Gynecologic Oncology 136 (2015) 54–59

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Sentinel node biopsy for the management of early stage endometrial cancer: Long-term results of the SENTI-ENDO study

Emile Daraï [a], Gil Dubernard [b], Anne-Sophie Bats [c], Denis Heitz [d], Patrice Mathevet [e], Henri Marret [f], Denis Querleu [g], François Golfier [h], Eric Leblanc [i], Roman Rouzier [a], Marcos Ballester [a,*]

[a] Department of Obstetrics and Gynecology, Tenon University Hospital, Paris, France
[b] Department of Obstetrics and Gynecology, Croix Rousse University Hospital, Lyon, France
[c] Department of Gynecology, Georges Pompidou University Hospital, Paris, France
[d] Department of Gynecology, Poissy-Saint Germain en Laye University Hospital, Poissy, France
[e] Department of Obstetrics and Gynecology, Edouard Herriot University Hospital, Lyon, France
[f] Department of Obstetrics and Gynecology, Bretonneau University Hospital, Tours, France
[g] Department of Surgical Oncology, Claudius Regaud Comprehensive Cancer Center, Toulouse, France
[h] Department of Obstetrics and Gynecology, Centre Hospitalier Lyon Sud, Lyon, France
[i] Department of Surgical Oncology, Centre Oscar Lambret, Lille, France

HIGHLIGHTS

- Long-term results of SENTI-ENDO evaluating the impact of sentinel lymph node biopsy on endometrial cancer management and survival
- No difference in RFS according to SLN status was observed.
- The relevance of SLN biopsy on surgical management and indications for adjuvant therapies should be confirmed.

ARTICLE INFO

Article history:
Received 7 April 2014
Accepted 12 September 2014
Available online 22 October 2014

Keywords:
Endometrial cancer
Sentinel lymph node biopsy
Lymphadenectomy
Ultrastaging
Recurrence free survival

ABSTRACT

Objective. We report the long-term results of the SENTI-ENDO study evaluating the impact of sentinel lymph node (SLN) biopsy on management and survival in patients with early stages of endometrial cancer (EC).

Methods. Patients with FIGO stage I–II EC underwent pelvic SLN biopsy after cervical dual injection (technetium and patent blue) and systematic pelvic node dissection. This study is a secondary endpoint reporting the long-term recurrence free survival (RFS) and the impact of the SLN procedure on adjuvant therapies.

Results. The median follow-up was 50 months (range: 3–77 months). Eighteen of the 125 patients (14.4%) experienced a recurrence. The 50-monthrecurrence-free survival (RFS) was 84.7% with no difference between patients with and without detected SLN ($p = 0.09$). Among patients with detected SLN (111), no difference in RFS was observed between those with and without positive SLN ($p = 0.5$). In the whole population, adjuvant therapy was performed in low-, intermediate- and high-risk groups in 31 of 64 patients (48.4%), 28 of 37 patients (75.7%) and 14 of 17 patients (82.3%), respectively ($p = 0.0001$). For the 111 patients with detected SLN, EBRT was performed in 27 of the 89 with negative SLN and in 11 of the 14 with positive SLN ($p = 0.001$). Chemotherapy was performed more frequently in patients with positive SLN (6/12, 50%) than in patients with negative SLN (7/56, 12.5%) ($p = 0.009$).

Conclusions. Our results support the impact of SLN biopsy on surgical management and indications for adjuvant therapies. Further studies are required to assess the clinical impact of the SLN biopsy in early stage EC.

Introduction

Endometrial cancer (EC) is the most frequent gynecological cancer in developed countries [1]. In France, more than 6500 new cases are diagnosed each year with an incidence similar to that observed in other European countries (UK), representing the seventh most common cause of death from cancer in women in western Europe [2].

At diagnosis, about three-quarters of patients with EC have disease confined to the uterine corpus. Classic management of early stages of EC is based on hysterectomy, bilateral salpingo-oophorectomy and pelvic +/− para-aortic lymphadenectomy [3]. Indications for adjuvant therapies depend on uterine findings and lymph node status [4].

* Corresponding author at: Service de Gynécologie-Obstétrique, Hôpital Tenon, 4 rue de la Chine, 75020 Paris, France. Fax: +33 1 56 01 73 17.
E-mail address: marcos.ballester@tnn.aphp.fr (M. Ballester).

http://dx.doi.org/10.1016/j.ygyno.2014.09.011
0090-8258/

Histological characteristics are recognized as being independent prognostic factors for survival and have given rise to the identification of three risk groups of relapse according to histology (type 1: endometrioid carcinoma, type 2: carcinosarcoma, clear cell or serous papillary carcinoma), tumor grade and depth of myometrial invasion [3,5]. The five-year overall survival is 75% for all FIGO stages, and as high as 95% for early stages confined to the uterus.

