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Incidence, patterns and prognosis of first distant recurrence after surgically treated early stage endometrial cancer: Results from the multicentre FRANCOGYN study group

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ABSTRACT

Patterns of distant metastatic failure of endometrial cancer (EC) by specific anatomic site are not well described in the literature. In this manuscript, we evaluated the metastatic patterns of EC cancer and analysed the potential distribution of metastatic disease in this malignancy.

Methods: A total of 1444 women with EC were identified. Of which we extracted women with locoregional and distant recurrence or with distant recurrence alone. Women were scored based on first site of metastasis: multiple versus one site: bone, brain, lung, liver or sus diaphragmatic lymph nodes.

Results: 110 women developed distant metastatic disease with (n = 37(33.6%)) or without (n = 73(66.4%)) locoregional recurrence, including 39 women with exclusive first site of metastatic disease and 34 women with multiple sites of metastatic disease. When considering all women, the most common exclusive first site of metastasis was lung (42.8%). The median time to develop distant metastases was shorter after the completion of treatment for exclusive brain metastatic disease compared with other sites of metastatic– disease (7 months vs, 9 for lung, 10 for liver, 19 for bone and 27 months for sus-diaphragmatic LN; $P = 0.004$). The rate of 3-year overall survival was higher in the sus-diaphragmatic LN metastase group (83.3% vs 50.6% for lung, 37.3% for bone, 16.7% for brain and 0% for liver; $P = 0.0059$).

Conclusion: The present study has demonstrated the site-specific patterns of metastases. These data support current clinical practice of screening for site-specific metastatic disease after initial treatment of early stage EC based on concerning women-specific signs or symptoms.

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Introduction

Endometrial cancer (EC) is the fourth cancer among women worldwide, after breast, lung & bronchus and colon & rectum [1,2]. The incidence of EC is rising worlwilde, and women are still dying from the disease with a 5-year overall survival reaching 85% [3,4].

Despite both most cases of EC are diagnosed at an early stage for which prognosis is very good and improvements in treatment strategy provided according to ESMO-ESGO-ESTRO guidelines, approximately 5–30% of women with early stage EC still experience distant metastases (i.e. brain, lung, liver, bone metastases, sus-diaphragmatic nodal metastases). Among those, it has been recognized that more than 70% of recurrences occur within the first 2–3 years after treatment [5,6]. Patients with recurrent disease will be candidates for systemic palliative therapy. The choice between surgical cytoreduction, hormonal treatment and chemotherapy relies on several factors, including histopathological and clinical features of the individual patient [5,7].

In this specific setting the pattern of metastatic failure of EC by specific anatomic site are not well described in the literature despite EC-related deaths are largely secondary to the impact of distant metastases [7] with a significant reduction in overall survival.

Therefore, the aim of the present study was to examine the incidence, pattern and prognosis of first distant recurrence after surgically treated early stage endometrial cancer based on the multicentre FRANCOGYN study Group database.

Materials and methods

Study population

Data of women with histologically proven EC who received primary surgical treatment between January 2001 and December 2013 and who experienced distant metastases with or without associated locoregional recurrences were abstracted from nine institutions with maintained EC databases in France (Tours University Hospital, Reims University Hospital, Dijon Cancer Center, Rennes University Hospital, Lille University Hospital, Tenon University Hospital, Creteil University Hospital, Poissy University Hospital and Jean Verdier Hospital) and from the Senti-Endo trial [8]. All the women had given informed written consent to participate in the study. The research protocol was approved by the Institutional Review Board of the French College of Obstetrics and Gynaecology (CEROG 2014-GYN-020).

All enrolled women underwent preoperative abdomino-pelvic magnetic resonance imaging (MRI) unless contraindicated, in which case a computed tomography (CT) scan was performed. Clinical, surgical, pathological data and adjuvant therapies were collected. All women were classified according to the FIGO 2009 classification [9] after final pathological analysis.

Histological characteristics and ESMO risk groups

In line with the ESMO guidelines, histological type 1 EC includes endometrioid tumours of any histological grade and histological type 2 includes clear cell adenocarcinomas, serous adenocarcinomas and carcinosarcoma [10]. Grade 3 tumours are those with more than 50% of non-squamous, non-morular growth pattern [11]. In addition to the non-squamous solid growth component, a markedly atypical nuclear pattern incongruous for the architectural grade could increase the final tumour grade by one. A tumour is considered lymphovascular space invasion (LVSI) positive when tumour emboli are found within a space clearly lined by endothelial cells on a haematoxylin and eosin (H&E)-stained section [12].

