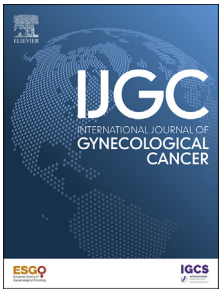
ORIGINAL RESEARCH

Co-existent endometrial and ovarian carcinoma: molecular and pathological features define low risk entity



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ABSTRACT

Objective: Most co-existent endometrial and ovarian carcinomas are clonally related and exhibit an indolent disease course. Pathologic assignment and clinical management of this entity vary greatly. The International Federation of Gynecology and Obstetrics (FIGO) 2023 endometrial carcinoma staging/risk stratification system introduced a new substage for co-existent endometrial and ovarian carcinomas that meet strict pathologic criteria (stage IA3, distinct from IIIA1). Our aim was to validate if FIGO IA3 identifies a subset of co-existent endometrial and ovarian carcinomas at very low risk of recurrence and determine whether further refinement, through molecular features and expanded ovarian pathologic criteria, could improve prognostic discernment and direct more patients for consideration of de-escalation.

Methods: Clinicopathologic, molecular, and outcome data were collected on patients with co-existent endometrial and ovarian carcinoma, extracted from pathology archives and molecularly classified endometrial carcinoma cohorts.

Results: Among the 154 co-existent endometrial and ovarian carcinoma patients, higher recurrence rates were observed with the p53abn (2/6, 33%), mismatch repair deficiency (MMRd) (7/34, 21%) or no specific molecular profile (NSMP) estrogen receptor (ER) negative-low (2/15, 13%) molecular sub-types, compared with patients with *POLE*mut or NSMP ER strong positive tumors. Thirty-two patients met FIGO IA3 criteria, with one recurrence and death event (MMRd). Eliminating patients with adverse molecular features (p53abn or MMRd endometrium or ovary, or NSMP ER negative-low endometrium) and expanding criteria to include any *POLE*mut or cases with bilateral ovarian involvement, intra- or pre-operative ovarian rupture, or ovarian surface involvement significantly improved risk stratification ($p = .008$) and added 48 co-existent endometrial and ovarian carcinoma patients (>2-fold increase) with no recurrence events (mean follow-up: 6 years). There was 91% concordance of molecular sub-type assignment between endometrial and ovarian tumors.

Conclusions: FIGO IA3 criteria identify a subset of co-existent endometrial and ovarian carcinomas with excellent outcomes. However, incorporating molecular features into the definition enables greater prognostic discernment and supports the inclusion of patients with a broader range of pathologic features with indolent disease (increased from 20% to 49% of the cohort, 0 recurrences) who may be candidates for treatment de-escalation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Co-existent endometrial and ovarian carcinomas are clonally related, representing metastases from the uterus to the ovary (eg, stage III), yet the clinical behavior is indolent and more aligned with early-stage (I) disease. The International Federation of Gynecology and Obstetrics (FIGO) 2023 endometrial cancer staging system provides a unique substage for co-existent endometrial and ovarian carcinomas (IA3); however, inconsistency in pathologic reporting and 'best' treatment recommendations persist.

WHAT THIS STUDY ADDS

We demonstrate that although FIGO IA3 does encompass patients with overall favorable clinical outcomes, greater prognostic discernment can be achieved through molecular classification (POLE, mismatch repair [MMR]/microsatellite instability, p53/TP53, and estrogen receptor [ER] status). Within a molecular framework, pathologic features currently excluded from the FIGO IA3 definition can be encompassed, resulting in the identification of many more patients at low risk of recurrence.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

*Binary stratification of co-existent endometrial and ovarian carcinomas, considering patients with molecular features associated with a low risk of recurrence (POLE*mut *or* NSMP *ER strong positive) as "indolent" and candidates for*

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de-escalation, while directing patients with molecular features associated with an intermediate-to-high risk of recurrence (MMRd, p53abn or NSMP *ER negative-low) to adjuvant treatment, requires validation in a prospective clinical trial.*

ORIGINAL RESEARCH

Keywords:
Co-Existent Endometrial and Ovarian Carcinoma; Endometrial Carcinoma; Ovarian Carcinoma; Molecular Classification; Treatment De-Escalation

INTRODUCTION

Molecular studies have shown that for co-existent endometrial and ovarian carcinomas of low-grade endometrioid histology, there is a clonal relationship between the endometrial and ovarian components in almost all cases.[1-5] This suggests that the tumor likely originates in the endometrium and secondarily extends to the ovary, ie, not "synchronous," driving a change in terminology.[6] Metastasis, however, appears to be restricted to the ovary, and outcomes are excellent.[4,7-10] Clinical guidelines on management have been inconsistent, with many patients receiving what may be overly aggressive adjuvant therapies.[7,11]

