A Proposal for a Classification for Recurrent Endometrial Cancer: Analysis of a French Multicenter Database From the FRANCOGYN Study Group

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Objective: Endometrial cancer (EC) recurrences are relatively common with no standardized way of describing them. We propose a new classification for them called locoregional, nodal, metastasis, carcinomatosis recurrences (rLMNC).

Patients and Methods: The data of 1230 women with EC who were initially treated by primary surgery were included in this French multicenter retrospective study. Recurrences were classified based on dissemination pathways: (1) locoregional recurrence (rL); (2) nodal recurrence (rN) for lymphatic pathway; (3) distant organ recurrence (rM) for hematogenous pathway; and (4) carcinomatosis recurrence (rC) for peritoneal pathway. These pathways were further divided into subgroups. We compared recurrence free survival and overall survival (OS) between the 4 groups (rL/rN/rM/rC).

Results: The median follow-up was 35.6 months (range, 1.70–167.60). One hundred ninety-eight women (18.2%) experienced a recurrence: 150 (75.8%) experienced a single-pathway recurrence and 48 (24.2%) a multiple-pathway recurrence. The 5-year OS was 34.1% (95% confidence interval [CI], 27.02%–43.1%), and the median time to first recurrence was 18.9 months (range, 0–152 months). The median survival after recurrence was 14.8 months (95% CI, 11.7–18.8). Among women with single pathway of recurrence, a difference in 5-year

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OS ($P < 0.001$) and survival after recurrence ($P < 0.01$) was found between the 4 rLNMC groups. The carcinomatosis group had the worst prognosis compared with other single recurrence pathways. Women with multiple recurrences had poorer 5-year OS ($P < 0.001$) and survival after recurrence ($P < 0.01$) than those with single metastasis recurrence, other than women with peritoneal carcinomatosis.

Conclusions: This easy-to-use and intuitive classification may be helpful to define EC recurrence risk groups and develop guidelines for the management of recurrence. Its prognosis value could also be a tool to select homogenous populations for further trials.

Key Words: Endometrial cancer, Recurrences, Relapses, Classification

Endometrial cancer (EC) is the most common gynecologic cancer worldwide with 320,000 new cases each year.[1] Around 75% of ECs are diagnosed at an early stage with a 5-year overall survival (OS) reaching 80%.[2] However, EC is a heterogeneous disease with some subsets of women displaying an increased risk of recurrence. Indeed, it causes almost 76,000 deaths per year.[1] The most usual identified risk factors for recurrence are the International Federation of Gynecology and Obstetrics (FIGO) stage, depth of myometrial invasion, histological type and grade, lymphovascular space invasion, and tumor size.[3] In this specific setting, the European Society for Medical Oncology (ESMO)/European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology group recently classified EC women into 4 subgroups according to the risk of recurrence (low risk, intermediate risk, high-intermediate risk, and high risk) to better adapt surgical staging and indications for adjuvant therapies.[4]

Although overall prognosis of women with surgically treated EC is good, Bendifallah et al[5] recently reported that at least 20% of them will experience a recurrence, impacting OS. Moreover, it is now well recognized that more than 70% of recurrences occur within the first 2 to 3 years after initial treatment.[6–8] Hence, recurrence events and their treatment are a crucial aspect in the management of women with EC. Most studies to date focus on predictive factors of recurrence, recurrence patterns, and specific treatments.[9–11] In this setting, most authors concur that locoregional recurrences are to be differentiated from distant recurrences.

However, there is currently no consensual standardized description of EC recurrence and definitions vary widely from one study to another.[12–16] This lack of homogeneity limits comparison of study results by rendering their interpretation somewhat blurred.

Hence, the purpose of this study was to describe the anatomical locations of EC recurrence with a view to developing an easy-to-use classification based on the 4 dissemination pathways (locoregional, lymphatic, blood, and peritoneal) to better assess prognosis.

PATIENTS AND METHODS

Study Population

From January 2001 to December 2013, data of women with histologically proven EC who received primary surgical treatment were abstracted from EC databases of 9 institutions in France (Tours University Hospital, Tenon University Hospital, Dijon Cancer Centre, Rennes University Hospital, Lille University Hospital, Reims University Hospital, Creteil University Hospital, Poissy University Hospital, and Jean Verdier University Hospital) and from the Senti-Endo trial.[17] The research protocol was approved by the Institutional Review Board of the Collège National des Gynécologues et Obstétriciens Français (CEROG 2014-GYN-020).