Treatment and follow-up

Women with histological proven EC had undergone primary surgical treatment including at least total hysterectomy with bilateral salpingo-oophorectomy. Some aspects of the management of high-risk EC changed within the study period: before 2010, nodal staging included pelvic (P-LND) ± para-aortic lymph node dissection (PA-LND); after 2010, both pelvic and para-aortic lymphadenectomy were recommended. Surgery was performed according to the Institut National du Cancer (INCa) French guidelines [11]. Adjuvant therapy was administered on an individual basis at the discretion of a multidisciplinary committee, based on the INCa guidelines and included vaginal brachytherapy (VBT) and/or external beam radiotherapy (EBRT) and/or chemotherapy (CT) [13]. Clinical follow-up consisted of physical examinations and the use of imaging techniques according to the findings. Routine tests were not advocated without symptoms. Post treatment imaging might have consisted of ultrasound, computed tomography and/or magnetic resonance imaging, and in the last decade, 18-Fluorodeoxy Glucose Positron Emission Tomography (18-FDG PET CT). Follow-up visits were conducted every 3 months for the first 2 years, every 6 months for the following 3 years, and once a year thereafter.

Distant recurrence event and distant recurrence-free survival

Disease recurrence was diagnosed by biopsy or imaging techniques adapted to clinical symptoms (computed tomography and/or magnetic resonance imaging, and in the last decade, 18-Fluorodeoxy Glucose Positron Emission Tomography (18-FDG PET CT). Time-to-event analyses were calculated from the date of primary surgery as the starting point and women who were alive and without recurrence were censored at the date of last follow-up. Data for survival curves were calculated using the Kaplan–Meier method with log-rank test. Recurrence free survival (RFS) and overall survival (OS) were analysed. In metastatic site-specific analysis, the event of distant metastasis was divided in: exclusive first site of metastasis (brain, bone, lung, liver and sus diaphragmatic LN metastases) or multiple sites of first metastases.

Other analyses

Women, tumour and treatment characteristics were analysed using Chi-square statistics or Fisher's exact test in case of categorical and *t*-test or analysis of variance (ANOVA) for continuous variables. Values of $p < 0.05$ were considered significant.

Multivariate Cox proportional hazards models included demographics, histological, surgical and management factors that were first tested individually for association with overall survival using univariate analysis. Factors with a p value ≤ 0.1 in univariate analysis and those with a demonstrated clinical correlation with survival were then included in the Cox Proportional Hazard multivariate model.

Data were managed with an Excel database (Microsoft, Redmond, WA, USA) and analysed using the R 2.15 software, available online.

Results

Demographic characteristics of the study population

During the study period, 1444 women with presumed early-stage EC were documented as having received primary surgical treatment in the nine institutions. Distant recurrences were observed in 110 out of the 1444 women (7.6%) and were included in the analysis according to the following distribution: Tours

University Hospital (n = 49, 44.5%), Creteil Hospital (n = 17; 15.4%), Reims University Hospital (n = 11; 10%), Dijon Cancer Center (n = 10; 9.1%), Rennes University Hospital (n = 7; 6.4%), Tenon University Hospital (n = 6; 5.4%), Jeanne de Flandre University hospital (n = 3; 2.7%), Jean Verdier Hospital (n = 1; 0.9%) and Senti-Endo trial (n = 6; 5.4%). The demographics and clinicopathologic characteristics of women and initial management according to the recurrence location are reported in Table 1.

We found no significant difference between groups. In women with locoregional + metastatic recurrence (n = 37), exclusive first site of metastases was observed in 24 women (64.8%) and multiple sites in 13 women (35.2%).

Second, we compared characteristics and management of women with distant metastasis not associated with locoregional recurrence according to the number of distant metastases sites (one versus multiple) Table 2.

We found no significant difference between groups.

Survival outcomes

The Kaplan-Meier 3-year and 5-year overall survival for the whole population were 49.2% and 30.8% (Fig. 1A).