In 2023, International Federation of Gynecology and Obstetrics (FIGO) created a new substage (IA3)[12] for co-existent endometrial and ovarian carcinomas fulfilling World Health Organization (WHO) pathologic criteria: 1) FIGO grade 1 or 2 (low-grade) tumors at both endometrial and ovarian sites, 2) $<$50% myometrial invasion, 3) no involvement of extra-uterine or extra-ovarian sites, and 4) absence of substantial lymphovascular space invasion (LVI).[13] FIGO 2023 stage IA3 (hereafter referred to as FIGO IA3) added two additional criteria: that the ovarian component be 5) unilateral and 6) without capsule invasion or pre-/intra-operative rupture.[12] This down-staging of FIGO IA3 (as distinct from IIIA1, endometrial cancer metastatic to the ovary) may help direct clinicians to consider treatment as they would for early-stage endometrial or early-stage ovarian cancers.[12]

Notably, both WHO and FIGO IA3 criteria do not account for molecular sub-type. This is despite the integration of molecular classification into the rest of the FIGO 2023 endometrial cancer staging system.[12] The original work in molecular classification identified 4 prognostic sub-types of endometrial carcinoma.[14-19] More recent research shows that molecular classification also discerns outcomes within endometrioid ovarian carcinoma.[20,21] *POLE* mutated (*POLE*mut) endometrial carcinomas and endometrioid ovarian carcinomas have excellent prognoses, with very rare recurrence events, even when high-grade or other aggressive pathologic features are present.[15,17-19,22,23] By contrast, mismatch repair (MMR) deficiency (MMRd) and p53 abnormal (p53abn) endometrial or endometrioid ovarian carcinomas have intermediate and poor outcomes, respectively. For the ~50% of no specific molecular profile (NSMP) endometrial cancers, estrogen receptor (ER) status subdivides patients into NSMP with strong ER expression (~85%), where clinical outcomes are as favorable as *POLE*mut endometrial carcinomas,[24,25] while the 15% of NSMP with less than strong ER expression have a high rate of recurrences and death from disease. The status of *POLE*, MMR, and p53 in combination with ER has not been previously assessed in co-existent endometrial and ovarian carcinomas.

Identification of a clinically relevant, biologically indolent subset of patients with co-existent endometrial and ovarian carcinomas is important, as these patients are candidates for treatment de-escalation, avoiding the side effects from therapies offered to patients with stage III endometrial carcinoma.[6] Studying a large cohort of co-existent endometrial and ovarian carcinomas, our aims were: 1) to validate that FIGO IA3 criteria identify a subset of patients who have low rates of recurrence; 2) to determine the prognostic significance of molecular sub-type in co-existent endometrial and ovarian carcinomas; and 3) to assess the prognostic value of additional clinicopathologic and molecular features in patients with co-existent endometrial and ovarian carcinomas, the results of which could expand the current FIGO IA3 criteria.

METHODS

Case Selection

With institutional ethics approval, patients diagnosed with co-existent endometrial and ovarian carcinomas were identified from pathology archives and retrospective cohorts that had undergone molecular classification (diagnosed 2000-2023). Patients with non-epithelial ovarian tumors or metastatic disease beyond the contiguous uterine corpus, cervix, ovaries/adnexa were excluded.

Molecular Testing

Among the 154 identified co-existent endometrial and ovarian carcinomas, 135 cases had undergone ProMisE molecular classification on the endometrial carcinoma (19 cases were excluded due to unavailable tumor blocks for molecular testing), and 43 on the matched ovarian carcinomas. Additional immunohistochemical (IHC) staining and mutational profiling results (ER, progesterone receptor [PR], L1CAM, *CTNNB1*) of the endometrial carcinomas were evaluated when available. ER was scored using the Allred semi-quantitative method for estimating the proportion and intensity of positive cells. Based on previous studies of ER staining in NSMP endometrial carcinomas,[26] ER was considered strong/positive for Allred scores of 7 to 8 ($>$66% of cells staining with moderate to strong intensity) and negative-low for Allred scores of $\leq$6.

Statistical Analyses

Univariable associations were assessed using Fisher's exact test and the Kruskal-Wallis rank sum test. Kaplan-Meier survival analysis and the log-rank test were used to compare oncologic

outcomes (progression-free survival [PFS], disease-specific survival [DSS], and overall survival [OS]). All analyses were performed using the R Project for Statistical Computing, with significance set at $\alpha = 0.05$.

In accordance with the journal's guidelines, we will provide our data for independent analysis by a team selected 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.

See Supplemental Methods for additional details.

RESULTS

Table shows the clinicopathologic parameters in the cohort of 154 patients with co-existent endometrial and ovarian carcinomas, as well as the differences between patients who met FIGO IA3 criteria ($n = 32$) and those who did not ($n = 122$). The mean age of FIGO IA3 co-existent endometrial and ovarian carcinoma patients was 49. Self-identified ethnicity data from 128 patients demonstrated a higher proportion of patients of East Asian descent with FIGO IA3 co-existent endometrial and ovarian carcinomas, compared to patients with endometrial cancer without ovarian involvement in the same geographic catchment (33% vs 13%, $p = .017$) (Table S).

Concurrent endometriosis was common, reported in 56% of all patients (63% of FIGO IA3). The use of adjuvant therapy differed, with 88% of the FIGO IA3 patients having surgery alone compared to 30% in non-FIGO IA3 patients ($p < .001$) (Table). Molecular sub-typing within FIGO IA3 showed that the majority were NSMP ($n = 23$, 82%) with 7% *POLE*mut ($n = 2$), 11% MMRd ($n = 3$), and no p53abn. Molecular sub-type distribution within non-FIGO IA3 was similar to what is seen in endometrial carcinoma without co-existent ovarian carcinoma, with 8% *POLE*mut ($n = 8$), 29% MMRd ($n = 31$), 58% NSMP ($n = 62$), and 6% p53abn ($n = 6$) (Fig. 1).