Recently, two trials and a meta-analysis have been published suggesting that pelvic lymphadenectomy has no impact on overall and disease-free survivals in patients with early stage EC while exposing patients to the risk of complications [6–8]. However, these results have been discussed in light of studies demonstrating that pelvic and para-aortic lymphadenectomy is associated with longer overall survival for patients with intermediate- or high-risk EC [9]. Moreover, none of these data took into account the contribution of sentinel lymph node (SLN) biopsy in improving metastasis detection through ultrastaging [10]. Indeed, in a multicenter study evaluating the contribution of SLN biopsy in early stage EC, 17% of women had lymph node metastasis suggesting that SLN biopsy adds significant data to uterine findings to tailor adjuvant therapy [11]. Finally, Kitchener concluded that SLN biopsy could be a trade-off between systematic lymphadenectomy and no lymphadenectomy [12]. However, the impact of SLN biopsy on surgical management and indications for adjuvant therapies, and hence potentially on recurrence, has been poorly investigated to date. We report the long-term results of a prospective multicenter study on SLN biopsy in patients with early stages EC (SENTI-ENDO).

Patients and methods

This prospective study was approved by our Institutional Review Committee (Ile de France 1, CPP 0711481) and registered on ClinicalTrials.gov under NCT00987051. From July 2007 to August 2009, all patients with EC seen at one of the nine participating centers were considered for enrollment. Inclusion criteria were: endometrial carcinoma confirmed by biopsy, patients over 18 years affiliated to the French Health Care System and speaking and reading French, invasive cancers (FIGO stages I and II according to the 1988 FIGO classification) [13], intention of surgical staging, and absence of pregnancy. Exclusion criteria were: FIGO stages III and IV, previous lymphadenectomy or surgery that could change the uterine lymphatic drainage (conization, myomectomy) and pregnancy. All patients underwent a preoperative MRI unless contraindicated in which case a CT scan was recommended [11]. All enrolled patients signed an informed consent.

As previously published, participating centers signed an agreement to strictly follow the protocol fortracer injection with lymphoscintigraphy and surgery and lymph node processing [11]. In accordance with French guidelines, the extent of lymphadenectomy was decided on according to preoperative pathological results [14]. For patients with type 1 EC, a pelvic lymphadenectomy was performed in all patients after the SLN biopsy. A para-aortic lymphadenectomy (PAAL) was recommended if metastases were detected on intraoperative histology or after definitive histology. For patients with type 2 EC, systematic pelvic and para-aortic lymphadenectomy was recommended whatever the SLN status. The usual boundaries of PAAL were respected with the left renal vein as the upper limit.

Adjuvant therapies and follow-up

Based on definitive histology, three risk groups according to the ESMO guidelines for EC were defined as follows [3]: low risk (type 1 EC, stage IA grade 1 or 2); intermediate risk (type 1 EC, stage IA grade 3, or stage IB grade 1 or 2); and high risk (type 1 EC, stage IB grade 3, or type 2 EC of any stage and grade). For patients with low-risk EC, no adjuvant therapy was recommended. For patients with intermediate-risk EC, a vaginal brachytherapy (VBT) was recommended. For patients with high-risk EC, a whole pelvic external beam radiotherapy (EBRT) (50 Gy in 25 fractions) and chemotherapy consisting of a cisplatin-based regimen for four to six cycles were recommended but depending on the center and the physician's discretion.

We assessed the patients before surgery, at the one-month postoperative visit, then every three months in the first year, every six months in years two and three, and every year thereafter. According to French guidelines, surveillance was based on routine pelvic examination [14]. Follow-up data collected included details on recurrence, treatments, side effects and survival.

Statistics

The primary end-point was to estimate the Negative Predictive Value (NPV) of pelvic SLN in endometrial cancer per hemipelvis and per patient. The secondary end-point was recurrence-free survival.

We defined recurrence-free survival as the time from surgery to first reappearance of EC or death from any cause. Patients who were known to be still alive and without recurrence at the time of the analysis were censored at the time of their last follow-up. We compared Kaplan–Meier curves for all time-to-event outcome measures with the standard (non-stratified) log-rank test. All p values are two-sided. Data were managed with an Access database (Microsoft, Redmond, WA) and analyzed using the R 2.11® software available freely online.

