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# Sentinel node mapping in endometrial cancer following Hysteroscopic injection of tracers: A single center evaluation over 200 cases

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#### HIGHLIGHTS

- SLNs detection rate after hysteroscopic injection is similar to cervical injection.
- Diagnostic accuracy after hysteroscopic injection is comparable to literature data.
- · Hysteroscopic injection leads to a nearly 50% mapping in the aortic area.
- ICG improves bilateral detection rate.
- · In half of patients with nodal metastases, the aortic area was involved.

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#### ABSTRACT

*Objectives.* To analyze detection-rate(DR) and diagnostic-accuracy (A) of sentinel-nodes(SLNs) mapping following hysteroscopic-injection of tracer. To compare DR and A between tracers: ICG and Tc99m.

Methods. Evaluation of endometrial-cancer patients who underwent SLNs mapping after hysteroscopic-peritumoral-injection of tracer  $\pm$  lymphadenectomy. Analysis of DR (overall-bilateral-aortic) and A in the entire cohort and comparison between tracers.

Results. 202 procedures were performed from January/2005 to February/2017. Mean age:60 years (28–82); mean BMI:  $26.8 \text{ kg/m}^2$  (15–47). In 133 cases (65.8%) hysterectomy and mapping procedure were performed laparoscopically. The overall-DR of the technique was 93.2% (179/192) (10 cases were excluded: 9 for technical-equipment failure; 1 for vagal reaction). Bilateral pelvic mapping was found in 59.7% of cases (107/179) and was more frequent in the ICG group (72.8% vs 53.3%; p: 0.012). In 50.8% of cases (91/179) SLNs were mapped both in pelvic and aortic nodes, and in 5 cases (2.8%) only in the aortic area. The mean number of detected SLNs was 3.7 (1-8)

22 patients (12.3%) had nodal involvement: 10-(45.5%)-macrometastases; 5-(22.7%)-micrometastases; 7-(31.8%)-ITCs. In 6 cases (27.3%) only aortic nodes were positive; in 5 cases (22.7%) both pelvic and aortic nodes and in 11 cases (50%) only pelvic nodes were involved.

Three false-negative results were found, all in the Tc99m group. All had isolated aortic metastases with negative pelvic nodes.

Overall-sensitivity was 86.4% (95%CI: 68.4-100) and overall-negative-predictive-value (NPV) was 96.4% (95%CI 86.7-100).

No differences in terms of overall-DR, overall-sensitivity and overall-NPV were found between the two tracers. *Conclusions*. Hysteroscopic-injection of tracer for SLNs mapping in endometrial cancer is as accurate as cervical injection with a higher DR in the aortic area. ICG improves bilateral-DR. Further investigation is warranted on this topic.

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#### 1. Introduction

Endometrial cancer is the most common gynecological neoplasm in western countries and its incidence is rising [1,2]. Sentinel node mapping has been widely used in the last years for staging purposes [3]. Even if it is not yet considered a standard procedure, SLNs mapping has gained popularity as a compromise between no lymphadenectomy and full lymphadenectomy [4,5,6,7,8]. According to a recent meta-analysis, the majority of reported series have been performed following cervical injection of tracers with a detection rate (DR) at 81%, bilateral DR at 50% and aortic DR at 17% [3]. When injected intracervically, indocyanine-green (ICG) has been found to have comparable DR to radiocolloid [9].

Since the first report in 2004, our group pursued the usage of hyster-oscopic injection of tracer for SLNs mapping in endometrial cancer [10, 11,12]. The present paper evaluates the largest series ever published on hysteroscopic injection of tracers for SLNs mapping in endometrial cancer. We sought to analyze DR, bilateral DR, aortic DR and diagnostic accuracy of SLNs mapping following hysteroscopic injection of tracer. Moreover we aimed to compare DR and accuracy between tracers (ICG and Tc99m).

#### 2. Material and methods

After Institutional Review Board approval from National Cancer Institute of Milan, data of a prospectively maintained database on SLNs mapping in endometrial cancer were retrieved.

Data of consecutive patients submitted to a SLNs procedure following hysteroscopic injection of Tc99m or ICG from January 2005 to February 2017 were analyzed. Included patients were women aged  $\geq$  18 years old, with no concomitant and/or previous cancer, and signed informed consent. Women with apparent early-stage endometrial cancer underwent a surgical treatment: hysterectomy  $\pm$  bilateral salpingo-oophorectomy and SLNs mapping  $\pm$  lymphadenectomy. Tumor histological classification and staging were performed according to FIGO 2009 criteria [13].

