










Prognostic factors in patients with endometrial cancer with isolated lymphatic recurrence

Ilaria Capasso ,^{1,2} Simone Garzon ,³ Sanjeev Kumar,⁴ Amy L Weaver,⁵ Michaela Mc Gree,⁵ Luigi Antonio De Vitis,¹ Stefano Uccella,³ Ivy Petersen,⁶ Gretchen Glaser ,¹ Carrie Langstraat ,¹ Giovanni Scambia ,² Francesco Fanfani ,² Andrea Mariani ¹

For numbered affiliations see end of article.

Correspondence to

Dr Andrea Mariani, Department of Gynecologic Oncology, Mayo Clinic, Rochester, MN 55905, USA; mariani.andrea@mayo.edu

IC and SG contributed equally.

IC and SG are joint first authors.

Received 2 March 2023

Accepted 2 June 2023

Published Online First

15 June 2023

ABSTRACT

Objective To analyze the clinicopathological features and outcomes in patients with endometrial cancer with isolated lymphatic recurrence after lymphadenectomy, stratified by different isolated lymphatic recurrence sites and treatment approaches.

Methods We retrospectively reviewed all surgically treated patients with endometrial cancer, identifying those with recurrence. We defined primary isolated lymphatic recurrence as the first and unique evidence of recurrence in lymph node-bearing areas, without concomitant vaginal, hematogenous, or peritoneal recurrence. Isolated lymphatic recurrences were classified as pelvic, para-aortic, distant, or multiple sites. Our primary outcome was cause-specific survival after diagnosis of the recurrence.

Results Among 4216 patients with surgically staged endometrial cancer, we identified 66 (1.6%) women with isolated lymphatic recurrence. The overall median cause-specific survival for patients with isolated lymphatic recurrence was 24 months. Although cause-specific survival was not significantly different between the four isolated lymphatic recurrence groups ($p=0.21$), 7 of 15 (47%) patients with isolated lymphatic recurrence in the para-aortic area were long-term survivors. At multivariate Cox regression, the absence of lymphovascular space invasion and grade 1 histology in the primary tumor were significantly associated with improved cause-specific survival. In addition, patients with isolated lymphatic recurrence who underwent surgery for recurrence (with/without other associated therapies) had improved cause-specific survival compared with patients who did not undergo surgery, also after adjusting for age.

Conclusions Low-grade histology and absence of lymphovascular space invasion in the primary tumor were predictors of improved prognosis in patients with endometrial cancer with isolated lymphatic recurrence. In addition, in this retrospective cohort, patients with isolated lymphatic recurrence who were selected for eradicated surgical treatment had improved cause-specific survival.

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy and the fourth cancer for incidence in adult women of Western countries.¹ Although endometrial cancer has a relatively good prognosis, because usually diagnosed when still confined to the

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Recurrence in endometrial cancer has already been studied, with evidence suggesting that both the number and location of recurrences may be associated with prognostic outcomes. However, there is very limited evidence regarding nodal recurrence and, particularly, isolated lymphatic recurrence.

WHAT THIS STUDY ADDS

⇒ Although the variables predicting lymphatic dissemination and recurrence have been extensively studied in endometrial cancer, survival outcomes after diagnosis of isolated lymphatic recurrence have not been well documented. This study aims to fill this gap in the literature and is specifically designed to analyze the clinicopathological features and outcomes in patients with endometrial cancer with isolated lymphatic recurrence, stratified by different recurrence sites and treatment approaches.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study will facilitate a deeper understanding of isolated lymphatic recurrences in endometrial cancer, based on their location and tumor characteristics. This knowledge will help to select patients who may benefit from surgical management of isolated lymphatic recurrence.

uterus,^{2,3} 10–23% of patients with early-stage disease will experience recurrence.^{4–6} Overall, the recurrence rate among all stages of endometrial cancer is approximately 20% for endometrioid histology and 50% for non-endometrioid histology.⁷ In recurrent cases, some studies have shown that local ablative therapy, such as surgery or stereotactic radiotherapy, may represent a definitive treatment option in the presence of 1–5 recurrence locations.^{8–12} Consistently, current guidelines define oligometastatic recurrent endometrial cancer as a state of limited metastatic tumor that may benefit from additional treatments.⁹ However, in addition to the number of concurrent recurrences, the site of relapse may play a key role, as shown for vaginal recurrences.^{13,14}



► <http://dx.doi.org/10.1136/ijgc-2023-004771>



© IGCS and ESGO 2023. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Capasso I, Garzon S, Kumar S, *et al.* *Int J Gynecol Cancer* 2023;**33**:1169–1178.

Original research

Among possible sites of recurrence, a lymphatic component is present in 4–20% of early-stage and up to 50% of advanced-stage endometrial cancers, in the absence of previous adjuvant radiotherapy.⁸ However, evidence focusing on the management of nodal recurrence is limited, with few studies reporting conflicting evidence on treatment-related outcomes of recurrence.^{15–17} To provide new evidence on the prognosis and management of nodal recurrence in endometrial cancer, the present study aimed to analyze the clinicopathological features and oncologic outcomes in patients who developed isolated lymphatic recurrence, stratified by recurrence sites and treatment approaches.

METHODS

This study used a prospectively maintained database of patients with endometrial cancer who underwent primary surgery (total hysterectomy and bilateral salpingo-oophorectomy) at Mayo Clinic, Rochester, Minnesota, between January 1984, and December 2017. This study was approved by Mayo Clinic Institutional Review Board (IRB number: 20–000174) and all participants gave informed consent before taking part to the study. All International Federation of Gynecology and Obstetrics (FIGO) stages of disease and all epithelial histologies (endometrioid, serous, clear cell, carcinosarcoma, undifferentiated, and mixed) were included in our analysis. Patients who underwent neoadjuvant therapy at the time of primary tumor diagnosis, had synchronous cancer, or did not have epithelial histology (leiomyosarcomas, rhabdomyosarcomas) at final pathology were excluded, along with patients who refused access to their medical records for research purposes.