Results

Impact of SLN biopsy on surgical management and adjuvant therapies

Among the 125 patients included in the study, preoperative assessment of EC risk groups was available in 82 (65.6%). Preoperative histological grade was not available in 43 cases (mainly due to insufficient tissue in Pipelle endometrial sampling). Among these patients, the number of patients with low-, intermediate- and high-risk EC was 35, 24 and 23 (64 type 1 and 18 type 2 EC), respectively. Ten of the 23 patients with high-risk EC underwent a systematic PAAL (Table 1).

Three (33.3%) of the nine patients with metastatic SLNs at intraoperative examination underwent immediate PAAL because of a type 2 EC at preoperative histology and four (44.4%) had type 1 EC and underwent PAAL exclusively due to metastatic SLNs. Two of these had positive

Table 1
Epidemiological and surgical characteristics of the 125 patients included in the study protocol.

	Patients (n = 125)
Age (years) (range)	63 (38–100)
BMI (kg/m^2) (range)	27 (18–54)
Preoperative FIGO 2009 stage—n(%)	
IA	82 (66%)
IB	42 (33%)
II	1 (1%)
Preoperative histology—n(%)	
Endometrioid	107 (86%)
Clear cell	3 (2%)
Serous papillary	7 (6%)
Undifferentiated	7 (6%)
Other	1 (1%)
SLN detection—n(%)	111 (89%)
Para-aortic lymphadenectomy—n(%)	15 (12%)
Preoperative risk groups—n(%)	
Low-risk	35 (28%)
Intermediate-risk	24 (19.2%)
High-risk	23 (18.4%)
Not available	43 (34.4%)
Postoperative risk groups—n(%)	
Low-risk	64 (51.2%)
Intermediate-risk	37 (29.6%)
High-risk	17 (13.6%)
Not available	7 (5.6%)

non-SLNs. PAAL was not performed in two cases due to severe morbidity.

Among the seven remaining patients with positive SLN at final histology not detected intraoperatively, only one underwent a second intention PAAL. No metastases were found in non-SLNs. For the remaining six patients who did not have a second PAAL, one patient with micrometastases on SLNs had a recurrence in the paraaortic area 12 months after initial surgical management.

In patients with detected SLN, 57 had low-risk, 33 intermediate-risk and 16 high-risk EC (not available in five cases). In those without detected SLN, seven had low-risk EC, four intermediate-risk and one high-risk (not available in two cases). No difference in the EC risk group was observed between patients with and without detected SLN ($p = 0.7$).

In the whole population, adjuvant therapy was performed in low-, intermediate- and high-risk groups in 31 of 64 patients (48.4%), 28 of 37 patients (75.7%) and 14 of 17 patients (82.3%), respectively ($p = 0.0001$). This difference was significant between low- and intermediate-risk groups and between low- and high-risk groups but without difference between intermediate- and high-risk groups. For the 111 patients with detected SLN, EBRT was performed in 27 of 89 patients with negative SLN and in 11 of 14 patients with positive SLN ($p = 0.001$) (not available in eight cases). Chemotherapy was performed more frequently in patients with positive SLN (6/12, 50%) than in patients with negative SLN (7/56, 12.5%) ($p = 0.009$).

SLN metastases were found in 16 of the 111 patients with detected SLN. Ultrastaging allowed the detection of SLN metastases in 9/16 patients with SLN metastases (macrometastases in one case, micrometastases and/or ITC in eight cases). EBRT and chemotherapy were respectively performed in 6/9 patients and 2/9 patients with SLN metastases diagnosed thanks to ultrastaging. Hence, ultrastaging allowed a change in adjuvant therapies in 6/16 (37.5%) patients with SLN metastases, 6/19 (31.5%) of patients with LN metastases and 6/111 (5.4%) of patients with detected SLN.

Recurrence rate and survival (Figs. 1, 2)

The median follow-up for the 125 patients included in the study was 50 months (range: 3–77 months). Eighteen patients (14.4%) experienced a recurrence (Table 2). Recurrence-free survival (RFS) in the whole population was 84.7% (Fig. 3a). The recurrence rate in patients with and without detected SLN was 12.6% (14/111) and 28.6% (4/14), respectively ($p = 0.23$). No difference in RFS was found between patients with and without detected SLN ($p = 0.09$) (Fig. 3b). No difference in RFS was observed between patients with and without lymph node metastases ($p = 0.17$). A difference in RFS was observed according to the risk group ($p < 0.0001$) (Fig. 4): it was higher for low- or intermediate-risk groups compared to the high-risk group but without difference between the two first groups. RFS was lower for patients with lymphovascular space involvement ($p = 0.02$).

