Gynecologic Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer

Noémie Body [a], Jean Grégoire [b], Marie-Claude Renaud [b], Alexandra Sebastianelli [b], Katherine Grondin [c], Marie Plante [b,*]

[a] Département de Chirurgie Gynécologique, Hôpital Anne de Bretagne, Centre Hospitalier Universitaire de Rennes, Université de Rennes 1, Rennes, France
[b] Gynecologic Oncology Division, L'Hôtel-Dieu de Québec, Centre Hospitalier Universitaire de Québec, Laval University, Quebec City, Canada
[c] Pathology Department, L'Hôtel-Dieu de Québec, Centre Hospitalier Universitaire de Québec, Laval University, Quebec City, Canada

HIGHLIGHTS

- ICG has excellent SLN detection rate, sensitivity and NPV in endometrial cancer.
- With the use of ICG, swollen green lymphatics can be mistaken for lymph nodes and contribute to failed detection.
- Spy and CSF mode, ex-vivo palpation of the nodes, frozen section and vigilance can reduce the rate of failed mapping.

ARTICLE INFO

Article history:
Received 7 May 2018
Received in revised form 30 May 2018
Accepted 1 June 2018
Available online xxxx

Keywords:
Endometrial cancer
Sentinel node mapping
Indocyanin green (ICG)

ABSTRACT

Objective. To determine the validity of sentinel lymph node (SLN) biopsy with ICG in endometrial cancer and to evaluate the factors associated with poor mapping or false negative.

Methods. We reviewed all patients who underwent primary surgery for endometrial carcinoma with SLN mapping using ICG followed by pelvic lymphadenectomy from February 2014 to December 2015. SLNs were ultrastaged on final pathology. Patients' demographics, surgical approach and histopathological factors were prospectively collected. Detection rate, sensitivity and negative predictive value (NPV) were calculated and univariate analysis was performed to evaluate factors associated with failed bilateral detection of SLNs.

Results. A total of 119 patients were included. The overall and bilateral detection rates were 93% and 74%. Sensitivity and NPV were 100% in patients with bilateral detection; 95% and 99% respectively in cases with at least unilateral detection. Advanced FIGO stage (III or IV) was the only factor related to failed bilateral detection ($p = 0.01$). In 14 hemi-pelvis, the specimen labelled as SLN did not contain nodal tissue on final pathology (only lymphatic channels), which represented 37% of the "failed detection" cases. One false negative occurred in a patient with an ipsilateral clinically suspicious enlarged lymph node.

Conclusion. ICG is an excellent tracer for SLN mapping in endometrial cancer. Advanced FIGO stage correlated with failed bilateral detection ($p = 0.01$). Suspicious lymph nodes should be removed regardless of the mapping. Care should be taken to ensure that SLN specimen actually contains nodal tissue and not only swollen lymphatic channels, as this represents a significant cause of failed SLN mapping.

1. Introduction

The advantages of sentinel lymph node (SLN) mapping in endometrial cancer are several: providing meaningful information regarding indication of adjuvant treatment, identifying aberrant drainage sites, performing ultrastaging to enhance the detection of low volume metastasis [1–3], while decreasing the surgical complication rates [4]. Similarly, in cervical cancer, SENTICOL 2 has recently shown a statistically improved quality of life (QoL) and reduced morbidity, namely lymphedema, in patients with cervical cancer who underwent SLN mapping alone compared to SLN mapping followed by complete lymphadenectomy [5].

The detection rate and false negative rate have been shown in endometrial cancer to be at least comparable to vulvar or breast cancer for which the sentinel lymph node concept has become standard of care [6, 7]. Still, there are no prospective randomized trial confirming that there is no difference in survival outcome between SLN alone vs complete lymphadenectomy. In the field of cervical cancer, there was no

* Corresponding author at: L'Hôtel-Dieu de Québec, Gynecologic Oncology Division, 11 Côte du Palais, Quebec City G1R-2J6, Canada.
E-mail address: marie.plante@crhdq.ulaval.ca (M. Plante).

https://doi.org/10.1016/j.ygyno.2018.06.001
0090-8258/

difference in survival outcome in the SENTICOL 2 study, however the study was not powered to show a difference in overall survival and recurrence free survival [5]. The SENTICOL 3 trial has recently been activated to address this issue. In endometrial cancer, the SENTIENDO study included 125 patients with SLN mapping with patent blue and Technetium-99 (Tc-99) followed by systematic lymphadenectomy. The long term results found no difference in terms of recurrence free survival in patients with or without detected SLN or in patients with or without positive SLN [6]. Again, the study was first aimed to assess the detection rate and SLN accuracy, and was not powered nor designed to detect survival differences. Nevertheless, NCCN and recent SGO guidelines support the implementation of sentinel lymph node mapping in the surgical staging of endometrial cancer, whereas the ESGO guideline considers SLN mapping as an acceptable option for early stage, intermediate risk endometrial cancer [2, 8, 9].

The technical aspect of sentinel lymph node has been addressed in numerous studies. Most have used a combination of blue dye and Tc-99, however Indocyanin green (ICG) has been increasingly used in recent years as a new tracer. In fact, many investigators now believe that ICG is becoming the new standard for SLN mapping in gynecologic cancers [1, 10]. However, it should be noted that the use of intradermal ICG injection for the purpose of SLN mapping is not currently FDA approved in the United States, nor in Canada or in European countries. Hopefully, data from the FILM study may soon lead to its definitive approval. However, If SLN mapping is to become "standard of care" and replace the traditional lymph node dissection, it is imperative that the bilateral detection rate and false negative rate are consistently high, and that lymph nodes removed and thought to be SLN actually contain lymph node tissue and not only lymphatic channels.

