Sentinel lymph nodes in endometrial cancer: is hysteroscopic injection valid?

D. Clement[1, 4], A.S. Bats[1, 4], N. Ghazzar-Pierquet[2], M.A. Le Frere Belda[3, 4], F. Larousserie[1, 4], C. Nos[1, 4], F. Lecuru[1, 4]

[1]Service de Chirurgie Gynécologique et Cancérologique, Hôpital Européen Georges Pompidou
[2]Département de Médecine Nucléaire, Hôpital Européen Georges Pompidou
[3]Service d'Anatomie Pathologique, Hôpital Européen Georges Pompidou
[4]Université Paris-Descartes, Faculté de Médecine, Paris (France)

Summary

We aimed to describe hysteroscopic peritumoral tracer injection for detecting sentinel lymph nodes (SLNs) in patients with endometrial cancer and to evaluate tolerance of the procedure, detection rate and location of SLNs. Five patients with early endometrial cancer underwent hysteroscopic radiotracer injection followed by lymphoscintigraphy, then by surgery with hysteroscopic peritumoral blue dye injection, and radioactivity measurement using an endoscopic handheld gamma probe. SLNs and other nodes were sent separately to the pathology laboratory. SLNs were evaluated by hematoxylin-eosin-saffron staining and, when negative, by immunohistochemistry. Tolerance of the injection by the patients was poor (mean visual analog scale score, 8/10). SLNs were detected in only two patients (external iliac and common iliac+paraaortic, respectively). Detection rates were 1/5 by radiotracer, 1/5 by dye, and 2/5 by the combined method. One SLN was involved in a patient whose other nodes were negative. In three patients no SLNs were found by radiotracer or blue dye. Of the 83 non sentinel nodes removed from these patients, none was involved. Hysteroscopic peritumoral injection may be more difficult than cervical injection and, in our experience, carries a lower SLN detection rate.

Key words: Endometrial cancer; Sentinel lymph node; Hysteroscopy; Paraaortic chain.

Introduction

Sentinel lymph node (SLN) detection in patients with endometrial cancer was first evaluated by Burke *et al*. in 1996 [1] with the goal of improving staging, most notably via better detection of paraaortic nodes. SLN detection also ensures identification of micrometastases. Most of the subsequent studies used intracervical radiotracer injection and blue dye, which proved effective in identifying pelvic SLNs [2-4]. However, paraaortic SLNs were rarely identified with this technique [2-4]. Injection around the tumor via hysteroscopy was used in a few studies to evaluate drainage of the tumor, as opposed to drainage of the cervix [5-8]. This method may be more appropriate for evaluating drainage toward the paraaortic nodes.

The objective of this study was to describe our preliminary experience with SLN detection by hysteroscopic radiotracer injection in patients with early endometrial cancer and to evaluate the SLN detection rate.

Materials and Methods

Between July 2005 and February 2006, five non-consecutive patients with early-stage endometrial cancer underwent SLN detection after hysteroscopic radiotracer injection. All patients gave their informed consent to the study before inclusion.

In all patients, the work-up included a physical examination, pelvic ultrasonography, magnetic resonance imaging, and endometrial biopsy or curettage. The results showed endometrial cancer with no evidence of spread beyond the uterus. The main patient characteristics are reported in Table 1.

On the day before surgery, 120 MBq of technetium-99m colloidal rhenium sulfide (Nanocis, Schering, CIS BIO International, Gif-sur-Yvette, France) was injected via a VERSAPOINT 5Fr hysteroscope (Gynecare, Issy les Moulineaux, France). Saline at hydrostatic pressure was used to dilate the uterus. The radiotracer was injected under the endometrium at four sites (anterior wall x 2, posterior wall x 2) around the tumor using a 17-gauge oocyte aspiration needle (Laboratoire CCD, Paris, France) (Figure 1). Although the injections induced no major complications, they were poorly tolerated by the patients (mean visual analog scale for pain score of 8/10). Lymphoscintigraphy was performed 12 hours after radiotracer injection, using a dual-head camera (Axis 2000°, Philips Medical Systems, Cleveland, OH). During surgery, 2 ml of patent blue dye (2.5% patent blue V dye, sodium salt, Guerbet, Roissy, France) was injected into the uterine cavity in the first four patients, using the same technique as for the radiotracer. In the fifth patient, blue dye was injected into the cervix, at 0, 3, 6, and 9 o'clock.

SLNs were looked for during laparoscopy. First, blue lymphatics were sought in the broad ligaments and in the pelvic and paraaortic node areas, with the peritoneum closed. A handheld gamma probe (CdTe probe, Europrobe°, Eurorad, Constellation Technology, Largo, FL) was then used to detect radioactivity, using the lymphoscintigram as a roadmap. The peritoneum was opened at the level of the iliac vessels, and the pelvic nodes were dissected to look for blue and/or radioactive nodes. Paraaortic SLNs were sought using the same procedure, with inspection for blue nodes followed by gamma probe detection based on lymphoscintigraphy findings. Then, the pelvic nodes were dissected routinely. Paraaortic dissection was to be performed in patients with paraaortic SLNs, adnexal involvement, pelvic node metastasis, Stage Ic disease, papillary serous or clear cell carcinoma. SLNs and other nodes were removed in a bag. All operative specimens were sent to the pathology laboratory.