Within this cohort, we identified all patients with endometrial cancer who developed a primary recurrence after surgery. Focusing on the site(s) at the time of recurrence, we defined isolated lymphatic recurrence as the first and unique evidence of recurrence in lymph node-bearing areas after primary surgery, without concomitant vaginal, hematogenous, or peritoneal recurrence. Based on the lymph node-bearing area involved, isolated lymphatic recurrences were classified as pelvic, para-aortic, distant (any other lymph node-bearing area), or multiple (more than one lymph node-bearing area, including pelvic and para-aortic, pelvic and distant, para-aortic and distant, pelvic and para-aortic and distant). The diagnosis of recurrence was in all cases by imaging with either CT or MRI; biopsy for histologic confirmation was performed whenever appropriate and at the clinician's discretion. The isolated lymphatic recurrence was defined as 'treatment-naïve' if the involved lymph node-bearing area had not been previously irradiated.

Data on clinical, surgical, and pathologic characteristics, adjuvant therapy, and follow-up information prior to recurrence diagnosis, as well as data on recurrence diagnosis, treatment, and subsequent follow-up, were retrieved from the prospectively collected database and medical records review. Histology, grade, and stage of the primary tumor were confirmed by a central pathology review by a pathologist with expertise in gynecologic oncology. Primary surgery, adjuvant therapy, and subsequent follow-up and recurrence management were performed according to the physician and patient's preferences following recommended institutional guidelines.

Statistical Analysis

Data on clinicopathological characteristics, surgery, adjuvant management, follow-up information, and recurrence diagnosis, treatment, and subsequent follow-up were summarized using standard descriptive statistics. The aforementioned variables were compared between the four groups defined by site of recurrence using the χ^2 or Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous or count variables.

The primary outcome of our study was death due to disease. The Kaplan-Meier method was used to estimate the cause-specific survival. Variables were evaluated for an association with death due to disease based on fitting univariate Cox proportional hazards regression models, both with and without adjusting for age at primary surgery. A full multivariable Cox model was fitted including all variables with $p < 0.10$ based on the univariate analysis along with age at primary surgery. Associations were summarized using hazard ratios (HRs) and 95% confidence intervals (CIs) estimated from the models. All calculated p values were two-sided, and $p < 0.05$ was considered statistically significant.

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.

RESULTS

Among 4216 patients with endometrial cancer who underwent surgery at Mayo Clinic during the study period and were included in our database, we identified 66 cases (1.6%) who developed an isolated lymphatic recurrence. Nine of these 66 patients had a pelvic isolated lymphatic recurrence (13.6%), 15 had a para-aortic isolated lymphatic recurrence (22.7%), 16 had a distant isolated lymphatic recurrence (24.2%), and 26 had multiple sites isolated lymphatic recurrence (39.4%). The group of distant isolated lymphatic recurrence included six supraclavicular, seven inguinal, one mediastinal, one axillary, and one para-esophageal. The group of multiple sites included 14 pelvic and para-aortic, 8 distant and para-aortic, and 4 distant and pelvic and para-aortic.

The recurrence was confirmed by pathologic evaluation for 44 patients (66.7%). For the remaining 22 cases (33.3%), the diagnosis was based on clinical and radiologic suspicion and further consolidated based on response to treatment for the recurrence. Of note, among these patients with no pathologic confirmation of the recurrence 12 (54.5%) of 22 have died due to disease within a year from the radiologic diagnosis of the recurrence, 5 (22.7%) of 22 have died due to disease between 1 and 3 years from the radiologic diagnosis of the recurrence, and 5 (22.7%) of 22 were long-term survivors (patients who survived more than 5 years after the recurrence).

Although not statistically significant, 93.8% of the patients who developed a distant isolated lymphatic recurrence had a primary FIGO stage III–IV, compared with 55.6%, 66.7%, and 80.8% of the pelvic, para-aortic, and multiple site groups, respectively. Neither age at primary surgery, nor any other primary tumor characteristics differed significantly among the four subgroups of recurrence (Table 1). The type of lymph node assessment during primary surgery was as follows: having both pelvic and para-aortic

Table 1 Isolated lymphatic recurrence in endometrial cancer: characteristics of patients, primary tumor, and related recurrence details

Characteristic	Site of recurrence					P* value
	All ILR n=66	Pelvic ILR n=9 (13.6%)	Para-aortic ILR n=15 (22.7%)	Distant ILR n=16 (24.2%)	Multiple ILR sites n=26 (39.4%)	
Age at primary surgery (years), mean (SD)	63.8 (10.1)	70.2 (11.8)	61.3 (12.8)	63.6 (7.1)	63.1 (8.8)	0.31
Tumor diameter (mm), median (IQR)	42 (32–65)	54 (40–72)	50 (36–65)	42 (30–70)	40 (30–62)	0.64
Tumor diameter, N (%)						0.35
<2 cm	5 (7.6)	–	–	3 (18.8)	2 (7.7)	
>2 cm	57 (86.4)	9 (100.0)	15 (100.0)	12 (75.0)	21 (80.8)	
Unknown	4 (6.1)	–	–	1 (6.3)	3 (11.5)	
Histology, N (%)						0.89
Endometrioid	41 (62.1)	5 (55.6)	10 (66.7)	9 (56.3)	17 (65.4)	
Non-endometrioid†	25 (37.9)	4 (44.4)	5 (33.3)	7 (43.8)	9 (34.6)	
FIGO stage, N (%)						0.10
I–II	15 (22.7)	4 (44.4)	5 (33.3)	1 (6.3)	5 (19.2)	
III–IV	51 (77.3)	5 (55.6)	10 (66.7)	15 (93.8)	21 (80.8)	
FIGO grade, N (%)						0.80
1	13 (19.7)	1 (11.1)	3 (20.0)	4 (25.0)	5 (19.2)	
2	14 (21.2)	1 (11.1)	5 (33.3)	2 (12.5)	6 (23.1)	
3	39 (59.1)	7 (77.8)	7 (46.7)	10 (62.5)	15 (57.7)	
LVSI, N (%)						0.51
No	30 (45.5)	4 (44.4)	10 (66.7)	5 (31.3)	11 (42.3)	
Yes	31 (47.0)	4 (44.4)	5 (33.3)	9 (56.3)	13 (50.0)	
Unknown	5 (7.6)	1 (11.1)	–	2 (12.5)	2 (7.7)	
Myometrial invasion, N (%)						0.83
<50%	26 (39.4)	3 (33.3)	5 (33.3)	6 (37.5)	12 (46.2)	
≥50%	40 (60.6)	6 (66.7)	10 (66.7)	10 (62.5)	14 (53.8)	
Lymph node assessment details						
Lymphadenectomy, N (%)						0.40
None	6 (9.1)	–	1 (6.7)	3 (18.8)	2 (7.7)	
Para-aortic only	1 (1.5)	–	–	–	1 (3.8)	
Pelvic only	20 (30.3)	1 (11.1)	5 (33.3)	3 (18.8)	11 (42.3)	
Pelvic and para-aortic	39 (59.1)	8 (88.9)	9 (60.0)	10 (62.5)	12 (46.2)	
Number of LNs removed via LND, median (IQR)‡						
Total	31 (18–45)	44 (40–46)	33 (22–49)	29 (6–45)	20 (10–35)	0.12
Pelvic	24 (13–33)	29 (25–33)	26 (21–35)	24 (6–34)	20 (12–30)	0.34
Para-aortic	10 (5–18)	13 (11–19)	15 (5–18)	8 (4–11)	6 (3–11)	0.25
Positive LNs via LND, N (%)						0.52
No LND	6 (9.1)	–	1 (6.7)	3 (18.8)	2 (7.7)	
LND with negative nodes	19 (28.8)	5 (55.6)	4 (26.7)	3 (18.8)	7 (26.9)	
LND with positive nodes	41 (62.1)	4 (44.4)	10 (66.7)	10 (62.5)	17 (65.4)	
Adjuvant therapy details						
Adjuvant therapy, N (%)						0.53

