Gynecologic Oncology 136 (2015) 60–64

Contents lists available at ScienceDirect

Gynecologic Oncology

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

# Relevance of sentinel lymph node procedure for patients with high-risk endometrial cancer

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## HIGHLIGHTS

- Relevance of SLN biopsy in high-risk endometrial cancer.
- Associate SLN to LVSI status to indicate adjuvant treatment.

## ARTICLE INFO

*Article history:*
Received 25 August 2014
Accepted 26 October 2014
Available online 31 October 2014

*Keywords:*
Endometrial cancer
Sentinel lymph node biopsy
ESMO group risk
High-risk group
Detection rate
False negative rate

## ABSTRACT

*Objective.* While the accuracy of the Sentinel Lymph Node (SLN) procedure has been validated in patients with early-stage endometrial cancer (EC) at low and intermediate risk of recurrence, its relevance for high-risk EC remains unknown. The aim of this study was to evaluate the contribution of SLN biopsy in staging patients with presumed high-risk EC.

*Methods.* This retrospective multicenter study, conducted from January 2001 to December 2012, included 180 patients with early-stage EC undergoing SLN biopsy. Detection rate and false negative rate were assessed according to risk groups of recurrence.

*Results.* SLNs were detected in 159/180 patients (88%) and were bilateral in 63% of cases. Of the 180 patients, 41 (22%) had a positive lymph node. Ultrastaging detected metastases undiagnosed by conventional histology in 17/41 patients (41%). The false negative rate was 6% (9/159); 2.3% in the low/intermediate risk group and 20% in the high-risk group ($p = 0.0008$). Lymphovascular space invasion (LVSI) was present in 48 patients (27%). Preoperative findings classified 146 patients as ESMO low/intermediate risk (81%) and 34 as high risk (19%). Ten of the 34 patients (29%) in the presumed high-risk group were downstaged on final histology and 5/18 patients (28%) initially diagnosed with type 2 were finally classified as having type 1 EC. Classification was more likely discordant for patients with preoperative type 2 EC ($p = 0.03$) and in the initial high-risk group ($p = 0.02$).

*Conclusions.* SLN biopsy associated with LVSI status can select which high-risk patients with EC would benefit from comprehensive staging.



## Introduction

Endometrial cancer (EC), the most common gynecological cancer in western countries, is a surgically staged disease [1]. Although lymph node status remains one of the main prognostic factors, two randomized trials and a meta-analysis concluded that pelvic lymphadenectomy had no impact on survival for patients with early-stage EC mainly corresponding to low and intermediate European Society of Medical Oncology (ESMO) risk groups [2–4]. In contrast, for patients in the ESMO high-risk group corresponding to type 1 EC, grade 3 endometrioid cancer with myometrial infiltration superior to 50% and type 2 EC (i.e. serous EC, carcinosarcoma and clear cell cancer), several studies have underlined the need for comprehensive staging including pelvic and para-aortic lymphadenectomy [5]. One such study, the SEPAL study, demonstrated that systematic pelvic and para-aortic lymphadenectomy for patients in the high-risk group was associated with increased overall and disease-free survival [6]. However, Kumar et al. reported that pelvic and pelvic and para-aortic lymph node metastases were observed in only 17% and 9% of the patients, respectively, suggesting that the vast majority of patients did not benefit from systematic lymphadenectomy. This is important to note as lymphadenectomy exposes patients to a risk of immediate postoperative complications which impact quality of life [4,7,8].

Previous studies on early-stage EC, including a multicenter prospective trial, have demonstrated the relevance of Sentinel Lymph Node

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http://dx.doi.org/10.1016/j.ygyno.2014.10.027
0090-8258/

(SLN) biopsy to detect lymph node metastasis in patients in the low and intermediate ESMO risk groups [9–11]. In this specific setting, SLN biopsy is judged to be a trade-off between systematic and no lymphadenectomy [2]. In contrast, little data are available on SLN biopsy in patients of the ESMO high-risk group [12]. Therefore, the aim of this multicentre study was to evaluate the relevance of SLN biopsy to predict lymph node status in patients of the ESMO high-risk group compared to those in the low/intermediate risk groups.

## Material and methods

Data of all patients with early-stage EC who received primary surgical treatment between January 2001 and December 2012, were abstracted from one institution with maintained EC databases (Tenon University Hospital) and from the Senti-Endo trial [9]. 180 patients who underwent SLN procedure were included. Among them, 146 were classified as having ESMO low/intermediate risk EC (81%) and 34 with ESMO high-risk EC (19%) on initial histology [5].

