Molecular and pathologic data to guide selection of patients with endometrioid endometrial cancer for ovarian preservation

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ABSTRACT

Objectives To investigate the association of molecular and pathologic factors with concurrent or recurrent ovarian disease to guide ovarian preservation in endometrioid endometrial cancer.

Methods Patients with endometrial cancer ≤50 years of age at diagnosis were grouped by elective oophorectomy versus ovarian preservation at staging (January 2010 to June 2021). Tumors were stratified by molecular sub-type and *CTNNB1* mutational status with next generation sequencing and immunohistochemistry. Germline data identified patients with Lynch syndrome. Associations between molecular/pathologic features and concurrent ovarian disease in patients electing oophorectomy were compared with the Wilcoxon rank-sum and Fisher's exact tests. Associations with isolated ovarian recurrences in patients who chose ovarian preservation were examined using survival analyses.

Results Among 317 patients with endometrial cancer who underwent bilateral oophorectomy, 27 (9%) had malignant ovarian tumors, of whom 11 (41%) had no gross ovarian involvement on intra-operative survey. For patients with sequencing, concurrent malignant ovarian tumors were diagnosed in 0/14 (0%) *POLE*, 2/48 (4%) copy number-low/no specific molecular profile, 10/22 (45%) microsatellite instability-high, and 3/6 (50%) copy number-high/*TP53*abnormal patients (p<0.001). Concurrent malignant ovarian tumors were present in 1/30 (3%) hotspot *CTNNB1*-mutated versus 10/60 (17%) wildtype/*CTNNB1* non-hotspot mutated endometrial cancer patients (p=0.11) and 7/28 (25%) Lynch versus 7/74 (9%) non-Lynch syndrome patients (p=0.06). Concurrent malignant ovarian tumors were present in patients with higher grade endometrial cancer (5% grade 1 vs 20% grade 2 and 24% grade 3; p<0.001), present versus absent lymphovascular space invasion (20% vs 6%; p=0.004), positive versus negative pelvic washings (28% vs 7%; p=0.016), and ≥50% versus <50% myoinvasion (24% vs 7%; p=0.004). Of 103 patients who chose ovarian preservation, four had isolated ovarian recurrences (two had high-risk pathologic features and two had high-risk molecular features).

Conclusions The integration of molecular and pathologic data may improve risk stratification of pre-menopausal patients with endometrial cancer and enhance candidate selection for ovarian preservation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In accordance with Society guidelines, ovarian preservation can be considered in select pre-menopausal women with early-stage, low-grade endometrioid endometrial cancer. These guidelines are based on clinical and pathologic features.

WHAT THIS STUDY ADDS

⇒ We assessed molecular tumor data in conjunction with pathologic data in patients with endometrioid endometrial cancer to determine the risk for the development of concurrent or recurrent ovarian disease. We found that patients with microsatellite instability-high/mismatch repair-deficient or copy number-high/TP53abnormal endometrial cancer were at increased risk of concurrent ovarian disease. The presence of lymphovascular space invasion and positive cytology were also associated with an increased risk.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study findings show that integrating molecular tumor profiling with pathologic characteristics of disease may help to better risk stratify pre-menopausal patients with endometrial cancer for ovarian preservation.

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in the USA, and approximately 12–21% of newly diagnosed cases occur in pre-menopausal women.[1] Population trends suggest the burden of this pre-menopausal disease will continue to increase in parallel with the obesity epidemic. Surgery for endometrial cancer traditionally includes bilateral oophorectomy, which induces surgical menopause in younger patients. A growing body of evidence suggests that deferring oophorectomy in well selected women with early-stage, low-grade endometrial cancer does not increase cancer-specific mortality.[2–7] In fact, early induction of surgical menopause is associated with an increased risk of heart disease, osteoporosis, and all-cause mortality.[1 8–11]

In 2018 the National Comprehensive Cancer Network (NCCN) guidelines introduced ovarian conservation as an option in select pre-menopausal women with early-stage endometrial cancer,