Continued

Original research

Table 1 Continued

Characteristic	Site of recurrence					P* value
	All ILR n=66	Pelvic ILR n=9 (13.6%)	Para-aortic ILR n=15 (22.7%)	Distant ILR n=16 (24.2%)	Multiple ILR sites n=26 (39.4%)	
Observation±VBT	19 (29.2)	4 (44.4)	5 (33.3)	2 (12.5)	8 (32.0)	
EBRT±VBT	22 (33.8)	2 (22.2)	7 (46.7)	7 (43.8)	6 (24.0)	
Chemotherapy±VBT	17 (26.2)	2 (22.2)	3 (20.0)	4 (25.0)	8 (32.0)	
Chemotherapy and EBRT±VBT	7 (10.8)	1 (11.1)	–	3 (18.8)	3 (12.0)	
Unknown	1	–	–	–	1	
Recurrence details						
Timing of recurrence following surgery (years), median (IQR)	1.0 (0.6–2.4)	1.2 (1.2–1.6)	1.2 (0.7–2.4)	0.7 (0.5–2.0)	0.8 (0.4–2.8)	0.62
LR in an area that was not previously irradiated,§ N (%)						0.005
No	11 (16.7)	3 (33.3)	–	–	8 (30.8)	
Yes	54 (81.8)	6 (66.7)	15 (100.0)	16 (100.0)	17 (65.4)	
Unknown	1 (1.5)	–	–	–	1 (3.8)	
Treatment of ILR						0.52
Observation or hormonal therapy only	15 (22.7)	2 (22.2)	3 (20.0)	3 (18.8)	7 (26.9)	
Chemotherapy and/or radiotherapy	33 (50.0)	4 (44.4)	5 (33.3)	9 (56.3)	15 (57.7)	
Surgery±other treatments	18 (27.3)	3 (33.3)	7 (46.7)	4 (25.0)	4 (15.4)	

*Kruskal-Wallis p value reported for continuous variables and χ^2 , or Fisher's exact p value reported for categorical variables obtained comparing the four groups with a different site of ILR.
†Non-endometrioid histology includes: 20 serous, 2 clear cell, 1 carcinosarcoma, 1 undifferentiated, and 1 mixed (endometrioid serous).
‡Among those who had the lymphadenectomy; one patient with an unknown number of nodes removed.
§In the case of multiple sites of ILR, such as pelvic and para-aortic recurrence, all the areas need to be not irradiated to consider the ILR as a recurrence in a non-irradiated area.
EBRT, external beam radiation therapy; FIGO, International Federation of Gynecology and Obstetrics; ILR, isolated lymphatic recurrence; LN, lymph node; LND, lymphadenectomy; LR, lymphatic recurrence; LVSI, lymphovascular space invasion; VBT, vaginal brachytherapy.

lymphadenectomy was the most common nodal assessment in all the groups, ranging from 46.2% in those with multiple sites to 88.9% in those with pelvic isolated lymphatic recurrence. Only one patient in the entire population underwent nodal staging by sentinel lymph node biopsy only, without further lymphadenectomy; this patient was included in the 'pelvic only' lymph node assessment group. Data on adjuvant treatment administered for the primary tumor are summarized in Table 1.

The median time from primary surgery to the diagnosis of isolated lymphatic recurrence was 1 year (IQR 0.6–2.4) and did not differ between recurrence sites (Table 1). Isolated lymphatic recurrences that developed in a not previously irradiated lymph node-bearing area were significantly more frequent in the para-aortic and distant groups (66.7% pelvic, 100% para-aortic, 100% distant, 65.4% multiple; $p=0.005$). Most patients who developed isolated lymphatic recurrence underwent some type of treatment for the recurrence. Data on treatment for recurrence are shown in Table 1. Among patients who underwent surgery with/without other treatments for isolated lymphatic recurrence, only one patient had surgery alone, three patients

had surgery+chemotherapy, nine patients had surgery+radiotherapy, three patients had surgery+chemotherapy+radiotherapy, one patient had surgery+hormonal therapy, and one patient had surgery+chemotherapy+hormonal therapy.

Among the 15 patients with para-aortic isolated lymphatic recurrence, one did not have lymphadenectomy at primary surgery, five had pelvic lymphadenectomy (one was node-negative, four were node-positive at pathologic evaluation), nine had pelvic and para-aortic lymphadenectomy (three were negative, six were node-positive). Among the six patients with positive nodes who had both pelvic and para-aortic lymphadenectomy, four had positive pelvic nodes only and two had positive pelvic and para-aortic nodes. None of the para-aortic isolated lymphatic recurrences receiving adjuvant external beam radiotherapy have also received extended radiotherapy in the para-aortic field.

