



Indocyanine green and infrared fluorescence in detection of sentinel lymph nodes in endometrial and cervical cancer staging – a systematic review



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ARTICLE INFO

Article history:

Received 3 April 2016

Received in revised form 19 September 2016

Accepted 22 September 2016

Keywords:

Sentinel lymph node

Indocyanine green

Endometrial or endometrium

Cervix

Gynecologic

Cancer/carcinoma/neoplasms

ABSTRACT

Objective: Sentinel lymph node (SLN) mapping for endometrial (EC) and cervical cancers (CC) is a current technique that could provide benefits over traditional lymphadenectomy. Near-infrared (NIR) fluorescence imaging is a promising technique to perform this procedure. We conducted a systematic review of the evidence regarding the technique and the effectiveness of indocyanine green (ICG) during SLN biopsy, using robotic and laparoscopic assisted surgery and laparotomy.

Materials and methods: We conducted a computer literature search for published English language studies in humans using PubMed since January 2010 up to May 2015. The initial search came up with 17 articles, of which 10 articles used ICG as tracer in SLN biopsy in EC and CC.

Results: 422 patients were included in 10 studies, ranging from 1 to 227 patients. The main surgical approach used in ICG SLN biopsy was robotic-assisted surgery in 368 patients. Laparotomy was performed in 39 patients and laparoscopy in 15. The detection rate in SLN mapping using ICG ranged from 78% to 100% for cervical injection and from 33% to 100% for hysteroscopic injection. Sensitivity and negative predictive value (NPV) vary from 50% to 100% and 88% to 100%, respectively. The most common site of injection was the cervix (two quadrants); this technique is correlated with a high detection rate (ranging from 78% to 95%). The cervical submucosal and stromal injections were the most frequent sites used. No complications related to ICG administration were described.

Conclusions: NIR fluorescence imaging using ICG is performed in robotic-assisted surgery in laparoscopy and in laparotomy, being a feasible, safe, time-efficient and seemingly reliable method for lymphatic mapping in early stage of CC and EC. Although it has promising results in SLN mapping, randomized studies, with larger patient samples, are needed.

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Introduction

Lymphadenectomy is an important step in the surgical management of cervical and endometrial cancers; however, it contributes to increased operative time, blood loss and is associated with short- and long-term complications such as nerve injury, lymphedema and lymphocyst formation [1–4]. Sentinel lymph node (SLN) sampling may reduce morbidity, hospital stay and healthcare costs for patients with cervical and endometrial

cancer by minimizing lymphatic disruption [5]. SLN biopsy was first described by Cabanas in 1977, and has gained increasing acceptance for the treatment of melanoma, breast and vulvar cancers [6,7].

Recently, several investigations have demonstrated the overall satisfactory efficacy and effectiveness of sentinel node biopsy in endometrial and cervical carcinomas [8,9]. The major apprehensions with SLN mapping involve the associated detection rate and false-negative rate. An acceptable false-negative rate (typically <5%) is imperative for SLN mapping to be considered a viable alternative to the current standard procedure, with the false-negative rate target being 0% [10]. Pelvic lymphatic mapping using colorimetric imaging with blue dyes [isosulfan blue (ISB), patent

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blue, and methylene blue] and/or radiocolloids (Technetium-99 (^{99m}Tc)) has been largely described [11,12] with pelvic SLN detection rates ranging between 80–85% for each tracer alone and 89–95% when blue dye and ^{99m}Tc are used together [13,14]. Recently, other medical dyes that fluoresce in light at the near-infrared (NIR) spectrum (700–900 nm) using laparotomic, laparoscopic and robotic imaging systems have been reported for use in lymphatic mapping of gastric, rectal, breast, vulvar, cervical, and endometrial cancers [15–17]. Indocyanine green (ICG) is the most clinically useful agent for NIR lymphatic mapping [18], and has been used clinically for two decades with an excellent safety profile.

In the literature, there are few and limited series using ICG as a tracer for SLN biopsy in EC and CC; therefore, there is no standardization for this procedure. Based on these considerations, this literature search investigates SLN mapping for endometrial and cervical cancer. Some promising results are presented with regard to the technique and effectiveness of indocyanine green.

Materials and methods

Data sources and study selection

A comprehensive, systematic computer literature search for published English language studies in humans was conducted using PubMed since January 2010 up to May 2015. Data were collected independently by two researchers and, in the end, were verified by a third researcher when there was disagreement in the collected data.

