Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Sentinel node mapping in endometrial cancer: Tips and tricks to improve bilateral detection rate. The sentitricks study, a monocentric experience ☆

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ARTICLE INFO

ABSTRACT

Objective: The objective of the study is to show some small tricks for bilateral sentinel lymph node (SLN) uptake in endometrial cancer.
Materials and methods: Each step of the sentinel lymph node technique was analyzed. The cervix was exposed through the use of vaginal valves and by Martin pliers stapling of the anterior cervical lip. Fifty mg Indocyanine Green (ICG) powder was diluted with 10 ml of physiological solution. The spinal needle was marked at 15 mm with a steri-strip. After 20 min from the administration, in case of no LNS identification, an additional 1 ml in the non-detected side was administered in the superficial cervical area. All cervical injections were made by a single (BR) surgeon experienced in oncological gynecology.
Results: Fifty patients undergoing sentinel lymph node research for endometrial cancer. The uptake of at least one side of the sentinel node was 98% (49 cases). Forty-six (92%) patients had bilateral lymph node uptake and 3 patients (6%) had unilateral uptake. Only one patient with pelvic and metastatic aortic lymph nodes had no sentinel nodal uptake.
Conclusions: Little tricks can increase the bilateral uptake of the SLN up to 92%. The reinjection could be a key element for the success of the SLN technique. Experienced surgeons could certainly play a funda-mental role in raising bilateral SLN detection. Further prospective randomized studies are needed to achieve the best SLN infiltration strategy.

Introduction

Since sentinel lymph node (SLN) technique was included in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in 2014, it has been increasingly accepted and globally adopted [1].

The rationale of the SLN technique consists in avoiding the complications of the systematic stage lymphadenectomy [2]. However, the technique still presents some critical points [3].

Since the first results reported by the FIRES trial, bilateral SLN detection immediately appeared to be a problem. The Authors re-ported a unilateral uptake of 86% and a bilateral uptake of 52% [4].

Regarding the studies reported in the literature, bilateral detection rate is extremely variable and ranges from 27 to 80% [5]. Further-more, as reported in the Society of Gynecologic Oncology (SGO) Clinical Practice Statement, bilateral uptake is reported in 55% of cases [6]. These data showed that about 50% of patients undergoing SLN technique experienced at least one hemipelvis lymphadenec-tomy [7].

Several aspects could be investigated as possible causes of nodal uptakes failure ranging from demographics to technical factors [8].

Nowadays, few studies have analyzed the possible causes of the sentinel lymph node failure [9—11]. Tortorella et al. identified predictors of unsuccessful SLN mapping, reporting that adhesiolysis and the presence of enlarged lymph nodes independently worsen bilateral dye uptake [12].

Our study aims to provide small tips and tricks to increase the success of the SLN technique in bilateral lymph nodal detection.

Materials and methods

Eighty-four patients with endometrial cancer afferent to the department of gynecological oncology of Parma from May 2017 to May 2019 were analyzed. Of these, patients not subject to sentinel lymph node technique, patients converted to open surgery or not able to sign informed consent were excluded from the study. Patients with any American Society of Anesthesiologists (ASA) status and any body mass index (BMI) were included in the analysis.

Of the 84 cases analyzed, 50 patients met the inclusion criteria.

Demographic factors

All patients subjected to the sentinel lymph node technique had early-stage endometrioid endometrial cancer according to the International Federation of Gynecology and Obstetrics (FIGO) classification. Patients at high risk of lymph node metastasis, with histotype other than endometrioid, and treated in laparotomy have been excluded from SLN research.

Tumor factors

Patients subjected to the SLN technique were patients at low/ intermediate risk of lymph node metastasis as required by the NCCN algorithm [1]. Patients at high risk of lymph nodal metastasis were defined according to the European Society for Medical Oncology, European Society of Gynaecological Oncology, and European Society for Radiotherapy and Oncology (ESMO-ESGO-ESTRO) Consensus conference criteria [7].

Technical factors

All patients underwent peritoneal washing, total hysterectomy, bilateral salpingo-oophorectomy, and search for sentinel lymph node with ultrastaging. All sentinel lymph nodes removed were processed using ultrastaging which included serial sectioning of 200 microns with revision of multiple Hematoxylin and Eosin stained slides and cytokeratin immunohistochemistry staining.

Pelvic and aortic lymphadenectomy was performed in case of mono- or bilateral sentinel node failure or in case of high risk factors to the frozen section analysis [13].