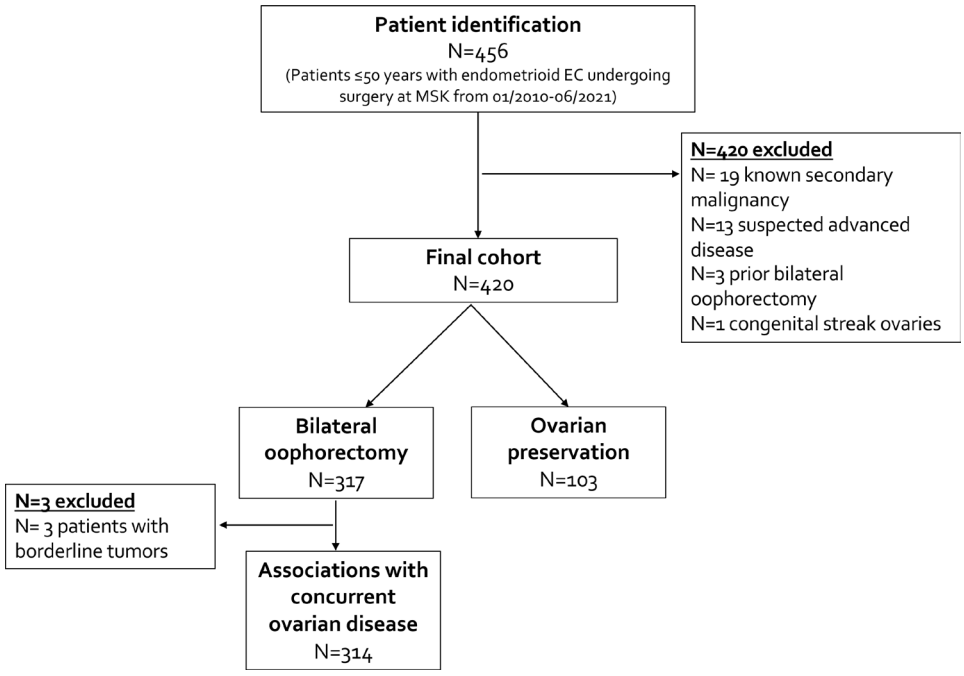

Figure 1 Study design.

normal-appearing ovaries, and no family history of breast/ovarian cancer or Lynch syndrome.[12] European groups have published similar recommendations, noting that ovarian preservation can be considered in patients <45 years of age with low-grade endometrioid endometrial cancer, <50% myometrial invasion, and no obvious ovarian or other extra-uterine disease.[13] Despite these recommendations, a sub-set of patients remain at risk of ovarian metastases and ovarian recurrence.[2 3 14]

The literature suggests that features such as grade 2/3 disease, lymphovascular space invasion (LVSI), and deep myometrial invasion are associated with co-existing ovarian neoplasms, although the evidence is mixed.[15–18] Few studies have specifically examined the relevant patient population—namely, pre-menopausal patients with endometrioid endometrial cancer.[16 18] In this study we sought to identify pathologic factors associated with concurrent or recurrent ovarian malignancy (either metastatic or synchronous) in patients with endometrial cancer aged ≤50 years at diagnosis. Recognizing the increasing relevance of molecular-based risk stratification in endometrial cancer, we investigated the association of ovarian involvement or recurrence across endometrial cancer molecular sub-types, and given data supporting its association with endometrial cancer recurrence/metastasis, *CTNNB1* (B-catenin) hotspot mutations, in young patients with endometrial cancer with tumor-normal panel-based sequencing.[19]

METHODS

After Memorial Sloan Kettering Cancer Center Institutional Review Board approval and informed consent, patients aged ≤50 years with endometrioid endometrial cancer diagnosed between January 2010 and June 2021 who underwent surgery at our institution were identified. Patients with a known diagnosis of a secondary malignancy such as colon, cervical, or ovarian cancer, suspected advanced disease based on pre-operative clinical or radiologic findings, prior bilateral salpingo-oophorectomy, or a history of streak ovaries were excluded.

