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Limits of lymphoscintigraphy for sentinel node biopsy in women with endometrial cancer

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ABSTRACT

Objective. Lymph node status in endometrial cancer is a major prognostic factor. Sentinel lymph node (SLN) biopsy using radiocolloid and blue dye labeling has emerged as an alternative to systematic lymphadenectomy. This technique requires a preoperative lymphoscintigraphy. The aim of this study was to evaluate the limits of day-before preoperative lymphoscintigraphy to SLN biopsy.

Methods. Between July 2002 and March 2007, 38 patients with endometrial cancer underwent laparoscopic SLN procedure using radiocolloid and blue dye. Those with early-stage I endometrial cancer (35 patients) underwent a SLN procedure followed by systematic pelvic lymphadenectomy and a hysterectomy with bilateral salpingo-oophorectomy while those with presumed stage IIB on MR imaging (3 patients) underwent a radical hysterectomy. Omentectomy and paraaortic lymphadenectomy were also performed for women with clear cell or serous papillary carcinoma (5 patients). The SLN identification rates and false-negative rates were studied.

Results. The detection rate of lymphoscintigraphy was 84.5% (32/38), with 1.9 nodes per patient. Eight of 17 patients (47%) with unilateral sentinel lymph node on lymphoscintigraphy had bilateral SLNs at surgery and three of 15 patients (20%) with bilateral SLN on lymphoscintigraphy had unilateral SLN at surgery. The correlation was poor (kappa = 0.266). When categorized in <2 and ≥ 2 sentinel nodes, the correlation between lymphoscintigraphic and surgical SLN mapping was moderate (kappa = 0.33).

Conclusion. Our results demonstrated the low correlation between day-before lymphoscintigraphy and surgical SLN mapping raising issues of its usefulness and cost-effectiveness in routine practice.

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Introduction

Uterine endometrial cancer is a major health problem in developed countries. In the USA alone there were 39000 new cases and 7400 related deaths in 2007 [1]. In addition to histological type, tumor grade and depth of myometrial invasion, lymph node status is a major prognostic factor and a decision criterion for adjuvant therapy [2,3].

Despite improvement in imaging techniques including CT scan, MR imaging and Pet-scan, preoperative assessment of lymph node status remains difficult and raises the issue of systematic lymphadenectomy. Pelvic/paraaortic lymphadenectomy is a source of potential severe complications especially in women with endometrial cancer who are often elderly, obese and with cardiovascular comorbidity [3,4]. In early stage endometrial cancer, the frequency of lymph node metastases varies from 0% to 34% [5]. Hence, the vast majority of women do not benefit from systematic lymphadenectomy. Due to a low incidence of lymph node metastases, Mariani et al. suggested that women with no myometrial invasion, low grade endometrioid carcinoma and no evidence of tumor outside the corpus should not undergo lymphadenectomy and that the procedure be reserved for those with advanced stages of the disease or with clear cell or serous papillary cancer [2,6].

The sentinel node (SLN) concept has been accepted as an alternative to lymphadenectomy in many malignancies including melanoma [7] and, more recently, breast cancer [8]. In gynecological malignancies, the SLN procedure is well established in vulvar cancer [9,10]. In endometrial cancer, using combined colorimetric and radiocolloid technique followed by a systematic lymphoscintigraphy, it gives a high detection rate of between 80% and 100% [11–15] and histologic validation has recently been demonstrated in this indication [16]. Moreover, Ballester et al. reported a high incidence of lymph node involvement, especially of micrometastases, by serial sectioning and immunohistochemical techniques on SLN even in women with early stages of endometrial cancer [17]. In cervical cancer though, Frumovitz et al. have recently underlined discrepancies existing between lymphoscintigraphic and surgical SLN mapping raising the issue of its usefulness [18]. No such data on the relevance of preoperative lymphoscintigraphy in women with endometrial cancer

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are available. We were thus prompted to retrospectively evaluate the relation between day-before lymphoscintigraphy and surgical localization of SLN in women with endometrial cancer.

Material and methods

Patients

Between July 2002 and March 2007, 46 women with suspicion of endometrial cancer were referred to the gynecology department of Tenon Hospital, France. All the women underwent an endometrial biopsy under hysteroscopic guidance to confirm the diagnosis of cancer, and then preoperative MR imaging to assess the stage.

The medical records were reviewed to determine age, the body mass index (BMI), history of prior abdominal surgery, tumor stage, histology, surgical procedure, intra- and postoperative complications, and the length of hospital stay. Outcome was obtained from the outpatient records. In accordance with the French law, no ethic committee approval is required for this retrospective study.

Therapeutic strategy

In accordance with our protocol, surgical management for stage I endometrial cancer included a peritoneal cytology followed by the SLN procedure with pelvic lymphadenectomy, bilateral salpingo-oophorectomy and hysterectomy by laparoscopy. For women with presumed stage IIB on MR imaging, a radical hysterectomy was performed instead of simple hysterectomy. For women with clear cell or serous papillary carcinoma, an omentectomy and paraaortic lymphadenectomy were recommended.