Among patients with detected SLN, no difference in RFS was observed between those with and without positive SLN ($p = 0.5$). A difference in RFS was observed according to the risk group ($p < 0.0001$). This difference was significant between low- and high-risk groups ($p < 0.001$) and between intermediate- and high-risk groups ($p = 0.03$) while no difference was observed between low- and intermediate-risk groups.

Discussion

Despite the publication of two randomized trials showing that there is no advantage in performing systematic lymphadenectomy in patients with early stage EC, there is persistent debate about the relevance of including lymphadenectomy in standard management of EC [6–8,11,12]. In our first report, we demonstrated that SLN biopsy adequately predicts lymph node status especially for patients with type 1 EC and that lymph node involvement was more accurately detected by ultrastaging [11]. However, the clinical relevance of this strategy was not proved. In the present study, patients with positive SLN underwent immediate PAAL and adjuvant EBRT and chemotherapy more frequently while no difference in RFS according to SLN status was observed. This absence of difference in RFS is probably related to lack of power of our study. Using the Surveillance Epidemiology and End Results dataset, Chino et al. reported that lymph node dissection (LND) was associated with a higher survival vs. no LND for patients at low risk whereas adjuvant therapy had no impact [15]. Using a multivariate propensity score analysis, Bendifallah et al. demonstrated that lymphadenectomy had a positive impact on disease specific survival

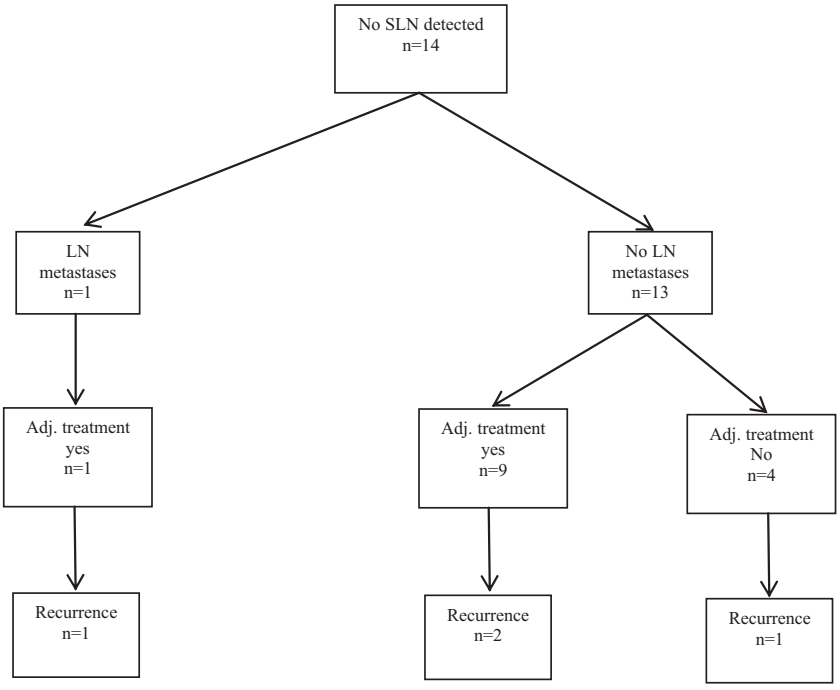

Fig. 1. Adjuvant therapies and recurrences for the 14 patients without SLN detection.