The median time to recurrence were 12; 15 and 13 months for locoregional + distant recurrences, exclusive first site of metastases and multiple sites of distant metastases, respectively. The 3-year and 5-year overall survival were not different between the three groups (41.2% and 28.8% for locoregional + distant recurrences, 56.9% and 36.4% for exclusive site of metastases group vs 43.7% and 19.9% in the multiple sites of metastases group, $P = 0.29$) (Fig. 1B). There was also no difference in the median survival after the occurrence of distant metastases regardless of additional treatment ($P = 0.60$) (Fig. 2).

Exclusive first sites of distant metastases

In women with only one site of distant metastasis without any locoregional recurrence (n = 39): 18 (46.1%) had lung metastases, 9 had bone metastases (23.1%), 6 (15.4%) had brain metastases, 3 (7.7%) had sus diaphragmatic LN metastases, 2 (5.1%) had liver metastases and one (2.5%) had cutaneous metastases.

When considering all women (with or without locoregional recurrence), at a median follow-up of 32 months, 63 (57.3%) women developed exclusive first site of metastatic disease and 47 women (42.7%) multiple sites of metastatic disease. The most common exclusive first site of distant metastasis was lung at every time point.

The five most common anatomic sites of distant metastases as the first exclusive event were lung (42.8%), bone (15.9%), liver (14.3%), sus diaphragmatic lymph nodes (14.3%) and brain (9.5%). Table 3 reports women and tumour characteristics stratified by these sites.

Women with bone metastases had higher age at the diagnosis of

Table 1
Demographic and clinicopathologic characteristics of women and initial management according to the recurrence location.

	Locoregional and distant recurrence n = 37	Distant recurrence n = 73	
Age (years)	69.9 ± 7.3 [55–86]	70.0 ± 8.9 [50–88]	0.95
Menopausal status	35 (94.6%)	62 (84.9%)	0.13
BMI (kg/m^2)	29.3 ± 7.5 [17–50.4]	28.5 ± 6.0 [16.4–43.7]	0.54
Hypertension	18 (48.6%)	25 (34.2%)	0.14
Diabetes	6 (16.2%)	8 (10.9%)	0.43
Personal history of breast cancer	5 (13.5%)	10 (13.7%)	0.97
Histological type			0.06
- Type I	16 (43.3%)	45(61.7%)	
- Type II	21 (56.7%)	28 (38.3%)	
Grade			0.54
- 1	5 (13.5%)	12 (16.4%)	
- 2	8 (21.6%)	19 (26.0%)	
- 3	23 (62.2%)	41 (56.2%)	
- Unknown	1 (2.7%)	1 (1.4%)	
Surgery route			0.30
- Laparoscopy	10 (27%)	24 (32.9%)	
- Laparotomy	20 (54%)	39 (53.4%)	
- Robotic surgery	2 (5.4%)	1 (1.4%)	
- Vaginally	3 (8.1%)	1 (1.4%)	
- Unknown	2 (5.4%)	8 (10.9%)	
Mean histological size (mm)	42.7	45.7	0.70
LVSI	26 (70%)	41 (56.2%)	0.15
Myometrial invasion >50%	24 (64.9%)	50 (68.5%)	0.70
ESMO			0.70
- Low	1 (2.7%)	3 (4.1%)	
- Intermediate	1 (2.7%)	3 (4.1%)	
- HIR	4 (10.8%)	8 (10.9%)	
- High	31 (83.8%)	59 (80.8%)	
Lymph node staging			0.08
- Pelvic lymphadenectomy	23 (62.2%)	40 (54.8%)	
- Pelvic and PA lymphadenectomy	8 (21.6%)	10 (13.7%)	
- No	6 (16.2%)	23 (31.5%)	
Lymph node status			0.13
- Positive	13 (41.9%)	13 (26%)	
- Negative	18(58.1%)	37(74%)	
Positive pelvic LN	12 (38.7%)	7 (14%)	0.01
Positive PA LN	5 (62.5%)	3 (30%)	0.36
Chemotherapy at initial treatment	16(51.6%)	25(34.2%)	0.35

BMI: Body Mass Index; LVSI lymphovascular space invasion; HIR high intermediate risk; PA para aortic, LN lymph nodes.

Table 2
Characteristics and management of women with distant metastasis not associated with locoregional recurrence according to the number of distant metastases sites (one versus multiple).

