Gynecologic Oncology 152 (2019) 38–45

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Risk-based stratification of carcinomas concurrently involving the endometrium and ovary

Gulisa Turashvili [a], Natalia R. Gómez-Hidalgo [b], Jessica Flynn [c], Mithat Gonen [c], Mario M. Leitao Jr [b,d], Robert A. Soslow [a], Rajmohan Murali [a,*]

[a] Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[b] Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[c] Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[d] Obstetrics and Gynecology, Weill Cornell Medical College, New York, NY, USA

HIGHLIGHTS

- Carcinomas may concurrently involve endometrium and ovary.
- We sought to separate women with these tumors into clinically low-risk and high-risk groups.
- We derived a risk-based classification based on pathologic features of the endometrial tumors.
- Risk-based classification allows prognostic stratification of women with concurrent endometrial/ovarian tumors.

ARTICLE INFO

Article history:
Received 5 September 2018
Received in revised form 19 October 2018
Accepted 23 October 2018
Available online 6 November 2018

Keywords:
Synchronous carcinomas
Endometrium
Endometrioid carcinoma
Non-endometrioid carcinoma
Ovary

ABSTRACT

Objective. Determining whether carcinomas concurrently involving endometrium and ovary are independent primary tumors (IPTs) or endometrial carcinomas with ovarian metastases (at least stage IIIA endometrial cancers, IIIA-EC) using clinicopathologic criteria is often challenging. Recent genomic studies showed that most such tumors are clonally related. We sought to identify clinicopathologic features associated with clinical outcomes, and to separate women with these tumors into clinically low-risk and high-risk groups.

Methods. We reviewed clinical and pathologic data from 74 women who, between 1993 and 2014, underwent primary surgery for endometrial cancer and had concurrent ovarian involvement.

Results. The endometrial carcinomas were endometrioid (EECs, $n = 41$) or non-endometrioid (ENECs, $n = 33$). Nineteen (26%) cases were originally classified as IPTs using clinicopathologic criteria. Multivariate analysis revealed that lymph node involvement (hazard ratio (HR) = 2.38, 95% CI 1.13–5.02, $p = 0.023$) and non-endometrioid endometrial tumor histology (HR = 6.27, 95% CI 2.6–15.13, $p < 0.001$) were associated with poorer progression-free survival (PFS). Multivariate analysis of 65 women with known lymph node status revealed two prognostically distinct groups: a high-risk group comprising ENECs with ≥50% myometrial invasion irrespective of lymph node status ($n = 21$; median PFS 12.7 months, 95% CI, 9.24–19.8); and a low-risk group consisting of all EECs, as well as lymph node-negative ENECs with <50% myometrial invasion ($n = 44$, median PFS not reached). The risk-based classification was superior to the original classification of endometrial cancers as IPTs vs. IIIA-EC for predicting PFS (log-rank test, $p < 0.001$ vs. $p = 0.07$).

Conclusion. Our proposed risk-based stratification enables categorization of women with concurrent endometrial and ovarian tumors according to their likely clinical outcomes.

1. Introduction

Staging, prognostic assessment and optimal clinical management of carcinomas concurrently involving the endometrium and ovary [1–4] depend on whether these neoplasms are independent primary tumors (IPTs) or endometrial cancers with ovarian metastases (at least stage IIIA endometrial cancers, IIIA-EC) [1,5,6]. Studies have shown that

* Corresponding author at: Department of Pathology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA.
E-mail address: MuraliR@mskcc.org (R. Murali).

https://doi.org/10.1016/j.ygyno.2018.10.033

endometrioid tumors classified as IPTs had a favorable prognosis compared to those classified as IIIA-ECs (86% vs. 58% 5-year survival rates) [1,2,6,7], thought to be consistent with the low clinical stage of each tumor in the former. However, accurate classification as IPT or IIIA-EC can be challenging in some cases, because as described below, surgical or histologic criteria that are currently used for this distinction do not consistently and unequivocally stratify women into low- and high-risk prognostic categories. This can lead to significant inter-institutional variability in the treatment of these women.

Currently, in the context of tumors concurrently involving endometrium and ovary, the term “synchronous” has been used to describe (mainly endometrioid) tumors associated with favorable prognosis or simultaneous endometrioid carcinomas in which the metastatic nature of the ovarian tumor cannot be completely ruled out. On the other hand, tumors exhibiting pathologic features strongly suggestive of ovarian metastasis (see below) are described as ovarian metastases.

Earlier studies attempted to identify specific histologic features that would allow classification and staging of concurrent endometrial and ovarian cancers. In a cohort of 34 women with both endometrioid and non-endometrioid carcinomas, the proposed criteria for favoring an endometrial primary included the following: either a major criterion (multinodular growth pattern in the ovary), or ≥2 minor criteria (including small size, <5 cm, of the ovary; bilateral ovarian involvement; deep myometrial invasion; lymphovascular invasion; and tubal luminal involvement) [8]. Scully et al.'s [9] pathologic criteria for classifying concurrent endometrial and ovarian tumors, described in 1998, are still used today. According to these criteria, the features suggestive of IPTs include the following: histologic dissimilarity of the tumors; absent or superficial myometrial invasion; presence of atypical hyperplasia in the endometrium; presence of endometriosis in the ovary; absence of lymphovascular invasion; absence of spread of endometrial tumor; unilateral ovarian involvement; ovarian parenchymal involvement without lymphovascular invasion; absence of spread of ovarian tumor; and dissimilar ploidy, molecular genetic or karyotypic abnormalities [9]. Features favoring an endometrial primary with ovarian metastasis (IIIA-EC) include the following: histologic similarity of the tumors; larger size of the endometrial tumor; presence of atypical endometrial hyperplasia and deep myometrial invasion with direct extension into adnexa and/or lymphovascular invasion; other evidence of spread of endometrial tumor; bilateral, multinodular, hilar or surface involvement of the ovary; absence of endometriosis; and similar ploidy, molecular genetic or karyotypic abnormalities [9]. However, despite the use of these criteria, classifying concurrent endometrial and ovarian tumors as IPTs or IIIA-ECs is not always easy in practice, particularly in the not uncommon setting in which the tumors exhibit one or more criteria favoring independent primaries as well as one or more criteria favoring metastasis. As a result, such cases are potentially at risk of being staged incorrectly and of being managed suboptimally.

