Impact of sentinel lymph node biopsy on the therapeutic management of early-stage endometrial cancer: Results of a retrospective multicenter study

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HIGHLIGHTS

• Sentinel lymph node biopsy applied to low- and intermediate-risk patients enables to detect 3 times more metastatic lymph node.
• Ultrastaging changed ESMO classification in half of the cases (10/22) and changed low- and intermediate-risk to high-risk group.
• Ultrastaging could recuperate patients with undiagnosed micrometastasis by lymphadenectomy and permit the administration of an EBRT.

Abstract

Objective. The aim of this study is to assess the impact of sentinel lymph node (SLN) mapping and ultrastaging on the therapeutic management of early-stage endometrial cancer.

Methods. This retrospective multicenter study covered the period from January 2000 through December 2012 and included 304 women with presumed low- or intermediate-risk endometrial cancer. Node staging, histology results, and the effects of both on therapeutic management were assessed in two groups: those who underwent the SLN mapping and ultrastaging procedure and those treated in accordance with French guidelines.

Results. The SLN procedure detected metastatic lymph nodes in three times more women than lymphadenectomy did (16.2% versus 5.1%, p = 0.03). Specifically, it found 7 macrometastases (5.1%) and 15 micrometastases (11%); 11 of the latter (8.1%) were detected by serial sectioning and immunohistochemistry (IHC), that is, pathologic ultrastaging. The SLN biopsy false-negative rate was 0% (95% CI: 0–1.6%). This ultrastaging enabled us to modify the adjuvant therapy for half the patients. Women with micrometastases detected by the SLN procedure were treated with external beam radiotherapy (EBRT), while those whose SLN biopsies were negative received vaginal brachytherapy (VBT) or clinical follow-up. SLN biopsies had no impact on recurrence-free survival.

Conclusion. SLN mapping and ultrastaging improved staging and made it possible to adapt adjuvant therapy to risk of recurrence.

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Introduction

Endometrial cancer is the most common gynecologic pelvic cancer in both the European Union and the United States. Prognosis is directly linked to histological type and grade and to surgical stage [1–3], and these factors guide the choice of adjuvant treatments. The prognostic relevance of assessing lymph node (LN) status by lymphadenectomy is, however, still a matter of debate. The recent recommendations for de-escalation of treatment in some patients [4] are based on results from two randomized trials and a meta-analysis, which have proved that pelvic lymphadenectomy has no effect on overall survival (OS) or relapse-free survival (RFS) but is associated with a higher incidence of early and late complications [5–7]. Nonetheless, 15% of the women whose cancer prognosis is considered good develop a recurrence, and its prognosis, in turn, is not well correlated with conventional histoprognostic factors [8].

Ballester et al. validated the feasibility, detection rates, and accuracy of the SLN mapping and ultrastaging procedure [8] as a possible alternative to pelvic lymphadenectomy in the early stages of endometrial
cancer [9]. We report the results of a retrospective multicenter study to assess the impact of this procedure in choosing adjuvant treatment for women with early-stage endometrial cancer.

Materials and methods

Patients

Our retrospective multicenter study is based on data from three participating French centers: Tenon Hospital in Paris, Reims University Hospital, and the Georges-François Leclerc Cancer Center in Dijon. Our data include all patients diagnosed with endometrial cancer at one of these hospitals between January 2000 and December 2012. Some of these women (n = 156) were included prospectively when they participated in the SENTI-ENDO protocol (a prospective, multicenter cohort study to assess the detection rate and diagnostic accuracy of the SLN procedure in predicting pelvic-node status in women with early-stage endometrial cancer) [9].

In accordance with the ESMO guidelines for endometrial cancer, we used the histology results of the biopsy samples to define three risk groups: low-risk (type 1 endometrial cancer, stage IA grade 1 or 2); intermediate risk (type 1 endometrial cancer, stage IA grade 3, or stage IB grade 1 or 2); and high-risk (type 1 endometrial cancer, stage IB grade 3, or type 2 endometrial cancer of any stage and grade) [10].

This study applied the following inclusion criteria: biopsy-confirmed endometrial carcinoma at low or intermediate risk, in a woman older than 18 years, affiliated with the French national health care system, and able to speak and read French.

Exclusion criteria included preoperative International Federation of Gynecology and Obstetrics (FIGO) staging as stage I high-risk, II, III, or IV, type 2 endometrial cancer, undetermined ESMO classification, or previous lymphadenectomy or surgery that might have modified uterine lymphatic drainage (conization or myomectomy).