	One site of distant metastasis n = 39	Multiple sites of distant metastasis n = 34	
Age (years)	70.6 [53–87]	66.9 [50–88]	0.08
Time to recurrence (months)	17.9 [1–59]	20.1 [1–77]	0.60
Recurrence treatment			0.09
- Chemotherapy	13 (33.3%)	21 (61.8%)	
- Surgery	2 (7.4%)	0 (0%)	
- Radiation therapy	5 (12.8%)	1 (2.9%)	
- Hormone therapy	3 (7.7%)	1 (2.9%)	
- Palliative	6 (15.4%)	4 (11.8%)	
- Unknown	10 (25.6%)	7 (20.6%)	
Time between occurrence of recurrence and death (months)	17.4 [1–75.3]	15.3 [1–108.6]	0.65
Death	20 (51.3%)	24 (70.6%)	0.14

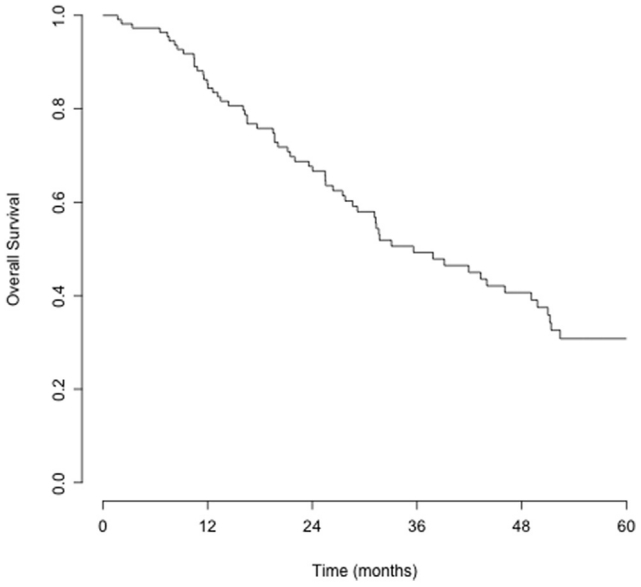

Fig. 1A. Overall survival for the whole population.

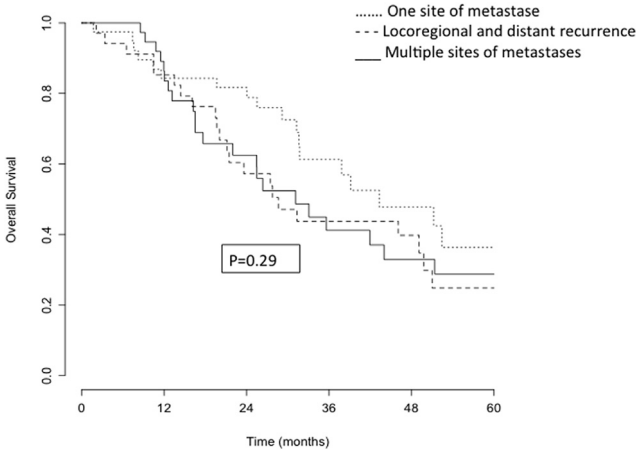

Fig. 1B. Overall survival according to three groups (locoregional + distant recurrence/ exclusive site of metastase/multiple sites of metastases).

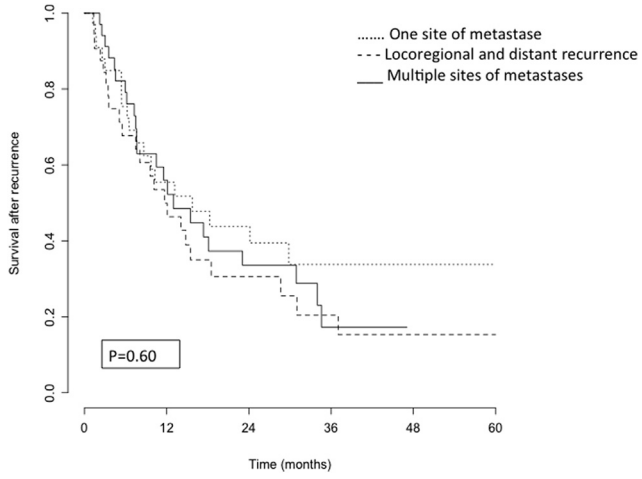

Fig. 2. Survival after the occurrence of distant metastases.