Genomic approaches have been used to explore the biological nature of concurrent ovarian and endometrial carcinomas. Early genetic studies of concurrent endometrial and ovarian tumors utilized assays of loss-of-heterozygosity [10], ploidy [11], microsatellite instability [12,13] and single gene mutations [12,13]. In these studies, the absence of common genetic alterations in concurrent endometrial and ovarian tumors was thought to indicate independent pathogenesis of the tumors at each site, supporting the concept that they were IPTs. However, shared alterations in at least some of the endometrial and ovarian tumors may not have been detected in these studies, since the assays used were focused on a limited portion of the genome. In contrast to these reports, two recent genomic studies described sporadic endometrioid tumors classified as IPTs to be frequently clonally related [14,15]. Whole-exome massively parallel sequencing of 5 cases revealed strikingly similar genetic abnormalities, including somatic mutations and copy number alterations. Clonal relationships were confirmed by high-depth targeted massively parallel sequencing in 17 additional women [14]. In another study, targeted and exome sequencing showed evidence of a clonal relationship in 17 of 18 cases of concurrent endometrial and ovarian tumors. Eleven cases fulfilled clinicopathologic criteria for IPTs, 10 of which were clonally related [15]. Although these clonal relationships suggest that many concurrent endometrial and ovarian tumors are not independent primary tumors, patients with these tumors often exhibit paradoxically good clinical outcomes. These data support the concept that ovarian metastases of endometrial tumors may, at least in some cases, represent a feature that is not invariably associated with adverse prognosis.

Since classification of concurrent endometrial and ovarian tumors using currently used clinicopathologic criteria or genomic approaches do not always reflect clinical outcomes, we sought to identify clinicopathologic features of these tumors that are directly associated with clinical outcomes, and thereby allowing separation of women with these tumors into prognostically low-risk and high-risk groups.

2. Materials and methods

2.1. Patient cohort

Through a query of our institutional database of 3812 women who underwent primary surgery for carcinomas of the endometrium between 1993 and 2014 at our institution, we identified patients who had concurrent endometrial and ovarian involvement. Histologic subtypes included endometrioid carcinomas and non-endometrioid carcinomas (serous carcinoma, clear cell carcinoma, carcinosarcoma, undifferentiated carcinoma, mixed carcinoma, squamous cell carcinomas [cervical origin was ruled out]) (Table 1). Women with stage IV disease were excluded. Surgical procedures consisted of total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and/or para-aortic lymph node sampling, omentectomy, pelvic and peritoneal biopsies, and cytology. The type of adjuvant therapy (pelvic radiation, chemotherapy, hormonal therapy) was individualized.

Pathology reports were reviewed to determine the original pathologists' classification as IPTs or IIIA-ECs. Clinical, macroscopic and microscopic data were reviewed, including patient age, body mass index (BMI), histotype of endometrial and ovarian tumors, binary histologic grade for endometrioid adenocarcinomas (low-grade included FIGO grades 1 and 2, while high-grade included FIGO grade 3), depth of myometrial invasion (none or <50% vs. ≥50%), lymph node status, presence of lymphovascular invasion in the uterus, peritoneal washing cytology result and presence of endometriosis in the ovary. Microscopic slides were not re-reviewed, as many of the cases were consultation cases which had been returned to the submitting institutions. The Institutional Review Board approved the study.

Table 1
Histologic subtypes of concurrent endometrial and ovarian tumors.

	Endometrial tumor							Total
Ovarian tumor	EC	SC	MMMT	CCC	MC	UC	SCC	
EC	**40**	2	0	0	0	1	0	43
SC	0	**17**	0	0	0	0	0	17
MMMT	0	0	**9**	0	0	0	0	9
CCC	1	0	0	**1**	0	0	0	2
MC	0	0	0	0	**1**	0	0	1
UC	0	0	0	0	0	**1**	0	1
SCC	0	0	0	0	0	0	**1**	1
Total	41	19	9	1	1	2	1	74

EC, endometrioid carcinoma; SC, serous carcinoma; MMMT, malignant mixed Mullerian tumor (carcinosarcoma); CCC, clear cell carcinoma; MC, mixed carcinoma (exhibiting endometrioid, serous and undifferentiated features); UC, undifferentiated carcinoma; SCC, squamous cell carcinoma.
The bold entries indicate cases in which the endometrial and ovarian tumors were of the same histologic subtype.

2.2. Statistical analysis

Disease-specific survival (DSS) was defined as the time from surgery to death from endometrial/ovarian cancer. Overall survival (OS) was defined as the time from surgery to death from any cause. Progression-free survival (PFS) was defined as the time from surgery to progression, or time from surgery to last follow-up, or death if progression did not occur. Five women died without progression and were censored at date of death. PFS probabilities were estimated using the Kaplan-Meier method and differences between groups were assessed using the log-rank test.

Cox proportional hazards regression was used to evaluate the associations between various clinicopathologic characteristics and PFS in a univariate fashion. Kendall rank correlation coefficients were used to assess correlation between covariates with the aim of excluding variables that were highly correlated with others from multivariate analysis. A stepwise approach was used to build a multivariate model starting from the variables that were significant in the univariate analysis and excluding those that were highly correlated.