All enrolled women underwent preoperative imaging examinations (abdominopelvic magnetic resonance imaging and/or computed tomography scan). The following clinical, surgical, pathological, and adjuvant therapy data were collected: women's age, body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters), surgical procedure, nodal staging, final pathological analysis (histological type and grade, depth of myometrial invasion, and lymphovascular space invasion status), and type of adjuvant therapy. Histological type 1 included endometrioid tumors (grades 1 to 3), and histological type 2 included serous or clear-cell carcinomas and carcinosarcomas. All women were classified according to the FIGO 2009 classification[18] after final pathological analysis and were classified into recurrence risk groups as defined by the ESMO/European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology guidelines.[4]

Treatment and Follow-up

All the women underwent primary surgical treatment including at least total hysterectomy with bilateral salpingo-oophorectomy, with or without nodal staging (sentinel lymph nodes ± pelvic ± para-aortic lymphadenectomy), as well as omentectomy. Adjuvant therapy and clinical follow-up were decided by a

multidisciplinary committee and based on the French guidelines. Adjuvant therapy could include vaginal brachytherapy and/or external beam radiotherapy (EBRT) and/or chemotherapy (CT). Clinical follow-up consisted of physical examinations and the use of imaging techniques according to the findings. 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.

Recurrence Events and Classification

Recurrent disease was assessed by physical examination and imaging techniques (computed tomography, magnetic resonance imaging, ultrasonography, bone scintigraphy, positron emission tomography with the fluorodesoxyglucose (18F) as well as histological findings when feasible. We applied a new classification, called the rLNMC classification, based on the pathway of dissemination: locoregional recurrence (rL), nodal recurrence (rN), distant organ recurrence (rM), and peritoneal recurrence with carcinomatosis (rC) (Table 1). Locoregional pathway recurrence was divided into 2 groups as follows: recurrence in the vaginal vault only (rL1) and rectal and/or bladder involvement (rL2). We defined a locoregional recurrence that could not be assessed (rLx) and no evidence of locoregional recurrence as rL0. Nodal recurrences were separated into 2 groups: for lymph node recurrence in the pelvic, inguinal, and/or infradiaphragmatic para-aortic area (rN1) and for mediastinal or other distance nodal recurrences (rN2). We defined a node recurrence that could not be assessed as rNx and no evidence of the recurrent node site as rN0. Hematogenous recurrences were also divided into 2 groups: single metastasis (rM1) and multiple metastasis (rM2). We defined a metastatic recurrence that could not be assessed as (rMx) and no evidence of the metastatic as (rM0). The peritoneal recurrence represented a single group for pelvic and/or abdominal carcinomatosis (rC1). We defined a peritoneal recurrence that could not be assessed as rCx and no evidence of carcinomatosis as (rC0). Single recurrence was defined as recurrence with only one pathway of dissemination. Multiple recurrences were defined as recurrences with more than one pathway of dissemination, Supplemental Digital Content 1, http://links.lww.com/IGC/A754;Supplemental Digital Content 2, http://links.lww.com/IGC/A755.

TABLE 1. rLMNC classification for EC recurrence

rLocoregional	
rLx	A recurrence tumor that cannot be assessed
rL0	No evidence of the recurrent tumor site
rL1	Recurrence tumor in the vaginal vault only
rL2	Centropelvic recurrence tumor with or without rectal and/or bladder involvement.
rNode	
rNx	The lymph node recurrence cannot be assessed
rN0	No lymph node recurrence
rN1	Lymphnode recurrence in pelvic, inguinal, and/or infradiaphragmatic para-aortic area
rN2	Mediastinal or other distance lymph node recurrence
rMetastasis	
rMx	Distant organ recurrence cannot be assessed
rM0	No distant organ recurrence
rM1	Distant recurrence in one organ
rM2	Distant recurrence in two or more organs.
rCarcinomatosis	
rCx	Carcinomatosis recurrence cannot be assessed
rC0	No carcinomatosis recurrence
rC1	Presence of carcinomatosis recurrence

Statistical Analysis

Recurrence free survival was defined as the length of time from the date of primary surgery to any EC recurrence and was censored at the date of the last follow-up or date of death without recurrence. Overall survival was defined as time from primary surgery to death as a result of any cause and survival after recurrence was defined as time from recurrence diagnostic to death. Kaplan-Meier estimates were used to estimate the event-time distributions, and log-rank test was used to compare the differences in terms of OS between the 4 groups (rL/rN/rM/rC). Values of $P < 0.05$ were considered to denote significant differences. Data were managed with an Excel database (Microsoft, Redmond, Wash) and analyzed using R 2.15 software, available online with caTools, rms, presence/absence, and verification libraries (https://www.r-project.org/).