Procedures

The SLN procedure was performed as previously described [9]. In brief, four intracervical injections of 0.2 mL (20 MBq each) of unfiltered technetium were administered the day before surgery. Scintigraphic images were obtained 2 h after the injections and then every 30 min to detect the SLN. Before starting surgery, under general anesthesia, patent blue was injected intracervically at 3 and 9 o’clock. The pelvic and lower para-aortic regions were inspected carefully for lymph ducts and LN dye uptake. Radioactive pelvic and para-aortic LNs were located with a gamma probe. After the SLNs were located, the peritoneum was opened, and each blue and/or radioactive LN was removed. Pelvic lymphadenectomy was systematically performed after the SLN procedure.

Experienced pathologists analyzed all SLNs: according to the previously reported procedure [10]. SLNs were cut perpendicular to the long axis and examined by intraoperative imprint cytology. Air-dried cytological smears were prepared by scraping the cut surfaces and staining with a rapid May–Grünewald–Giemsa method. Each half-SLN was sectioned at 3-mm intervals. Each 3-mm section was analyzed at four parallel divisions of 200 μm; one was used for hematoxylin and eosin staining (H&E), and H&E-negative sections were examined by IHC with an anticytokeratin antibody cocktail (cytokeratins AE1–AE3; Dako Corporation, Glostrup, Denmark) [11]. Non-SLNs were submitted whole and blocked individually after 3-mm sectioning and H&S.

Patients who did not undergo this SLN procedure were treated in accordance with French guidelines. The decision to perform pelvic lymphadenectomy was based on the preoperative pathology results [4]. Pelvic LNs were submitted whole and blocked individually after 3-mm sectioning and H&S.

Statistical analysis

The aim of this study was to assess the impact of SLN mapping and ultrastaging on therapeutic management in early-stage endometrial cancer. The primary objective was to determine the SLN status and the contribution of ultrastaging to the diagnosis of SLN metastases, and the secondary objective was to assess the effect of SLN status on the ESMO classification and on adjuvant therapy.

The detection rate and invasion type (macro- and micro-metastases) were calculated. The false negative rate was calculated with its 95% confidence interval (95% CI). The statistical analysis used Student’s t test for parametric continuous variables, the Wilcoxon test for non-parametric continuous variables, and the Chi-square test or Fisher’s exact test, as appropriate, for categorical variables. The Kruskal–Wallis test was performed to compare means (> 2).

Survival curves were estimated by the Kaplan–Meier method and compared with the log-rank test. We defined OS as the time from surgery to death from any cause. We defined RFS and distant metastasis-free survival (DMFS) as the time from surgery to the first locoregional recurrence or distant recurrence. Cox regression analysis was used to calculate hazard ratios with their 95% CIs. We compared 5-year RFS and DMFS for women who did and did not undergo the SLN procedure, but also among those who did, according to whether a LN metastasis was present. We compared RFS and DMFS for women who underwent any SLN procedure and those with no metastases in SLN, and 5-year RFS and DMFS for women who underwent pelvic lymphadenectomy and those who did not. Values of p < 0.05 were considered to be significant.

Data were managed with an Excel database (Microsoft, Redmond, WA) and analyzed by the R 2.15.3 software (package and library Veriﬁcation, Hmisc, survival, rms and stats), available online (http://lib.stat.cmu.edu/R/CRAN/).

Results

From January 2000 to December 2012, the three participating centers enrolled 494 women, 190 of whom were excluded because of: preoperative diagnosis of type 2 endometrial cancer (n = 87), MRI staging as FIGO stage I high-risk, II, III, or IV and indeterminate (n = 92), and preoperative ESMO classification as undetermined (n = 11). This study therefore included 304 women (Fig. 1). The SLN procedure was followed by pelvic lymphadenectomy for 156 women (51.3%); 95 women had pelvic lymphadenectomy alone (31.2%), and 53 (17.4%) women had no nodal staging. Table 1 summarizes the patients’ characteristics.

SLN procedure

Of the 156 patients who underwent the SLN procedure, 136 had at least one SLN detected, for a detection rate of 87.2%. The 20 women with no SLN detected had pelvic lymphadenectomy, and conventional histological analysis showed LN metastasis for one of them (5%). Among the women with at least one SLN detected, location was bilateral for 89 (65.4%) and unilateral for 46 women (33.8%), with laterality unknown for one. The total number of SLNs detected and removed was 382, for a mean of 2.5 per procedure (range: 1–10).