We further investigated the presence of significant risk factors based on the histologic subtype of endometrial carcinomas: endometrial endometrioid carcinomas (EECs) vs. endometrial non-endometrioid carcinomas (ENECs). The analysis was centered on endometrial histology for two reasons: 1) all women underwent primary surgery for endometrial carcinomas and were found to have ovarian involvement; 2) endometrial and ovarian tumors had identical morphology in 95% of cases (see below). We followed the same strategy of univariate analysis, followed by stepwise multivariate regression. This analysis led to the identification of low- and high-risk groups. The PFS differences between these groups were assessed by the log-rank test. All statistical analyses were performed in R version 3.4 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Analysis of the whole cohort

We identified 74 women with tumors concurrently involving the endometrium and ovary (Table 2). The median patient age was 61 years (range 32–89). There were 41 (55%) EECs and 33 (45%) ENECs. The depth of myometrial invasion was ≥50% in 36 cases (49%). Lymphovascular invasion was identified in 55 (74%) cases, and 26 women (35%) had lymph node metastases. The endometrial and ovarian carcinomas had similar morphology in the majority of cases (70/74, 95%) (Table 3). A total of 23 (31%) women had positive peritoneal washings, and ovarian endometriosis was present in 13 cases (18%). Tumors were classified by the reporting pathologists as IPTs in 19 (26%) cases, and as IIIA-ECs in 55 (74%) cases. Most IPTs (16/19, 84%) were endometrioid adenocarcinomas. Disease progression occurred in 35 (47%) women, including 26% (5/19) of IPTs, while 23 (31%) women died (median follow-up 60.7 months). Of the 5 patients with IPTs, the pathologic features were as follows: 2 high-grade endometrioid adenocarcinomas, 2 low-grade endometrioid adenocarcinomas and 1 serous carcinoma, while ovarian tumors were all endometrioid; only 2 tumors (1 endometrioid, 1 serous) showed ≥50% myometrial invasion, and only 1 endometrioid carcinoma was lymph node positive; lymphovascular invasion was identified in 4 cases (1 serous, 3 endometrioid). The 3- and 5-year PFS rates were 58% and 56%, while the 3- and 5-year DSS rates were 85% and 80% (Supplementary Table 1).

Univariate Cox proportional hazards analysis revealed that increasing patient age, lymph node involvement, histology of endometrial and ovarian carcinomas (endometrioid vs. non-endometrioid), and higher grade of endometrial carcinoma (ENECs and high-grade EECs vs. low-grade EECs) were associated with disease progression ($p \leq 0.02$) (Table 2, Fig. 1). Peritoneal washing cytology and depth of myometrial invasion did not show statistically significant associations with disease progression.

Given that histotype of endometrial carcinomas was highly correlated with histologic grade and histotype of ovarian carcinomas (Kendall $r = 0.87$, $r = 0.89$, respectively), the multivariable analysis was performed using endometrial histotype as the most clinically relevant variable. This analysis demonstrated that there were only two statistically significant predictors of PFS in the whole cohort – lymph node

Table 2
Summary of clinicopathologic variables and univariate Cox proportional hazard analysis (progression used as outcome variable) in the whole cohort.

	Total (n = 74)	HR (95% CI)	p-Value
Age; median (range)	61 (32–89)	1.05 (1.01–1.08)	0.008[a]
BMI; median (range)	28 (18–62)	1.01 (0.98–1.05)	0.482
Depth of myometrial invasion, n (%)			0.069
≥50%	36 (48.6)	1.89 (0.95–3.7)	
None or <50%	38 (51.4)	1.00	
Lymph node status, n (%)			0.022[a]
Negative	39 (52.7)	1.00	
Positive	26 (35.1)	2.32 (1.13–4.77)	
N/A	9 (12.2)		
Histology endometrial, n (%)			<0.001[a]
EEC	41 (55.4)	1.00	
ENEC	33 (44.6)	4.9 (2.32–10.38)	
Grade endometrial, n (%)			<0.001[a]
High[b]	38 (51.4)	1.00	
Low	36 (48.6)	0.23 (0.11–0.5)	
Histology ovarian, n (%)			<0.001[a]
Endometrioid	43 (58.1)	1.00	
Non-endometrioid	31 (41.9)	4.64 (2.25–9.58)	
Lymphovascular invasion, n (%)			0.618
No	19 (25.7)	1.00	
Yes	55 (74.3)	1.23 (0.55–2.72)	
Peritoneal washing, n (%)			0.11
Negative	31 (41.9)	1.00	
Positive	23 (31.1)	1.86 (0.87–4)	
N/A	20 (27.0)		
Endometriosis, n (%)			0.12
No	61 (82.4)	1.00	
Yes	13 (17.6)	0.39 (0.12–1.28)	
Endometrial vs. ovarian histology, n (%)			0.382
Different	4 (5.4)	1.00	
Similar	70 (94.6)	2.43 (0.33–17.76)	
Adjuvant treatment, n (%)			
None	1 (1.4)		
Hormonal therapy	2 (2.7)		
Radiation + hormonal therapy	2 (2.7)		
Radiation therapy	9 (12.2)		
Systemic therapy	60 (81.1)		
Progression, n (%)			
No	39 (52.7)		
Yes	35 (47.3)		

BMI, body mass index; CI, confidence interval; EEC, endometrial endometrioid carcinoma; ENEC, endometrial non-endometrioid carcinoma; HR, hazard ratio; N/A, not applicable.
[a] Statistically significant variables.
[b] High grade endometrioid adenocarcinomas and all non-endometrioid adenocarcinomas.