Medical records were reviewed for demographic, histologic, radiology, and outcomes data. Body mass index (BMI) was classified as normal (18.5–<25.0 kg/m^2), overweight (25.0–<30.0 kg/m^2), or obese (≥30.0 kg/m^2) following the World Health Organization classification.[20] All endometrioid endometrial cancers were reviewed by a gynecologic pathologist and assigned an International Federation of Gynecology and Obstetrics (FIGO) tumor grade.[21] As chosen by clinician discretion, a sub-set of patients underwent clinical panel-based sequencing of their endometrial cancer with matched normal blood using Memorial Sloan Kettering Cancer Center–Integrated Mutation Profiling of Actionable Cancer Targets, targeting 410–468 cancer-related genes.[22 23] For these patients, germline data were not reported in patients who declined germline testing. The genomic data derived from the sequencing assay were used for molecular sub-type classification using an integrated molecular-immunohistochemistry approach, as previously described,[24 25] to identify microsatellite instability-high/mismatch repair-deficient (MMRd), *POLE*-mutated (*POLE*mut), copy number-high/*TP53*abnormal (TP53abn), and copy number-low/no special molecular profile (NSMP) groups.[26] Additionally, *CTNNB1* hotspot mutations were identified in endometrial cancer according to Cheng et al.[22] Patients who consented to and had germline sequencing were assessed for pathogenic germline variants according to the American College of Medical Genetics; variants of unknown significance were not reported.[27]

Patients were stratified into two groups for analyses: (1) those who underwent bilateral oophorectomy, for whom associations with concurrent ovarian disease were generated; and (2) those who underwent ovarian preservation, for whom associations with recurrent ovarian disease were generated (Figure 1). A shared decision-making framework was used for surgical planning for oophorectomy following institutional and national guidelines, as previously described.[28]

For the oophorectomy group, associations of pathologic and molecular features with concurrent ovarian malignancy were compared using Wilcoxon rank-sum and Fisher's exact tests where appropriate. Factors associated with a diagnosis of concurrent ovarian disease were examined using logistic regression univariately. A multivariate logistic model was built based on clinically relevant variables selected from those found to be significant in the univariate setting.

For the ovarian preservation group, time to ovarian recurrence or development of a second primary ovarian tumor were analyzed as a time-to-event outcome, referred to as progression-free survival and calculated from the date of surgery to the date of recurrence/last follow-up.

For analysis, p values were obtained using the log-rank test with permutation for categorical variables due to the small sample size and the Wald test based on the Cox proportional hazards model for continuous variables.[29] All p values are two-sided and statistical analyses were performed using R 4.1.2 (https://www.R-project.org/).

RESULTS

Clinicopathologic Characteristics: Bilateral Oophorectomy Group

Of 456 patients with endometrial cancer, those with a known diagnosis of a secondary malignancy such as colon, cervical, or ovarian cancer (n=19), suspected advanced disease (n=13), prior bilateral salpingo-oophorectomy (n=3), or a history of streak ovaries (n=1) were excluded, leaving 420 patients for analysis. In total, 317 patients (75%) underwent bilateral oophorectomy at the time of endometrial cancer surgery. In the bilateral oophorectomy group, median patient age at diagnosis was 47 years (range 27–50); 68% (n=188/276) self-identified as White, 22% (n=65/301) were overweight (BMI ≥25 kg/m^2), and 51% (n=154/301) were obese (BMI ≥30 kg/m^2). FIGO grade distribution was as follows: grade 1, n=235 (74%); grade 2, n=44 (14%); and grade 3, n=38 (12%) (Table 1).