RESULTS

Characteristics of the Population

During the study period, 1230 women with EC who were initially treated by primary surgery were included in this multicenter retrospective study. Two hundred twenty-four women (18.2%) experienced a recurrence. Among them, 26 were excluded owing to incomplete data leaving 198 women for final analysis. The median age of the women with recurrence was 68.5 years (range, 32–88 years), and their BMI was 29.09 kg/m^2 (range, 14–50.4 kg/m^2). The median follow-up was 35.6 months (range, 1.70–167.60 months) after primary diagnosis and 10.2 months (range, 1–109 months) after recurrence. The median recurrence free survival was 18.9 months (range, 0–152 months). The 5-year OS was 34.1% (95% CI, 27.02%–43.1%). The median survival after recurrence was 14.8 months (95% CI, 11.7–18.8). One hundred nineteen women (60%) died, and 65 (55%) of these deaths were due to EC recurrence. For the remaining 54 women, the cause of the death was not recorded. The characteristics of the women with recurrence are reported in Table 2.

TABLE 2. Characteristics of women who experienced a recurrence

Characteristics	Population, n = 198
Age, median (range), y	68.49 (32–88)
BMI, median (range), kg/m^2	29.09 (14–50.4)
Follow-up, median (range), mo	35.6 (1.70–167.60)
Histological type	n (%)
Type 1	115 (58)
Type 2	83 (42)
ESMO classification	n (%)
Low risk	18 (9.1)
Intermediate risk	9 (4.5)
Intermediate-high risk	18 (9.1)
High risk	151 (76.3)
NA	2 (1)
FIGO stage at definitive histology	n (%)
I	86 (43.4)
II	26 (13.1)
III	73 (36.9)
IV	13 (6.6) (13)
Adjuvant therapies before recurrence	n (%)
No adjuvant therapy	30 (15.2)
Vaginal brachytherapy alone	13 (6.6)
EBRT + brachytherapy	64 (32.3)
CT + EBRT	21 (10.6)
CT alone	28 (14.1)
EBRT + brachytherapy + CT	27 (13.6)
EBRT alone	14 (7.1)
Brachytherapy + CT	1 (0.5)

NA, not available.

Patterns of Recurrence According to the rLNMC Classification

Among the 198 women who experienced recurrence: 52 (21.1%) experienced a locoregional recurrence (vaginal vault [rL1] in 22 cases [8.9%], centropelvic recurrence [rL2] in 30 cases [12.2%]); 50 (20.3%) experienced a nodal recurrence (pelvic, inguinal, and/or para-aortic node recurrence [rN1] in 41 cases [16.7%] and mediastinal or distant nodes [rN2] in 9 cases [3.8%]); 95 (38.6%) experienced a metastatic pathway recurrence (rM1) in 49 cases (19.9%) and rM2 in 46 cases (18.7%); and 49 (19.9%) experienced a peritoneal carcinomatosis recurrence (rC1).

Among the women who experienced a single recurrence (n = 150, 75.8%): 30 (20%) experienced a tumor site recurrence (vaginal recurrence [rL1N0M0C0] in 14 cases [46.7%], centropelvic recurrence [rL2N0M0C0] in 16 cases [53.3%]); 26 (17.3%) experienced a nodal recurrence (pelvic, para-aortic, or inguinal areas [rL0N1M0C0] in 18 cases [69.2%] and mediastinal or distance nodes [rL0N2M0C0] in 8 cases [30.8%]); and 65 (43.3%) experienced a metastatic recurrence (only 1 localization [rL0N0M1C0] in 32 cases [49.2%] [15 lung, 8 bone, 6 brain, 2 liver, 1 unspecified], more than 1 [rL0N0M2C0] in 33 cases [50.8%], and peritoneal carcinomatosis recurrence (rL0N0M0C1) in 29 cases [19.4%]).