Table 3
Comparison of histologic subtypes of endometrial and ovarian carcinomas.

Ovarian histology	Endometrial histology	
	EEC (n = 41)	ENEC (n = 33)
Endometrioid (n = 43)	40 (93% ovarian; 98% endometrial)	3 (7% ovarian; 9% endometrial)
Non-endometrioid (n = 31)	1 (3% ovarian; 2% endometrial)	30 (97% ovarian; 91% endometrial)

EEC, endometrial endometrioid carcinoma; ENEC, endometrial non-endometrioid carcinoma.

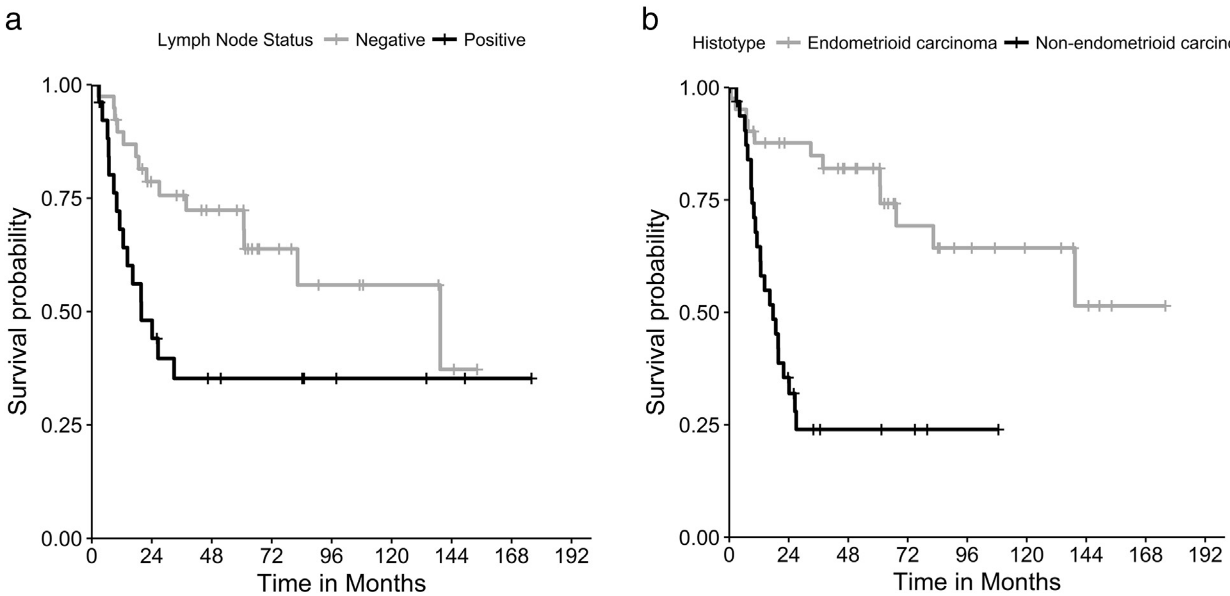

Fig. 1. PFS analysis by lymph node status (a) and histology of endometrial carcinoma (b) in the whole cohort (Log Rank $p = 0.019$ and $p < 0.001$) (PFS, progression-free survival).

involvement (HR = 2.38, 95% CI 1.13–5.02, $p = 0.023$) and endometrial tumor histotype (endometrioid vs. non-endometrioid) (HR = 6.27, 95% CI 2.6–15.13, $p < 0.001$).

3.2. Comparison of clinicopathologic features in women with EECs and ENECs

Ovarian and endometrial carcinomas had similar morphology in most cases: 98% (40/41) for EECs and 91% (30/33) for ENECs (Table 3). Of 41 EECs, most cases (36, 87.8%) were low-grade, and only 5 (12.2%) were high-grade in both sites. Table 4 details the clinicopathologic features of EECs and ENECs. The median age was 53 years (range 32–89) for women with EECs and 66 years (range 45–88) for women with ENECs ($p = 0.003$). Only 3 (9%) ENECs were considered IPTs by the original pathologists, compared with 16 (39%) EECs ($p = 0.004$).

Clinicopathologic variables and univariate Cox proportional hazard analysis for PFS in EECs and ENECs are described in Table 4. Disease progression occurred in 12 (29%) EECs and 23 (70%) ENECs (HR = 4.9, 95% CI, 2.32–10.38, $p < 0.001$). Ten women (24%) with EECs and 13 women

Table 4
Clinicopathologic variables and univariate Cox proportional hazard analysis (progression used as outcome variable) in EECs and ENECs.