Among patients who underwent bilateral oophorectomy, median endometrial tumor size was 2.5 cm (range 0.0–10.2), 90% (n=277/306) had <50% myoinvasion, 84% (n=266/316) had no LVSI, and 89% (n=270/302) had negative washings (Table 1). Overall, 92 (29%) of the 317 patients underwent clinical tumor-normal sequencing and 104 patients (33%) consented to germline testing for Lynch syndrome. Among the 92 sequenced tumors, 14 (15%) were *POLE*mut, 48 (52%) copy number-low/NSMP, 24 (26%) microsatellite instability-high/MMRd, and 6 (7%) copy number-high/TP53abn. Thirty-one (34%) harbored a pathogenic *CTNNB1* alteration, specifically in S37 (n=19), S33 (n=5), G34 (n=4), D32 (n=2), and T41 (n=1) hotspots. Twenty-nine (28%) of the 104 patients who consented to germline sequencing were diagnosed with Lynch syndrome.

Associations with Ovarian Tumors: Bilateral Oophorectomy Group

Among the 317 patients who underwent bilateral oophorectomy there were 30 (9%) concurrent ovarian tumors (27 malignant and 3 borderline). On intra-operative survey, 11 (41%) of the 27 patients with malignant tumors on final pathology had no gross ovarian involvement. Pathologic factors associated with concurrent ovarian

Table 1 Clinical characteristics of patients undergoing bilateral oophorectomy

Characteristic	Overall (n=317)
Age, years (range)	47 (27–50)
Self-identified race/ethnicity	
White non-Hispanic	188 (68%)
Black	19 (7%)
Asian	44 (16%)
White or non-White Hispanic	25 (9%)
Missing	41
Body mass index, kg/m^2	
Normal (<25 kg/m^2)	82 (27%)
Overweight (25–30 kg/m^2)	65 (22%)
Obese (≥30 kg/m^2)	154 (51%)
Missing	16
FIGO tumor grade	
Grade 1	235 (74%)
Grade 2	44 (14%)
Grade 3	38 (12%)
FIGO stage (2009)	
I	272 (86%)
II	15 (5%)
III/IV	30 (10%)
Endometrial tumor size, cm (range)	2.5 (0.0–10.2)
Depth of invasion	
None	203 (66%)
<50%	74 (24%)
≥50%	29 (10%)
Missing	11
Lymphovascular space invasion	
Absent	266 (84%)
Present	50 (16%)
Missing	1
Washing	
Negative	270 (89%)
Positive	18 (6%)
Atypical/suspicious	14 (5%)
Missing	15
Molecular classification	
CN-H/TP53abn	6 (7%)
CN-L/NSMP	48 (52%)
MSI-H/MMRd	24 (26%)
POLEmut	14 (15%)
Not available	225
CTNNB1	
Wildtype	61 (66%)
Pathogenic hotspot mutation	31 (34%)
Missing	228

Continued

Table 1 Continued

Characteristic	Overall (n=317)
Lynch syndrome	
No	75 (72%)
Yes	29 (28%)
Not assessed	213

Values presented as median (range) or n (%).
CN-H, copy number-high; CN-L, copy number-low; FIGO, International Federation of Gynecology and Obstetrics; MMRd, mismatch repair-deficient; MSI-H, microsatellite instability-high; NSMP, no specific molecular profile; POLE, DNA polymerase epsilon mutated; TP53abn, TP53abnormal.

malignant tumors were investigated in 314 patients; the three patients with borderline tumors were excluded (Table 2). Grade of endometrial cancer (5% for grade 1 vs 19% for grade 2 vs 22% for grade 3; p<0.001), present versus absent LVSI (20% vs 6%; p=0.004), positive versus negative peritoneal cytology (28% vs 7%; p=0.016), and ≥50% versus <50% myoinvasion (24% vs 7%; p=0.004) were all associated with ovarian malignancy, either metastatic or synchronous, at the time of oophorectomy.

In the sub-group of patients with molecularly classified endometrial cancer who underwent oophorectomy, excluding patients with borderline disease (n=90), concurrent ovarian malignancy was diagnosed in 0/14 (0%) *POLE*mut, 2/48 (4%) copy number-low/NSMP, 10/22 (45%) microsatellite instability-high/MMRd, and 3/6 (50%) copy number-high/TP53abn endometrial cancers (p<0.001) (Figure 2). Concurrent ovarian disease was present in 1/30 (3%) hotspot *CTNNB1*-mutated versus 10/60 (16%) wildtype/*CTNNB1* non-hotspot-mutated endometrial cancers (p=0.09). Among patients with germline data, 7/28 (25%) with Lynch syndrome versus 7/74 (9%) without Lynch syndrome had concurrent ovarian tumors (p=0.06).