Among the women who experienced a multiple recurrence (n = 48 [24.2%]): 22 (45.8%) experienced a locoregional recurrence (vaginal vault [rL1] in 8 cases [36.4%], centropelvic [rL2] in 14 cases [63.6%]); 24 (50%) experienced a nodal recurrence (involving pelvic, para-aortic, or inguinal area nodes [rN1] in 23 cases [95.8%] and mediastinal area or distance nodes [rN2] in 1 case [4.2%]); and 30 (62.5%) experienced a metastatic recurrence (1 metastasis [8 lung, 7 liver, 1 unspecified, 1 bone] [rM1] in 17 cases [56.7%], more than 1 metastatic recurrence [rM2] in 13 cases [43.3%] [Table 3], and peritoneal carcinomatosis [rC1] in 20 cases [41.7%]).

Survival Outcomes

The 5-year OS was 34.1% (95% CI, 27,02–43,1%) (Fig. 1A). The median survival after recurrence was 14.8 months (95% CI, 11.7–18.8) (Fig. 1B). Among women with single pathway of recurrence, a difference in 5-year OS (Fig. 2A) and survival after recurrence (Fig. 2B) was found between the 4 rLNMC groups. The carcinomatosis group (rL0N0M0C1) had the worst prognosis compared with other single recurrence pathways. When considering women with multiple recurrences, a difference in 5-year OS (Fig. 3A) and survival after recurrence (Fig. 3B) was found between the rLNMC groups.

DISCUSSION

Our study confirms that the patterns of recurrence in EC are multiple. Moreover, it shows that recurrence sites can be isolated or associated with each other: we identified 246 different recurrences among the 198 women who experienced recurrence with 75.8% experiencing single recurrence and (24.2%) multiple recurrences. These results are in agreement with those of Sohaib et al[12] who report 48% of multiple-site recurrences. This is why the rLNMC classification we propose here includes the different pathways of spread: locoregional

TABLE 3. Women with single or multipathways of recurrence with rLNMC classification

Single recurrence on locoregional site (rL)	30 (15.2%)
rL1N0M0C0	14
rL2N0M0C0	16
Single-nodes recurrence (rN)	26 (13.2%)
rL0N1M0C0	18
rL0N2M0C0	8
Single-metastasis recurrence (rM)	65 (32.8%)
rL0N0M1C0	32
rL0N0M2C0	33
Single-carcinomatosis recurrence (Rc)	29 (14.6%)
rL0N0M0C1	29
Multiple-pathways recurrence (rMpath)	48 (24.2%)

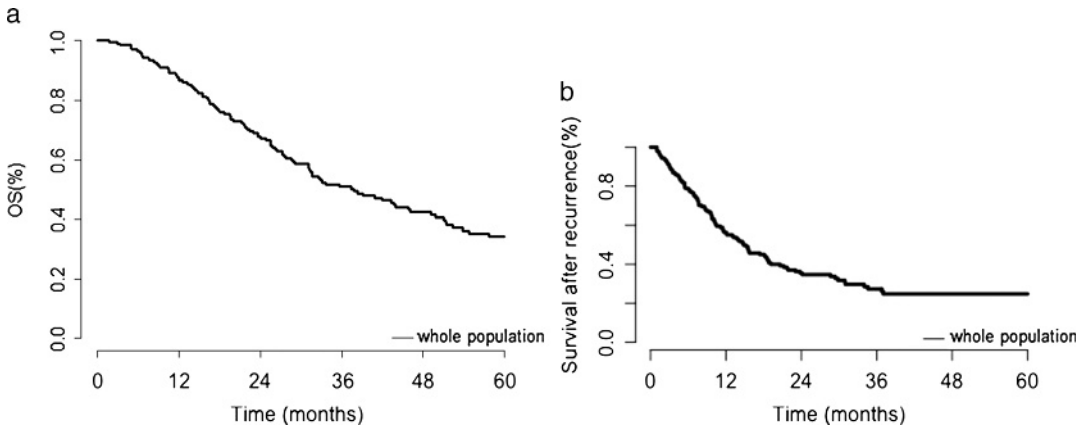

FIGURE 1. A, Five-year cumulative survival rates for the whole population. B, Cumulative survival rates after recurrence for the whole population.

extension (contiguous extension), lymphatic dissemination (nodal recurrences), hematogenous dissemination (metastatic recurrences), and peritoneal seeding (carcinomatosis). It is based on clinical and/or imaging data found during the follow-up period with or without histological confirmation and describes localization, type, and focality of recurrences. Moreover, localization of recurrence is not the only prognostic factor; prognosis may also depend on the type of recurrence treatment, which is conditioned by (1) initial treatment (radiotherapy), (2) the interval between initial diagnosis and recurrence, and (3) the initial histology and tumor grade.[13] Hence, our classification could be completed by the type of early adjuvant treatment used. Consequently, the prefixes Ra for radiotherapy, Ch for CT, and Ht for hormonotherapy could also be recorded in the classification.