There were more *CTNNB1* mutations in the endometrial carcinomas of patients with FIGO IA3 compared to non-FIGO IA3 (77% vs 32%, $p = .005$), but no differences were observed in ER, PR, or L1CAM IHC expression (Table). Endometrial carcinoma components were strongly ER positive (Allred 7-8) in 61% (37/61 tested) and PR positive in 91% (52/57 tested). ER-negative status (Allred 0) was seen in only 3 patients, and reduced staining (Allred 1-6) in 21, including 2 patients assigned as FIGO IA3. L1CAM IHC expression levels were low overall, with only 3% showing overexpression (Table). Thirty-five percent of MMRd patients were identified to have Lynch syndrome.

The mean and median follow-up time for this study were 6 and 4.5 years, respectively (range; 0.05-23). There was only 1 patient in the FIGO IA3 cohort who experienced recurrence and died of disease (3%), compared to 16 recurrences (13%), 9 of whom died from disease (7.5%), in the non-FIGO IA3 group (Table). The one patient with recurrent FIGO IA3 tumor harbored an MMRd ovarian carcinoma with MLH1 loss and an NSMP endometrial carcinoma with low ER expression (Allred 6). Of the 16 non-FIGO IA3 patients who recurred, 7 were MMRd, 2 p53abn, 5 NSMP, and 2 had missing molecular sub-type data. Six recurrent tumors were high-grade and 4 were low-grade; 1 with substantial LVI in the endometrium, and 3 with low ER expression (Allred 2-6). Kaplan-Meier survival analyses showed a trend toward improved DSS/PFS in patients with FIGO IA3 disease compared to those in the non-FIGO IA3 group, but this was not statistically significant (Fig. S). Figure 1 shows molecular sub-type distribution and disease recurrences in FIGO IA3 and non-FIGO IA3 patients. The FIGO IA3 cohort had no patients with p53abn tumors in either the endometrium or ovary in cases where this had been tested, but they could exist in untested cases. FIGO IA3 did include 3 patients with MMRd tumors. Among the 10 patients with *POLE*mut endometrial carcinoma, there were no recurrences or deaths, despite high grade ($n = 1$), deep myometrial invasion ($n = 1$), substantial LVI ($n = 1$), with only 2 patients meeting FIGO IA3 criteria. The highest recurrence rates were observed in patients with p53 abnormalities (2/6 [33%]) and MMRd (7/34 [21%]). Six events occurred in NSMP cases: 2 in NSMP ER-negative-low (1 of which was MMRd in the ovary and NSMP in endometrium), 2 in NSMP with ER unknown, and 2 in ER-positive NSMP (both higher stage; stage II endometrial carcinoma/stage IIB ovarian carcinoma).

Kaplan-Meier comparison of outcomes based on binarized molecular features, *POLE*mut in the endometrium and/or ovary, and NSMP ER strong positive in the endometrium versus MMRd or p53abn in the endometrium and/or ovary or NSMP ER negative-low in the endometrium, demonstrated a statistically significant difference in PFS ($p = .008$; Fig. 2).

Molecular sub-type was concordant in 39 of 43 cases (91%, kappa statistic 0.79), where data were available in both the endometrial and ovarian tumors (Fig. 1). Of the 4 discordant cases, 3 demonstrated a difference in MMR status, with MLH1 loss in either the endometrial (1) or ovarian (2) carcinomas, and 1 had p53wt expression in the endometrial carcinoma (grade 1 endometrioid) but was p53abn in the ovarian tumor (mixed endometrioid and serous).

Expanding FIGO IA3 criteria to include any *POLE*mut endometrial or ovarian carcinomas added an additional 8 patients with no recurrences. Excluding molecular sub-types associated with higher recurrence (MMRd and p53abn, or NSMP ER negative-low endometrial carcinomas) would have identified the single FIGO IA3 case associated with recurrence and death. After exclusion of molecular subtypes associated with higher risk, the following pathological features were not associated with recurrence or death due to disease: i) bilateral ovarian involvement, ii) intra-operative ovarian rupture, iii) pre-operative rupture, and even iv) positive ovarian surface involvement in the absence of positive washings or ascites. The proposed molecular refinement, discerning favorable versus unfavorable molecular subtypes in the endometrium or ovary, and expanding the pathological criteria would result in an additional 48 patients (8 *POLE*mut, 40 expanded pathology criteria) identified with no recurrences or disease-specific death events (Fig. 3). These changes increased the number of patients identified as having excellent clinical outcomes who may be candidates for treatment de-escalation, from 32 (20% of cohort) to 75 (49% of cohort). Recurrence was observed in 1 patient with intra-operative rupture and 1 patient with ovarian surface involvement, but both had MMRd carcinomas and thus would have been excluded from expanded FIGO IA3 criteria based on molecular refinement. Even with the removal of MMRd and p53abn, 2 of 8 (25%) patients with positive peritoneal washings experienced recurrences; therefore, this ovarian pathologic feature should not be considered for inclusion in expanded IA3 criteria. Among the 79 patients with co-existent endometrial and ovarian carcinomas (74 from the original cohort and 5 from the FIGO IA3 cohort) who did not meet our refined