Clinicopathologic Characteristics: Ovarian Conservation Group

Among the 103 patients who chose ovarian conservation, median patient age at diagnosis was 40 years (range 25–50); 46% (n=32/70) self-identified as White non-Hispanic, 19% (n=19/100) were overweight, and 44% (n=44/100) were obese (see online supplemental table 1).

After a median follow-up of 17.2 months (range 0.3–116.9), four of the 103 patients developed an ovarian malignancy or recurrence in the ovary (online supplemental table 2). The first patient was a para 2 woman in her 40s with Lynch syndrome (MLH1 germline mutation) who declined bilateral oophorectomy due to concern for surgical menopause despite clinical recommendations against ovarian preservation. She underwent a hysterectomy, bilateral salpingectomy, and sub-total colectomy and was diagnosed with a T2N0 adenocarcinoma of the cecum as well as a stage IA, grade 1 endometrioid endometrial cancer arising in a polyp. Four years later she underwent bilateral oophorectomy for a 4 cm left adnexal lesion and was diagnosed with a stage II clear cell carcinoma arising in endometriosis. The second patient was a para 0 woman in her 20s who underwent a hysterectomy and bilateral salpingectomy for stage IA, grade 2 endometrioid endometrial cancer with no LVSI

Table 2 Pathologic and molecular factors associated with concurrent malignant tumor of the ovary in patients with endometrial cancer undergoing bilateral oophorectomy

Characteristic	Patients (n=314)	Event (n=27)	OR	95% CI	P value
Age at diagnosis (years)					0.8
≤40	61	6	—	—	
>40	253	21	0.83	0.34 to 2.35	
Self-reported race/ethnicity	**273**	**24**			0.57
White non-Hispanic	186	14	—	—	
Black	18	3	2.46	0.53 to 8.62	
Asian	44	4	1.23	0.33 to 3.64	
White or non-White Hispanic	25	3	1.68	0.37 to 5.65	
Body mass index, kg/m^2	**298**	**26**			0.4
Normal (<25 kg/m^2)	82	9	—	—	
Overweight/obese (≥25 kg/m^2)	216	17	0.69	0.30 to 1.69	
FIGO tumor grade	**314**	**27**			**<0.001**
Grade 1	234	11	—	—	
Grade 2	43	8	4.63	1.69 to 12.3	
Grade 3	37	8	5.59	2.02 to 15.0	
Endometrial tumor size, cm	**297**	**24**	1.25	1.04 to 1.51	**0.022**
Depth of myoinvasion	**303**	**26**			**0.004**
None	202	11	—	—	
<50%	72	8	2.17	0.81 to 5.60	
≥50%	29	7	5.52	1.87 to 15.6	
Lymphovascular space invasion	**313**	**27**			**0.004**
No	263	17	—	—	
Yes	50	10	3.62	1.50 to 8.36	
Washing	**299**	**25**			**0.016**
Negative	267	20	—	—	
Positive/atypical	32	5	2.29	0.72 to 6.19	
Molecular classification	**90**	**15**			**<0.001**
CN-H/TP53abn	6	3	—	—	
CN-L/NSMP	48	2	0.04	0.00 to 0.35	
MSI-H/MMRd	22	10	0.83	0.13 to 5.40	
POLEmut	14	0			
CTNNB1	**90**	**15**			0.09
Wildtype	60	10	—	—	
Pathogenic hotspot mutation	30	1	0.19	0.01 to 1.07	
Lynch syndrome	**104**	**14**			0.06
No	74	7	—	—	
Yes	28	7	3.19	0.99 to 10.4	

CN-H, copy number-high; CN-L, copy number-low; FIGO, International Federation of Gynecology and Obstetrics; MMRd, mismatch repair-deficient; MSI-H, microsatellite instability-high; NSMP, no specific molecular profile; POLE, DNA polymerase epsilon mutated; TP53abn, TP53abnormal.

