Comparison of laparoscopic intraoperative sentinel lymph node detection rates obtainable with vital dye or radioactive colloid in early stage endometrial cancer. A preliminary prospective trial

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Summary

***Aims*. The objective of this preliminary study was to specifically compare sentinel lymph nodes (SLNs) detection rates obtainable by injecting blue dye or radioactive tracer in women with endometrial cancer undergoing laparoscopic staging.**
***Methods*. Seven patients with early stage endometrial cancer were enrolled. The assessment of SLNs was done laparoscopically. The radioactive tracer was injected into the cervix 24 hours before surgery. Blue dye was injected into the cervix the day of surgery. Radioactive SLNs were identified with a gamma-scintiprobe. Both SLNs and non-SLNs were evaluated for micrometastases.**
***Results*. The SLNs detection rate was 100% for the radioactive tracer and 71% for blue dye. All the four patients (100%) with lymph node metastases had SLNs identified by the radioactive tracer whereas only two (50%) had SLNs identified by blue dye.**
***Conclusions*. Radioactive tracer seems to be more reliable to predict lymph node status in women with endometrial cancer undergoing laparoscopic staging.**

KEY WORDS: sentinel lymph node, laparoscopy, endometrial cancer, blue dye, radioactive tracer.

Introduction

The primary treatment for women with endometrial cancer is surgical, including total hysterectomy, removal of adnexal structures, and staging with lymphadenectomy (1,2). The traditional approach is surgery via an open, laparotomy incision, but surgical treatment can be also performed via standard laparoscopy or robotic surgery (1,2). These minimally invasive approaches have helped to reduce both the morbidity of women with early-stage cancer and surgery costs (1,2).
A staging system is essential to an evidence-based approach to cancer. It should assist the clinician in planning treatment and in evaluating the results of treatment, should provide indications of prognosis, and should facilitate the exchange of information. Endometrial cancer is staged surgically only since 1988 when the FIGO Committee on Gynecologic Oncology decided to accept the results of several studies evaluating by surgery the pathological spread pattern of the carcinoma outside of the uterus (lymph node metastasis, adnexal disease, intraperitoneal spread and/or malignant cells in peritoneal washings) (2). Therefore, since 1988 surgical staging for endometrial cancer became routinely adopted by the majority of Gynecologic Oncology centers all over the world. However, controversies exist in surgical staging of lymphatic spread because approximately 80% of endometrial cancers are diagnosed at an early stage and systematic pelvic and para-aortic lymphadenectomy may produce additional morbidity without the benefit of appropriate surgical staging (2).
In the effort to avoid complete systematic lymphadenectomy whenever possible, the Sentinel Lymph Node (SLN) biopsy has been proposed (2). Several studies have examined the feasibility of SLNs biopsy after intraoperative lymphatic mapping with both vital dyes and radioactive colloids in women with endometrial cancer but none of the studies specifically compared the SLN detection rates obtainable by using a blue dye or a radioactive tracer (2).
We recently performed a prospective trial with allocation of women with endometrial cancer to laparotomy or laparoscopy to compare the SLN detection rates obtainable by the two surgical accesses after the injection of a blue dye into the uterine cervix showing that the detection rate was significantly higher for laparoscopy but cases of failed mapping were observed both in the

laparoscopy and in the laparotomy group using blue dye (3). We therefore decided to perform a new preliminary prospective trial injecting both a blue dye and a radioactive colloid into the uterine cervix of women with endometrial cancer undergoing laparoscopic staging to compare the SLNs detection rate of the two tracers.

Materials and Methods

Women undergoing surgical staging through laparoscopy for endometrial cancer at clinical stage I-II were enrolled in this prospective study. Surgery was performed in Italy in a teaching hospital from February to July 2010.

The study was approved by the Institutional Review Board of the Department at the University of Cagliari, Italy. The procedure followed was in accordance with the Helsinki Declaration of 1975, as revised in 1983, and was explained to each patient. Written informed consent was obtained from all patients included in the study and only patients who agreed to be a part of the study were enrolled.

Before surgery all patients underwent a complete physical examination, routine laboratory tests, and a radiological workup that included CT scan of the abdomen and pelvis as well as a pelvic sonogram.

Women having enlarged retroperitoneal nodes at CT scan were not enrolled.

As suggested by Pelosi et al. (4), 37 MBq of 99 m-Technetium (Tc-99m)-labelled albumin colloidal particles were administered to the patients 24 hours before surgery in a volume of 0.4 ml. The radioactive tracer was injected directly into the substance of the cervix at 3, 6, 9, and 12 o'clock (depth of injection 0.5 to 1 cm) by using a 22-gauge spinal needle.

In the same patients 4 ml of Patent Blue Violet (PBV; Bleu Patente' V 2.5% sodique) were injected directly into the substance of the cervix on the day of surgery after the induction of general anesthesia. PBV was injected at 3, 6, 9, and 12 o'clock (depth of injection 0.5 to 1 cm) by using a 22-gauge spinal needle as previously reported (3).