Table Clinicopathologic, Treatment, and Outcome Data (A) and Molecular Features (B) for the Total Cohort of Co-Existent Endometrial and Ovarian Carcinomas and Comparing Those Who Met Criteria for FIGO IA3 and Those Who Did Not (non-FIGO IA3)

A: Clinicopathologic and outcome data	**Total cohort *n* = 154**	**Non-FIGO IA3 criteria *n* = 122**	**FIGO IA3 criteria *n* = 32**	***p*-Value**
Age (y) mean (IQR)	52 (46-56)	52 (46-57)	49 (44-52)	.13
BMI, mean (IQR)	29 (23-34)	29 (23-34)	29 (24-34)	.54
Endometrial grade				**.033**
Grade 1	108 (70.1%)	80 (65.6%)	28 (87.5%)	
Grade 2	34 (22.1%)	30 (24.6%)	4 (12.5%)	
Grade 3	12 (7.8%)	12 (9.8%)	0 (0.0%)	
Ovarian grade				**<.001**
Grade 1	83 (56.1%)	57 (48.7%)	26 (83.9%)	
Grade 2	40 (27.0%)	35 (29.9%)	5 (16.1%)	
Grade 3	25 (16.9%)	25 (21.4%)	0 (0.0%)	
Endometrial histotype				.85
Endometrioid	145 (94.2%)	113 (92.6%)	32 (100.0%)	
Non-endometrioid	9 (5.2%)	9 (7.4%)	0 (0.0%)	
Ovarian histotype				**.029**
Endometrioid	129 (83.8%)	98 (80.3%)	31 (100.0%)	
Non-endometrioid	25 (16.2%)	25 (19.7%)	0 (0.0%)	
LVI				.36
Negative	125 (84.5%)	95 (81.9%)	30 (93.8%)	
Focal	10 (6.8%)	8 (6.9%)	2 (6.3%)	
Positive (not specified)	8 (5.4%)	8 (6.9%)	0 (0.0%)	
Extensive	5 (3.4%)	5 (4.3%)	0 (0.0%)	
Myoinvasion				**.013**
None	77 (50.0%)	57 (46.7%)	20 (62.5%)	
<50%	55 (35.7%)	43 (35.2%)	12 (37.5%)	
>50%	22 (14.3%)	22 (18.0%)	0 (0.0%)	
Ovarian surface involvement (yes)	44 (28.9%)	44 (36.1%)	0 (0.0%)	**<.001**
Bilateral ovarian involvement (yes)	29 (18.8%)	29 (23.8%)	0 (0.0%)	**<.001**
Positive washings (yes)	31 (20.3%)	31 (25.4%)	0 (0.0%)	**<.001**
Intra-op rupture (yes)	38 (25.0%)	37 (30.8%)	0 (0.0%)	**<.001**
Pre-op rupture (yes)	4 (2.6%)	4 (3.3%)	0 (0.0%)	.58
Adjuvant therapy				**<.001**
None	64 (41.6%)	36 (29.5%)	28 (87.5%)	
VB	1 (0.6%)	1 (0.8%)	0 (0.0%)	
EBRT ± VB	5 (3.2%)	5 (4.1%)	0 (0.0%)	
Chemo + RT	46 (29.9%)	46 (37.7%)	0 (0.0%)	
Chemo alone	38 (24.7%)	34 (27.9%)	4 (12.5%)	
Recurrence				.20
No	137 (89.0%)	106 (86.9%)	31 (96.9%)	
Yes	17 (11.0%)	16 (13.1%)	1 (3.1%)	
Death from disease				.69
No	144 (93.5%)	113 (92.6%)	31 (96.9%)	
Yes	10 (6.5%)	9 (7.4%)	1 (3.1%)	
Follow-up				
Mean	6.01 y			
Median	4.47 y			

B: Molecular data	Total cohort $n = 154$	Non-FIGO IA3 criteria $n = 122$	FIGO IA3 criteria $n = 32$	p-Value
ER IHC (Allred)				.57
0	3 (4.9%)	3 (6.5%)	0 (0.0%)	
1-6	21 (34.4%)	15 (32.6%)	6 (40.0%)	
7-8	37 (60.7%)	28 (60.9%)	9 (60.0%)	
PR IHC				.31
Positive	52 (91.2%)	37 (88.1%)	15 (100.0%)	
Negative	5 (8.8%)	5 (11.9%)	0 (0.0%)	
L1CAM (≥10%)				>.99
<10%	61 (96.8%)	46 (95.8%)	15 (100.0%)	
≥10%	2 (3.2%)	2 (4.2%)	0 (0.0%)	
L1CAM (>50%)				>.99
≤50%	61 (96.8%)	46 (95.8%)	15 (100.0%)	
>50%	2 (3.2%)	2 (4.2%)	0 (0.0%)	
CTNNB1				**.005**
Wildtype	37 (58.7%)	34 (68.0%)	3 (23.1%)	
Mutated	26 (41.3%)	16 (32.0%)	10 (76.9%)	
Molecular sub-type (endometrial tumor)				.08
*POLE*mut	10 (7.4%)	8 (7.5%)	2 (7.1%)	
MMRd	34 (25.2%)	31 (29.0%)	3 (10.7%)	
NSMP	85 (63.0%)	62 (57.9%)	23 (82.1%)	
p53abn	6 (4.4%)	6 (5.6%)	0 (0.0%)	
Molecular sub-type (ovarian tumor)				.33
*POLE*mut	2 (2.2%)	2 (2.9%)	0 (0.0%)	
MMRd	12 (26.7%)	11 (31.4%)	1 (10.0%)	
NSMP	28 (62.2%)	19 (54.3%)	9 (90.0%)	
p53abn	4 (8.9%)	4 (11.4%)	0 (0.0%)	