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Table 1. — *Main characteristics of the five patients.*

Patient	Age	BMI	Final stage	Histology	Grade	Surgical approach
1	57	24	Ib	Endometroid	II	Laparoscopy
2	87	22	Ic	Endometroid	II	Laparoscopy
3	61	37	Ic	Endometroid	I	Laparoscopy
4	63	38	Ib	Endometroid	I	Laparoscopy
5	60	30	IIIc	Endometroid	I	Laparoscopy

BMI: body mass index.

Table 2. — *Detection of sentinel lymph nodes after hysteroscopic injection of radiotracer and blue dye.*

Patient	Depth invaded by preoperative MRI	Tumor size by preoperative MRI	Hysteroscopic injection of 99m Tc	SLNs by lymphoscintigraphy	SLNs by blue dye	Location of SLNs (n)
1	< 1/2	Focal	Yes	0	0	None detected
2	< 1/2	Focal	Yes	0	0	None detected
3	< 1/2	Focal	Yes	2	0	Left common iliac (2) and paraaortic (1)
4	< 1/2	Entire cavity	Yes	0	0	None detected
5	< 1/2	Entire cavity	Yes	0	1*	Right external iliac (1)

MRI: magnetic resonance imaging; SLN: sentinel lymph node; *: blue dye was injected in the cervix.

SLNs were embedded in paraffin. Five sections were obtained at 250-µ intervals. Four sections were stained with hematoxylin-eosin-saffron (HES) and examined by light microscopy. When these sections were negative, the fifth section was used for immunohistochemistry with the broad-spectrum monoclonal antikeratin antibody KL1 (Immunotec, Marseille, France). Non-sentinel nodes were evaluated by light microscopy examination of a single HES-stained section after paraffin embedding.

Results

Although the injections induced no major complications, they were poorly tolerated by the patients (mean visual analog scale for pain score of 8/10).

SLNs were detected in only two of the five patients (Table 2). One patient (#2) had three SLNs, two in the common left iliac territory and one in the paraaortic territory (preaortic and inframesenteric). The SLNs were identified by lymphoscintigraphy and gamma probe detection. All three SLNs were negative for cancer cells. The six pelvic nodes and nine paraaortic nodes removed during routine node detection were also negative. In the other patient (#5), the radiotracer failed to detect SLNs but intracervical blue-dye injection identified an SLN in the right external iliac chain. This SLN contained a metastasis, whereas the other 15 iliac nodes and the 11 paraaortic nodes were negative. Neither radiotracer injection nor blue dye showed SLNs in the other three patients. Thus, the radiotracer detection rate was 1/5, the dye detection rate was 1/5, and the combined detection rate was 2/5. In all, 83 nodes were removed from the five patients. No nodal metastases were found in non sentinel nodes. Peritoneal cytology was negative in all five patients. No intra- or postoperative complications were recorded.

Discussion

Evaluation of the lymph nodes is a crucial step in the management of endometrial cancer [9], which can metastasize to the pelvic and/or paraaortic chains. The staging procedure recommended by the FIGO involves routine assessment of pelvic and paraaortic nodes [9]. However, routine removal of the paraaortic nodes remains controversial, and the relative merits of full dissection versus selective dissection are unclear [10]. SLN detection may offer a solution by determining which nodes must be removed.

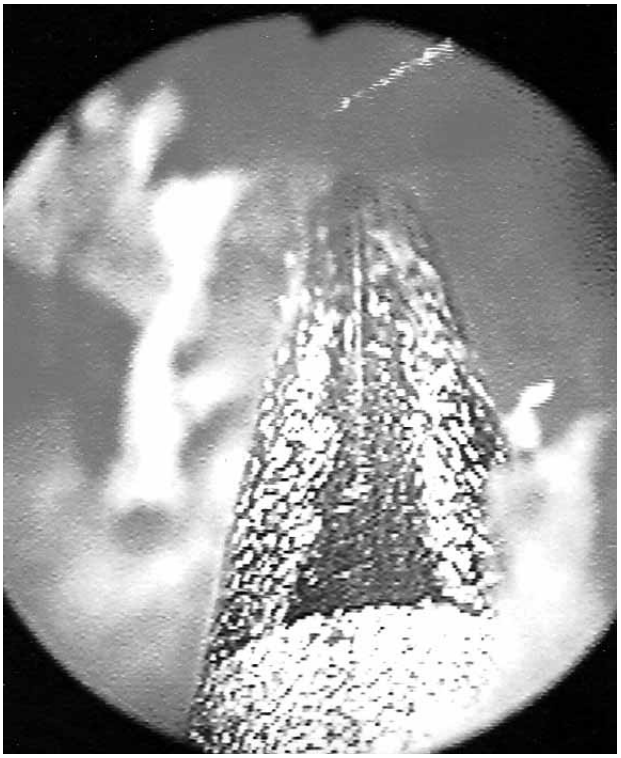

Figure 1. — Peritumoral injection of isotope in the anterior wall.