	EEC ($n = 41$)	HR (95% CI)	*p*-Value	ENEC ($n = 33$)	HR (95% CI)	*p*-Value
Age; median (range)	53 (32, 89)	1.01 (0.95–1.07)	0.753	66 (45, 88)	1.07 (1–1.14)	0.047[a]
BMI; median (range)	28 (18, 61)	1.03 (0.97–1.09)	0.308	27 (18, 62)	1 (0.95–1.04)	0.912
Depth of myometrial invasion, *n* (%)			0.857			0.001[a]
≥50%	19 (46.3)	1.00		17 (51.5)	4.35 (1.81–11.1)	
None or <50%	22 (53.7)	1.12 (0.34–3.69)		16 (48.5)	1.00	
Lymph node status, *n* (%)			0.483			0.006[a]
Negative	25 (61)	1.00		14 (42.4)	1.00	
Positive	10 (24.4)	0.57 (0.12–2.76)		16 (48.5)	3.99 (1.5–10.63)	
N/A	6 (14.6)			3 (9.1)		
Grade endometrial, *n* (%)			0.477			N/A
High[b]	5 (12.2)	1.00		33 (100)	N/A	
Low	36 (87.8)	0.6 (0.15–2.42)			N/A	
Histology ovarian, *n* (%)			N/A			0.173
Endometrioid	40 (97.6)	N/A		3 (9.1)	1.00	
Non-endometrioid	1 (2.4)	N/A		30 (90.9)	4.04 (0.54–30.15)	
Lymphovascular invasion, *n* (%)			0.316			0.952
No	15 (36.6)	1.00		4 (12.1)	1.00	
Yes	26 (63.4)	0.56 (0.18–1.75)		29 (87.9)	1.05 (0.24–4.52)	
Peritoneal washing, *n* (%)			0.386			0.902
Negative	18 (43.9)	1.00		13 (39.4)	1.00	
Positive	7 (17.1)	2.17 (0.38–12.51)		16 (48.5)	1.06 (0.45–2.49)	
N/A	16 (39.0)			4 (12.1)		
Endometriosis, *n* (%)			0.729			0.422
No	30 (73.2)	1.00		31 (93.9)	1.00	
Yes	11 (26.8)	0.76 (0.16–3.56)		2 (6.1)	0.44 (0.06–3.27)	
Progression, *n* (%)						
No	29 (70.7)			10 (30.3)		
Yes	12 (29.3)			23 (69.7)		

BMI, body mass index; CI, confidence interval; EEC, endometrial endometrioid carcinoma; ENEC, endometrial non-endometrioid carcinoma; HR, hazard ratio; N/A, not applicable. Some *p*-values are N/A due to insufficient sample size at each level.

[a] Statistically significant variables.

[b] High grade endometrioid adenocarcinomas and all non-endometrioid adenocarcinomas.

(39%) with ENECs died. The 3- and 5-year PFS rates were 85% vs. 24%, respectively and 82% vs. 24%, respectively; the 3- and 5-year DSS rates for women with EECs and ENECs were 92% vs. 73%, respectively and 89% vs. 65%, respectively (Supplementary Table 1).

Subset analysis of EECs and ENECs revealed that there were no risk factors that could separate favorable and unfavorable prognostic groups in women with EEC (Table 4). In contrast, in women with ENECs, three variables were significantly associated with PFS: patient age (HR = 1.07, 95% CI, 1–1.14, $p = 0.047$), depth of myometrial invasion (HR = 4.35, 95% CI, 1.81–11.1, $p = 0.001$), and lymph node status ((HR = 3.99, 95% CI, 1.5–10.63, $p = 0.006$) (Table 4, Fig. 2).

Multivariable analysis including patient age, depth of myometrial invasion and lymph node status showed that there were two significant predictors of PFS in ENECs – lymph node involvement (HR = 3.56, 95% CI, 1.3–9.74, $p = 0.014$), and ≥50% depth of myometrial invasion (HR = 4.55, 95% CI, 1.69–11.11, $p = 0.002$).

3.3. Identification of low- and high-risk groups

In a multivariate analysis including 65 women with known lymph node status, EECs were compared to ENECs stratified by lymph node status and depth of myometrial invasion (Supplementary Fig. 1). EECs and lymph node negative ENECs with <50% myometrial invasion had more favorable outcomes ($n = 44$, median PFS and DSS not reached) and were categorized as a low-risk group. All other ENEC patients (i.e. ENECs with ≥50% myometrial invasion with or without positive lymph nodes) had a poorer PFS ($n = 21$; median PFS 12.7 months, 95% CI, 9.24–19.8) and DSS (median DFS not reached) and were categorized as a high-risk group. The survival difference between the low-risk and high-risk groups was statistically significant (PFS $p < 0.001$, Fig. 3a; DSS $p = 0.005$, Fig. 3b).

In contrast to the risk-based stratification, PFS analysis based on the original pathologists` classification of endometrial tumors as IPTs or IIIA-ECs failed to reveal statistically significant differences between subgroups (PFS $p = 0.07$, Fig. 3c; DSS $p = 0.15$, Fig. 3d). Comparison of the newly assigned risk groups to this original classification showed that 31 cases (42%) were reclassified/restaged: 2 cases originally classified as IPTs were reclassified as high-risk, and 29 cases originally classified as IIIA-ECs were reclassified as low-risk. Clinicopathologic characteristics of low- and high-risk groups are summarized in Table 5.

Comparing clinical outcomes of low- vs. high-risk groups, the 3- and 5-year PFS rates were 83% vs. 8% and 80% vs. 8%; the 3- and 5-year DSS rates were 95% vs. 60% and 89% vs. 60% (Supplementary Table 1).

4. Discussion

Our study presents a risk-based stratification of endometrial cancers in women with concurrent endometrial and ovarian cancers. Traditionally, histologic criteria first proposed by Ulbright and Roth [8] and further refined by Scully et al. [9] have been applied to carcinomas concurrently involving the endometrium and ovary for primary site assignment and staging. Tumors that are classifiable as IPTs are typically low-grade endometrioid adenocarcinomas in both sites in 90% of cases [1,5,16]. Affected women tend to be young (premenopausal), overweight and nulliparous, and have a favorable prognosis with a median survival of nearly 10 years [1,2,5,16–18], further supporting their classification as two low-stage tumors rather than IIIA-ECs, which are characterized by 5-year and 10-year OS rates of 43–58% [19,20] and 37% [21], respectively. However, the clinical significance and relationships between some of the Scully criteria are questionable. For example, in the setting of positive lymph nodes, an ovarian tumor would most likely represent metastasis from an endometrial primary even in the absence of lymphovascular invasion or deep myometrial invasion [22]. Consequently, even after considering all of the features, the primary site cannot be assigned confidently in a significant proportion of cases [22], particularly in tumors with some features favoring "synchronous" tumors (i.e. IPTs) and others favoring "metastasis". Furthermore, independent validation studies of the above criteria have not been performed. Therefore, risk-based stratification of women with concurrent endometrial and ovarian tumors is likely to be more useful clinically than definitive identification of the primary site.