Abbreviations: BMI, body mass index; Chemo, chemotherapy; EBRT, external beam radiotherapy; ER, estrogen receptor; FIGO, International Federation of Gynecology and Obstetrics; IHC, immunohistochemistry; IQR, interquartile range; LVI, lymphovascular space invasion; MMRd, mismatch repair protein deficiency; NSMP no specific molecular profile; p53abn, p53 abnormal; *POLE*mut, *POLE* mutated; PR, progesterone receptor; RT, radiotherapy; VB, vaginal brachytherapy.
Total cases within each parameter measured may be less than total numbers due to missing data.

molecular and pathologic criteria, 17 (22%) recurred and 10 (13%) died from disease.

DISCUSSION

Summary of Main Results

This study is the first attempt to assess molecular classification with the addition of ER stratification in a large cohort of co-existent endometrial and ovarian carcinomas and to consider molecular subtype in the context of the recently proposed FIGO stage IA3 criteria. We validate that the new FIGO stage IA3 identifies a cohort with a low risk of recurrence. Importantly, this study also demonstrates that, in the context of molecular stratification, the current FIGO IA3 definition may be too restrictive, failing to identify a large additional cohort of patients who may be able to safely receive de-escalated treatment without risk of disease recurrence or death. These data support the criteria proposed by the WHO and FIGO but go further by incorporating molecular classification, a validated prognostic marker in the context of single-site carcinomas.

Results in the Context of Published Literature

Applying this newly proposed definition of indolent co-existent endometrial and ovarian carcinomas to our cohort of 154 patients identified an additional 48 patients who would potentially be downstaged (to IA3). These changes more than doubled the number of patients identified as having excellent clinical outcomes who may be candidates for treatment de-escalation, from 32 (20% of the cohort) to 75 (49% of the cohort). Twenty-five of these 48 patients had received adjuvant treatment, including vaginal brachytherapy (VB) (1), external beam radiation ± VB (4), chemotherapy (8), or chemoradiation (12), and we are unable to determine whether treatment or tumor biology/behavior is responsible for their favorable outcomes.

In assessing the prognostic role of molecular testing in co-existent endometrial and ovarian carcinomas, a difference in outcomes was observed between patients with MMRd or p53 abnormalities in either/both the endometrial or ovarian carcinoma or NSMP ER negative-low status in the endometrium, as compared to *POLE*mut or NSMP ER strong positive patients. This difference in outcomes (unfavorable vs favorable based on molecular features) aligns with the abundance of data in endometrial carcinoma (without ovarian involvement) and data from endometrioid ovarian carcinoma (without endometrial involvement).[14-21,24,25,27,28] Based on these data, we suggest a binary stratification of co-existent endometrial and ovarian carcinomas, considering patients with molecular features associated with a low risk of recurrence (*POLE*mut cancers in the endometrium and ovary, as well as NSMP ER strong positive in the endometrium) as 'indolent' and candidates for de-escalation but directing patients with molecular features associated with an intermediate-high risk of recurrence (MMRd or p53abn carcinomas in the endometrium or ovary, or NSMP ER negative-low carcinoma in the endometrium) to adjuvant treatment (Fig. 4). No role is appreciated for additional testing with other molecular features assessed in this series (PR, L1CAM, *CTNNB1*).

This series confirmed observations previously reported in the co-existent endometrial and ovarian carcinomas literature, with a young age of diagnosis (median 49) and good clinical outcomes.[4,5,7-10] Lynch syndrome was found in 35% of MMRd co-existent endometrial and ovarian carcinoma patients tested, which is higher than the rates of Lynch syndrome in MMRd endometrial carcinoma without ovarian involvement (10%).[29] We share new ethnicity data showing a higher proportion of East Asian patients with co-existent versus endometrial primaries. Molecular subtype concordance between endometrial and ovarian carcinomas was observed to be high (91%) in the subset of patients where results were available on both samples, consistent with previous publications.[1-4] We identified 3 cases of discordant MMR status between the endometrial and ovarian tumors, associated with MLH1 methylation. Heterogeneity of MMR status is a known feature in endometrial carcinoma[30,31] and colorectal carcinoma,[32] most commonly due to MLH1 loss secondary to promoter methylation, which may not result in complete loss of MLH1 expression. It is our opinion that until more data are available on molecular classification in patients with co-existent endometrial and ovarian carcinomas, both endometrial and ovarian sites need to be tested. We recommend that if MMRd or p53abn is identified in either the endometrial or ovarian carcinoma site, the patient should not be categorized as FIGO IA3 and should not be considered at low risk of recurrence. The priority must remain ensuring that no patient is inappropriately downstaged/miscategorized as indolent and de-escalated, as this could result in a missed opportunity for adjuvant therapy. Although we were missing ER status on many patients in our cohort, we did identify patients with NSMP ER negative-low endometrial carcinomas with recurrences, and therefore, this