Intra operative SLNs assessment was done as first step of a systematic laparoscopic pelvic lymphadenectomy performed immediately before a laparoscopic-assisted vaginal hysterectomy (LAVH). As previously reported (3), the laparoscopic approach was transumbilical and transperitoneal in all cases. Radioactive SLNs were identified by using a laparoscopic gamma-scintiprobe (MR 100 type 11, Tc-99 m settled, Pol. Hi. Tech., Carsoli, Italy).

In the cases where one or more lymph nodes were immediately visible as blue-dyed but not radioactive on the right or left sides, they were removed before starting systematic dissection and identified with a label as b-SLN for post-surgical pathology. In the cases where one or more lymph nodes were found by the gamma-scintiprobe to be radioactive but not blue-dyed, they were also removed before starting systematic dissection and identified with a label as r-SLN for post-surgical pathology. In the cases where one or more lymph nodes were both blue-dyed and radioactive they were identified with a label as b/r-SLN for post-surgical pathology. Thereafter, the systematic lymph node dissection was performed as usual on the right side and nodes were identified with a label as non-SLN for post-surgical pathology. After completion of the right side dissection the same procedure was done on the left side.

In the cases where no b-SLN or r-SLN or b/r-SLN were immediately found, the systematic dissection was performed from front to back of the medial external iliac nodes, intermediate external iliac nodes, lateral external and common iliac nodes, and nodes located in the lateral root of the paracervical ligament (3). If b-SLN or r-SLN or b/r-SLN were identified during systematic dissection, they were taken separately from the global anatomical material and identified with the appropriate label for post-surgical pathology.

Histopathological examination of b-SLNs, r-SLNs, b/r-SLNs, and non-SLNs was performed by haematoxylin and eosin (H&E) staining followed by immunohistochemical (IHC) staining. Nodes were examined by sections at reduced intervals to identify micro metastases by IHC. Specimens sent for pathology as b-SLNs or r-SLNs or b/r-SLNs where defined "false" SLNs when they did not contain lymphatic tissue but only retroperitoneal fat tissue (3).

The following data were collected for each patient: main demographics, disease characteristics, intraoperative workup findings, number and topography of b-SLNs, r-SLNs or b/r-SLNs, presence of metastases in b-SLNs, r-SLNs or b/r-SLNs, and presence of metastases in non-SLNs obtained by systematic dissection. TNM classification of malignant tumors was used for cancer stage (3).

The study was an exploratory trial so the sample size was not derived from statistical considerations. Descriptive statistics and inferential methods were used to analyze data (5).

Results

Post-surgical tumor classification was T1b in 6 women and T3a in one woman. The histological type was endometrioid in 6 women and clear cell in one woman

Table 1. Women demographics and disease characteristics.

Number of women	7
Age range (years)	58-69
Tumor classification	
T1b	6
T3a	1
Histotype	
Endometrioid	6
Clear cell	1
Grade	
G1	5
G2	1
G3	1
Site	
Fundus	2
Anterior wall	1
Multiple or diffuse	4

(Tab. 1).
Pelvic lymph nodes dissection was initiated 20-30 min after PBV injection. All blue-dyed SLNs were also radioactive (b/r-SLNs) while some SLNs were only radioactive (r-SLNs). Therefore, patient identification rates were 71% for PBV and 100% for Tc-99m-labelled albumin colloidal particles (Tab. 2).
In one woman a "false" SLN was found. The specimen did not contain lymphatic tissue but only retroperitoneal fat tissue and was both blue-dyed and radioactive (Tabs. 2 and 3).
At final post surgical pathology pelvic lymph node metastases were present in 4 out of 7 women. No SLNs were labelled by PBV in 2 (50%) out of these 4 women while all of them (100%) had at least one SLN detected by Tc-99m-labelled albumin colloidal particles (Tabs. 2 and 3).

Discussion

The results of the present trial confirm that intraoperative SNL detection by blue dye only is not reliable in patients with endometrial cancer undergoing laparoscopic

Table 2. Findings in the seven women undergoing sentinel lymph node (SLN) detection by both Patent Blue Violet (PBV) and 99m-Technetium-labeled albumin colloidal particles (Tc-99).

TPLNC [a] (range)	4-14
Number of women with SLN labelled by PBV	5 (71%)
Number of women with SLN labelled by Tc-99	7 (100%)
Number of women with "false" SLN by PBV [b]	1
Number of women with "false" SLN by Tc-99 [b]	1
SLN per patient labelled by PBV (range)	0-2
SLN per patient labelled by Tc-99 (range)	1-2
Number of women with MPLN [c]	4
Number of women with MPLN and no SLN labelled by PBV	2
Number of women with MPLN and no SLN labelled by Tc-99	0

[a] Total Pelvic Lymph Node Count
[b] Same specimen in the same woman
[c] Metastatic Pelvic Lymph Nodes at final post-surgical pathology

Table 3. Findings in the four women having metastatic pelvic lymph nodes at final post-surgical pathology.