Intracervical injection of a radiotracer with or without blue dye was used in the studies of SLN detection in patients with endometrial cancer. This method is generally described as easy to perform, well tolerated by the patients, and effective in identifying SLNs in over 80% of cases [2-4]. However, the SLNs detected using this technique are usually located in the iliac and obturator chains. In our experience, SLNs may be found in the paraaortic chains, although pelvic SLNs are usually detected also [4], in keeping with the fact that cervical injection produces a drainage map of the cervix, as opposed to the uterine body or tumor.

Burke *et al*. [1] used blue-dye injection into the subserosal myometrium during surgery. Results were judged poor with this approach [11]. Subsequently, other groups used hysteroscopic peritumoral injections, and reported good acceptability, high detection rates and low false-negative rates [5-7].

In contrast, tolerance and detection rates were low in our study. The reasons for this failure are unclear. First we used a similar technique to previous reports, so that the lymphatic drainage should have been similar [5-7]. Second, we recorded no detection in 3/5 patients, whatever the technique used (radiotracer, blue dye). It appears that the use of blue dye alone by hysteroscopy limited the

Table 3. — *Main results of studies of hysteroscopic injection for detecting sentinel lymph nodes in patients with endometrial cancer.*

Author (n)	Tolerance	Lymphoscintigraphic SLN detection rate	Intraoperative SLN detection rate	SLN location (n), SLN metastases (n)
Raspagliesi (18)	Vagal malaise: 2 Failure: 1 Bleeding: 1	100%	100%	23 I, 2 + 10 CI, 1 + 12 PA, 1 +
Maccauro (26)*	Vagal malaise: 2 Bleeding: 1	100%	92%	27 I, 2+ 12 CI, 1+ 14 PA, 1+
Niikura (28)	Not recorded	68%	82%	37 I , 1 + 4 CI, 0+ 30 PA, 0+
Gien (16)	Not recorded	Not done	56% (blue only)	13 I, 0+ (1 FN) 3 CI, 0+ 1 PA, 0+

SLN: sentinel lymph node; PA: paraaortic; CI: common iliac; I: iliac (external iliac, internal iliac, and/or obturator); FN: false negative; (n): number of patients in the study.

SLN detection rate [5, 7, 8] (Table 3). This does not explain the failure with the radiotracer. Third, although there may be a learning curve, we have extensive experience with outpatient hysteroscopy, operative hysteroscopy, and cervical radiotracer and dye injection for endometrial or cervical cancer. Furthermore, no learning curve effect was reported for hysteroscopic injection by other groups [5-7]. Fourth, time interval between the injection and the detection (lymphoscintigraphy and peroperative detection) as well as the radiotracer size do not appear as determinant since different approaches provided similar results [5-7]. Fifth, depth of myometrial invasion could decrease the detection rate [6].

Radiotracer injection on the day before surgery was poorly tolerated by the patients. We did not use general or local anesthesia. In contrast, Niikura *et al*. (28 patients) reported good tolerance and Maccauro *et al*. (26 patients) mentioned only transient vagal symptoms in two patients [5, 6]. Raspagliesi *et al*. (18 patients) reported one failure and one case of procedure-limiting intrauterine bleeding [7]. In fact, patient tolerance was not evaluated in previous studies, whereas we evaluated the pain due to the hysteroscopy with a visual analog scale. We found that hysteroscopic injection considerably complicated the SLN-detection procedure in patients with early-stage endometrial cancer, whose management is now simple and well standardized [12].

The main goal of hysteroscopic injection is detection of both pelvic and paraaortic SLNs and metastases. Results in our patient #2 show that this goal can be achieved. Maccauro *et al*. reported 21% of SLNs in the paraaortic area; one being metastatic without pelvic involvement [7]. Similarly, Nikura *et al*. reported SLNs in the paraaortic chain in 72% of patients (SLNs were distributed in all paraaortic areas) [6]. SLNs were exclusively paraaortic in 13% of patients [6]. However, neither report provides information on tumor stage, most notably on whether pelvic node disease or cervical spread was found. These factors could influence the risk of paraaortic involvement [13, 14].

Another group reported negative results with the hysteroscopic approach [8]. In this series of 16 patients, only the first three injections were performed by hysteroscopy, the subsequent having a combination of hysteroscopic and subserosal or simply subserosal injection of blue dye. Detection rate was of 0% after hysteroscopy alone (0/3) [8].

Conclusion

We suggest that the feasibility and relevance of the present hysteroscopic tracer injection for SLN detection in endometrial cancer may be in doubt. This approach has to be compared to intracervical injections, in terms of detection rate and node areas explored.

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Address reprint requests to:
F. LÉCURU, M.D.
Service de Chirurgie Gynécologique
et Cancérologique,
Hôpital Européen Georges Pompidou,
20 rue Leblanc - 75015 Paris (France)
e-mail: fabrice.lecuru@egp.aphp.fr