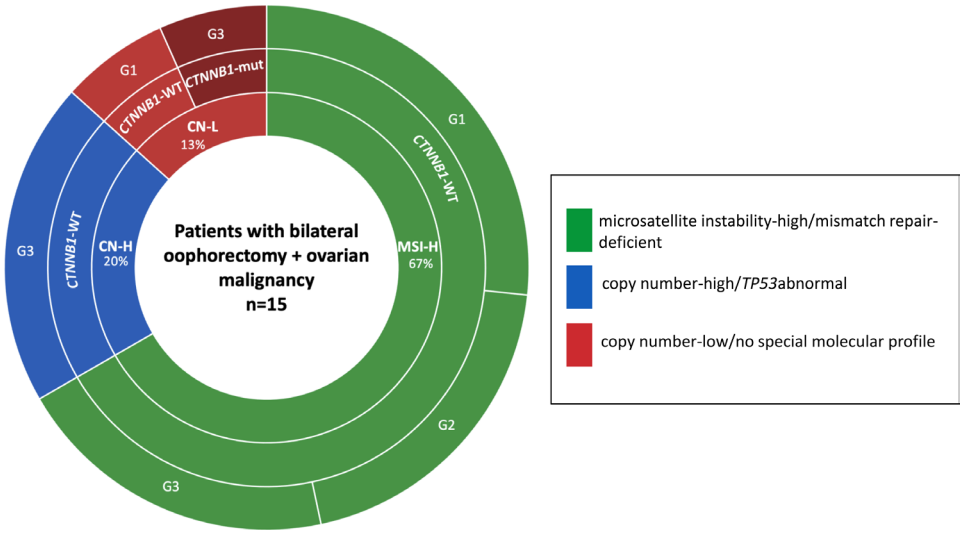

Figure 2 Distribution of patients with concurrent ovarian malignancy and tumor sequencing.

and negative washings. The tumor harbored a pathogenic *CTNNB1* D32N alteration and was considered copy number-low/NSMP; the patient had negative germline testing. One year later she developed increasing pelvic pain and was diagnosed with recurrent grade 3 endometrioid endometrial cancer present in both ovaries and a left obturator lymph node. The third patient was a para 0 woman in her 30s who underwent a hysterectomy and bilateral salpingectomy for stage IA, grade 1 endometrioid endometrial cancer with no LVSI and negative washings. The tumor harbored a pathogenic *CTNNB1* G34R alteration and was copy number-low/NSMP; the patient had negative germline testing. Two years later she was diagnosed with stage IA, grade 1 endometrioid ovarian cancer arising in an endometrioid borderline tumor. The fourth patient was a para 0 woman in her 40s who underwent a hysterectomy and bilateral salpingectomy for stage IA, grade 1, MMR-proficient endometrioid endometrial cancer with no LVSI and negative washings. The patient had negative germline testing but no somatic mutation testing was performed. Two years later she developed abdominal discomfort and had an 18 cm left ovarian mass removed. She was diagnosed with a grade 1 endometrioid carcinoma morphologically similar to her endometrial cancer.

DISCUSSION

Summary of Main Results

Our findings suggest the addition of molecular data to histopathology helps identify patients who desire ovarian preservation but are at increased risk for concurrent, recurrent, or new ovarian tumors. In our study cohort the rates of concurrent ovarian tumors among patients with microsatellite instability-high/MMRd or copy number-high/TP53abn endometrial cancer approached 50% compared with 0–4% in patients with *POLE*mut or copy number-low/NSMP endometrial cancer, suggesting ovarian preservation is safest in patients with low-risk molecular sub-types. Of note, two of the four patients who elected ovarian preservation and subsequently developed ovarian tumors had copy number-low/NSMP endometrial cancer; however, with such a small number of recurrences in this group, the significance of this is unclear.