SLN biopsies enabled us to diagnose 22 metastatic SLNs: macrometastases in 7 cases (31.8%) and micrometastases in 15 (68.2%). All macrometastases were diagnosed by H&E. Of the SLNs with micrometastases, 11 cases (73.3%) were diagnosed by serial sections by
IHC (pathologic ultrastaging). The pelvic lymphadenectomies performed after the SLN procedure showed LN metastases in 2 cases (9.1%), but the H&N of those SLNs had showed macrometastases. The SLN biopsy false-negative rate was 0% (95% CI: 0–1.6%), that is, all negative SLNs were followed by pelvic lymphadenectomies that were also negative. All women for whom isolated tumor cells were found also had at least one micro- or macro-metastasis and were so classified.

Among the 136 women for whom SLNs were detected, the procedure resulted in a change in the ESMO classification for 20 (14.7%). The micrometastasis diagnosis changed the risk level in 9 cases (60%), raising 4 low-risk and 5 intermediate-risk classifications to high risk. The other 6 women with micrometastases had factors besides their nodal status that caused them to be classified as high risk. One woman with a macrometastasis in a SLN had her ESMO classification changed from low to high risk (14.3%). The other four already had factors that ranked them at high risk of recurrence. Thus the LN metastasis identified by SLN mapping and upstaging identified 22 women, and the risk group was raised for 10 of them.

The adjuvant therapy administered to women with macrometastases identified by SLN mapping was external beam radiotherapy (EBRT) alone (n = 1), EBRT combined with vaginal brachytherapy (VBT) (n = 2), EBRT combined with chemotherapy (n = 2), or a combination of the three (n = 1); one woman had only clinical follow-up. Adjuvant therapy for the women with SLN-identified micrometastases was EBRT alone (n = 4), EBRT combined with VBT (n = 2) or EBRT with chemotherapy (n = 5), while two women had all three treatments, and the treatment received by two others (13.3%) was not known. The SLN procedure and in particular the presence of a metastasis changed the type of adjuvant therapy administered, compared with women who had either pelvic lymphadenectomy or no LN staging (p < 0.001) (Table 2).

Of the 22 patients with metastatic SLNs, 2 (9%) had recurrences. The mean time to recurrence was 14.5 months [12–17].

Table 1

<table>
<thead>
<tr>
<th>Patients’ characteristics.</th>
<th>Center</th>
<th>Total</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tenon (51.3%)</td>
<td>CGFL (31.6%)</td>
<td>Reims (17.1%)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>156</td>
<td>96</td>
<td>52</td>
</tr>
<tr>
<td>Age (years, mean (min–max))</td>
<td>65 (38–98)</td>
<td>66 (31–87)</td>
<td>67 (46–86)</td>
</tr>
<tr>
<td>BMI (kg/m², mean (min–max))</td>
<td>27.2 (17–54)</td>
<td>30.2 (20–50)</td>
<td>31.7 (19–61)</td>
</tr>
<tr>
<td>FIGO 2009 stage at preoperative IRM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>111 (36.5%)</td>
<td>80 (26.3%)</td>
<td>52 (17.1%)</td>
</tr>
<tr>
<td>IB</td>
<td>45 (14.8%)</td>
<td>16 (5.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Preoperative histological grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>71 (23.3%)</td>
<td>61 (20.1%)</td>
<td>23 (7.6%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>39 (12.8%)</td>
<td>29 (9.5%)</td>
<td>19 (6.2%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>6 (2%)</td>
<td>6 (2%)</td>
<td>5 (1.6%)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>40 (13.1%)</td>
<td>0</td>
<td>5 (1.6%)</td>
</tr>
</tbody>
</table>

CGFL = Centre Georges Frangois Leclerc. FIGO = International Federation of Gynecology and Obstetrics. BMI = body-mass index.
a macrometastasis and distant recurrence 12 months after the diagnosis and received adjuvant therapy with EBRT and VBT. The second had a micrometastasis with a distant recurrence 17 months after diagnosis; she died 9 months later. She had received adjuvant therapy with EBRT and chemotherapy. However, of the 94 patients with no metastasis, 11 (11.7%) had local (n = 1) or distant (n = 9) recurrences (with the location of the recurrence unknown for one). The mean time to recurrence was 16.6 months (5–27). Their adjuvant therapy had been clinical follow-up (n = 2), VBT alone (n = 1), EBRT alone (n = 4), EBRT associated with chemotherapy (n = 2), or EBRT with VBT (n = 1). The adjuvant therapy administered to one was unknown. Among this group, 2 women had died, 24 and 31 months after diagnosis. One had received EBRT alone, the other EBRT with VBT.