In the classification we present here, locoregional recurrence (rL) concerns recurrences localized in the locoregional area and related to contiguous dissemination (from the initial EC tumor site). In this specific setting, we decided to exclude parenchimatous recurrences from this group and include them in the hematogenous pathway (metastasis) group, even if such recurrences can involve abdominal or pelvic organs. Our division into 2 different subgroups (rL1, rL2) is supported by its impact on OS: a trend for poorer prognosis was found for centropelvic recurrences (rL2, N0, M0, C0) compared with vaginal vault recurrences (rL1, N0, M0, C0). Therapeutic options are an additional parameter supporting this distribution. Indeed, surgical treatment can be more difficult and sometimes not possible for centropelvic recurrences as opposed to isolated vaginal vault recurrence, which can often be salvaged with surgical excision and/or radiotherapy. In this setting, Ackerman et al[19] reported a local control rate of up to 79% for isolated vaginal vault recurrences. Moreover, several studies report that survival is better in women with recurrence confined within the vaginal vault rather than in the true pelvis[13,20–22] or other sites.[23] However, these results must be interpreted with caution because the prognosis seems to be the poorest for women who initially received external beam radiotherapy.[13] Concerning centropelvic recurrences (rL2), the extent of recurrence appears to be an important prognostic factor for local control and survival.[24] In a series of 209 women with recurrence, Sartori et al[23] reported that the 5-year OS for vaginal, pelvic, and distant recurrence was 68%, 29%, and 8%, respectively.

Concerning the lymphatic pathway, nodal recurrences represented 20.3% of the total recurrence sites in our study and were isolated in 13.1% of cases. These findings are in contradiction with those of Sohaib et al[12] who found that nodal recurrences were the most frequent recurrence site (47%).

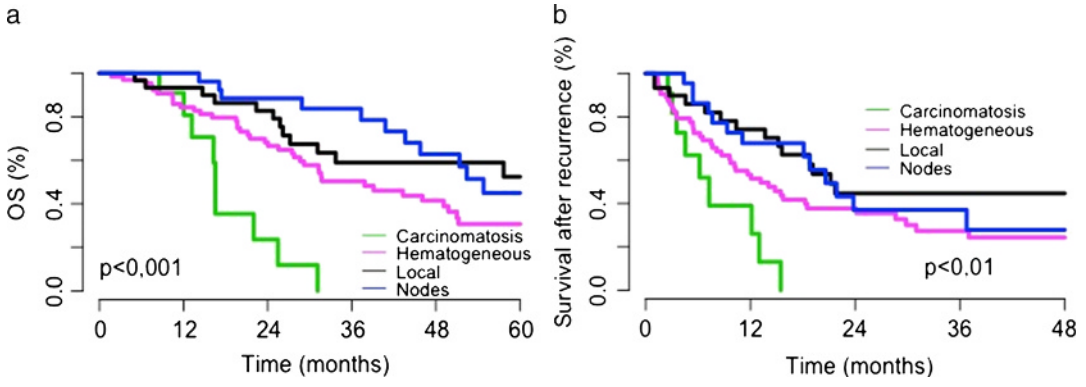

FIGURE 2. A, Five-year cumulative survival rates for the different single recurrences. B, Cumulative survival rates after recurrence for different single recurrences.

