.9%; POLE mutated 14.2%; NSMP 10.8%). According to our findings, this greater likelihood of these two groups (p53abn and MMRd) of having positive SLNs could be influenced by the higher rate of deep

myometrial invasion in the MMRd group or the greater prevalence of LVSI-positive high-grade non-endometrioid tumors in the p53abn group.

Finally, we have defined the rate of sentinel lymph node involvement for each of the risk groups of the new ESGO prognostic risk classification. This rate of nodal involvement is similar to that described by Persson et al for the high-risk group in the SHREC trial (22.5% vs 21.0%),[4] but there were differences for the intermediate group with respect to that described by Bjørnholt et al in the SENTIREC trial (6.6% vs 22.5%).[23] These differences might be due to the definition of intermediate risk in the SENTIREC study, which did not consider molecular classification or lymphovascular status. These variables, as demonstrated in the latest 2023 FIGO classification,[24] are fundamental to define the stage of the patients adequately. In fact, in a recent analysis performed by Schwameis et al, 27.6% of the stages changed with respect to the 2009 FIGO classification when these variables were taken into account. Particularly in early-stage disease, the new substages (including molecular subtypes) added further prognostic granularity and identified treatment relevant subgroups.[25]

Strengths and Weaknesses

Overall, the strengths of this study include a collaborative effort of 66 institutions from 16 countries where comprehensive data were collected on 2139 patients. Another strength of our study was that all patients were staged following the SLN algorithm. It is also important to emphasize that our study is, to the best of our knowledge, the first study with a large cohort of patients showing that patients with stage I–II (FIGO 2009) endometrial cancer differ in sentinel node involvement with respect to molecular profile as well as prognostic risk group. However, we recognize that such groups, by definition, might already be at a lower risk of lymph node involvement.

Our study has several weaknesses due to the retrospective nature, including the fact that there was no formal auditing of the data. To account for these limitations, we provided the participating sites with a strict list of inclusion and exclusion criteria, and all investigators declared that the reported information adhered to the data in the reviewed charts. In addition, there is a 43.2% of incomplete molecular profile (without ultramutated POLE analysis) due to the presence of low-risk or intermediate-risk endometrial cancer with low-grade histologies; therefore, within the NSMP group there could potentially be some patients belonging to the ultramutated POLE group. While our study benefited from being able to collect data from multiple centers worldwide, it is essential to acknowledge the variability inherent in the equipment used for DNA sequencing methodologies and antibodies used for immunohistochemical determinations across these centers. Nonetheless, it is worth noting that each center has undergone rigorous quality assurance measures, contributing to the reliability of their respective results. However, it should be remarked that we did not perform a centralized data review. There are also 24.9% of patients with lymph nodes affected by isolated tumor cells with uncertain impact on oncologic outcomes. This, together with the small number of events, represents a further limitation.

Implications for Practice and Future Research

Molecular classification represents a paradigm shift in the knowledge of endometrial cancer. Currently, evidence is lacking on how molecular profiling impacts surgical staging. Correct staging of the disease is crucial to properly manage these patients and avoid undertreatment or overtreatment. The present study shows that there are two molecular groups (p53abn and MMRd) with a greater tendency to have lymph node involvement. However, molecular profiling did not improve the prediction of nodal status when compared with classic risk factors (FIGO stage and final histology) since the rate of nodal involvement remained very similar between groups with no significant differences in the area under the curve between the two models. For that reason, lymph node staging should not yet be adopted based on molecular profiling as prospective studies are needed to validate whether these differences affect survival.[26]

This trend was also observed in the prospective PROME trial,[27] in which 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-mut; OR=0.788, 95% CI 0.32 to 1.98, p=0.602 for p53abn; OR=1.14, 95% CI 0.53 to 2.42, p=0.733 for MMRd/microsatellite instability-high). Bogani et al observed at multivariable analysis that 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) were correlated with the increased risk of positive nodes.

Furthermore, we have defined the rate of sentinel lymph node involvement for each ESGO prognostic risk group. We believe that these data will be helpful for tailoring the surgery of these complex patients due to frequent obesity and adhesions. In this sense we would like to emphasize the importance of implementing the preoperative definition of the molecular profile as it has been shown to have a good correlation with the definitive biopsy.[28] This could be useful to define pre-operatively the prognostic risk groups and therefore facilitate decision-making during surgery.[29]

For all these reasons, the present study should be considered as a hypothesis-generating study to stimulate an international collaboration to prospectively investigate the potential role of molecular classification in the surgical staging of patients with endometrial cancer,[30] validating the results obtained by our group. In the meantime, we believe that from now on, in all prospective and retrospective studies on sentinel lymph node biopsy and endometrial cancer, the definition of the molecular profile should be considered as a variable to be weighted for the risk of lymph node involvement.

CONCLUSIONS

In this retrospective study, significant differences were found for nodal involvement in patients with stage I–II endometrial cancer (FIGO 2009) according to molecular profile. Patients belonging to the p53abn and MMRd groups were associated with a higher rate of sentinel lymph node involvement.

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