All enrolled patients underwent a preoperative MRI unless contraindicated, in which case a CT scan was performed. Patients with histologically-proven EC were staged on the basis of final pathological findings according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) classification. Clinical and pathological variables included patient's age, body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), surgical procedure, 2009 FIGO stage, preoperative and final pathological analyses (histological type and grade, depth of myometrial invasion, and lymphovascular space invasion (LVSI) status), adjuvant treatments and recurrence. The research protocol was approved by the Ethical review committee of the French college of obstetricians and gynecologists (CEROG 2014-GYN-0207).

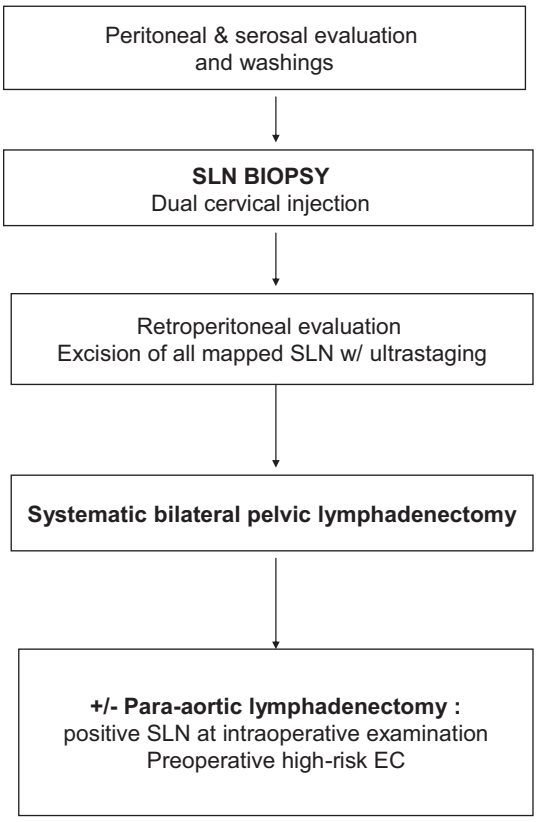


**Fig. 1.** Surgical algorithm for endometrial cancer.

### *Surgical treatment*

Patients were included if they had had primary surgical treatment including at least total hysterectomy with bilateral salpingo-oophorectomy and SLN procedure completed by a systematic pelvic lymphadenectomy [9]. Para-aortic lymphadenectomy (PAAL) was recommended for patients with positive SLN at intraoperative examination or final histology and for those with high-risk EC according to the current guidelines [13].

### *Sentinel lymph node procedure*

SLN procedure was performed as previously described [9]. For the SLN biopsy, a dual cervical injection was performed intracervically based on the histological validation of SLN by Delpech et al [14]. Lymph nodes with macroscopic metastases were sectioned. Normal-appearing SLNs were cut perpendicular to the long axis. All the SLNs were submitted to intraoperative imprint cytology or frozen section. Air-dried specimens were stained with a rapid May–Grünwald–Giemsa method. Each half-SLN was sectioned at 3-mm intervals. Each 3-mm section was analyzed at four additional levels of 150 μm and four parallel sections. One was used for hematoxylin and eosin (H&E) staining and H&E-negative sections were examined by immunohistochemistry (IHC) with an anticytokeratin antibody cocktail (cytokeratins AE1-AE3; Dako Corporation, Glostrup, Denmark). Non-SLNs were submitted totally and blocked individually after 3-mm sectioning and H&E staining. In accordance with previous study on sentinel node mapping in endometrial cancer, Fig. 1 illustrates the surgical algorithm for management of patients with EC.

Macrometastasis was defined as being a single focus of metastatic disease per node measuring more than 2 mm, micrometastasis as a focus of metastatic disease ranging from 0.2 mm to no more than 2 mm and, in accordance with previous studies [15,16], isolated tumor cells as metastases measuring no more than 0.2 mm including the presence of a single non-cohesive tumor cell. SLNs and non-SLNs were considered positive when they contained macrometastases, micrometastases or isolated tumor cells.

### *Statistical analysis*

The detection rate was calculated as the number of patients with at least one detected pelvic SLN divided by the total number of patients who underwent labeling and SLN mapping. False negative cases were defined as patients with negative SLNs at definitive histology with at least one metastatic non-SLN. Statistical analysis was based on Student's *t*-test and the Mann–Whitney test for parametric and nonparametric continuous variables, respectively, and the Chi-square test or Fisher's exact test, as appropriate, for categorical variables. Values of $p < 0.05$ were considered to denote significance.

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

## Results

### *Population characteristics*

The epidemiological and surgical characteristics of the 180 patients included in the study are shown in Table 1. Median age was 65 years [38–98] and BMI 25 kg/m$^2$ [18–54]. All the patients underwent total hysterectomy, bilateral salpingo-oophorectomy and SLN procedure completed by systematic pelvic lymphadenectomy. PAAL was performed in 25 patients (14%).

Final histology diagnosed type 1 EC in 154 patients (86%) and type 2 EC in 26 patients (14%). LVSI was present in 48 patients (27%).