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

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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.

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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].

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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%)