#### 2.1. Mapping technique

Detailed description of mapping techniques have been reported in previous papers [11,12,14]. Tc99m was the tracer until ICG equipment became available at our center. Briefly:

#### Tc99m mapping (01/2005-11/2013)

The same day of surgery (no > 6 h before surgery) an office hysteroscopy without cervical dilation and without local and/or general anesthesia was carried out. Uterine distension was obtained with saline solution maintaining an intracavitary pressure lower than 40 mm Hg, to avoid the possible risk of spillage [15]. 111 MBq of technetium 99 m-labeled human albumin colloid particles (Nanocoll, GE Healtcare, Fairfield, CT, USA) eluted in 5 ml saline were injected subendometrially. In the case of a single lesion injection was performed at 3, 6, 9 and 12 o'clock, while if the entire cavity was involved by the tumor, anterior, posterior, lateral walls and fundus were injected. A total hysterectomy and adnexectomy with frozen section evaluation of myometrial invasion and tumor grade was performed by laparotomy or by laparoscopy (since 2010). SLNs mapping was carried out with a gamma-probe (C-Track System, Care-Wise, CA, USA) for open surgery or (OmniProbe™ Care-Wise, CA, USA) for laparoscopic procedures. The acoustic signal emitted by the probe was used to guide isolation and removal of the nodes. Completion lymphadenectomy (pelvic  $\pm$  aortic) was based on identification of tumor risk factors and clinical judgment or according to "diagnostic accuracy 2005-2010" study protocol [11] (patients with a stage IBG2 (FIGO 1988) or higher were submitted to sentinel nodes detection followed by systematic pelvic and paraaortic lymphadenectomy).

#### ICG mapping (12/2013-02/2017)

Under general anesthesia, laparoscopy was performed to exclude peritoneal carcinomatosis. Tubal occlusion was carried out via bipolar coagulation of the corunal os to avoid any peritoneal spillage during the hysteroscopic procedure. That prevented also any ICG spillage that could have masked the operating field if all had become fluorescent. The hysteroscopy was carried out, without cervical dilation. Uterine distension was obtained with saline solution. 4 ml of 25 mg ICG (pulsion medical System SE, Feldkirchen – Germany) eluted in 20 ml of sterile water (1.25 mg/ml total of 5 mg) were injected subendometrially. In case of a single lesion injections were performed at 3, 6, 9 and 12 o'clock, while, if the entire cavity was involved by the tumor, anterior, posterior, lateral walls and fundus were injected. Real-time laparoscopic identification of SLNs was performed using SPIE-System (Storz-Professional-Image-Enhancement-System). Fluorescent nodes were then sampled. A total laparoscopic hysterectomy and bilateral salpingo-oophorectomy were then performed. The uterus was sent for frozen section. Completion lymphadenectomy was based on identification of tumor risk factors and clinical judgment. Patients with poorly differentiated endometrial cancers and deeply invasive tumors, underwent a completion pelvic and aortic lymphadenectomy. Patients with well/moderated differentiated cancers confined to the inner half of the myometrium underwent a SLNs biopsy only.

#### 2.2. Pathological assessment of SLNs

Standard pathological evaluations were performed by pathologists who are experts in gynecological cancers, as reported in our previous experience [11,12]. In detail: lymph nodes were isolated from the fatty tissue without freezing or preservation and were examined by standard techniques. Nodes of major axis > 0.5 cm were dissected, nodes smaller than 0.5 cm were entirely fixed and embedded. Three sections were obtained from each node at different levels (100–500  $\mu m$  apart), and stained with hematoxilin and eosin (H&E). Immunohistochemistry for cytokeratins (CK) (AE1-AE3, Dako corporation Glostrup, Denmark) was assessed in the same number of sections of SLN that resulted negative for metastasis at H&E evaluation.

SLNs were considered positive if they contained macrometastasis or micrometastasis, or isolated tumor cells (ITCs), according to the combined evaluation using H&E and immunohistochemistry [16].

Among the study period, seven surgeons were involved in mapping and surgical procedures.

This single center review includes all patients with endometrial cancer who underwent hysteroscopic injection of tracer for SLNs mapping. Demographics (age and body mass index) and pathological data (stage, histological type and grade) were extracted from our prospectively kept database and analyzed. SLNs were examined for the number and location of the nodes. Only first draining nodes were considered as SLNs, while "echelon" or "secondary" nodes were not considered as SLNs. Absolute and percentage frequencies were used to describe categorical items, while mean values and ranges were assessed for continuous variables. The statistical outcome measures were reported as recently proposed in a systematic review, including the "overall outcomes (DR, sensitivity, negative predictive value, false negative rate)" [17]. Accuracy was calculated only among patients submitted to completion lymphadenectomy. Chi-square, Fisher exact test or Student t-test were used for comparison between the two cohort (ICG and Tc99m) when appropriate. Statistics were performed using SPSS 15.0 (SPSS, Inc., Chicago, IL). All calculated p values were two-sided, and p values < 0.05 were considered statistically significant.

#### 3. Results

A total of 202 procedures were performed. Mean age was 60 years (28–82) and mean BMI was 26.8 kg/m $^2$  (15–47). In 133 cases (65.8%) hysterectomy and mapping procedure were performed laparoscopically Two conversions to laparotomy occurred. At least one SLN was detected

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