Among the nine patients with pelvic isolated lymphatic recurrence, one patient had pelvic lymphadenectomy at primary surgery (node-negative at pathologic evaluation), four patients had pelvic and para-aortic lymphadenectomy (all node-negative), four patients had pelvic and para-aortic lymphadenectomy (three with positive

Table 2 Clinical characteristics of long-term survivors (ie, patients that survived at least 5 years or more after the ILR)

Patient	Age* (years)	FIGO grade	LVSI	Adjuvant therapy	LR in an area that was not previously irradiated†	Isolated lymphatic recurrence site	Time of recurrence following surgery (years)	Treatment of ILR	Years from ILR to last follow-up	Status at last follow-up
1	39	3	No	EBRT+VBT	Yes	PA	2.5	Surgery+EBRT	24.0	Alive
2	52	3	Yes	CHT	Yes	Multiple (PA and supraclavicular)	0.4	Surgery+CHT	11.4	Alive
3	53	1	No	CHT	Yes	PA	2.5	Surgery+EBRT	13.0	Alive
4‡	59	2	No	VBT	Yes	PA	2.4	EBRT	6.8	Alive
5	53	3	Yes	EBRT+VBT	Yes	PA	2.0	Surgery+CHT	13.8	Alive
6	50	2	No	EBRT+VBT	Yes	PA	0.6	Surgery, EBRT, and CHT	11.3	Alive
7	70	2	No	VBT	Yes	PA	0.9	Surgery+CHT	6.6	Alive
8	57	1	No	None	Yes	PA	0.4	EBRT	7.0	Alive
9‡	58	1	Yes	EBRT	No	Multiple (P and PA)	0.5	HT	7.2	Dead
10‡	87	2	n/a	EBRT	No	P	0.4	HT	6.5	Dead
11	84	1	No	None	Yes	Distant	2.1	Surgery+EBRT	5.2	Dead
12‡	50	1	No	EBRT	Yes	Distant	0.8	EBRT	19.0	Dead
13‡	62	3	Yes	EBRT	Yes	Distant	0.3	HT	8.6	Dead
14	63	1	No	None	Yes	Multiple (N/A)	6.7	Surgery+HT	14.9	Dead
15	68	1	No	VBT	Yes	Multiple (PA and mediastinal)	0.7	CHT and EBRT	5.9	Dead

All patients had endometrioid histology, except for patient number 13, whose tumor was non-endometrioid.
 *At primary surgery.
 †In the case of multiple sites of ILR, such as pelvic and para-aortic recurrence, all the areas need to be not irradiated to consider the ILR as a recurrence in a non-irradiated area.
 ‡No pathologic confirmation of the recurrence. Diagnosis of recurrence was based on clinical and radiologic suspicion and further consolidated based on response to treatment for the recurrence.
 CHT, chemotherapy; EBRT, external beam radiation therapy; FIGO, International Federation of Gynecology and Obstetrics; HT, hormonal therapy; ILR, isolated lymphatic recurrence; LR, lymphatic recurrence; LVSI, lymphovascular space invasion; N/A, not available; P, pelvic; PA, para-aortic; VBT, vaginal brachytherapy.

pelvic nodes only, and one patient had positive pelvic and para-aortic nodes).

The group of multiple site isolated lymphatic recurrences included 14 pelvic and para-aortic, eight distant and para-aortic, and four distant and pelvic and para-aortic. Among the 14 pelvic and para-aortic isolated lymphatic recurrences, seven did not receive adjuvant radiotherapy, seven had adjuvant radiotherapy (five pelvic radiation only, two pelvic and para-aortic radiation). All these seven patients receiving radiotherapy (pelvic or pelvic+para-aortic radiation) had an in-field recurrence.

Of the 66 patients, 56 patients had died at the time of last follow-up, including 46 patients who died due to disease after diagnosis of isolated lymphatic recurrence. The median follow-up after diagnosis of recurrence for the remaining 10 patients who were not deceased at last follow-up was 9.2 (IQR 6.6–13.0) years.

Focusing on the group of the 15 long-term survivors (women who survived at least 5 years from the diagnosis of isolated lymphatic recurrence), seven patients (46.7%) had para-aortic recurrence, four (26.7%) had multiple sites recurrence, three (20.0%) had distant recurrence, and only one (6.7%) had pelvic recurrence. Also, eight of the 15 long term survivors (53.3%) were selected for surgery with/without other treatment for isolated lymphatic recurrence. Moreover, 7 of 15 (46.7%) recurrences in the para-aortic area were long-term survivors (Table 2). Among the group of long-term survivors, two patients had developed an in-field recurrence in areas that had been irradiated in the adjuvant setting, after receiving systematic pelvic and para-aortic lymphadenectomy at

primary surgery. In contrast, none of the seven para-aortic isolated lymphatic recurrence long-term survivors have received radiotherapy extended to the para-aortic region in the adjuvant setting, and six of seven have received pelvic and para-aortic nodal staging at primary surgery.

Median cause-specific survival after diagnosis of isolated lymphatic recurrence was 2 years overall, and survival did not differ significantly among the four recurrence groups (Figure 1A). At univariate analysis (Table 3), FIGO grade 2 and 3 and the presence of lymphovascular space invasion in the primary tumor were significantly associated with worse cause-specific survival (Figure 1B,C). Treatment of isolated lymphatic recurrence was also significantly associated with survival, such that patients who underwent surgery had a more favorable survival (Figure 1D). This latter association was attenuated after adjusting for age at primary surgery (Table 3, $p=0.045$). This confounding effect of age is anticipated, considering the role of age in the treatment decision. The mean age at the time of the recurrence diagnosis was 60.9 years (SD 10.3) for the 18 patients who underwent surgery compared with 65.7 (8.4) years for the 33 patients who received chemotherapy±radiotherapy, and 70.2 (11.0) years for the 15 patients who received no treatment or hormonal therapy alone.

A multivariable model was fitted, including all variables with $p<0.10$ based on univariate analysis and age at primary surgery (Table 4). The presence of FIGO grade 2 and 3, lymphovascular space invasion in the primary tumor, and the type of treatment for the isolated lymphatic recurrence maintained their statistically significant ($p<0.05$) association with cause-specific survival.