The SLN procedure did not improve RFS (HR = 0.89; 95% CI: 0.42–1.90; p = 0.77). Specifically, the early detection of SLN metastasis (HR = 0.82; 95% CI: 0.18–3.64; p = 0.8) and especially of a micrometastasis (HR = 0.46; 95% CI: 0.03–7.42; p = 0.59) did not improve RFS (Fig. 2 and Table 3).

Pelvic lymphadenectomy

Lymph node exploration of 115 patients consisted of a pelvic lymphadenectomy (95 immediately and 20 after SLN detection failed); 1160 LNs were removed, for a mean of 10.1 per patient (0–44). Conventional histology identified LN metastases in 7 of them (6.1%). This nodal status resulted in a change in the ESMO classification of one woman from intermediate to high risk. The postoperative histological data of the others had already placed them in the high-risk group.

The adjuvant therapy administered to these 7 women with LN metastasis was EBRT alone (n = 1), EBRT combined with chemotherapy (n = 2), EBRT with VBT (n = 2), or EBRT with both; one woman had only clinical follow-up. The adjuvant therapy administered did not differ according to the histological results of the pelvic lymphadenectomy (p = 0.14) (Table 2).

One of these seven women (14.3%) had a recurrence. She had pelvic lymphadenectomy after failure of the SLN mapping procedure and EBRT as an adjuvant treatment. This local recurrence was detected 5 months after the initial diagnosis, and she died 16 months later.

Of the 108 women with no metastasis, 11 (10.2%) had recurrences: distant (n = 7), locoregional (n = 3), or site unknown (n = 1). The mean time to recurrence was 17 months (3–55). Their adjuvant treatment had been chemotherapy (n = 2), EBRT alone (n = 1), EBRT combined with chemotherapy (n = 1), EBRT with VBT (n = 2), or EBRT with both (n = 4) (and that for one woman was unknown (9.1%)). Three of these women died after distant recurrence, at a mean of 21.3 months (7–35) after diagnosis and after adjuvant chemotherapy (n = 1), a combination of EBRT, VBT, and chemotherapy (n = 1), or unknown in the last case.

No LN staging

In accordance with the French guidelines, no LN exploration was performed in 53 women (17.4%). In this group, the postoperative ESMO classification was raised from low to high risk for 14 (26.4%) (invasion of the lymphovascular space (n = 11), stage IB grade 3 (n = 2), stage II (n = 1)).

These women received as adjuvant therapy VBT alone (n = 17), EBRT alone (n = 1), EBRT combined with VBT (n = 12), EBRT with chemotherapy (n = 1), or EBRT with both. Nineteen women had clinical follow-up only.

Recurrence was diagnosed for 4 patients (7.5%): 2 distant recurrences, one local recurrence, and one of unknown location. The mean time to recurrence was 44.7 months (2–152). One woman with distant recurrence had received VBT, and the other clinical follow-up; the woman with a local recurrence had received a combination of three treatments and died 33 months after recurrence, at 43 months after the initial diagnosis. The woman with recurrence at an unknown location had received VBT and chemotherapy.

The absence of LN exploration did not influence survival (overall, RFS, or DMFS), but it did change the type of adjuvant therapy administered. Tables 2 and 4 summarize the different adjuvant treatments administered and the recurrence site depending on the type of node staging and the histology results.

Discussion

In this study, SLN mapping and ultrastaging applied to low- and intermediate-risk patients made it possible to detect metastatic LNs three times more often than complete pelvic lymphadenectomy (16.2% versus 5.1%, p = 0.03). Ultrastaging changed the ESMO classification in half of the cases.
vant therapy to these women. Yabushita et al. demonstrated that this understaging makes it impossible to administer appropriate adjuvant therapy or adjuvant therapy [4]. These recommendations are based on a Cochrane meta-analysis including two randomized trials (ASTEC and Benedetti) that showed that in the early stages of endometrial cancer, pelvic lymphadenectomy has no effect on OS (HR = 1.07; 95% CI: 0.81–1.43) or RFS (HR = 1.23; 95% CI: 0.96–1.58) [5,6,13]. Previous studies have reported a 0–5% rate of lymph node metastasis in women classified at low or intermediate risk, as determined by conventional histology (H&E) analysis of pelvic lymph node metastases. Our results are consistent with the literature, since 7 macrometastases (5.1%) were diagnosed by the SLN mapping and biopsy process. Overall, however, this technique, used with ultrastaging by serial sectioning and IHC, diagnosed three times more metastases (16.2%) than the standard procedure.