The following keywords were used: “sentinel lymph node” and “indocyanine green” and “endometrial or endometrium” or “cervix” or “gynecologic” or “cancer/carcinoma/neoplasms”. Publications using ICG as a tracer were selected. The list of articles was supplemented by extensive crosschecking of reference lists of the identified articles. Review articles, letters and comments, were excluded. Our systematic review was submitted to the PROSPERO register and published on the database, with registration number CRD42015019528. We recorded data from each of the selected studies. In each article, we collected the following items: (1) authors and year of publication; (2) sample size; (3) type of cancer; (4) type of surgery approach; (5) FIGO staging; (6) technique details of indocyanine use (needle size, ICG means of dilution, time

of injection, volume, ICG dose, ICG concentration, place and depth of injection); (7) other tracers and methods used for SLN procedures; (8) ICG total mapping time; (9) mean number of SLNs resected per study; (10) mean number of non-SLNs resected per study; (11) detection rate of SLNs for each study and (12) pathological assessment.

To assess sensitivity, specificity and negative predictive value (NPV), we excluded patients in whom SLN mapping failed. Sensitivity was estimated as the proportion of true positives (patients with positive SLNs) among the patients with positive lymph nodes. Specificity was found by dividing the number of patients with negative SLNs by the number of all patients without lymph nodes metastasis. NPV was calculated as a proportion of true negatives (patients with normal lymph nodes) and patients with negative SLNs. Both sensitivity and specificity were calculated only in patients in whom complete lymph node dissection was performed. In our review, we included robotic-assisted surgery, laparotomy and laparoscopy.

Results

Until May 2015, the initial search came up with 17 articles. After screening, there were 10 articles using ICG as tracer in SLN biopsy in EC and CC as demonstrated in [Diagram 1](#).

A total of 422 patients were included in 9 reviewed studies. The number of patients per study ranged from 1 to 227. One study described only the technique.

SNL was evaluated for EC in 5 articles and for CC in 6; in 2 articles, both localizations were studied. A total of 361 patients with EC and 61 with CC were included ([Table 1](#)).

In 3 studies, including both CC and EC, women enrolled were FIGO stage I exclusively (Van der Vorst et al., Rossi et al., 2012, and Schaafsma et al.). In another 2 studies, II, III or IV FIGO stages (Rossi et al., 2013 and Sinno et al.) were included. In Holloway et al., 26 (74.6%) of the patients had “Mayo Clinic high-risk” features for lymphatic metastasis on final pathologic analysis [15].

The main surgical approach used in ICG SLN biopsy was robotic-assisted surgery in 368 patients (5 studies). Laparotomy was performed in 39 patients (3 studies) and laparoscopy in 15 (3 studies) patients. In Rossi et al. (2012, 2013), both surgical approaches were used. As the robotic surgery is the approach more frequently described during sentinel node mapping with ICG, Da

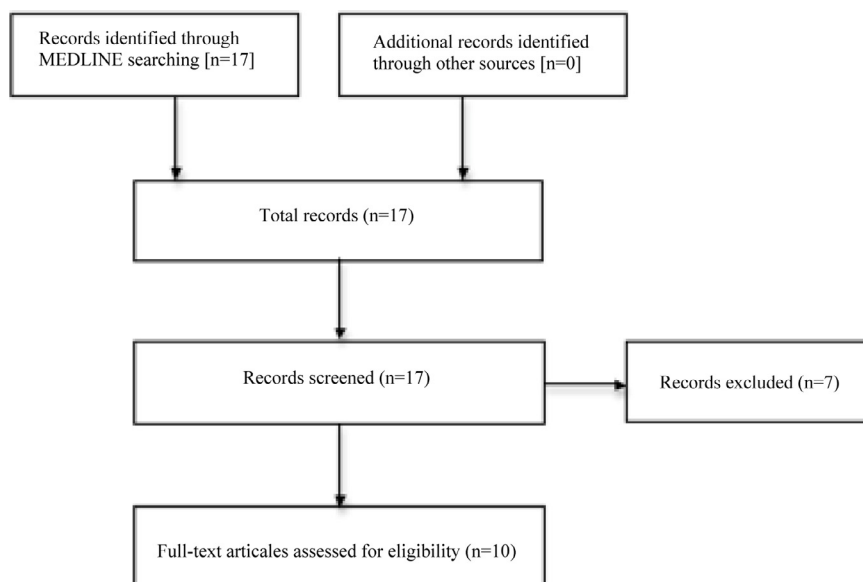


Diagram 1. Flow diagram of data selection process.

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