Original research

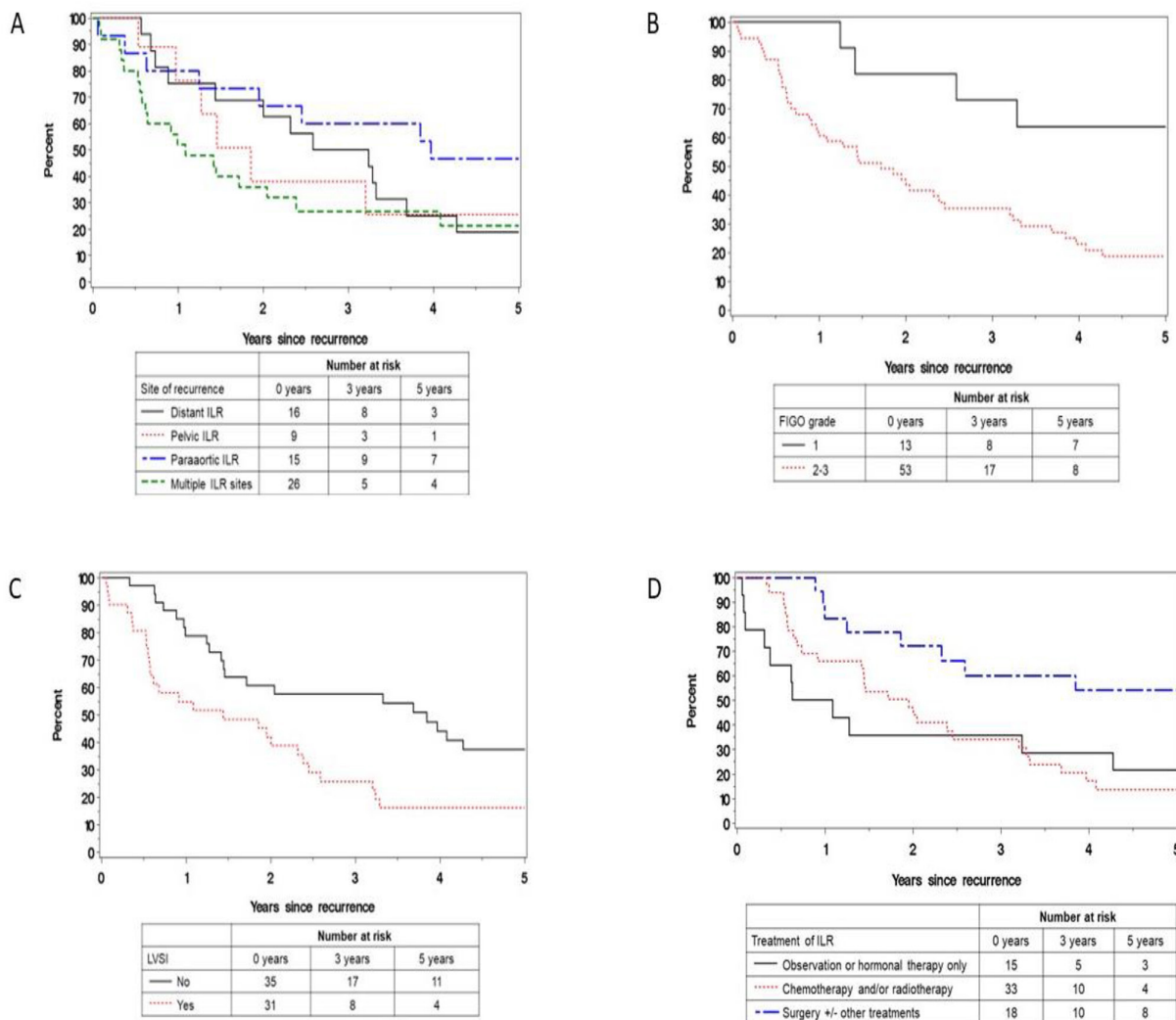


Figure 1 Cause-specific survival curves, according to site of isolated lymphatic recurrence, clinical characteristics, and treatment at the time of isolated lymphatic recurrence. (A) Cause-specific survival according to sites of isolated lymphatic recurrence. (B) Cause-specific survival in patients with isolated lymphatic recurrence by FIGO grade (1 vs 2–3 in the primary tumor). (C) Cause-specific survival in patients with isolated lymphatic recurrence according to presence of lymphovascular space invasion in the primary tumor. (D) Cause-specific survival in patients with isolated lymphatic recurrence stratified by treatment of isolated lymphatic recurrence. ILR, isolated lymphatic recurrence; LVS, lymphovascular space invasion.

DISCUSSION

Summary of Main Results

In our analysis, we demonstrated that isolated lymphatic recurrence in endometrial cancer is a rare finding. In fact, in our population, only 66 (1.6%) of 4216 patients with endometrial cancer developed an isolated lymphatic recurrence. In addition, we observed that low-grade disease (FIGO grade 1), absence of lymphovascular space invasion in the primary tumor, and/or being treated with surgery (with/without other treatments) for the recurrence were significantly associated with improved cause-specific survival at multivariate analysis, further adjusted for age. In addition, nearly half of patients with recurrence in the para-aortic area were long-term survivors.

Results in the Context of Published Literature

The type of treatment for isolated lymphatic recurrence was independently associated with survival in our study. Patients who were

carefully selected for surgery (with/without other associated treatments) had a decreased risk of death due to disease compared with patients with non-surgical therapies. The subgroup of patients who underwent surgery in our study is small and does not allow further sub-analysis to draw conclusions on which combination of associated treatments has the best survival outcomes when combined with surgery. However, our results are consistent with previous evidence showing a better prognosis in patients undergoing secondary surgery compared with other treatment modalities^{16–18}; even though these previous studies had considered only distant isolated lymphatic recurrence^{16 17} or combination of different recurrence sites in their populations.¹⁸

Other studies have shown that surgery with or without radiotherapy should be considered for bulky but resectable nodal recurrences. Specifically, if the recurrence has developed in a previously irradiated field, surgical resection alone may be indicated; alternatively, radical resection combined with intra-operative radiation

