Gineco.eu [14] 110-112 [2018]
DOI: 10.18643/gieu.2018.110
@ 2018 Romanian Society of Ultrasonography in Obstetrics and Gynecology

Indocyanine green utility for sentinel lymph node biopsy in early stage endometrial cancer. A literature review

Irina Balescu[1], Nicolae Bacalbasa[2,3,4], Mihaela Vilcu[2,3], Iulian Brezean[2,3], Diana Gheorghiu[5]

1. "Ponderas" Academic Hospital, Bucharest, Romania

2. "Ion Cantacuzino" Clinical Hospital, Bucharest, Romania

3. "Carol Davila" University of Medicine and Pharmacy, Bucharest,

4. Center of Excellence in Translational Institute, Fundeni Clinical Institute, Bucharest, Romania

5. Obstetrics and Gynecology Clinic, "Sf. Pantelimon" Urgency Hospital, Romania

Correspondence:
Dr. Irina Balescu
E-mail address: irina.balescu@ponderas-ah.ro

Abstract

Applying the concept of sentinel lymph node biopsy in patients diagnosed with early stage endometrial cancer has been associated with several benefits such as providing an adequate ultra-staging of the malignant process, identifying the aberrant routes of lymphatic spread as well as the micrometastatic lymph nodes. Due to all these benefits in association with an acceptable rate of false negative results the method has been widely accepted. In order to maximize the efficacy of the method especially in cases submitted to laparoscopic approach, recent studies have demonstrated the utility of indocyanine green as a tracer for detecting the sentinel lymph nodes in early stage endometrial cancer. This is a literature review of the most recent papers evaluating the safety and feasibility of the method

Keywords: *early stage endometrial cancer, indocyanine green, sentinel lymph node biopsy*

Introduction

Endometrial cancer remains one of the most commonly encountered gynecologic malignancies being frequently seen in postmenopausal women; due to the early apparition of worrying signs such as vaginal postmenopausal bleeding, a significant number of patients will self-refer to their gynecologist very soon after the apparition of the symptoms, leading to a high rate of early diagnostic. In such cases a favorable long term outcome is expected[1,2]. When it comes to the most efficient therapeutic strategy for early stage endometrial cancer, it consists of total hysterectomy with bilateral adnexectomy and, in certain cases association of pelvic lymph node dissection. However, in a significant number of cases the histopathological studies will reveal the absence of metastatic disease at the level of the retrieved lymph nodes. In the meantime, performing a complete pelvic lymph node dissection will induce the development of postoperative complications such as chronic lymphedema of the inferior limbs. Due to these reasons attention was focused on establishing whether performing sentinel lymph node biopsy (SLNB) could minimize the number of patients submitted to an un-necessary lymph node dissection procedure. Preliminary studies showed that both the detection rate as well as the false negative rate of SLNB in endometrial cancer are similar to those reported in patients with vulvar or breast cancer[3,4]. Initially SLNB was performed after injecting blue dye or Technetium-99. Recent studies have demonstrated that utilization of indocyanine green (ICG) is at least as efficient when compared to standard tracers; unfortunately, ICG mapping through intradermal injection has not been approved yet by the Food and Drug Administration in the United States of America, Canada or Europe[5]. When it comes to intracervical administration, it seems that ICG injection tends to become the new standard of care for SLN detection in gynecological cancer[5-7].

Received: *June 05, 2018*
Revised: *July 18, 2018*
Accepted: *August 25, 2018*

Technique of ICG Injection in Endometrial Cancer Mapping

The technique of ICG injection consists of dissolving the 25 mg of ICG powder in 10 cm3 of sterile water and injecting 4 cm3 of the resulting solution into the cervical stroma at the three and nine o'clock points, superficially and deeper (at each injection 1 cm3 of solution being administrated). The administration should be performed just before beginning the surgical procedure; the sentinel lymph nodes are to be searched after opening the retroperitoneal space by using the near infrared mode as well as the spy mode and the color segmented fluorescence mode[5,8].

Other authors routinely recommend a two steps procedure of ICG injection; during the first step 2 ml of solution into each uterine cornu by inserting a laparoscopic needle into the corneal myometrial layer at a depth of 1 cm in order to detect the sentinel para-aortic lymph nodes. The second step consists of ICG injection into the uterine cervix similarly to the above described technique (i.e. at three and nine o'clock) in order to detect the presence of pelvic sentinel lymph nodes[9].