The objectives of our study are to report the detection rate of sentinel lymph node mapping using ICG alone in endometrial cancer, to assess the diagnostic performance, to evaluate the factors associated with failure of this technique and to provide some insights regarding some of the "pitfalls" of the technique.

2. Methods

2.1. Patients

SLN mapping using ICG dye fluorescence was first introduced in our centre in February 2014. Fluorescence was detected using the Pinpoint Endoscopic Fluorescence Imaging system (Pinpoint, Novadaq Technologies, Bonita, Springs, FL). From February 2014 to December 2015, 119 consecutive patients with a biopsy proven endometrial cancer who underwent SLN mapping at L'Hotel-Dieu de Québec hospital were included. All patients underwent total hysterectomy and bilateral salpingo-oophorectomy and a complete pelvic lymph node dissection following SLN mapping. Paraaortic node dissection was performed at the surgeon's discretion. The project received IRB approval.

2.2. Procedure

Vials containing 25 mg of ICG powder were reconstituted with 10cm^3 of aqueous sterile water (2.5 mg/mL). A total of 4 cm^3 was used for the intracervical injection with a 25-gauge spinal needle. 1 cm^3 of ICG was injected superficially and 1 cm^3 was injected deeper into the cervical stroma at the 3 and 9 o'clock position immediately before the surgery. Our technique has been described elsewhere [11] but, briefly, sentinel nodes are carefully searched for after opening the retroperitoneum by activating the infrared button on the camera head. The main mode used was the Near Infrared mode (NIR), but two additional modes were also used as needed: spy mode (black and white mode) or color segmented fluorescence mode (CSF) in the form of a color gradient. Surgeons can switch back and forth between the different modes as often as needed (Fig. 2a). The same Pinpoint laparoscopic device was used for abdominal and robotic surgeries [11]. The position of each SLN was recorded immediately on a standardized form.

2.3. Histopathology

SLNs were not routinely submitted for frozen section unless there was a suspicion of metastatic disease on gross inspection. For ultrastaging, SLNs were cut perpendicular to the long axis at 3 mm intervals and embedded in paraffin. Six 4 μm sections at 40 μm intervals were cut from the paraffin blocks and stained with hematoxylin and eosin (H&E). An additional section was taken adjacent to the 3rd H&E cut and used for immunohistochemistry using anti-cytokeratin AE1/AE3 (DAKO, Agilent, CA). The non-sentinel lymph nodes (non-SLNs) were bisected parallel to the long axis and examined with routine H&E on one level. SLNs and non-SLNs were analyzed by pathologists experienced in SLN ultrastaging who were also previously involved in the validation of the technique in a previous study of SLN biopsy in cervical cancer [12].

2.4. Statistical analysis

All data were collected from a prospectively maintained institutional database. Demographics (age, body mass index (BMI), menopausal status, cesarean section, surgical approach, location of sentinel lymph node) and histopathological data (stage, histologic type and grade, presence of lymphovascular space invasion (LVSI), lymph node metastasis) were extracted and analyzed. In patients with absence or unilateral detection of SLN, each histopathology reports were retrospectively reviewed by one of the co-authors (NB) to identify the cause for the mapping failure. Descriptive statistics were performed using STATA version 13 software (Stata Corp, College Station, TX). Sensitivity, negative predictive value and detection rates were calculated. Univariate analysis with Chi square test, Fisher or *t*-test as appropriate, was performed to evaluate factors associated with failed bilateral SLN mapping.

3. Results

A total of 119 patients with endometrial cancer were included in the study. The mean age of the patients was 65.5 years (49–91) and the mean BMI was 31 kg/m2 (18–56). The majority had stage I disease (99/119, 83%), most were endometrioid (101/119, 85%) and grade 1 or 2 (94/119, 79%). The majority of patients had minimally invasive surgery (76%) either by robotic (50%) or laparoscopic (26%) approach (Table 1). A total of 267 SLNs were retrieved. The median number of SLN identified per patient was 2 (0–7) and the median number of pelvic nodes removed was 15 (5–43). SLNs were located primarily in the external iliac node basin (70% of cases), usually on or just under the medial aspect of the external iliac vein near the bifurcation, followed by the obturator area (23%). Unusual locations (6%) were the common iliac area [11], the parametrium [4], the paraaortic [2] or the presacral area [1].

SLN were detected bilaterally in 89 patients (74%) and unilaterally in 22 patients (19%). No SLN were identified in 8 patients (6%). Thus, the overall SLN detection rate was 93% (111/119), and the failed bilateral detection occurred in 25% (30/119) of patients (Fig. 1). As can be seen in Fig. 1, these 30 cases of failed bilateral SLN detection are the sum of unilateral mapping only (22/119) and complete absence of mapping (8/119). These cases include all causes of failed mapping, such as failed dye migration, excessive fluorescence (diffuse smearing) and cases of swollen lymphatics or "empty specimen" on final pathology.

In terms of hemipelvis, sentinel lymph nodes were detected in 84% (200/238) of hemipelvis, and not detected in 16% (38/238). Reasons for failed mapping included diffuse smearing of ICG or complete absence of dye migration in respectively 4 and 14 hemipelvis. However, in 14 hemipelvis, a SLN was "identified" and the specimen

Please cite this article as: N. Body, et al., Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer, Gynecol Oncol (2018), https://doi.org/10.1016/j.ygyno.2018.06.001