All women were staged according to the International Federation of Gynaecology and Obstetrics (FIGO) classification. For women with stage IA independently of grade, no adjuvant therapy was recommended. Brachytherapy was performed for women with stage IB, IC, IIA or IIB and external pelvic radiotherapy for those with a stage above or equal to III.

Brachytherapy consisted of 20 grays (Gy) given 5–6 weeks after surgery. External pelvic radiation therapy consisted of 40 Gy using 2.25 Gy per fraction, 4 days a week. All fields were treated daily with 15 Megavoltage units. Women requiring concurrent chemoradiotherapy received chemotherapy during the first and fourth weeks of radiation therapy. This consisted of a continuous 5-fluorouracil infusion (750 mg/m^2/day) and a cisplatin bolus (20–25 mg/m^2/day) 1 h before radiotherapy on days 1, 2, 4 and 5. Patients with positive aortic nodes received extended-field radiation up to the level of T12-L1.

Technique

Sentinel node procedure

Four cervical injections at 3, 6, 9 and 12 o'clock of 0.2 mL (20 MBq each) of unfiltered technetium sulphur colloid (median particle size is 100 nm) (Nanocis; CIS Bio International, Saclay, France), were administered with a 25-gauge spinal needle the day before surgery. Scintigraphic images were obtained 2 h after the injections and then every 30 min two or three times to detect the SLN with a triple-head gamma camera (Irix; Marconi Corporation, Cleveland, OH). Five-minute static, anterior and lateral projections were acquired with a matrix size of 512×512 pixels.

The patients were placed in a low lithotomy position under general anesthesia. A speculum was placed in the vagina and patent blue (Bleu Patenté; V; Guerbet Laboratory, Issy les Moulineaux, France) injected cervically through a 25-gauge spinal needle at 3 and 9 o'clock (1 mL per injection). Antimicrobial chemoprophylaxis (cefazoline 2 g intravenously) was administered at the beginning of the operation. Prophylactic subcutaneous heparin was administered the day before surgery. For the laparoscopic procedure, after pneumoperitoneal insufflation using a Veress needle, a 10 mm laparoscope was inserted through an umbilical incision and connected to a video monitor. Three stab incisions were made in the suprapubic area for the trocars: one 12-mm incision in the median suprapubic area and one 5.5-mm incision in each iliac fossa.

Pelvic and lower paraaortic regions were inspected carefully for lymph ducts and dye uptake by lymph nodes. Radioactive pelvic and paraaortic lymph nodes were located by using an endoscopic gamma probe (Eurorad, Strasbourg, France) inserted through the 12-mm suprapubic trocar. Radioactive lymph nodes were sought before opening the peritoneum. The gamma probe was angled laterally to avoid detecting radioactivity at the injection site.

After locating the SLN, the peritoneum was opened and each blue and/or radioactive lymph node was removed separately in endoscopic bags. The position of each SLN was recorded relative to the major pelvic vessels, vena cava or aorta.

After the SLN procedure, systematic pelvic lymphadenectomy was performed. All lymphatic tissue was removed and extracted in an endoscopic bag. The absence of residual pelvic or paraaortic radioactivity was verified after lymphadenectomy.

Histology

SLNs and non-SLNs were analyzed by a pathologist. Lymph nodes with macroscopic metastases were sectioned. Normal-appearing SLNs were cut perpendicular to the long axis. All SLNs were submitted to intra-operative imprint cytology. Air-dried cytological smears were prepared by scraping the cut surfaces and staining with a rapid May-Grünwald-Giemsa method. Each half-SLN was sectioned at 3-mm intervals and 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 whole and blocked individually after 3-mm sectioning and H&E staining.

The size of lymph node metastases was estimated with an eyepiece micrometer. A micrometastasis was defined as a single focus of metastatic disease per lymph node, measuring no more than 2 mm. The presence of metastases less than 0.2 mm or single non-cohesive tumor cells was recorded and defined as submicrometastasis. An SLN was considered positive when it contained macrometastases, micrometastases, or submicrometastasis.

SLN analysis

SLNs were recorded as blue-stained and/or radioactive (if the *in vivo* count exceeded three times the background). The false-negative rate was defined as the number of procedures with a negative SLN and one or more positive non-SLNs, divided by the number of procedures with any positive pelvic lymph or paraaortic node.

Statistical analysis

Statistical analysis was based on Student's *t*-test and the Mann–Whitney test for parametric and non parametric continuous variables, respectively, and the Chi square test or Fisher's exact test, as appropriate, for categorical variables. The Mac Nemar test for paired samples was used to compare detection method performances. *P* values $<.05$ were considered to denote significant differences.

Results

Epidemiological characteristics of the population

Thirty-eight of the 46 patients (82.6%) underwent a combined technique with radiocolloid and colorimetric SLN detection. All these patients underwent a preoperative lymphoscintigraphy. Eight patients underwent a colorimetric technique alone and were excluded from the study.

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