SLN micrometastases were diagnosed in 15 women (11%), with 11 (8.1%) of these diagnoses possible only because of the serial sectioning and IHC. Our results are thus consistent with those of Kim et al., who showed that half of the metastatic SLNs identified were detected by pathologic ultrastaging that could pinpoint micrometastases [14]. Nonetheless, despite the favorable prognosis of women with no LN metastases, 15% of them have recurrences. We currently do not know enough of the prognostic factors to allow us to predict these recurrences. One hypothesis to explain them might be understaging of the initial disease. LN micrometastases cannot be detected by conventional histology (H&E). This understaging makes it impossible to administer appropriate adjuvant therapy to these women. Yabushita et al. demonstrated that micrometastases are an independent risk factor for recurrence in early stages of endometrial cancer [15]. Our results support this hypothesis, since SLN biopsies showed approximately 10% more LN metastases, which had not been detected by pelvic lymphadenectomy.

In our study, the multidisciplinary staff conferences decided to define micrometastatic invasion as stage IIIC1. This diagnosis in these women earlier classified as at low and intermediate risk led to their reclassification in the high-risk group. In our study, of the 22 women with metastatic SLNs, 10 were classified at high risk of recurrence (i.e., IIIC1). However, according to current French guidelines, treatment for the groups at low and intermediate risk should be clinical follow-up or VBT, while in the high-risk group, it should be EBRT, often combined with VBT or chemotherapy or both [4]. The modification of the ESMO classification by the diagnosis of micrometastasis modifies the adjuvant therapy administered. In our study, patients with micrometastases received the same treatment as those with macrometastases, and EBRT was administered in 86.7% of the cases, in contrast to patients with no metastases or without lymph node exploration, who had clinical follow-up in 32.6% of the cases and VBT in 57.1%. This management raises the question of whether overtreatment or adaptation of adjuvant therapy to ultrastaging should be considered. However, our results are consistent with the conclusion of the PORTEC-2 study, which found that patients at intermediate and high risk levels without lymphadenectomy had a higher rate of pelvic recurrence after VBT (4.4%: 8/183 patients) than EBRT (0.5%: 1/183), despite their similar efficacy in vaginal disease control. There was, however, no difference in survival (either OS or RFS) [16]. Our results confirm that SLN biopsies can be used to select the patients to receive these two adjuvant therapies: women with no micrometastases should receive VBT or clinical follow-up, and those with micrometastases should receive EBRT.

Ultrastaging could identify the women with micrometastases diagnosed by lymphadenectomy and enable their treatment by EBRT. Our results are consistent with the meta-analysis by Kong et al., who concluded that VBT reduces the risk of local recurrence with fewer side effects than EBRT in the low- and intermediate-risk groups. Nevertheless, due to insufficient statistical power, they could not rule out the potential of a small survival benefit with EBRT in the stage I high-risk group [17].

In our study, the SLN procedure did not improve RFS (HR = 0.89; 95% CI: 0.42–1.90; p = 0.77). The discovery of a metastasis did not improve survival (HR = 0.82; 95% CI: 0.18–3.64; p = 0.8), nor did the discovery of a micrometastasis (HR = 0.46; 95% CI: 0.03–7.42; p = 0.59). A possible explanation for these results is that we administered EBRT in cases with LN micrometastases. The findings of Yabushita et al. reinforce this hypothesis, as they showed that micrometastasis removal was associated with significant increase in RFS [15]. However, to confirm our hypothesis it would be necessary to conduct a randomized study comparing the effect of EBRT versus surgery alone in women with micrometastases. Our study confirms that this treatment provided

### Table 3
Relapse-free survival and distant metastasis free survival at 5 years in patients at low and intermediate risk of recurrence based on the performance of a SLN procedure.