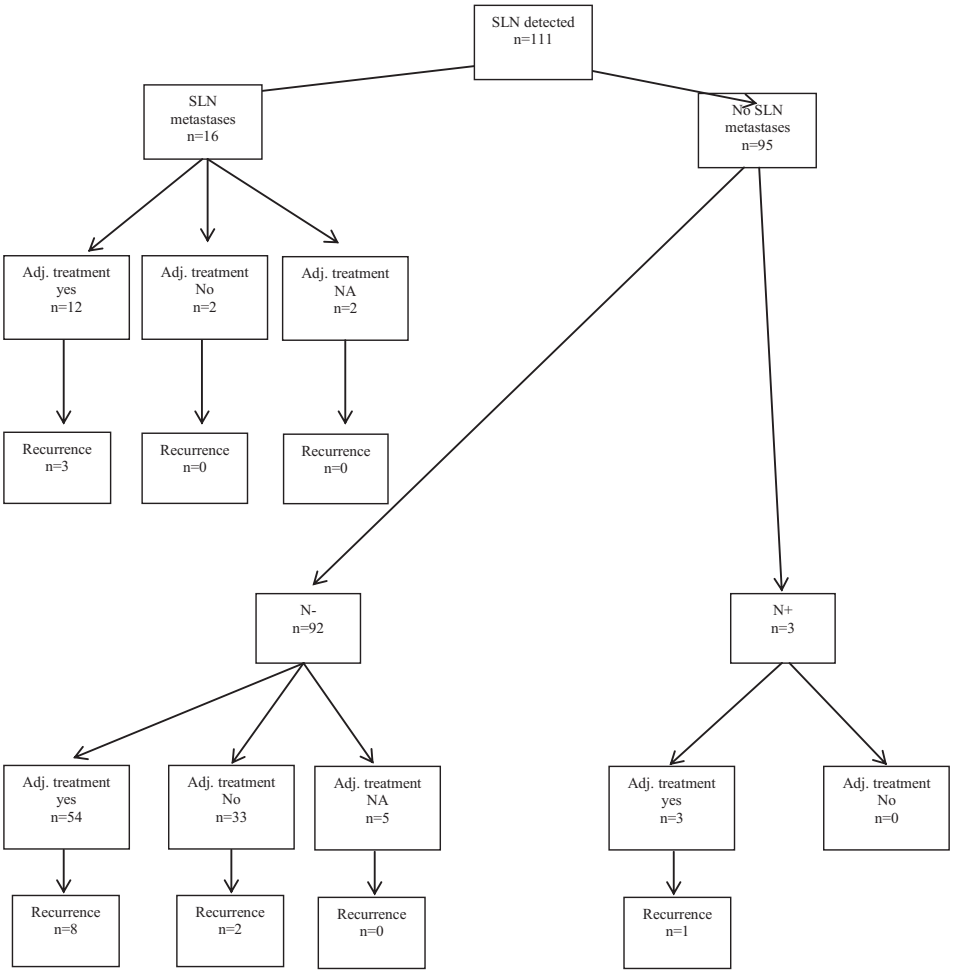

Fig. 2. Adjuvant therapies and recurrences for the 111 patients with detected SLN.

for patients with stage I-grade 3 EC [16]. Using a model evaluating the risk of lymphatic spread and the effects of treatment on patients with EC, Naumann suggested that the ASTEC trial was unable to detect a difference in outcome as no stratification of adjuvant therapies was planned according to lymph node status [17]. In accordance with previous study, with an estimated 9% of lymph node metastases detected by

Table 2
Characteristics of the 18 patients who experienced a recurrence.

Patient	SLN detected	Postoperative risk	Positive SLN	Positive lymph node	Type of metastasis	Adjuvant treatment	RFS (months)	Type of recurrence
1	Yes	High	No	Yes	Micro	Radiotherapy	18	Nodal
2	Yes	High	No	No	–	Radiotherapy + chemotherapy	10	Nodal + lung
3	Yes	Intermediate	No	No	–	Brachytherapy	6	Nodal
4	No	Low	No	Yes	Macro	NA	15	Peritoneal carcinomatosis
5	No	Intermediate	No	Yes	Macro	Radiotherapy	5	Vaginal
6	Yes	Low	No	No	–	Brachytherapy	15	Abdominal wall
7	Yes	Intermediate	No	No	–	Radiotherapy	19	Peritoneal carcinomatosis
8	Yes	Low	No	No	–	NA	11	Nodal + bone
9	Yes	High	No	No	–	Radiotherapy	12	Nodal + peritoneal carcinomatosis
10	No	Intermediate	No	No	–	Radiotherapy	27	Suburethral
11	Yes	Low	No	No	–	NA	24	Nodal
12	Yes	High	Yes	Yes	Macro	Radiotherapy + chemotherapy	18	Lung
13	Yes	High	Yes	Yes	Macro	Brachytherapy + radiotherapy	12	Nodal + peritoneal carcinomatosis
14	Yes	High	No	No	–	Radiotherapy	14	Lung
15	Yes	High	No	No	–	Radiotherapy	27	Lung
16	Yes	Intermediate	No	No	–	Brachytherapy	12	bone
17	No	High	No	No	–	Brachytherapy	20	Suburethral + nodal (groin)
18	Yes	High	Yes	Yes	Macro	Brachytherapy + radiotherapy + chemotherapy	24	Lung + brain

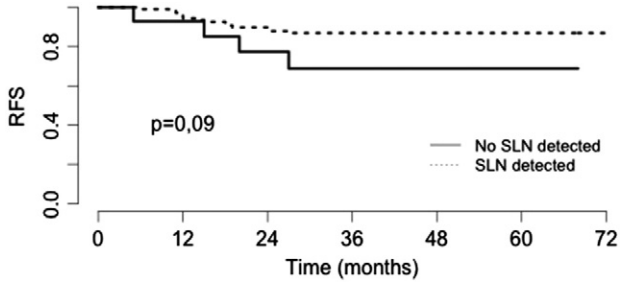

Fig. 3. Recurrence-free survival in the whole population according to SLN detection.

routine histology in the ASTEC trial, a difference in 3-year survival of 7% would be observed when comparing standard treatment with and without lymphadenectomy [17]. Conversely, SLN biopsy detected 17% of patients with lymph node metastases with an estimated difference in 3-year survival reaching 12%.