Patient	**1**	**2**	**3**	**4**
Age (years)	60	58	58	69
Tumor				
Classification	T1b	T1b	T1b	T3a
Histotype	Endom [a]	Endom [a]	Endom [a]	Clear cell
Grade	G1	G1	G2	G3
Site	Multiple or diffuse	Multiple or diffuse	Multiple or diffuse	Multiple or diffuse
TPLNC [b]	10	14	4	7
SLN [c] **by PBV** [d]	1 (Right)	0	1 (Left)	0
Location	Int Iliac [e]		Int Iliac [e]	-
"False" SLN [c] **by PBV** [d]	0	1 (Right)	0	0
Location	-	Int Iliac [e]	-	-
SLN [c] **by Tc-99** [f]	2 (Bilateral)	1 (left)	2 (Bilateral)	2 (Bilateral)
Location	Int Iliac [e]	Int Iliac [e]	Int Iliac [e]	Int Iliac [e]
"False" SLN [c] **by Tc-99** [f]	0	1 (Right)	0	0
Location	-	Int Iliac [e]	-	-
MPLN [g]	2 (Bilateral)	1 (Left)	2 (Bilateral)	1 (Right)
Location	Int Iliac [e]	Int Iliac [e]	Int Iliac [e]	Int Iliac [e]

[a] Endometrioid
[b] Total Pelvic Lymph Node Count
[c] Sentinel Lymph Node
[d] Patent Blue Violet
[e] Internal Iliac
[f] 99m-Technetium-labeled albumin colloidal particles
[g] Metastatic pelvic lymph nodes at final post-surgical pathology

staging because the low detection rate and the finding of "false" blue-dyed SLNs implies that it is impossible to correctly identify more than one half of the patients having a real lymphatic spreading of a clinical early stage endometrial cancer (3). As a matter of fact, a low SLN global detection rate by blue dye injection has been reported in all previously published papers (2).

To our knowledge this is the first trial performed in women with endometrial cancer specifically aimed at comparing the SLN detection rate obtainable through laparoscopy by injecting into the substance of the cervix blue dye or Tc-99m-labelled albumin colloidal particles. From 2002 to 2009 many authors reported on intraoperative SLN detection by injecting both blue dye and radioactive tracers in women with endometrial cancer (2, 4, 6-20). However, the injection sites of the tracers and the surgical accesses for surgical staging varied widely among studies and the majority of them reported the SLN global detection rate without comparing the blue stain detection rate with the radioactive tracer detection rate (2, 4, 6-20).

From the results obtained in this preliminary trial one could infer that the injection of a radioactive tracer into the cervix should be followed by a very high detection rate. This finding is in agreement with findings of several authors who reported a high detection rate by using the injection of Tc-99m–labelled colloidal particles into the substance of the cervix (4,7-10). By contrast, some authors who injected radioactive tracers into the endometrium reported a low detection rate (21-24).

In the present study all blue-dyed SLNs were also radioactive. However, in other reports some of the blue-dyed SLNs were not radioactive and the negative predictive value was reported to be identical with the use of blue dye or radioactive tracer (6, 10, 13-20). However, these reports were not specifically aimed at comparing the SLN detection rates obtainable by injecting blue dye or radioactive tracers (6,10,13-20).

Despite the small sample size of the present exploratory trial, at final post surgical pathology pelvic lymph node metastases were present in 4 out of 7 patients. This finding raises the question of possible biases due to enrollment of a high risk population because many authors with larger global sample sizes had a similar number of patients with pelvic lymph node metastases (2,6,10,13-20).

The patients enrolled in the present trial underwent systematic lymphadenectomy of pelvic nodes only in agreement with the majority of previous papers focusing on the feasibility of SLN detection in women with endometrial cancer (2). Systematic lymphadenectomy of both pelvic and para-aortic nodes to the level of renal veins was performed by few authors only (2). Some authors performed systematic pelvic and selective para-aortic lymphadenectomy (2). As a matter of facts, McMeekin et al. (25) reported that para-aortic nodal metastatic involvement without pelvic nodal involvement occurred in only 7 out of 607 patients with endometrial cancer.

In conclusion, the injection of a radioactive tracer into the substance of the cervix seems to be the more reliable method to detect SLNs in women with endometrial cancer undergoing laparoscopic staging. However, a recent large, prospective, multicentre cohort study reported 97% negative predictive value with cervical dual labelling with both blue stain and radioactive tracer (26). Therefore, the reliability of radiocolloid injection only for SLNs detection in women with endometrial cancer needs to be confirmed in future prospective and comparative large-scale clinical trials.

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