EC ($p = 0.01$) and were less likely to receive chemotherapy at EC initial treatment ($p = 0.05$). Women with brain metastases had a lower median time of distant recurrence (7 months) than women with lung, liver, bone and susdiaphramatic LN (9, 10, 19 and 27 months), (p = 0.004), respectively. Women with sus diaphragmatic LN had a higher 3-year overall survival (83.3%) than women with lung, bone, brain and liver metastases (50.6%, 37.3%, 16.7% and 0%), (p = 0.0059) (Fig. 3), respectively. There was no significant difference in the median survival after the occurrence of distant metastases regardless of additional treatment ($P = 0.34$).

Survival analyses for the whole population showed that pelvic and vaginal vault recurrences (when compared to peritoneal carcinomatosis) and sus-diaphragmatic LN metastasis as compared to other exclusive first site of distant metastases, are independent predictive factor of better overall survival (Table 4).

Discussion

In this large multicentre study, we report specific patterns of first distant metastasis in terms of site-specific and timing. Although EC is a disease with generally a good outcome, women presenting distant metastatic disease have less favorable outcomes. We underline the poor prognosis related to multiple or unique sites of metastases with or without locoregional recurrence but with no significant differences in 3-year and 5-year OS between these groups. The timing of distant failure also did not differed between women within the groups. Although all patients with liver or brain

Table 3
Women and tumour characteristics stratified by the exclusive first site of metastases.

	Lung (n = 27)	Bone (n = 10)	Liver (n = 9)	Sus diaphragmatic LN (n = 9)	Brain (n = 6)	p
Age (years)	70.8 ± [53–81]	75.5 ± [66–87]	66.4 ± [60–77]	66.0 ± [61–71]	66.1 ± [55–79]	0.01
BMI (kg/m^2)	28.9 ± [16.8–50.5]	26.8 ± [16.4–38.8]	30.6 ± [20–43]	39.2± [15–61]	27.2 ± [18–35]	0.16
Menopausal status	27 (100%)	10 (100%)	9 (100%)	9 (100%)	6 (100%)	1
Hormonal Replacement Therapy	5 (18.5%)	2 (20%)	2 (22.2%)	1 (11.1%)	0 (0%)	0.80
Surgery route						0.60
- Laparoscopy	8 (29.6%)	3 (30%)	2 (22.2%)	3(33.3%)	0	
- Laparotomy	14(51.8%)	0	0	5(55.5%)	4 (66.7%)	
- Robotic surgery	1(3.7%)	7 (70%)	5 (55.5%)	0	1 (16.7%)	
- Vaginally	1(3.7%)	0	1(11.1%)	1(11.1%)	0	
- Unknown	3(11.1%)	0	1(11.1%)	0	1 (16.7%)	
Mean histological size (mm)	61.5	20.8	17.5	47.5	50	0.15
Pelvic lymphadenectomy	20 (74.1%)	7 (70%)	8 (88.9%)	9 (100%)	3 (50%)	0.16
Positive pelvic LN	3 (28.6%)	1 (14.3%)	3 (37.5%)	3 (33.3%)	1 (33.3%)	0.87
PA lymphadenectomy	4 (14.8%)	1 (10%)	3 (33.3%)	2 (22.2%)	0 (0%)	0.54
Positive PA LN	2 (50%)	0 (0%)	1 (33.3%)	1 (50%)	0 (0%)	1
Positive LN	6 (30%)	1 (14.3%)	2 (25%)	5 (55.6%)	1 (33.3%)	0.51
Type II	15 (55.6%)	3 (30%)	6 (66.7%)	4 (44.4%)	3 (50%)	0.55
MI >50%	20 (74.1%)	6 (60%)	3 (33.3%)	5 (55.6%)	5 (83.3%)	0.16
Grade						0.34
- 1	3 (11.1%)	1 (10%)	1 (11.1%)	2 (22.2%)	2 (33.3%)	
- 2	7 (25.9%)	3 (30%)	1 (11.1%)	2 (22.2%)	1 (16.7%)	
- 3	17 (63%)	6 (60%)	6 (66.7%)	5 (55.6%)	3 (50%)	
- Unknown	0 (0%)	0 (0%)	1 (11.1%)	0 (0%)	0 (0%)	
ESMO						0.09
- Low	0	0	1 (11.1%)	0	0	
- Intermediate	0	0	0	0	0	
- HIR	1 (3.7%)	3 (30%)	1 (11.1%)	1 (11.1%)	0	
- High	26 (96.3%)	7 (70%)	7 (77.8%)	8 (88.9%)	6 (100%)	
LVSI	16 (59.2%)	6 (60%)	4 (44.4%)	7 (77.8%)	4 (57.1%)	0.77
Chemotherapy	9 (33.3%)	0 (0%)	5 (55.6%)	4 (44.4%)	3 (50%)	0.05
Initial treatment						0.25
- Surveillance	2 (7.4%)	2 (20%)	0	0	0	
- Brachytherapy	1 (3.7%)	1 (10%)	1 (11.1%)	1 (11.1%)	1 (16.7%)	
- Radiation/brachy	15 (55.6%)	7 (70%)	3 (33.3%)	4 (44.4%)	2 (33.3%)	
- Chemoradiation	5 (18.5%)	0	3 (33.3%)	4 (44.4%)	1 (16.7%)	
- Chemotherapy	4 (14.8%)	0	2 (22.2%)	0	2 (33.3%)	