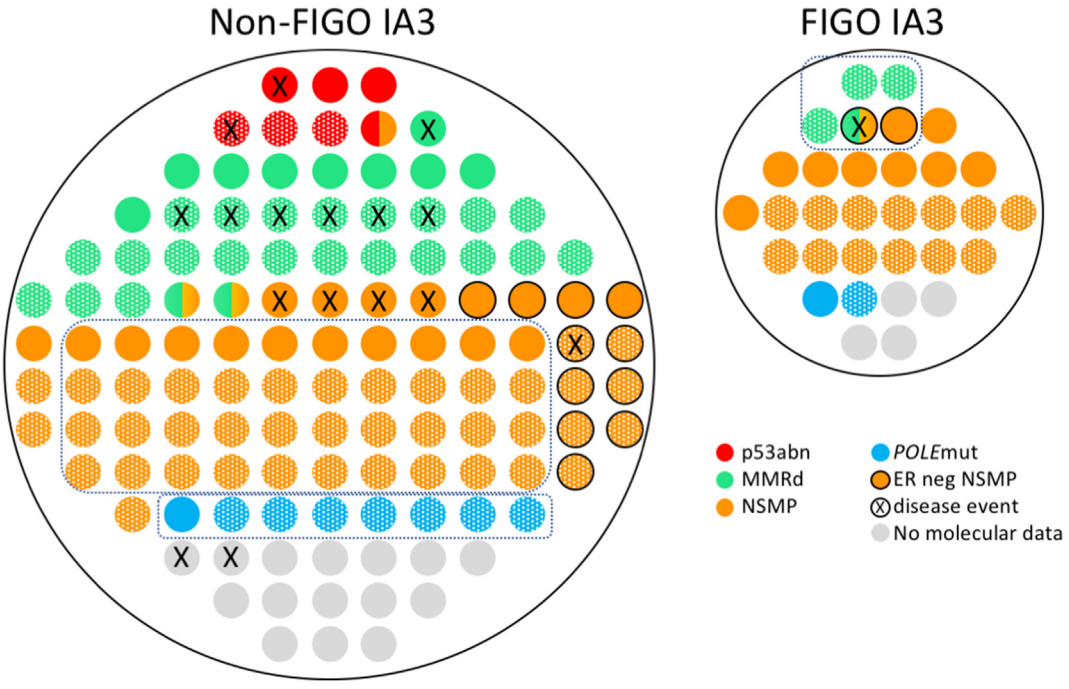

Figure 1 Molecular sub-types in 154 co-existent endometrial and ovarian carcinomas patients, including non-FIGO ($n = 122$) and FIGO IA3 ($n = 32$) with disease recurrence events (**X**). Solid circles indicate molecular classification concordance between the endometrium and ovary, and stippled circles indicate molecular classification was available for the endometrium only. There were 4 cases with discordant molecular classification between the 2 tumor sites, indicated with circles of 2 colors (left color: ovary, right color: endometrium). NSMP ER negative-low are indicated with outlined circles; the remaining NSMP cases either had positive ER or unknown ER status. Molecular classification was not available in either the ovary or endometrium for 19 cases (gray circles). The dashed boxes in the left-hand circle indicate the additional 48 cases that would meet our molecular and pathology criteria for possible treatment de-escalation. The dashed box in the right-hand circle indicates the 5 cases that would not qualify for treatment de-escalation by our criteria (MMRd or NSMP ER negative-low). Importantly, the single recurrence in the FIGO IA3 cohort would not qualify for treatment de-escalation by our criteria.