Utility of ICG Injection in Endometrial Cancer Mapping

The main studies which investigated the utility of ICG injection in endometrial cancer mapping are summarized in Table 1.

Table 1 Studies investigating the utility of ICG injection in endometrial cancer mapping

Name, year	No of patients, mean age	Mean BMI value (kg/m^2)	FIGO stage	Histology	Location of SLN	Unilateral/ bilateral	Sensitivity	Negative predictive value
Body, 2018(5)	119 pts, 65.5 yrs	31	IA – 58% IB – 25% II – 3% IIIA – 3% IIIC1 – 7% IIIC2 – 3% IVB – 1%	Endometroid: 85% Serous: 7% Undifferentiated: 2% Clear cell: 3% Carcinosarcoma: 3%	External iliac: 70% Obturatory area: 23% Other locations – common iliac, para-aortic, presacral area: 6%	UL – 19% BL – 74% No SLN – 6%	100% in pts with bilateral detection, 95% in pts with unilateral detection	98.8%
Eoh, 2108(9)	50 pts, 52 yrs	24	IA – 76.0% IB – 10.0% II – 2.0% IIIA – 2.0% IIIB – 2.0% IIIC1 – 4.0% IIIC2 – 4.0%	Endometrioid: 90.0% Serous: 4.0% Clear cell: 2.0% Carcinosarcoma: 2.0% Mixed: 2.0%	Medial to external iliac region Ventral area of the hypogastric region Superior part of the obturatory region	BL pelvic nodes – 94%	100%	100%
Mendivil, 2018(10)	87 pts, 61.5 yrs	32.9	IA – 50.6 IB – 27.6 II – 9.2 IIIA – 5.7 IIIC1 – 6.9	Endometrioid: 78,5% Mixed: 6.8% Carcinosarcoma: 4.6% Serous: 4.6% Adenosarcoma: 2.2% Clear cell: 1.1% Mucinous: 1.1% Endometrial stromal sarcoma: 1.1%	Internaliliac: 31.8% Externaliliac: 31% Obturator: 18.4% Pre-sacral region: 11.8 % Common iliac: 3.7% Infra-mesenteric: 3.3%	BL – 81.6%	NR	NR
Taskin, 2017(11)	71 pts, 62 yrs	29	IA – 56.3 IB – 30.9 IIIA – 1.4 IIIC1 – 7 IIIC2 – 4.2	Endometroid: 92.9% Serous: 4.2% Carcinosarcoma: 2,8%	External iliac: 56.7% Obturatory: 39.3% Para-aortic: 0.8% Presacral: 1.2% Common iliac: 2%	BL – 77.4% UL – 18.3% None – 4.3%	87.5%	98.4%

BMI= body mass index; SLN= sentinel lymph node; yrs= years; UL=unilateral; BL=bilateral; pts= patients.

Benefits of ICG Mapping in Endometrial Cancer when Compared to other Agents

When compared to other agents (e.g. such as blue dye) it seems that ICG mapping is associated with a lesser spread in the surrounding tissues providing in this way a clearer operative field[10]. Therefore, identification of SLNB was more facile after ICG injection due to the fact that the image was not influenced by the development of surrounding bleeding; this fact was explained by the possibility of using the near-infrared mode of the telescope. This aspect presents a particular interest especially in morbidly obese cases which usually present a well-developed retroperitoneal fat[11]. All these advantages are translated into a higher rate of SLNB detection after ICG injection when compared with those reported after technetium colloid or blue dye agent[12]. Moreover, ICG utilization does not require performing other investigations such as lymphoscintigraphy[11].

Pitfalls of ICG Mapping in Endometrial Cancer

One of the most fearful complications induced by ICG usage consists of mapping failure; this phenomenon is explained by the fact that ICG is albumin bound, leading to a higher amount of interstitial fluid absorption into the lymphatic channels. Therefore these channels will have a swollen aspect, with a diameter similar to the one of the lymph nodes. In this way confusion between lymph nodes and lymph channels might occur; the surgeon might be tempted to retrieve the structures presenting the larger diameter, structures which might prove to be only lymph channels and not lymph nodes[5]. The so called "empty specimen" situation might predispose to an unsatisfactory staging of the disease; in such cases the surgeon has two options: to re-operate the patient in order to perform a complete staging procedure or to decide upon the necessity of administrating an adjuvant treatment based