BMI: Body Mass Index; LVSI lymphovascular space invasion; HIR high intermediate risk; PA para aortic, LN lymph nodes.

metastases experienced treatment failure within 2 years of completion of initial treatment, 8 of 27 patients with lung metastases (29.6%), 5 of 9 patients with sus diaphragmatic LN metastases (55.5%), and 3 of 10 patients with bone metastases (30%) developed distant metastases more than 2 years after definitive treatment.

This finding is consistent with those of previous studies reported that over 70% of recurrences occur within the first 2–3 years after initial treatment but these studies reported only the timing of any known recurrence, which was locoregional in most of the patients. We also showed in this study that vaginal vault recurrence (when compared to peritoneal carcinomatosis) and sus-diaphragmatic LN metastasis as compared to other exclusive first site of distant metastases, are independent predictive factor of better overall survival.

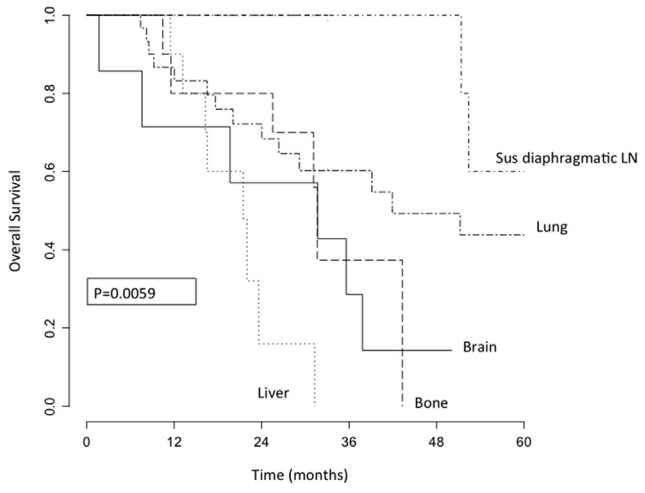

Fig. 3. Overall survival according to the five most common anatomic sites of distant metastases as the first exclusive event.

To our knowledge, the specific patterns of EC recurrence especially distant recurrence, in terms of location, timing and prognosis are poorly reported [14,15].

Distant metastases adversely impact survival. Women with metastatic disease at either initial diagnosis or relapse have traditionally been considered incurable with conventional treatment. It is important to underline that the recent ESMO-ESGO-ESTRO guidelines do not suggest a specific follow-up scheme for women with EC underlining the need to promote specific tools to better identify recurrences [10,16,17]. In contrast, the National Comprehensive Cancer Network (NCCN) guidelines, updated in 2015 (version 2.2015), recommend that a physical exam be performed every 3–6 months for 2–3 years then every 6 months or annually, but little is known about the clinical impact of such follow-up scheme (18).

In the current study, we also highlight heterogeneity in terms of location of first distant metastasis although being in the context of early stage endometrial cancer surgically treated with high proportion of lymph node staging and adapted adjuvant therapies. These findings suggest that locoregional treatments do not prevent distant metastasis. In this context, the major issue is the place of surgery in case of operability in women with only one site of distant

Table 4
Prognostic factors for overall survival.