Our study showed that the risk-based classification of endometrial cancers is superior to the original classification as IPTs vs. IIIA-EC for predicting PFS. Comparison of low-risk and high-risk groups demonstrates significant differences in clinical outcomes (5-year OS: 82% vs. 46%; 5-year DSS: 89% vs. 60%; 5-year PFS: 80% vs. 8%). Despite the variability in reported end points (PFS vs. OS), histotypes and categorization of tumors as IPTs based on Scully et al. criteria [9], our survival rates appear similar to most previous studies. A 5-year OS rate of 46% for the high-risk group is within the reported range of 43–58% for women with IIIA-EC [19,20]. A 5-year OS rate of 82% for the low-risk group is

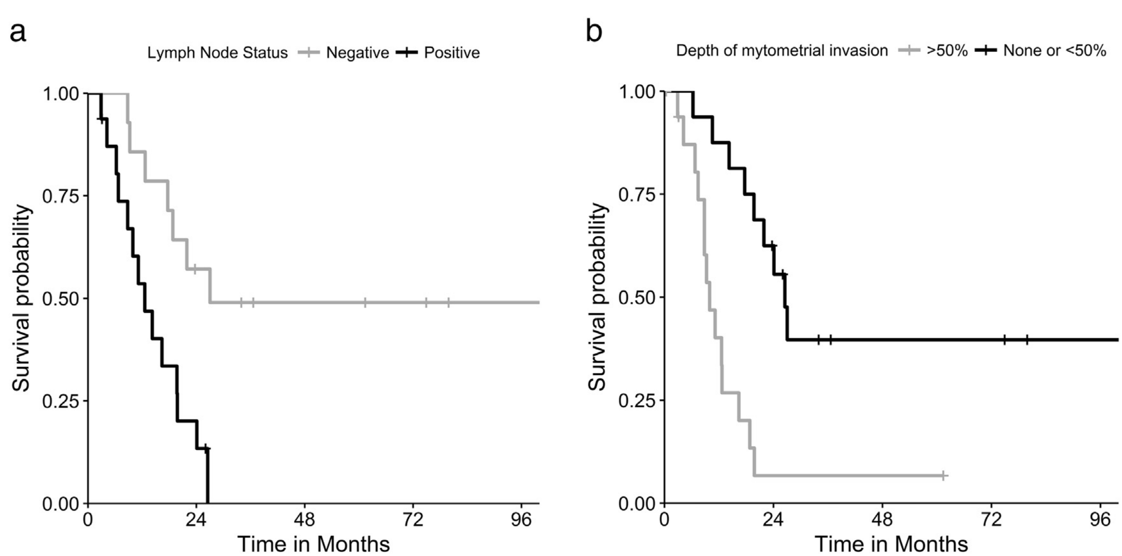

Fig. 2. PFS analysis by lymph node status (a) and depth of myometrial invasion (b) in women with ENEC (Log Rank $p = 0.003$ and $p < 0.001$, respectively) (ENEC, endometrial non-endometrioid carcinoma; PFS, progression-free survival).