on the preoperative imagistic studies. If the decision is to re-operate the patient, it should not be omitted the fact that surgery might be more difficult. Working in a recently opened retroperitoneal and pelvic space might be more difficult for the surgeon, especially in endometrial cancer patients which usually associate obesity, cardiovascular diseases and diabetes. Moreover, the healing of such a patient might be delayed, inducing in this way postponing the administration of the adjuvant therapy[5]. Few tricks which might help the surgeon to distinguish between a swollen lymphatic channel and a true lymph node are represented by: the first one consists of a carefully analyze of the shape of the structure, channels being rather linear while nodes are rather rounder in shape. Another trick which might help the surgeon to distinguish between the two structures is represented by the change of the regimen of the telescope (using the SPY module or the color segmented fluorescence module might provide a better identification of the nodes). At last but not at least, the retrieved specimen might be carefully examined ex vivo by palpation and might be sent to frozen section examination in order to confirm the presence of a lymph node in the retrieved structures[5].

Conclusions

ICG utilization for SLNB detection in endometrial cancer represents a novel method which seems to be associated with high sensitivity and negative predictive value. Moreover, the possibility of using a multi-modal telescope seems to increase the rate of detection of SLNB, decreasing the inconvenient of a poor retroperitoneal image due to the subsequent bleeding. However, it should not be omitted the fact that ICG injection might induce a dilatation of the lymphatic vessels predisposing in certain cases to the confusion between the dilated lymphatic channels and the true lymph nodes. ■

Conflict of interests: The authors declare no conflict of interests.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin.* 2017, 67(1), 7-30.
2. Creasman WT, DeGeest K, DiSaia PJ, Zaino RJ. Significance of true surgical pathologic staging: a Gynecologic Oncology Group Study. *Am J Obstet Gynecol.* 1999; 181(1), 31-4.
3. Ballester M, Dubernard G, Lecuru F, Heitz D, Mathevet P, Marret H. et al. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO). *Lancet Oncol.* 2011, 12(5), 469-76.
4. Rossi EC, Kowalski LD, Scalici J, Cantrell L, Schuler K, Hanna RK. et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. *Lancet Oncol.* 2017, 18(3), 384-92.
5. Body N, Gregoire J, Renaud MC, Sebastianelli A, Grondin K, Plante M. Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer. *Gynecol Oncol.* 2018, 150(2), 267-73.
6. Bodurtha Smith AJ, Fader AN, Tanner EJ. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. *Am J Obstet Gynecol.* 2017, 216(5), 459-76.
7. Darin MC, Gomez-Hidalgo NR, Westin SN, Soliman PT, Escobar PF, Frumovitz M et al. Role of Indocyanine Green in Sentinel Node Mapping in Gynecologic Cancer: Is Fluorescence Imaging the New Standard? *J Minim Invasive Gynecol.* 2016, 23(2), 186-93.
8. Plante M, Touhami O, Trinh XB, Renaud MC, Sebastianelli A, Grondin K et al. Sentinel node mapping with indocyanine green and endoscopic near-infrared fluorescence imaging in endometrial cancer. A pilot study and review of the literature. *Gynecol Oncol.* 2015, 137(3), 443-7.
9. Eoh KJ, Lee YJ, Kim HS, Lee JY, Nam EJ, Kim S, Kim YT, Kim SW. Two-step sentinel lymph node mapping strategy in endometrial cancer staging using fluorescent imaging: A novel sentinel lymph node tracer injection procedure. *Surgical Oncology.* 2018, 27, 514-9.
10. Mendivil AA, Abaid LN, Brown JV, III, Mori KM, Beck TL, Epstein HD. et al. The safety and feasibility of minimally invasive sentinel lymph node staging using indocyanine green in the management of endometrial cancer. *Eur J Obstet GynecolReprod Biol.* 2018, 224, 29-32.
11. Taskin S, Sukur YE, Altin D, Ersoz CC, Turgay B, Kankaya D. et al. Laparoscopic near-infrared fluorescent imaging as an alternative option for sentinel lymph node mapping in endometrial cancer: A prospective study. *Int J Surg.* 2017, 47, 13-7.
12. Papadia A, Zapardiel I, Bussi B, Ghezzi F, Ceccaroni M, De Ponti E. et al. Sentinel lymph node mapping in patients with stage I endometrial carcinoma: a focus on bilateral mapping identification by comparing radiotracer Tc99(m) with blue dye versus indocyanine green fluorescent dye. *J Cancer Res ClinOncol.* 2017, 143(3), 475-80.