	Univariate analysis HR [95%CI]	p	Multivariate analysis HR [95%CI]	p
Age	1.01[0.98–1.04]	0.41	–	
Menopause	0.56[0.17–1.82]	0.33	–	
BMI	0.99[0.95–1.03]	0.81		
Parity	0.89[0.73–1.10]	0.30	–	
Surgical route				
Laparotomy	1.02[0.59–1.75]	0.93		
Type II	1.81[1.12–2.95]	**0.01**	0.15[0.01–2.17]	0.16
Histological size	1.0[0.99–1.02]	0.63		
Grade	1.67[1.15–2.42]	**0.007**	7.35[0.53–100]	0.13
LVSI	1.49[0.87–2.57]	0.14	–	
ESMO				
- HIR	1.20[0.57–2.55]	0.62	–	
- Intermediate	0.27[0.04–0.69]	0.19		
- Low	0.80[0.25–2.58]	0.71		
Distant recurrence vs locoregional and distant				
Locoregional recurrence	0.75[0.45–1.25]	0.28	–	
- Carcinosis	Ref			
- LN	0.16[0.05–0.50]	**0.001**	1.01[0.14–7.18]	0.99
- Pelvic	0.16[0.04–0.69]	0.14	0.19[0.04–0.86]	**0.03**
- Vaginal vault	0.14[0.03–0.59]	**0.007**	0.04[0.002–0.84]	**0.004**
One site of distant metastases vs multiple				
Exclusive first site of metastases	0.87[0.54–1.41]	0.58	–	
- Brain	Ref			
- Liver	1.52[0.46–5.07]	0.49	1.15[0.22–5.88]	0.86
- Sus diaphragmatic LN	0.14[0.03–0.66]	**0.01**	0.22[0.0007–0.42]	**0.006**
- Bone	0.66[0.19–2.18]	0.49	0.14[0.006–3.24]	0.22
- Lung	0.38[0.13–1.13]	0.08	0.37[0.12–1.12]	0.08

BMI: Body Mass Index; LVSI lymphovascular space invasion; HIR high intermediate risk; PA para aortic, LN lymph nodes.

metastasis with or without any locoregional recurrence. The recent ESMO-ESGO-ESTRO guidelines underline the fact that there is no standard of care for recurrence cases with several options according to the nature of the recurrence and histopathological tumor and clinical features of the individual patient. It may be helpful to standardize the way of describing EC recurrences to define risk groups and develop guidelines for the management of recurrences: bricou et al.(5), proposed a classification based on dissemination pathways: 1) locoregional recurrence; 2) nodal recurrence for lymphatic pathway; 3) distant organ recurrence for hematogenous pathway and 4) carcinomatosis recurrence for peritoneal pathway. These pathways were further divided into subgroups with a prognostic value that could be a tool to discuss a curative treatment option especially in young and fit women depending on site of EC recurrence especially when metastases concern lung or liver (both together representing the majority of exclusive first site of metastases).

All these finding fuels the persistent debate about the rationale of adjuvant chemotherapy in standard management EC (high-intermediate and high-risk) with metastases having low median time of occurrence making chemotherapy indications more questionable. The recent European guidelines state that adjuvant systemic therapy is still under investigation for women with type 1 EC at increased risk of recurrence with negative nodal staging or without nodal staging.

The strengths of our study lie in its multicentre nature and the large number of women included. However, some limits deserve to be mentioned. First, we cannot exclude an inherent bias linked to its retrospective nature especially concerning the recurrence treatment which represents a major concern. However, all included women were treated in regional referral centres applying the current French/European guidelines after systematic multidisciplinary committee approval. Second, during the data collection period, modifications occurred in staging modalities (FIGO classification) and the indications for nodal staging and for adjuvant therapies [10,11]. Third, the participating institutions may not have recorded in full data regarding subsequent sites of distant metastases after initial distant failure; although such information may be more readily available in a retrospective institution review.

In summary, we can say that women who present with metastatic disease are a complex cohort of patients, ranging from those who are young and fit to those who are older and have life-threatening comorbidities. Within our series, there was heterogeneity of treatment, as many patients had significant comorbidities preventing aggressive approaches to management.

This retrospective cohort review demonstrates the pattern of distant metastatic failure in EC after definitive treatment. There was no significant difference between interval to distant metastases between women with locoregional and distant recurrence, one or multiple sites of failure but in the group of women with exclusive first site, women with sus diaphragmatic LN disease have a longer interval to distant metastases than those with other unique first site, with a significant number of women experiencing distant failure more than 2 years after completion of treatment. These data support current clinical practice of screening for site-specific metastatic disease after initial treatment of early stage EC based on concerning women-specific signs or symptoms.

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