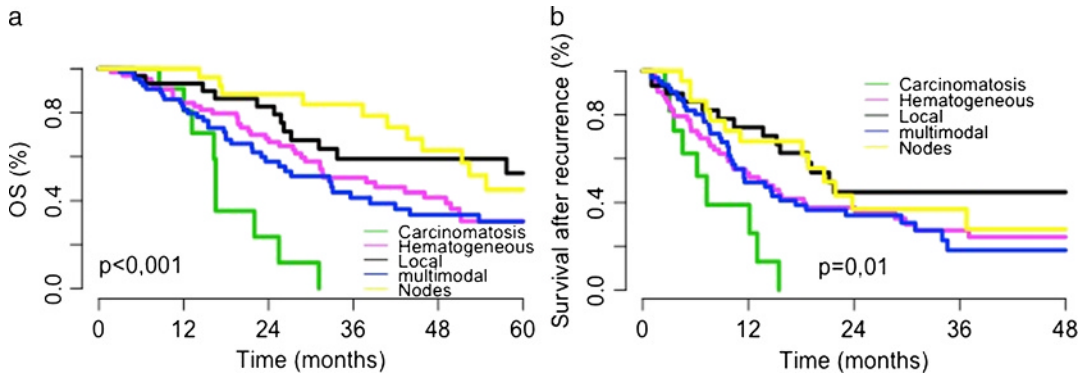

FIGURE 3. A, Five-year cumulative survival rates for single and multiple recurrences. B, Cumulative survival rates after recurrences for single and multiple recurrences.

However, their study included 86 patients among whom only 40 (46.5%) had undergone nodal dissection during primary surgery.[12] We distinguish between 2 types nodal recurrence in our classification: rN1 for all pelvic, inguinal, and/or infradiaphragmatic para-aortic area node recurrence and rN2 for mediastinal or other distant lymph node recurrence. This distinction is based on the possibility of surgical removal for the rN1 group compared with the rN2 group. However, we were not able to distinguish pelvic node involvement from infradiaphragmatic para-aortic or inguinal nodal involvement in the database. Moreover, we did not find any difference in survival between the rN1 and the rN2 groups, when isolated. This can be explained by the fact that isolated rN2 recurrences are rare and that nodal recurrences are often associated with other recurrence sites. However, a few studies in the literature have attempted to distinguish between type of nodal involvement and what we consider to be the rN2 group is often classified as distant recurrence sites.[5,21,22,25]

In our study, metastases represented the first pathway of recurrence and was found in 95 women (38.6%) with a similar distribution between isolated and multiple metastases. This rate is in complete agreement with that reported by Sohaid et al[12] who found that metastases occurred in 36% of recurrences and represented a major predictor factor for poor survival. In the current classification, we decided to classify metastatic recurrences as single (rM1) or multiple (rM2). We believe that single metastases could be, in selected cases, eligible for local control (surgery or interventional imaging) with a view to increasing the symptom-free interval, which is less feasible for multiple-site metastases. In contrast, we decided not to distinguish between the different anatomical sites because this would detract from the clarity and ease-of-use of the classification.

In our study, the presence of peritoneal carcinomatosis was linked to a significant decrease in 5-years OS and survival after recurrence. That is why we decided to create a single group because it may represent a specific pathway of dissemination. In the current literature, the real impact of peritoneal carcinomatosis on survival remains unclear because it is often associated with other recurrence sites such as distant metastases, extravaginal recurrences, or abdominal recurrences.[22,26–28] Indeed, Ouldamer et al[29] recently reported a nomogram to predict poor prognosis recurrences (ie, peritoneal carcinomatosis and distant metastases) with a 3-year OS of 33.1% for the peritoneal carcinomatosis group. Finally, the treatment options may differ depending on whether the peritoneal carcinomatosis is isolated or associated to another pathway of dissemination. In this setting, in case of isolated carcinomatosis, the place of cytoreductive surgery with hyperthermic intraperitonal CT is a matter of major interest.

The strengths of our study lie in its multicenter nature and the large number of women with EC recurrence included. However, we cannot exclude an inherent bias linked to its retrospective nature. Indeed, among the 224 women who experienced a recurrence, 26 (11.6%) were excluded owing to incomplete data. Moreover, our database did not allow to differentiate pelvic nodes involvement, infradiaphragmatic para-aortic area nodes involvement, and inguinal nodes involvement. Finally, during the data collection period, modifications occurred in surgical techniques such as lymph node staging and indications for adjuvant therapies with potential impact on prognosis. However, all women were managed in regional referral centers with a systematic multidisciplinary committee approval in accordance with French/Europeans guidelines.[30]

In conclusion, EC recurrences represent a heterogeneous group of women with various histological characteristics, initial treatments, and anatomical sites of recurrence. Such heterogeneity has been widely described, but, to our knowledge, this is the first study to propose a classification including standardized definitions of recurrence based on the different pathways of dissemination. A consensual classification would not only make it easier to better define risk groups and develop guidelines for the surgical or medical management of EC recurrence but also help select homogenous populations for further trials. This first classification for EC recurrence should, naturally, be further developed and updated.

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