Table 3 Univariate Cox-regression analysis for cause-specific survival after ILR

Characteristic	No. of events per level of each characteristic	Unadjusted		Adjusted for age at primary surgery	
		HR (95% CI)	P value	HR (95% CI)	P value
Age at primary surgery (years)*	--	1.26 (0.96 to 1.67)	0.10	--	--
Tumor diameter (mm)*	--	1.01 (0.79 to 1.28)	0.97	1.06 (0.81 to 1.38)	0.66
Tumor diameter			0.62		0.35
<2 cm	3/5	Reference		Reference	
>2 cm	40/57	1.45 (0.45 to 4.70)		1.88 (0.57 to 6.26)	
Unknown	3/4	2.24 (0.45 to 11.17)		3.37 (0.65 to 17.53)	
Histology			0.16		0.17
Endometrioid	25/41	Reference		Reference	
Non-endometrioid	21/25	1.52 (0.84 to 2.73)		1.51 (0.84 to 2.72)	
FIGO stage			0.27		0.11
I-II	9/15	Reference		Reference	
II-IV	37/51	1.51 (0.73 to 3.14)		1.84 (0.87 to 3.90)	
FIGO grade			0.01		0.01
1	4/13	Reference		Reference	
2-3	42/53	3.76 (1.34 to 10.54)		3.61 (1.28 to 10.13)	
LVSI			0.03		0.02
No	16/30	Reference		Reference	
Yes	26/31	2.37 (1.26 to 4.44)		2.42 (1.29 to 4.54)	
Unknown	4/5	1.81 (0.61 to 5.42)		1.40 (0.45 to 4.40)	
Myometrial invasion			0.29		0.30
<50%	16/26	Reference		Reference	
≥50%	30/40	1.39 (0.76 to 2.55)		1.38 (0.75 to 2.54)	
Total number of LNs removed via LND†	--	1.00 (0.98 to 1.01)	0.41	1.00 (0.98 to 1.01)	0.51
Positive LNs via LND			0.20		0.11
No LND	3/6	Reference		Reference	
LND with negative nodes	12/19	1.73 (0.49 to 6.17)		1.92 (0.53 to 6.87)	
LND with positive nodes	31/41	2.56 (0.78 to 8.44)		3.03 (0.91 to 10.10)	
Adjuvant therapy			0.41		0.27
Observation±VBT	12/19	Reference		Reference	
EBRT±VBT	14/22	0.96 (0.44 to 2.07)		1.17 (0.53 to 2.57)	
Chemotherapy±VBT	13/17	1.54 (0.70 to 3.40)		1.79 (0.80 to 4.00)	
Chemotherapy and EBRT±VBT	6/7	1.85 (0.68 to 4.99)		2.41 (0.85 to 6.77)	
Unknown	1/1	--		--	
Site of ILR			0.21		0.26
Pelvic	6/9	Reference		Reference	
Para-aortic	8/15	0.56 (0.19 to 1.62)		0.75 (0.24 to 2.37)	
Distant	13/16	0.95 (0.36 to 2.51)		1.16 (0.42 to 3.19)	
Multiple ILR sites	19/26	1.37 (0.55 to 3.44)		1.67 (0.63 to 4.41)	
Recurrence details					
Timing of recurrence following surgery*	--	0.94 (0.74 to 1.19)	0.60	0.94 (0.74 to 1.19)	0.62
LR in an area that was not previously irradiated‡			0.84		0.92
No	7/11	Reference		Reference	

Continued

Table 3 Continued

Characteristic	No. of events per level of each characteristic	Unadjusted		Adjusted for age at primary surgery	
		HR (95% CI)	P value	HR (95% CI)	P value
Yes	38/54	0.92 (0.41 to 2.06)		1.04 (0.46 to 2.37)	
Unknown	1/1	–			
Treatment of ILR			0.02		0.045
Observation or hormonal therapy only	11/15	3.08 (1.24 to 7.67)		2.74 (1.06 to 7.04)	
Chemotherapy and/or radiotherapy	27/33	2.81 (1.27 to 6.23)		2.67 (1.20 to 5.95)	
Surgery±other treatments	8/18	Reference		Reference	

*HR per 10 year increase for age and per doubling for tumor diameter and timing of recurrence following surgery.

†Among those who had the lymphadenectomy; one patient with an unknown number of nodes removed.

‡In the case of multiple sites of ILR, such as pelvic and para-aortic recurrence, all the areas need to be not irradiated to consider the ILR as a recurrence in a non-irradiated area.

EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; ILR, isolated lymphatic recurrence; LND, lymphadenectomy; LNs, lymph nodes; LR, lymphatic recurrence; LVSI, lymphovascular space invasion; VBT, vaginal brachytherapy.

therapy or radiofrequency ablation may be viable options.¹⁹ In addition, a recently published systematic review on the management of recurrent endometrial cancer²⁰ suggested the following therapeutic management for single/locoregional nodal recurrences: if the recurrence is considered resectable, both surgery and stereotactic radiotherapy represent viable options, whereas if the recurrence is considered unresectable, chemotherapy needs to be considered.

Our study is retrospective, and our population is not large enough to provide robust evidence in favor of surgery for the management of isolated lymphatic recurrence. Moreover, patients undergoing

surgical treatment have been specifically selected based on good performance status and higher possibility of achieving a radical resection, thus introducing a bias in the association between surgery and increased survival. However, from the analysis of our results and previous evidence,²⁰ it seems reasonable to state that surgery, with or without other treatment, could represent a viable effective strategy for patients with isolated lymphatic recurrence who have been carefully selected based on their overall health and site of recurrence, whenever the tumor is considered surgically resectable.

The role of substantial lymphovascular space invasion in predicting both nodal and distant recurrence and worse overall survival has already been suggested by previous studies.^{21 22} In our analysis, the presence of lymphovascular space invasion in the primary tumor showed its negative prognostic influence on survival in the specific subset who had developed an isolated lymphatic recurrence. The presence of lymphovascular space invasion mirrors the higher biological aggressiveness of the primary tumor and the increased likelihood of lymphatic and systemic spread of the disease; thus, directly impacting survival outcomes. Therefore, it seems reasonable that those tumors with a higher propensity for systemic spread would also develop recurrences with a biologically aggressive behavior. Among the other pathologic features, FIGO grade 1 was significantly associated with improved survival on both univariate and multivariate analysis. This finding probably reflects the more indolent biological behavior of the primary tumor in these isolated lymphatic recurrences.