<table>
<thead>
<tr>
<th>Group or variable</th>
<th>n</th>
<th>Relapse free survival</th>
<th>Distant metastasis free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Survival 5 years</td>
<td>HR 95% CI p</td>
</tr>
<tr>
<td>SLN procedure</td>
<td>156</td>
<td>88.4% 0.89 0.42–1.90 0.77 91.2%</td>
<td>1.05 0.42–2.57 0.92</td>
</tr>
<tr>
<td>No SLN procedure</td>
<td>148</td>
<td>84.2% 0.82 0.18–3.64 0.8 90.3%</td>
<td>1.19 0.25–5.52 0.82</td>
</tr>
<tr>
<td>Metastatic SLN</td>
<td>22</td>
<td>90.5% 0.82 0.18–3.64 0.8 90.3%</td>
<td>1.19 0.25–5.52 0.82</td>
</tr>
<tr>
<td>No metastatic SLN</td>
<td>114</td>
<td>88% 0.82 0.18–3.64 0.8 90.3%</td>
<td>1.19 0.25–5.52 0.82</td>
</tr>
<tr>
<td>Presence of metastasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrometastatic SLN</td>
<td>7</td>
<td>85.7% 0.46 0.03–7.42 0.59 85.7%</td>
<td>0.46 0.01–14.9 0.59</td>
</tr>
<tr>
<td>Micrometastatic SLN</td>
<td>15</td>
<td>92.9% 1.08 0.50–2.35 0.84 89.2%</td>
<td>0.97 0.38–2.48 0.95</td>
</tr>
<tr>
<td>No SLN procedure</td>
<td>148</td>
<td>84.2% 1.08 0.50–2.35 0.84 89.2%</td>
<td>0.97 0.38–2.48 0.95</td>
</tr>
<tr>
<td>No metastatic SLN</td>
<td>114</td>
<td>88% 1.08 0.50–2.35 0.84 89.2%</td>
<td>0.97 0.38–2.48 0.95</td>
</tr>
<tr>
<td>Pelvic lymphadenectomy</td>
<td>251</td>
<td>86.6% 1.13 0.34–3.76 0.84 90.2%</td>
<td>1.29 0.30–5.59 0.73</td>
</tr>
<tr>
<td>No pelvic lymphadenectomy</td>
<td>53</td>
<td>90.8% 1.13 0.34–3.76 0.84 90.2%</td>
<td>1.29 0.30–5.59 0.73</td>
</tr>
</tbody>
</table>

CI: confidence interval, HR: hazard ratio, SLN: sentinel lymph node.

### Table 4
Location of recurrence based on the histology of lymph node exploration for patients at low and intermediate risk of recurrence.

<table>
<thead>
<tr>
<th>Recurrence location</th>
<th>No lymph node staging (n = 53)</th>
<th>SLN procedure</th>
<th>Pelvic lymphadenectomy</th>
<th>Total (n = 304)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative* (n = 114)</td>
<td>Positive (n = 22)</td>
<td>Negative (n = 108)</td>
<td>Positive (n = 7)</td>
</tr>
<tr>
<td>Loco/regional</td>
<td>1 (1.9%)</td>
<td>1 (0.9%)</td>
<td>3 (2.8%)</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>2 (3.8%)</td>
<td>9 (7.9%)</td>
<td>7 (6.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>1 (1.9%)</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Negative pelvic lymphadenectomy, SLN: sentinel lymph node.
good local control, as most of the recurrences were distant (69%). The impact of micrometastases on RFS was very difficult to identify because of their low incidence and their association with lymphadenectomy and EBRT (like macrometastases).

Another advantage of the SLN procedure in the early stages of endometrial cancer is to prevent secondary lymphadenectomy. Many studies have emphasized the difference between pre- and postoperative histology [18,19]. No imaging or histological examination has a sensitivity and specificity sufficient to allow an always accurate preoperative staging, particularly of LN invasion [20,21]. Pre- and postoperative discrepancies require a secondary lymphadenectomy in some cases [22]. But patients with endometrial cancer are often obese and have multiple comorbidities. In these conditions, lymphadenectomy is technically more difficult and at risk of complications, and therefore to be avoided. The SLN procedure and ultrastaging would enable it to be avoided safely.

This study has limitations that we must note. First, the low- and intermediate-risk groups were analyzed together. However, the likelihood that patients at intermediate risk would have had lymphadenectomy according the guidelines is low in this study. Analyzing these two groups separately would not change the results, except to reduce the study power. Secondly, we used pericervical dual labeling, which may not reflect the lymphatic drainage of the corpus uteri. However, the studies that provide histological and clinical validation of the SLN procedure in endometrial cancer have all used only cervical injection [9]. Furthermore, in our study chemotherapy was used less often than at other centers, although it may play an important role in addition to radiation in case of node metastasis.

These results suggest that the SLN procedure in early stages of endometrial cancer could provide a benefit by enabling staging of micrometastases. This improved staging would enable better selection of adjuvant therapy: women at low and intermediate risk with no metastases could receive clinical follow-up or VBT, and those with metastases could receive EBRT.

Conflicts of interest
The authors declared no conflicts of interest.

References

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