We sought to complement our molecular findings with pathologic features of endometrial tumors and simultaneous ovarian disease in a pre-menopausal patient population. We found that higher grade, the presence of LVSI, tumor size, positive washings, and ≥50% myoinvasion were associated with concurrent ovarian disease in

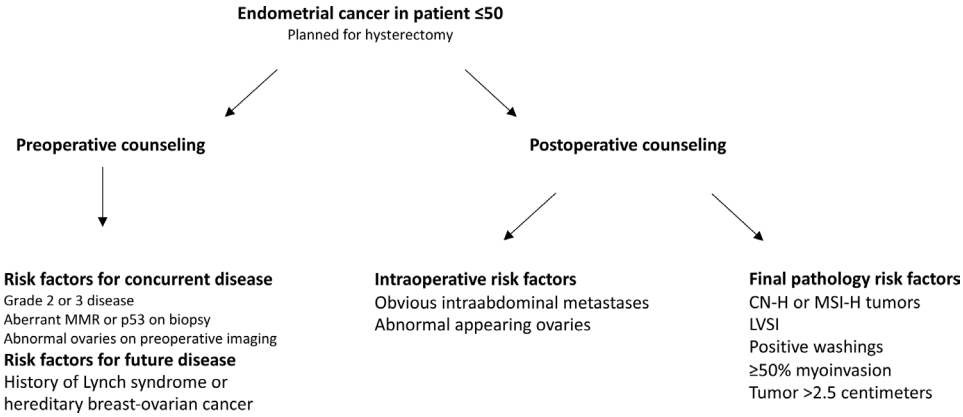

Figure 3 Proposed clinical framework for patient counseling on ovarian conservation. CN-H, copy number-high; LVSI, lymphovascular space invasion; MMR, mismatch repair; MSI-H, microsatellite instability-high.

young patients with endometrial cancer, consistent with current guidelines recommending against ovarian preservation for these patients. Future investigations examining the interaction between pathologic and molecular features are warranted, such as whether patients with low-risk pathologic features but high-risk molecular sub-type are at an even greater risk for ovarian disease.

Current NCCN guidelines state that ovarian preservation may be considered in pre-menopausal patients with early-stage endometrioid endometrial cancer, normal-appearing ovaries, and no family history of breast/ovarian cancer or Lynch syndrome.[12] Current European Society for Medical Oncology (ESMO) guidelines state that "preservation of ovaries can be considered in premenopausal patients with FIGO stage IA grade 1 endometrioid endometrial cancer" and do not address the question of myoinvasion.[30] In the current study we found that 19% of patients with FIGO grade 2 disease had concurrent ovarian tumors compared with 5% with FIGO grade 1 disease. Our data also showed that 24% of patients with ≥50% myoinvasive endometrial cancer had concurrent ovarian tumors compared with 11% with <50% myoinvasion.[16 31] NCCN and ESMO guidelines do not provide recommendations regarding ovarian preservation in patients with high-risk features such as positive washings or LVSI, in part because of a lack of available data. Investigators have sought to define the patient-specific risk of ovarian preservation; however, many studies are hindered by the inclusion of post-menopausal patients who would not derive the same clinical benefit from ovarian preservation or have used national databases lacking granular histopathologic data.[1 15 17 32 33]

Our study adds to the literature by providing a large and well-annotated cohort of patients with pathologic and clinical features integrated with molecular sub-typing. We have proposed a clinical framework based on our data that can be used to guide counseling regarding ovarian preservation in young patients with endometrioid endometrial cancer in the pre- and post-operative settings (Figure 3).