In the present study, a lower RFS was observed for patients in the high-risk group compared to those in the low- and intermediate-risk groups. For patients at low risk, using routine histology on the lymph nodes, previous studies reported nodal metastases in only 3–5% [18]. In the current study, SLN detected 11% of lymph node metastases with a potential difference in 3-year survival of 11%. For low-risk patients, all lymph node metastases were exclusively detected on SLN without positive non-SLN suggesting the therapeutic effect of SLN biopsy. However, our results also underline the risk of para-aortic lymph node recurrence when pelvic micrometastases are detected on SLN justifying the possibility of PAAL in this case. In the SEPAL study, using routine histology, no benefit of adding para-aortic to pelvic lymphadenectomy for patients at low-risk EC was observed [9]. However, some reports have suggested a relation between the presence of micrometastases and the risk of recurrence [19]. Therefore, further studies taking into account the detection of micrometastases are required to better define surgical strategy.

Exclusion of lymph node involvement is also crucial to identify patients that would not benefit from adjuvant therapy. In the present study, for patients with no detected SLN, despite a high incidence of adjuvant therapy (71% of the patients), the recurrence rate was 28.6% vs. 12.6% in patients with detected SLN suggesting that criteria based on uterine specimen and lymphadenectomy without ultrastaging are insufficient to plan adjuvant therapy. This is in agreement with the data of Nugent et al. showing that uterine factors were less likely to be predictive of recurrence than lymph node status [20]. Moreover, the Benedetti-Panici trial and the SEPAL study reported a lower rate of postoperative radiotherapy when full staging was performed [8,9]. Finally, in a series of 1077 patients with EC, Trovik et al. observed improved overall and disease specific survivals linked to a shift from standard surgery (hysterectomy with bilateral salpingo-oophorectomy) to a more extensive surgery with lymphadenectomy along with a reduction in adjuvant radiotherapy [21]. Since the publications of the PORTEC-1 and 2 and GOG-99 trials, there has been an escalation in indications for adjuvant therapies [22–24]. However, these trials, focusing on

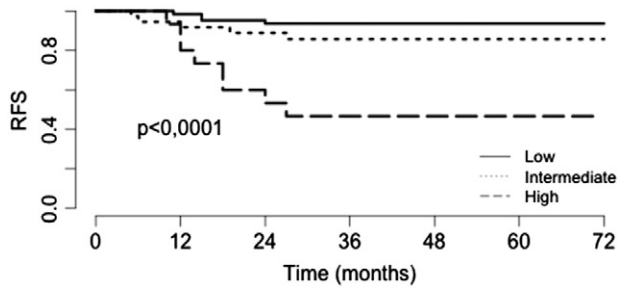

Fig. 4. Recurrence-free survival in the whole population according to risk groups.

patients of intermediate/high-risk groups, had various definitions of this risk group rendering indications for VBT and EBRT somewhat blurred. In our low-risk group, representing more than half of the population, the overall recurrence rate was 5.2% with no recurrence for the six patients with positive SLN after adjuvant therapy. One recurrence on the abdominal wall was observed among the 21 low-risk patients with negative SLN and adjuvant therapy (4.7%) and two recurrences among the 29 patients with negative SLN and no adjuvant therapy (6.9%). These results compare favorably with those of Nugent et al. using the criteria of the PORTEC-1 trial and reporting 4% of low-risk patients with lymph node metastases but a recurrence rate of 14% [20]. Similarly, using the criteria of the GOG-99 trial, the lymph node involvement rate was 3% for low-risk patients, but the recurrence rate 24% [22]. In addition, the meta-analysis of Kong et al. demonstrated that adding an EBRT did not impact on disease-free survival for low-risk patients while an increased cancer-related death rate was found [25]. When considering our patients in the intermediate- or high-risk groups, the overall recurrence rate was 13.5% and 42.8% when the patients with type 2 EC were excluded. In the PORTEC-1 trial including patients of intermediate–high risk after standard surgical treatment without lymphadenectomy, the 5-year recurrence rate was 4% in the surgery and EBRT group versus 14% in the surgery alone group, but without difference in overall survival [23]. In the PORTEC-2 trial including patients with type 1 EC of intermediate/high-risk after standard surgery and comparing EBRT to VBT, no difference in estimated 5-year rates of vaginal recurrence and distance metastases was found [24]. However, an increased risk of pelvic recurrence probably related to lymph node relapse was observed in the VBT group (HR 8.29, 95% CI 1.04–66.4; $p = 0.02$) confirming the relevance of assessing lymph node status to adapt adjuvant therapy and particularly EBRT.