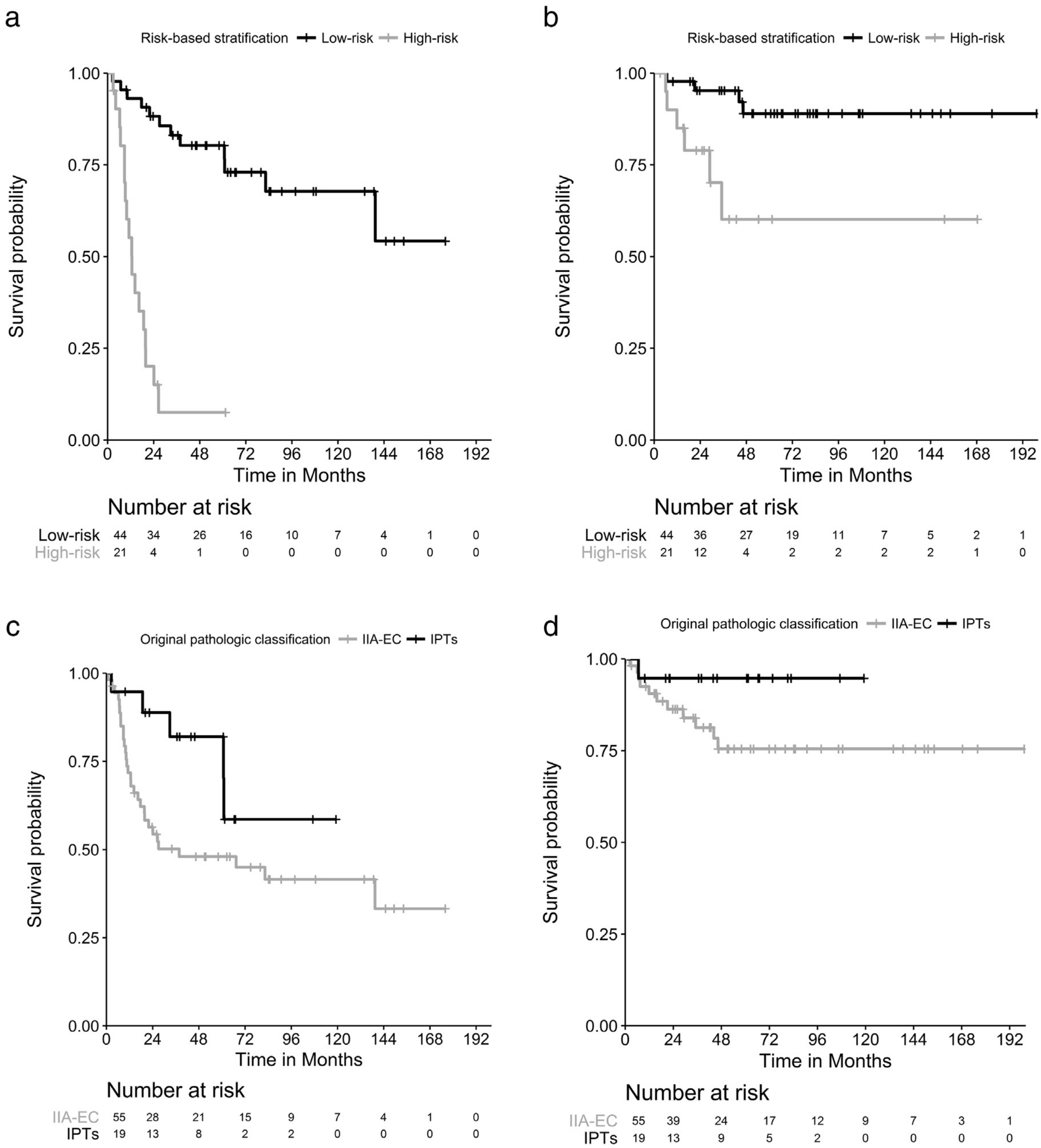

Fig. 3. a) PFS by low- and high-risk groups (Log Rank $p < 0.001$); b) DSS by low- and high-risk groups (Log Rank $p = 0.005$); c) PFS based on the original pathologists` classification of endometrial tumors as IPTs or IIIA-EC (Log Rank $p = 0.07$); d) DSS based on the original pathologists` classification of endometrial tumors as IPTs or IIIA-EC (Log Rank $p = 0.15$). (EEC, endometrial endometrioid carcinoma; ENEC, endometrial non-endometrioid carcinoma; IPTs, independent primary tumors; DSS, disease-specific survival; PFS, progression-free survival, IIIA-EC, stage IIIA endometrial carcinoma).

comparable to clinical outcomes of so-called "synchronous" tumors in the literature [23,24]. Of note, even in the studies with the best survivals, a subset of women with IPTs can still recur or die [21,23,24], indicating that equating the term "synchronous" with two FIGO stage 1 tumors does not entirely eliminate the risk of poor outcome. Therefore, risk-based stratification represents a more robust approach for estimating clinical outcomes compared to the traditional classification.

In our retrospective cohort of 41 (55%) EECs and 33 (45%) ENECs, only 19 cases (26%) were considered IPTs at initial diagnosis, and 70 (95%) tumors had similar morphology in both sites, in agreement with prior studies [1,17,24-26]. Most EECs were low-grade (88%, 36/41), as reported previously in tumors classified as IPTs [21,23,27]. In our study, women with ENECs had poorer PFS than those with EECs, and endometrial histology (EEC vs. ENEC) and lymph node status were associated with clinical outcomes in multivariable analysis. Tumor histotype was not associated with clinical outcomes in some studies [1,18,26,28]. However, an earlier study by Eifel et al. showed that 55% (6/11) of women with ENECs died of disease compared to none of the 16 women with EECs [17]. In a cohort of 90 women, those with EECs had a better 5-year survival probability than those with ENECs (0.89 vs. 0.69, $p = 0.02$) [6].

Analysis of 41 EECs in our study failed to identify any variables that could separate EECs into favorable and unfavorable prognostic groups. Zaino et al. previously showed the association between the risk of recurrence and higher histologic grade [1]. Even endometriosis, which was identified in 18% of cases and represents one of the 12 features proposed by Scully et al. and confirmed by other authors [9,23], was not helpful for assigning a primary site. This may be related to common occurrence of endometriosis in the ovary without a necessarily causative role in ovarian EECs.

Table 5
Clinicopathologic variables for the high- vs. low-risk groups (65 women included; 9 women were not classified due to lack of lymph node status data).

	High-risk (*n* = 21)	Low-risk (*n* = 44)
Age; median (range)	65 (46, 79)	53.5 (32, 89)
BMI; median (range)	28 (18, 41)	27.5 (18, 62)
Lymph node status, *n* (%)		
Negative	5 (23.8)	34 (77.3)
Positive	16 (76.2)	10 (22.7)
Depth of myometrial invasion, *n* (%)		
>50%	15 (71.4)	15 (34.1)
None or <50%	6 (28.6)	29 (65.9)
Histology endometrial, *n* (%)		
EEC	0 (0)	35 (79.5)
ENEC	21 (100)	9 (20.5)
Grade endometrial, *n* (%)		
High[a]	21 (100)	13 (39.5)
Low	0 (0)	31 (70.5)
Histology ovarian, *n* (%)		
Endometrioid	2 (9.5)	35 (79.5)
Non-endometrioid	19 (90.5)	9 (20.5)
Lymphovascular invasion, *n* (%)		
No	2 (9.5)	12 (27.3)
Yes	19 (90.5)	32 (72.7)
Peritoneal washing, *n* (%)		
Negative	10 (47.6)	19 (43.2)
Positive	9 (42.9)	11 (25)
N/A	2 (9.5)	14 (31.8)
Endometriosis, *n* (%)		
No	19 (90.5)	33 (75)
Yes	2 (9.5)	11 (25)
Endometrial vs. ovarian histology, *n* (%)		
Different	2 (9.5)	2 (4.5)
Similar	19 (90.5)	42 (95.5)
Progression, *n* (%)		
No	3 (14.3)	32 (72.7)
Yes	18 (85.7)	12 (27.3)

BMI, body mass index; EEC, endometrial endometrioid carcinoma; ENEC, endometrial non-endometrioid carcinoma; N/A, not applicable.
[a] High grade endometrioid adenocarcinomas and all non-endometrioid adenocarcinomas.

