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Contribution of lymphoscintigraphy to intraoperative sentinel lymph node detection in early cervical cancer: Analysis of the prospective multicenter SENTICOL cohort

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HIGHLIGHTS

- We conducted a multicenter prospective study to evaluate contribution of lymphoscintigraphy in SLN procedure in early cervical cancer. We report low agreement with intraoperative lymphatic mapping. Lymphoscintigraphy identified substantial proportions of unusual drainage pathways. It might help decrease the false-negative rate.

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ABSTRACT

Purpose. To evaluate the contribution of preoperative lymphoscintigraphy to intraoperative lymphatic mapping (ILM) in early cervical cancer

Methods. We conducted an ancillary analysis of the multicenter prospective SENTICOL study in early cervical cancer. Radiocolloid was injected intracervically on the day before (long protocol) or morning of (short protocol) surgery, lymphoscintigraphy was performed, and the results of a centralized image review were communicated to the surgeons. ILM was performed on combined radioactivity/patent blue detection. Sentinel lymph nodes (SLNs) were electively sampled before routine bilateral pelvic lymphadenectomy by laparoscopy.

Results. Of 139 patients in the modified intention-to-diagnose analysis, 114 had centrally reviewed lymphoscintigrams, which showed 352 SLNs in 100 patients. Lymphoscintigraphy and ILM detection rates were 87.8% and 97.8%, respectively. Agreement between lymphoscintigraphy and ILM was low for the number of SLNs ($\kappa = 0.23$; -0.04; 0.49) and bilateral SLNs ($\kappa = 0.36$; 0.2; 0.52). No patient without SLNs by ILM had SLNs by lymphoscintigraphy. Lymphoscintigraphy identified substantial proportions of unusual drainage pathways. No patients with metastatic nodes had SLNs by lymphoscintigraphy but not by ILM in the relevant territory. In 1

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of the 2 patients with false-negative SLN results, SLNs were bilateral by lymphoscintigraphy and unilateral by ILM.

Conclusion. Although the detection rate was lower by lymphoscintigraphy than by ILM, the substantial proportions of SLNs in unusual territories provided valuable guidance for the surgical exploration. Awareness of the limited agreement between lymphoscintigraphic and surgical detection might help surgeons decrease the false-negative rate.

Introduction

Sentinel lymph node (SLN) biopsy, which is standard practice for breast cancer, may also hold promise for the surgical management of early cervical cancer [1–3]. Lymph node involvement is found in fewer than 20% of patients with early cervical cancer but has a major adverse impact on the prognosis [4,5]. Pelvic lymphadenectomy is associated with a substantial risk of lymphedema. Moreover, SLN detection can identify aberrant drainage pathways that might otherwise be the site of nodal recurrences [6]. Finally, nodal metastases are often small and best detected by ultrastaging, which is performed routinely to assess SLNs [7]. Studies have established the feasibility of SLN biopsy in early cervical cancer and shown high detection rates and good diagnostic value [8].

The available data support the use of both radioactive tracer and blue dye injection to ensure accurate intraoperative lymphatic mapping (ILM) [9,10]. Preoperative SLN detection by lymphoscintigraphy is usually performed to guide ILM, thereby increasing the SLN detection rate. However, preoperative lymphoscintigraphy is time-consuming and costly and should therefore be used only if proof of benefit is obtained. The scarce data published to date leave room for controversy about the benefits of lymphoscintigraphy.

Here, our purpose was to use data from the large SENTICOL study of patients with early cervical cancer to evaluate the agreement between lymphoscintigraphic and intraoperative SLN detection and to clarify the contribution of lymphoscintigraphy to ILM.

Material and methods

Material

We conducted an ancillary analysis of the prospective multicenter SENTICOL (January 2005–June 2007) [8,11,12]. Inclusion criteria were squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma of the uterine cervix, FIGO stage IA1 with emboli to IB1, and confirmation of the diagnosis by biopsy or cone biopsy, clinical examination, and pelvic MRI. Non-inclusion criteria were downstaging following chemotherapy or radiotherapy, documented allergy to patent blue or rhenium sulfide, history of severe allergy, age younger than 18 years, and pregnancy. Patients whose preoperative imaging studies suggested lymph node involvement were not included. All patients gave their written informed consent before inclusion in the study, which was approved by our ethics committee (Comité de Protection des Personnes HEGP-Broussais, Paris).

Methods

An injection of 60 or 120 MBq of radiocolloid (^{99m}Tc-labeled rhenium sulfide, Nanocis®, Cis Bio International, Gif sur Yvette, France) was performed into the four cardinal points of the cervix, on the day before (long protocol) or morning of (short protocol) surgery.

Lymphoscintigraphy was performed routinely and the results were communicated to the surgeons before the surgical procedure.

At the beginning of the surgical procedure, 2 mL of diluted patent blue (2.5% in 2 mL of saline) was injected into the four cardinal points of the cervix. ILM and pathological examination are reported elsewhere [8,11,12].

We recorded the number of SLNs detected by lymphoscintigraphy and ILM, as well as their locations according to Marnitz et al. [13]. External and inter-iliac nodes were considered to be located in typical sites. All the other locations were atypical. Nodal tumor diameter was used to distinguish isolated tumor cells (<0.2 mm), micrometastases (0.2–2 mm), and macrometastases (>2 mm) [14].

All lymphoscintigrams included in the analysis were subjected to centralized review by two nuclear physicians (MF, IO) and three surgeons (ASB, FL, PM). For each patient, the following lymphoscintigram data were recorded: total number of SLNs, median number of SLNs per patient, overall SLN detection rate, bilateral SLN detection rate, and anatomic location of SLNs. The same data were collected for ILM. As far as pre-operative SLNs' location is concerned, external, inter-iliac, and internal iliac nodes were analyzed together.

Statistical analysis

The sample size ($n = 120$ patients) estimation has been previously described [8,15], and the study was carried out using the modified intention-to-diagnose approach. The detection rate was first determined. All variables were normally distributed. Continuous variables were compared using Student's *t*-test and categorical variables using the chi-square test or Fisher's exact test, as appropriate. P values < 0.05 were considered significant.

Agreement between lymphoscintigraphy and ILM was assessed using Cohen's κ coefficient and its confidence interval. We assessed agreement for detection of at least one SLN, bilateral detection of SLNs, and number of detected SLNs. The κ values were categorized as follows: 0, no agreement; 0–0.2, very low agreement; 0.21–0.4, low agreement; 0.41–0.6, moderate agreement; 0.61–0.8, full agreement; and 0.81, almost perfect agreement. Differences between SLN locations detected by lymphoscintigraphy and by surgery were evaluated using the chi-square test.

Results

Characteristics of the population

As previously described [8], 139 patients were included in the modified intention-to-diagnose population. Among them, 11 had major protocol deviations: 6 did not receive the radiocolloid injection,

Table 1
Characteristics of the population and tumors.

Characteristics	N = 139 (%)
Age in years, mean (±SD)	44.4 (±13.6)
BMI in kg/m^2, mean (±SD)	23.7 (±5.5)
Histology, n (%)	
Squamous cell carcinoma	103 (74.1)
Adenocarcinoma	34 (24.4)
Adenosquamous carcinoma	2 (1.4)
FIGO stage, n (%)	
IA1 with emboli	5 (3.6)
IA2	12 (8.6)
IB1	121 (87.1)
IIA	1 (0.7)

Abbreviations: BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics.

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