Another challenge for physicians faced with patients with EC is to assess their presumed preoperative risk group to adapt treatment taking into account morbidity factors such as the age of the patient and obesity. As previously observed in retrospective studies, there is a high discrepancy in risk group evaluation between preoperative assessment based on endometrial biopsy and MRI, and final histology [26]. For patients at preoperative low risk upstaged to final intermediate–high risk, despite a low incidence of lymph node involvement when SLN biopsy is not performed, the impact of surgical management is a key issue mainly concerning the indication of a second surgery for comprehensive lymphadenectomy [27]. In the present study the overall discrepancy rate was 33%. For the 31 patients at low risk on preoperative findings, 23 patients were of intermediate-high risk at final histology. In the SEPAL study, it was demonstrated that overall survival was significantly longer when pelvic and PAAL was performed compared to pelvic lymphadenectomy alone particularly for patients at intermediate- or high-risk ($p = 0.0009$) [9]. However, it is important to note that the rate of patients with positive lymph nodes in the pelvic lymphadenectomy group and in the para-aortic and pelvic lymphadenectomy group was respectively 14% and 18% suggesting that most of the patients had no benefit of systematic lymphadenectomy while exposing them to an increased risk of short- and long-term complications such as lymphoedema and lymphocyst. In this specific setting, SLN biopsy allows us to identify patients who would potentially benefit from undergoing an extended lymphadenectomy to the para-aortic area in the case of intraoperative positivity of SLN as the estimated risk of avoiding metastases is 1% [28]. In the present study, among the six patients with type 1 EC and positive SLN on intraoperative histology, four underwent an immediate PAAL exclusively based on SLN status showing two patients with metastases on non-SLNs.

Some limits of the present trial have to be underlined. First, as in the ASTEC trial, no stratification for adjuvant therapy was planned which means that we cannot draw definite conclusions about which risk group would benefit from an adjuvant therapy. However, in agreement with a previous study, in the absence of positive SLN, our results support that no adjuvant therapy is required for patients in the low-

risk group. For low-risk patients with micrometastases or ITC, the therapeutic effect of lymphadenectomy and potentially of the SLN biopsy alone can plead on behalf of no adjuvant therapy as all non-SLNs were negative. Second, a higher rate of recurrence was observed in the present study compared to the ASTEC and the Benedetti-Panici et al. trial, probably linked to a higher incidence of high-risk patients with type 2 EC and a longer follow-up [6,8]. Finally, despite a high incidence of lymph node involvement mainly corresponding to micrometastases, our sample size cannot conclude on their impact on RFS.

In conclusion, our results support the relevance of SLN biopsy on surgical management and indications for adjuvant therapies. Hence, despite the absence of a difference in RFS, probably linked to the sample size, further studies focusing on management of EC should take into account not only SLN biopsy results but also stratifying adjuvant therapies according to SLN status.

Role of the funding source

The SENTI-ENDOstudy was funded by a grant from the Programme Hospitalier de Recherche Clinique PHRC 2006 (Ministère de la Santé), and sponsored by “Assistance publique — Hôpitaux de Paris”. Data was collected by the Unité de Recherche Clinique de l'Est Parisien (URCEST: TS, NM, IZ, SB, FA), and analyzed and interpreted independently. The report writing was led by ED. The corresponding author had full access to all of the data and the final responsibility to submit for publication. All authors were responsible for the final decision to submit the report for publication.

Conflict of interest statement

All authors confirm that they have no conflict of interest.