There are conflicting data in the literature regarding oncologic outcomes in patients with endometrial cancer with recurrent disease. Even the few available studies that focus on isolated lymphatic recurrence^{16 17} do not stratify patients by different recurrence sites. Therefore, a comparison between our data and previous studies is not possible. Indeed, some studies showed no significant difference in survival when comparing different subgroups of both nodal and non-nodal sites of recurrence.^{15–17 23–28} Others reported that both the

Table 4 Multivariable analysis for cause-specific survival after ILR

Characteristic	Adjusted HR (95% CI)	P value
Age at primary surgery (years)*	1.13 (0.80 to 1.58)	0.49
FIGO grade		0.028
1	Reference	
2–3	3.24 (1.13 to 9.25)	
LVSI		0.016
No	Reference	
Yes	2.10 (1.15 to 3.86)	
Treatment of ILR		0.0499
Observation or hormonal therapy only	2.36 (0.90 to 6.14)	
Chemotherapy and/or radiotherapy	2.83 (1.23 to 6.52)	
Surgery±other treatments	Reference	

*HR per 10-year increase for age.

FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; ILR, isolated lymphatic recurrence.

number and the multiple sites of recurrence were independent predictors of survival.^{29 30} The reason for this conflicting evidence may be due to the heterogeneity of the study populations. Most studies have analyzed altogether patients with recurrences in different sites (nodal, peritoneal, abdominal); therefore, making a comparison with the available evidence challenging.

The median time to recurrence of 1 year in our study was consistent with previous studies and similar among the different subgroups of isolated lymphatic recurrence.^{28 31} In our population, almost half (47%) of the long-term survivors had para-aortic isolated lymphatic recurrence. Conversely, 7 of 15 (47%) patients with para-aortic isolated lymphatic recurrences were long-term survivors (compared with <20% in the other subgroups). Very limited information is available in the literature on patients with isolated lymphatic recurrence in the para-aortic area. Nakamura et al³² observed that patients with para-aortic isolated lymphatic recurrence benefit from cytoreductive surgery, with a significant improvement in their prognosis.³² Similarly, our results reported longer survival in the para-aortic group, among which five of seven patients had received surgery for recurrence management (Table 2). Our data on longer survival outcomes of para-aortic isolated lymphatic recurrence compared with the other recurrence sites should be reframed in the context of the minimally invasive surgery era and reinforce the already existing evidence showing that surgical radicality in the para-aortic area for staging purposes may not add significant survival benefit, while potentially increasing the risk of peri-operative complications. Indeed, Aloisi et al³³ have demonstrated in a large population of FIGO stage IIIC1 endometrial cancers not receiving para-aortic nodal assessment at primary surgery that isolated lymphatic recurrence in the para-aortic region is a rare event (less than 4%). Moreover, no significant differences in rates or patterns of recurrence have been reported in Aloisi's study when stratifying for the adjuvant treatment received for the primary tumor. Of note, in the subset of patients receiving extended field radiation to the para-aortic region (n=8), none have developed para-aortic isolated lymphatic recurrence, thus suggesting a potential role of extended radiotherapy in prevention of nodal recurrences in the para-aortic region in this setting, even though this subset was small, and no conclusions can be drawn in this regard. However, it must be highlighted again that in our study the majority of patients (59%) received both pelvic and para-aortic nodal staging at primary surgery; more specifically, 89% of the pelvic group, 60% of the para-aortic group, 63% of the distant group, and 46% of the multiple sites group.

Strengths and Weaknesses

This is one of the largest populations of patients with isolated lymphatic recurrence reported in the literature to date. However, the retrospective nature of our study and the small sample size represent a limitation. Isolated lymphatic recurrence is a rare finding in endometrial cancer, and patients undergoing surgical treatment have been specifically selected based on good performance status and higher possibility of achieving a radical resection, thus introducing a bias in the association between surgery and increased survival. Moreover, pathologic confirmation of the recurrence was not performed in 33.3% of the long-term survivors.

Implication for Practice and Future Research

This study lays the foundation for a deeper understanding of isolated lymphatic recurrence in patients with endometrial cancer. Patients with isolated lymphatic recurrence and grade 1 histology and absence of lymphovascular space invasion in the primary tumor are less likely to have poor prognosis. Also, almost half of the patients with isolated lymphatic recurrence in the para-aortic area were long-term survivors. The above features (grade 1 with no lymphovascular space invasion, especially in case of isolated para-aortic recurrence) may help in the selection of patients who can be considered surgical candidates.

CONCLUSIONS

In the present study, we observed that the absence of lymphovascular space invasion and FIGO grade 1 in the primary tumor positively influenced prognosis in patients with isolated lymphatic recurrence. We also observed that, in carefully selected patients with isolated lymphatic recurrence, surgical management (with or without other associated therapies) could increase survival. Additional studies may help to confirm our results and strengthen our conclusions.

Author affiliations

¹Department of Gynecologic Oncology, Mayo Clinic, Rochester, Minnesota, USA

²Department of Women, Children and Public Health Sciences, Gynecologic Oncology Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Lazio, Italy

³Department of Obstetrics and Gynecology, AOUI Verona, University of Verona, Verona, Italy

⁴Department of Gynecologic Oncology, Baptist Memorial Hospital for Women, Memphis, Tennessee, USA

⁵Division of Clinical Trials and Biostatistics, Mayo Clinic, Rochester, Minnesota, USA

⁶Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota, USA

Twitter Luigi Antonio De Vitis @LuigiDEvitis and Francesco Fanfani @fracfanfani

Contributors IC and SG contributed equally and are joint first authors. All listed authors have contributed to the manuscript preparation. Guarantor: AM. Conceived and designed the study: IC, SG, SK, SU, AM. Data collection, analysis, and interpretation: IC, SG, SK, ALW, MM, LADV, SU. Writing, review, and editing: all authors.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Mayo Clinic Institutional Review Board. IRB number: 20-000174. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs

Ilaria Capasso <http://orcid.org/0000-0001-5987-6654>

Simone Garzon <http://orcid.org/0000-0002-5840-699X>

Gretchen Glaser <http://orcid.org/0000-0001-9413-316X>

Carrie Langstraat <http://orcid.org/0000-0001-9361-8392>

Giovanni Scambia <http://orcid.org/0000-0003-2758-1063>

Francesco Fanfani <http://orcid.org/0000-0003-1991-7284>

Andrea Mariani <http://orcid.org/0000-0001-8059-1602>

REFERENCES

- 1 Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. *CA Cancer J Clin* 2022;72:7–33.