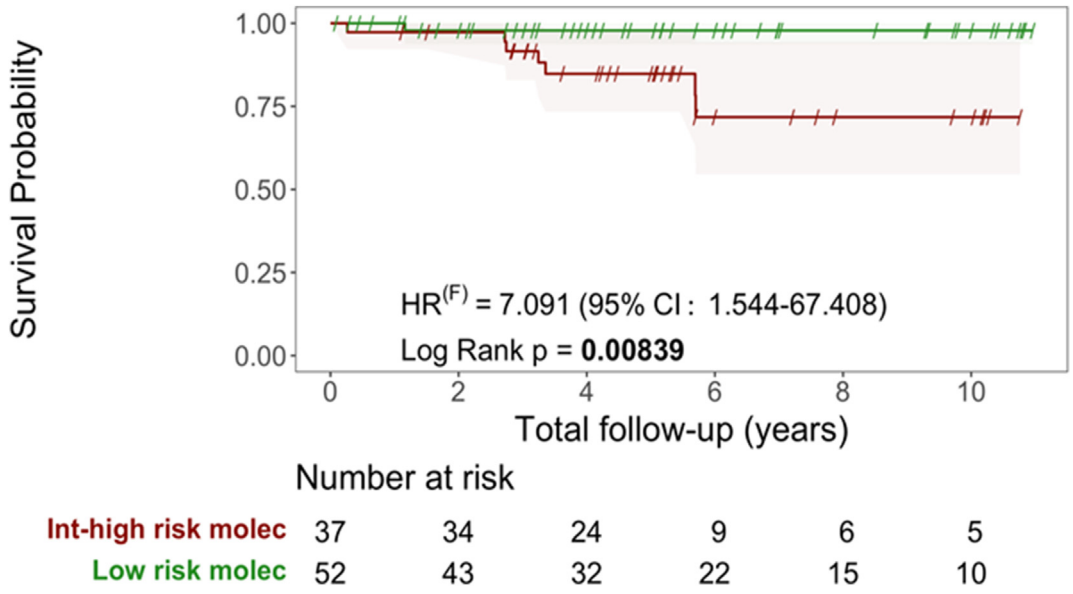

Figure 2 Kaplan-Meier survival analysis for molecular subset of co-existent endometrial and ovarian carcinomas at low risk of recurrence (*POLE*mut in the endometrium and/or ovary or NSMP ER strong positive in the endometrium) as compared to molecular subset at intermediate and high risk of recurrence (MMRd or p53abn in the endometrium and/or ovary or NSMP ER negative-low in the endometrium) demonstrates a significant difference in progression-free survival.

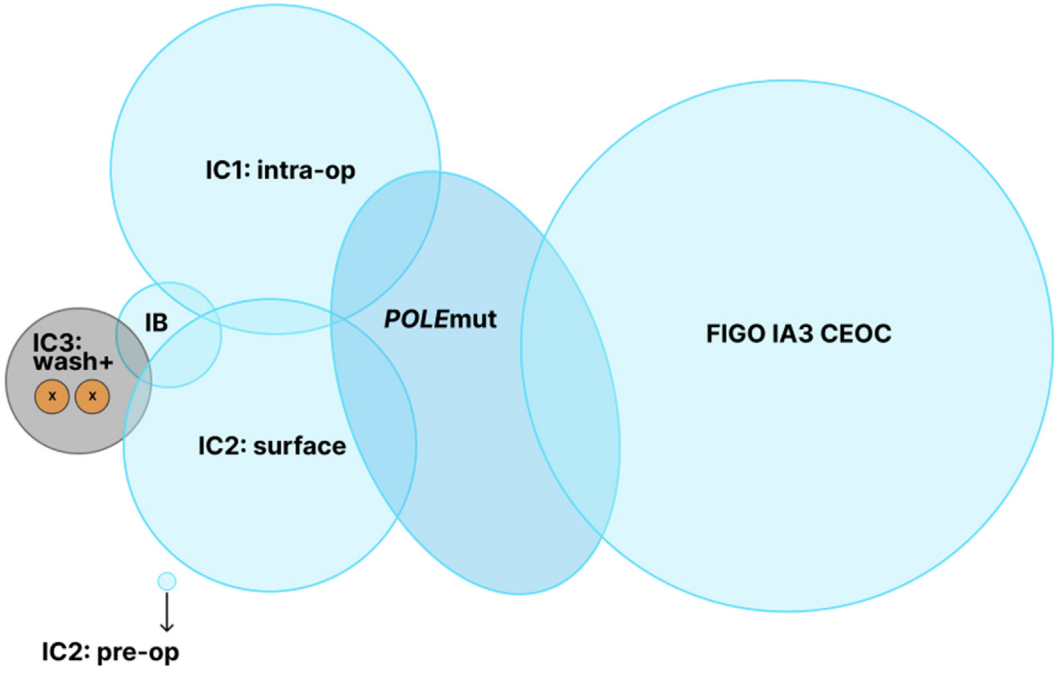

Figure 3 VENN diagram showing the overlap and relative proportion of pathologic and molecular features not included in FIGO IA3 criteria. By removing patients with ovarian or endometrial MMRd or p53abn carcinomas or NSMP ER negative-low endometrial carcinomas we can add cases with i) bilateral ovarian involvement (IB, $n = 5$, ii) intra-op rupture (IC1, $n = 18$), iii) pre-op rupture (IC2, $n=1$), iv) ovarian surface involvement (IC2: surface, $n = 16$) as well as any patients with *POLE*mut carcinomas (*POLE*mut, $n = 8$ not included in FIGO IA3) without observing any recurrences or deaths from disease. This adds 48 patients (>2-fold increase) that could be considered for de-escalation. Even with the removal of MMRd and p53abn, 2 of 8 (25%) patients with positive peritoneal washings (stage IC3) experienced a recurrence; therefore, this pathologic criterion would not be considered for inclusion in our expanded IA3 criteria.