References

[1] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11–30.
[2] Belot A, Grosclaude P, Bossard N, Jougla E, Benhamou E, Delafosse P, et al. Cancer incidence and mortality in France over the period 1980–2005. Rev Dépidémiologie Santé Publique 2008;56:159–75.
[3] Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, Marini C, et al. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol ESMO 2011;22(Suppl. 6):vi35–9.
[4] Petru E, Lück H-J, Stuart G, Gaffney D, Millan D, Vergote I, et al. Gynecologic Cancer Intergroup (GCIG) proposals for changes of the current FIGO staging system. Eur J Obstet Gynecol Reprod Biol 2009;143:69–74.
[5] Fujimoto T, Nanjyo H, Fukuda J, Nakamura A, Mizunuma H, Yaegashi N, et al. Endometrioid uterine cancer: histopathological risk factors of local and distant recurrence. Gynecol Oncol 2009;112:342–7.
[6] ASTEC study group, Kitchener H, Swart AMC, Qian Q, Amos C, Parmar MKB. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 2009;373:125–36.
[7] May K, Bryant A, Dickinson HO, Kehoe S, Morrison J, May K, Bryant A, Dickinson HO, Kehoe S, Morrison J. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev 2010:CD007585.
[8] Benedetti Panici P, Basile S, Maneschi F, Alberto Lissoni A, Signorelli M, Scambia G, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst 2008;100:1707–16.
[9] Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. Lancet 2010;375:1165–72.
[10] Kang S, Yoo HJ, Hwang JH, Lim M-C, Seo S-S, Park S-Y. Sentinel lymph node biopsy in endometrial cancer: meta-analysis of 26 studies. Gynecol Oncol 2011;123:522–7.
[11] Ballester M, Dubernard G, Lécuru F, Heitz D, Mathevet P, Marret H, et al. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO). Lancet Oncol 2011;12:469–76.
[12] Kitchener HC. Sentinel-node biopsy in endometrial cancer: a win–win scenario? Lancet Oncol 2011;12:413–4.
[13] Mikuta JJ. International Federation of Gynecology and Obstetrics staging of endometrial cancer 1988. Cancer 1993;71:1460–3.
[14] Querleu D, Planchamp F, Narducci F, Morice P, Joly F, Genestie C, et al. Clinical practice guidelines for the management of patients with endometrial cancer in France: recommendations of the Institut National du Cancer and the Société Française d'Oncologie Gynécologique. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc 2011;21:945–50.
[15] Chino JP, Jones E, Berchuck A, Secord AA, Havrilesky LJ. The influence of radiation modality and lymph node dissection on survival in early-stage endometrial cancer. Int J Radiat Oncol Biol Phys 2012;82:1872–9.
[16] Bendifallah S, Koskas M, Ballester M, Genin A-S, Darai E, Rouzier R. The survival impact of systematic lymphadenectomy in endometrial cancer with the use of propensity score matching analysis. Am J Obstet Gynecol 2012;206(500):e1-11.
[17] Naumann RW. The role of lymphadenectomy in endometrial cancer: was the ASTEC trial doomed by design and are we destined to repeat that mistake? Gynecol Oncol 2012;126:5–11.
[18] Cragun JM, Havrilesky LJ, Calingaert B, Synan I, Secord AA, Soper JT, et al. Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer. J Clin Oncol Off J Am Soc Clin Oncol 2005;23:3668–75.
[19] Yabushita H, Shimazu M, Yamada H, Sawaguchi K, Noguchi M, Nakanishi M, et al. Occult lymph node metastases detected by cytokeratin immunohistochemistry predict recurrence in node-negative endometrial cancer. Gynecol Oncol 2001;80:139–44.
[20] Nugent EK, Bishop EA, Mathews CA, Moxley KM, Tenney M, Mannel RS, et al. Do uterine risk factors or lymph node metastasis more significantly affect recurrence in patients with endometrioid adenocarcinoma? Gynecol Oncol 2012;125:94–8.
[21] Trovik J, Mauland KK, Werner HMJ, Wik E, Helland H, Salvesen HB. Improved survival related to changes in endometrial cancer treatment, a 30-year population based perspective. Gynecol Oncol 2012;125:381–7.
[22] Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92:744–51.
[23] Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000;355:1404–11.
[24] Nout RA, Smit VTHBM, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens LCHW, 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.
[25] Kong A, Johnson N, Kitchener HC, Lawrie TA. Adjuvant radiotherapy for stage I endometrial cancer: an updated Cochrane systematic review and meta-analysis. J Natl Cancer Inst 2012;104:1625–34.
[26] Ballester M, Koskas M, Coutant C, Chéreau E, Seror J, Rouzier R, et al. Does the use of the 2009 FIGO classification of endometrial cancer impact on indications of the sentinel node biopsy? BMC Cancer 2010;10:465.
[27] Koskas M, Chereau E, Ballester M, Dubernard G, Lécuru F, Heitz D, et al. Accuracy of a nomogram for prediction of lymph-node metastasis detected with conventional histopathology and ultrastaging in endometrial cancer. Br J Cancer 2013;108:1267–72.
[28] Abu-Rustum NR, Gomez JD, Alektiar KM, Soslow RA, Hensley ML, Leitao Jr MM, et al. The incidence of isolated paraaortic nodal metastasis in surgically staged endometrial cancer patients with negative pelvic lymph nodes. Gynecol Oncol 2009;115:236–8.