Results in the Context of Published Literature

Previous literature has sought to propose a two-step ovarian preservation model that uses both pre- and intra-operative factors.[1] This two-step model states that ovarian preservation can be offered in women ≤45 years of age with clinical stage I, FIGO grade 1 endometrioid endometrial cancer, low-risk personal and family history of hereditary malignancy, normal tumor markers, and microsatellite instability-low disease. The authors suggested that ovaries should be preserved in women with uterine-confined, low-grade, non-myoinvasive endometrial cancer with small tumors, normal-appearing ovaries, and no endometriosis or secondary cancers. Our data support more dynamic counseling for patients who are initially eligible to pursue ovarian preservation but may have risk factors identified on final pathology or molecular sub-type that warrant revisiting oophorectomy. Our approach requires clear counseling prior to staging surgery that there may be risk factors found on final pathology that could result in a second surgery for completion oophorectomy.

Strengths and Weaknesses

Our study is strengthened by only including women ≤50 years of age who underwent endometrial cancer surgery at our institution, many of whom also underwent tumor-normal sequencing, thus providing histopathologic and molecular tumor data. We included only patients who underwent primary endometrial cancer surgery at our institution to reduce selection bias associated with referral from outside institutions for endometrial cancer recurrence or those with synchronous or metastatic tumors. As a result of these strict inclusion criteria, however, the study size was limited and did not allow for a more comprehensive multivariate analysis to more comprehensively elucidate the interaction between demonstrated molecular and clinicopathologic risk factors such as grade, LVSI, myoinvasion, positive washings, and molecular sub-type. Furthermore, the limited numbers of recurrences precluded a progression-free survival or overall survival analysis.

Our study is limited by its retrospective single-institution design. Molecular data were only available for 29% of patients included in this study as molecular testing is performed at the clinician's discretion. At our institution, reporting these data requires patient consent for molecular testing of endometrial cancer as well as consent for retrospective research related to this testing. Additionally, universal molecular testing of endometrial cancer did not become available at our institution until 2017 when FDA approval was granted for our in-house molecular testing platform, further limiting the availability of data. Furthermore, panel-based sequencing of endometrial cancer is not universally available, making the use of immunohistochemistry-based surrogates an important area of investigation for broader applicability. These surrogates, including p53 and MMR immunohistochemistry, have demonstrated effectiveness in accurately classifying endometrial cancer as NSMP or MMRd.[34] Our ability to investigate the development of a recurrence or second primary in women choosing ovarian conservation was limited as these women were in the minority due to comprehensive risk counseling and institutional guidelines.[28] This same premise underpins the importance of a careful intra-operative survey, which identified approximately 50% of patients with concurrent ovarian tumors. Of note, our guideline-based selection resulted in a small percentage of patients (3–4%) who ultimately developed either an ovarian recurrence or second ovarian primary. We must acknowledge our inability to characterize the clonal relation of endometrial and ovarian tumors to distinguish between synchronous and metastatic disease, as this would have required massive parallel sequencing of both endometrial and ovarian tumors to allow for clonal decomposition analyses.[35 36] We contend that the clinically relevant outcome is removal of all malignant disease, and the identification of co-existing adnexal malignancies remains an appropriate endpoint, consistent with prior publications.[33]

Implications for Practice and Future Research

We have proposed a clinically relevant framework for patient counseling within a shared decision-making process that integrates post-operative pathology and molecular classification to better refine patient selection for ovarian preservation. These results warrant further study and validation, with practice-changing implications.

CONCLUSION

Our study shows that patients with microsatellite instability-high/MMRd or copy number-high/TP53abn endometrial cancer are at an increased risk for concurrent ovarian disease. We also found that

patient selection for ovarian conservation may be refined with the inclusion of LVSI and positive cytology, with additional discussion on the risks and benefits associated with removing retained ovaries in patients with extensive LVSI or positive cytology.

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Correction notice This article has been corrected since it was first published. A typo in the Results section of the Abstract has been corrected.

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Contributors Conceptualization: BMG, JM. Data curation: ERD. Formal analysis: QCZ, AI. Methodology: BMG, JM. Roles/Writing - original draft: BMG, JM. Writing - review and editing: all authors. Guarantor: JM.

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Data availability statement Data are available upon reasonable request. In accordance with the journal's guidelines, we will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

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