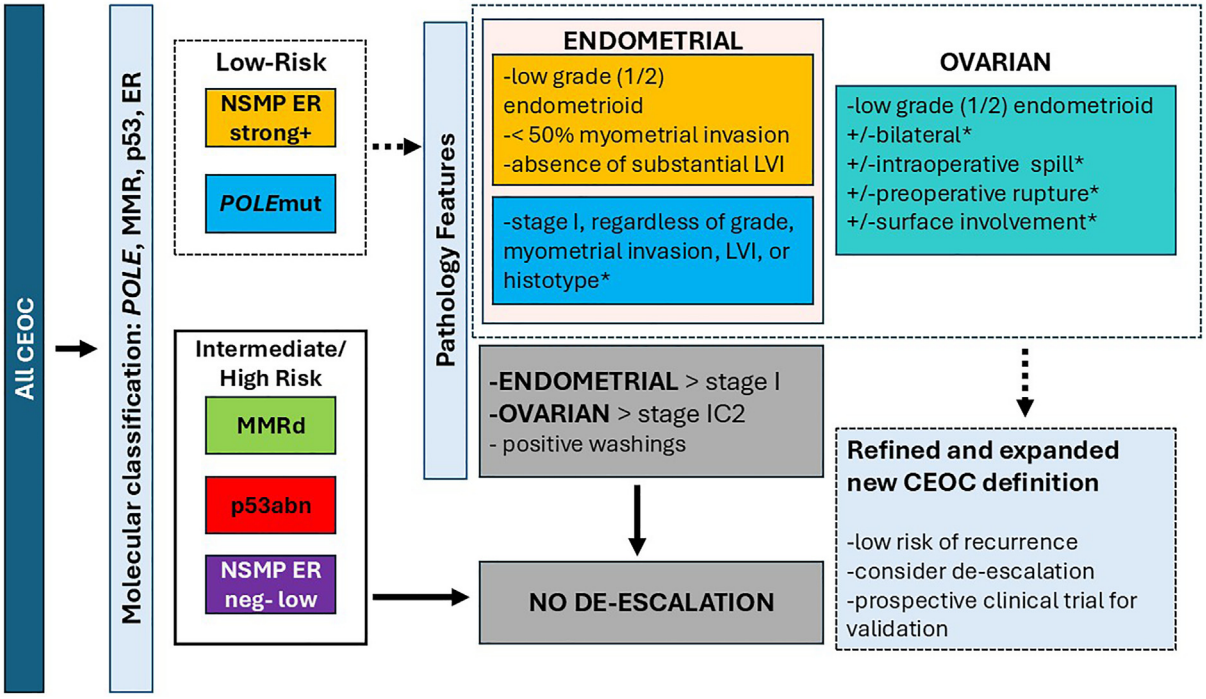

Figure 4 The proposed refinement using molecular subtype to identify high-risk co-existent endometrial and ovarian carcinomas (CEOC) and expanding the pathologic criteria associated with low risk of recurrence. All patients undergo molecular classification. Patients with MMRd or p53abn (either site), or NSMP ER negative-low (endometrial) will be excluded from FIGO stage IA3 and not offered de-escalated treatment. NSMP or *POLE*mut (either site) patients will be considered for de-escalation if endometrial pathology criteria (orange box [NSMP ER] strong positive or blue box [*POLE*mut]) and ovarian pathology criteria (teal box for both) are met. The * indicates pathology features that are expanded beyond the current FIGO IA3 criteria.

additional stratification feature is recommended when interpreting the endometrial components of these patients.

Strengths and Weaknesses

Strengths of this series include the first attempt to assess the role of molecular classification with the addition of ER stratification in the endometrium in a large cohort of co-existent endometrial and ovarian carcinomas, in the context of the new FIGO IA3 endometrial cancer staging criteria. The weaknesses include low overall numbers of patients and a low number of recurrence and death events to draw comparisons. Molecular data were not able to be assessed in all patients, nor were they available in both endometrial and ovarian tumors in all patients. Our data are retrospective, and we were unable to assess why patients received adjuvant treatment or what role treatment played in their disease outcomes. Validation of these molecular and pathologic criteria in an independent cohort is needed.

Implications for Practice and Future Research

We have validated that FIGO IA3 endometrial cancer criteria identify a cohort of patients at very low risk of recurrence. We demonstrate that further discernment of outcomes can be provided by molecular testing. This ensures that patients with molecular features associated with intermediate-high rates of recurrence (MMRd and p53abn in the ovary or endometrium, or NSMP ER negative-low endometrial carcinoma) are excluded from stage IA3 assignment and are not offered de-escalated therapy. Molecular refinement also provides an opportunity to expand the diagnosis of FIGO IA3 to include patients with *POLE* mutations and additional pathologic features, such as bilateral ovarian involvement or intra-operative/pre-operative ovarian rupture, directing more patients toward de-escalated adjuvant therapy. The value of stratification of co-existent endometrial and ovarian carcinoma by molecular sub-type (IHC or DNA-based testing, at minimum for MMR, p53, and ER) demonstrated in this series, and the expansion of the FIGO IA3 criteria, requires validation in a prospective clinical trial.

CONCLUSIONS

Molecular classification, including assessment of *POLE*, MMR/MSI, p53/*TP53,* and ER status, enables prognostic stratification of co-existent endometrial and ovarian carcinomas. Incorporation of refined molecular and pathologic criteria for FIGO IA3 will provide greater consistency in diagnosis and may safely direct more patients to de-escalated treatment.

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