- 2 Rose PG, Ali S, Moslemi-Kebria M, *et al*. Paclitaxel, carboplatin, and bevacizumab in advanced and recurrent endometrial carcinoma. *Int J Gynecol Cancer* 2017;27:452–8.
- 3 Perrone E, Capasso I, Pasciuto T, *et al*. Laparoscopic vs. robotic-assisted laparoscopy in endometrial cancer staging: large retrospective single-institution study. *J Gynecol Oncol* 2021;32:e45.
- 4 Aalders JG, Abeler V, Kolstad P. Recurrent adenocarcinoma of the endometrium: a clinical and histopathological study of 379 patients. *Gynecol Oncol* 1984;17:85–103.
- 5 Abu-Rustum NR, Chi DS, Leitao M, *et al*. What is the incidence of isolated paraaortic nodal recurrence in grade 1 endometrial carcinoma. *Gynecol Oncol* 2008;111:46–8.
- 6 Mariani A, Dowdy SC, Keeney GL, *et al*. High-risk endometrial cancer subgroups: candidates for target-based adjuvant therapy. *Gynecol Oncol* 2004;95:120–6.
- 7 Creutzberg CL, Nout RA, Lybeert MLM, *et al*. Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. *Int J Radiat Oncol Biol Phys* 2011;81:e631–8.
- 8 Bradford LS, Rauh-Hain JA, Schorge J, *et al*. Advances in the management of recurrent endometrial cancer. *Am J Clin Oncol* 2015;38:206–12.
- 9 Concin N, Matias-Guiu X, Vergote I, *et al*. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. *Int J Gynecol Cancer* 2021;31:12–39.
- 10 Lodeweges JE, Klinkenberg TJ, Ubbels JF, *et al*. Long-term outcome of surgery or stereotactic radiotherapy for lung oligometastases. *J Thorac Oncol* 2017;12:1442–5.
- 11 Palma DA, Olson R, Harrow S, *et al*. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet* 2019;393:2051–8.
- 12 Turan T, Tasci T, Karalok A, *et al*. Salvage cytoreductive surgery for recurrent endometrial cancer. *Int J Gynecol Cancer* 2015;25:1623–32.
- 13 Nout RA, Smit VTHBM, Putter H, *et al*. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. *Lancet* 2010;375:816–23.
- 14 Wortman BG, Creutzberg CL, Putter H, *et al*. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. *Br J Cancer* 2018;119:1067–74.
- 15 Ho JC, Allen PK, Jhingran A, *et al*. Management of nodal recurrences of endometrial cancer with IMRT. *Gynecol Oncol* 2015;139:40–6.
- 16 Kılıç F, Kimyon Cömert G, Akar S, *et al*. Evaluation of peripheral nodal recurrence in patients with endometrial cancer. *J Turk Ger Gynecol Assoc* 2022;23:38–50.
- 17 Foote RL, Schray MF, Wilson TO, *et al*. Isolated peripheral lymph node recurrence of endometrial carcinoma. *Cancer* 1988;61:2561–5.
- 18 Shikama A, Minaguchi T, Takao W, *et al*. Predictors of favorable survival after secondary cytoreductive surgery for recurrent endometrial cancer. *Int J Clin Oncol* 2019;24:1256–63.
- 19 Del Carmen MG, Boruta DM, Schorge JO. Recurrent endometrial cancer. *Clin Obstet Gynecol* 2011;54:266–77.
- 20 Restaino S, Dinoui G, La Fera E, *et al*. Recurrent endometrial cancer: which is the best treatment? Systematic review of the literature. *Cancers (Basel)* 2022;14:4176.
- 21 Bosse T, Peters EEM, Creutzberg CL, *et al*. Substantial lympho-vascular space invasion (LVS) is a significant risk factor for recurrence in endometrial cancer—a pooled analysis of PORTEC 1 and 2 trials. *Eur J Cancer* 2015;51:1742–50.
- 22 Restaino S, Tortorella L, Dinoui G, *et al*. Semiquantitative evaluation of lympho-vascular space invasion in patients affected by endometrial cancer: prognostic and clinical implications. *Eur J Cancer* 2021;142:29–37.
- 23 Mariani A, Webb MJ, Keeney GL, *et al*. Predictors of lymphatic failure in endometrial cancer. *Gynecol Oncol* 2002;84:437–42.
- 24 Corn BW, Lanciano RM, Greven KM, *et al*. Endometrial cancer with para-aortic adenopathy: patterns of failure and opportunities for cure. *Int J Radiat Oncol Biol Phys* 1992;24:223–7.
- 25 Mariani A, Webb MJ, Galli L, *et al*. Potential therapeutic role of para-aortic lymphadenectomy in node-positive endometrial cancer. *Gynecol Oncol* 2000;76:348–56.
- 26 Mariani A, Webb MJ, Rao SK, *et al*. Significance of pathologic patterns of pelvic lymph node metastases in endometrial cancer. *Gynecol Oncol* 2001;80:113–20.
- 27 Kilts TP, Glaser GE, Langstraat CL, *et al*. Comparing risk stratification criteria for predicting lymphatic dissemination in endometrial cancer. *Gynecol Oncol* 2019;155:21–6.
- 28 Bricou A, Bendifallah S, Daix-Moreux M, *et al*. A proposal for a classification for recurrent endometrial cancer: analysis of a French multicenter database from the FRANCOGYN study group. *Int J Gynecol Cancer* 2018;28:1278–84.
- 29 Shim S-H, Kim D-Y, Kim HJ, *et al*. Stratification of risk groups according to survival after recurrence in endometrial cancer patients. *Medicine (Baltimore)* 2017;96:e6920.
- 30 Sohaib SA, Houghton SL, Meroni R, *et al*. Recurrent endometrial cancer: patterns of recurrent disease and assessment of prognosis. *Clin Radiol* 2007;62:28–34.
- 31 Bendifallah S, Ouldamer L, Lavoue V, *et al*. Patterns of recurrence and outcomes in surgically treated women with endometrial cancer according to ESMO-ESGO-ESTRO consensus conference risk groups: results from the FRANCOGYN study group. *Gynecol Oncol* 2017;144:107–12.
- 32 Nakamura H, Takehara K, Samura O, *et al*. Cytoreductive surgery for isolated para-aortic lymph node recurrence of endometrial cancer: report of four cases and a review of the literature. *Eur J Gynaecol Oncol* 2014;35:535–8.
- 33 Aloisi A, Casanova JM, Tseng JH, *et al*. Patterns of FIRST recurrence of stage IIC1 endometrial cancer with no PARAAORTIC nodal assessment. *Gynecol Oncol* 2018;151:395–400.