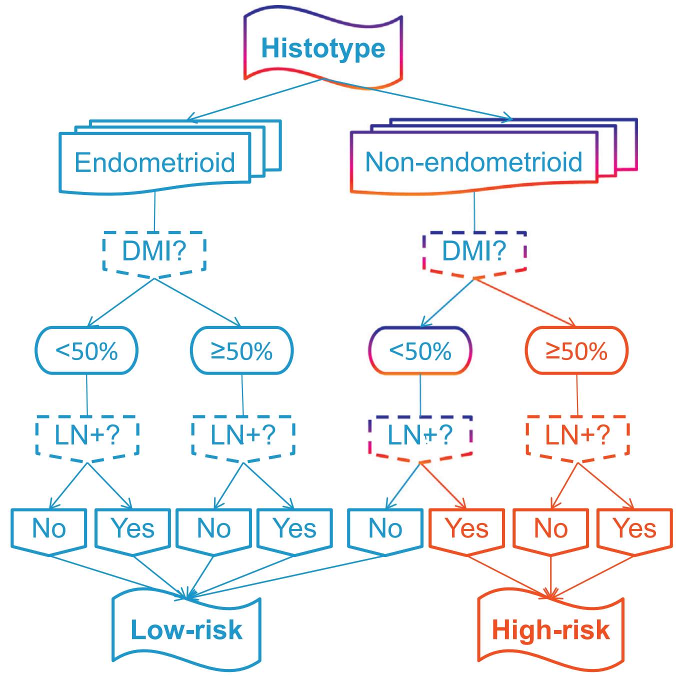

Fig. 4. A schematic diagram to illustrate risk-based stratification of carcinomas concurrently involving the endometrium and ovary (histotype refers to endometrial carcinomas; DMI, depth of myometrial invasion; LN+, lymph node positive).

In our cohort of 33 ENECs, significant predictors of PFS were lymph node status and depth of myometrial invasion ((HR = 3.56 95% CI, 1.3–9.74, $p = 0.014$; and HR = 0.22, 95% CI, 0.09–0.59, $p = 0.002$, respectively) on multivariate analysis. The significance of lymph node status was further confirmed by multivariate analysis comparing all EECs and ENECs based on the depth of myometrial invasion and lymph node status. Clinical outcomes of ENECs with negative lymph nodes and <50% myometrial invasion were similar to all EECs irrespective of lymph node status and depth of myometrial invasion, and median survival was not reached for this group. In contrast, ENECs with ≥50% myometrial invasion had a decreased PFS irrespective of lymph node status (median survival 12.7 months). The association between the depth of myometrial invasion and clinical outcomes has been reported previously. Deep myometrial invasion was associated with recurrence or death from all histotypes of endometrial carcinoma in 77% (57/74) of women in a study by Zaino et al. [1]. Metastatic disease including positive lymph nodes has been reported be associated with decreased survival in several studies [1,21,29].

A total of 35 (47%) women developed tumor recurrences in our cohort including 26% (5/19) of women originally categorized as IPTs. The 5-year OS and PFS rates were 69% and 56% for the whole cohort, and 80% vs. 54% and 82% vs. 24% for EECs vs. ENECs, respectively. Risk-based stratification of our cases with concurrent endometrial and ovarian involvement demonstrated that ENECs with ≥50% myometrial invasion, irrespective of lymph node status, represent high-risk tumors. Given the similar favorable clinical outcomes in our cohort, all EECs and lymph-node negative ENECs with <50% myometrial invasion (in the setting of concurrent endometrial and ovarian involvement) represent low-risk tumors (Fig. 4). It is possible that at least some ENECs with favorable prognosis may not be non-endometrioid subtypes and could represent MSI-high or *POLE*-mutated subtype of endometrioid adenocarcinoma [30]. Although *POLE* mutations can only be detected by sequencing, the MSI-high subtype can easily be identified by immunohistochemical studies for DNA mismatch repair proteins. Unfortunately, given the archival nature of the cases in our cohort, these additional analyses were not feasible.

In summary, our study suggests that clinical outcomes of carcinomas concurrently involving the endometrium and ovary are strongly associated with the histotype of endometrial carcinoma, depth of myometrial invasion and lymph node status. Carcinomas of non-endometrioid histology with ≥50% myometrial invasion with or without positive lymph nodes represent high-risk tumors. In contrast, endometrioid carcinomas (irrespective of depth of myometrial invasion or lymph node status) as well as lymph node-negative non-endometrioid carcinomas with <50% myometrial invasion are low-risk tumors for the purposes of clinical management. This simple risk-based stratification will allow classification of tumors according to their likely clinical behavior and will facilitate optimization of their follow-up regimens. It is simple, easily applicable, and has practical utility for pathologists and clinicians. In addition, it eliminates the need for applying imprecise clinicopathologic criteria or expensive and resource-intensive sequencing/clonality analyses.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2018.10.033.

Author contributions

Study design and supervision (RAS, MML, RM); Data acquisition, analysis and interpretation (GT, NRG-H, MML, RAS, RM); Statistical analysis (JF, MG); Preparation of manuscript (GT, JF, RM); Review and approval of final manuscript (all authors).

Conflict of interest statement

The authors declare that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

Acknowledgments and funding source

The authors would like to thank Malcolm Pike and Prusha Patel for their assistance with the initial data analysis. This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

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