The cervix was exposed through the use of vaginal valves and by Martin pliers stapling of the anterior cervical lip.

Fifty mg Indocyanine Green (ICG) powder was diluted with 10 ml of physiological solution.

Four ml of ICG were injected with a 19 Gauge (G) needle at 3 and 9 o'clock, 1 ml deep (15 mm), and 1 ml superficial (2—3 mm) per side. The site of the infiltration had been between the outer uterine orifice and the vaginal fornix. The infusion was carried out slowly, 10 s per milliliter of infiltrated dye. The needle was marked at 15 mm with a steri-strip for greater precision of the deep infiltration into the cervix (see Fig. 1).

Each cervix was measured with a KC-Sizer clamp in narcosis before surgery began. A Rumi manipulator was positioned at the end of cervical infiltration [14].

After 20 min from the dye administration, in case of no LNS identification, an additional 1 ml in the non-detected side was infiltrated in the superficial cervical area.

Surgeon factors

All cervical injections were made by a single (BR) surgeon experienced in oncological gynecology.

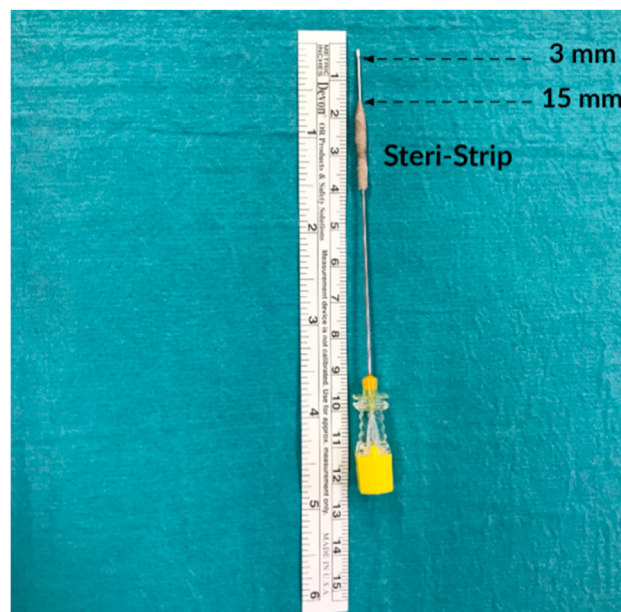No resident performed tracer infiltration.

Fig. 1. A 19-G spinal needle, with a Steri-Strip positioned 15 mm away from the tip.

Instrumentation

Indocyanine Green powder 50 mg;
Physiological Solution 10 mL;
Near-infrared laparoscopic optic (Storz Endoscopic IMAGE 1SH3-link TC300 and Light source Storz D-light P 20133720).

Ethical approval

The local ethics committee approved the study with the protocol code: 477/2019/OSS/AOUPR (Number 0000365).

Results

Of the 84 cases undergoing surgical treatment for endometrial cancer in the study period, 50 patients were included in the study. The median age was 66.5 years, and median BMI was 27. The patients' demographic characteristics are reported in Table 1.

Table 1
Patients' demographic characteristics.

Total cases	50
Age (years) median	66.5
BMI (Kg/m^2) median	27
FIGO STAGE	
IA	33
IB	10
IIIA	1
IIIC1	5
IIIC2	1
Hystotype	
Endometrioid	50
Grading	
G1	27
G2	16
G3	7
Lymphadenectomy	
Pelvic	4
Aortic	1

BMI: Body Mass Index.

The uptake of at least one side of the sentinel node was found in 98% of cases (49 patients). Forty-six (92%) patients had bilateral lymph node uptake and 3 (6%) unilateral uptake. Only one patient with pelvic and metastatic aortic lymph nodes had no sentinel nodal uptake. In 9 patients 5 mL of tracer were infiltrated due to SLN failure in a hemipelvis. Of these, in 6 cases the sentinel node of the non-capturing hemipelvis was identified, and in 3 cases the sentinel node was not identified despite the reinjection. Of the 3 non-captive cases that underwent unilateral lymphadenectomy, one patient had metastatic pelvic lymph nodes.

In 3 patients, 6 ml of dye were injected due to the absence of bilateral uptake. In 2 cases the pelvic sentinel node was identified after reinjection. Furthermore, in the latter case, no sentinel node was identified and lymphadenectomy showed both pelvic and aortic nodal metastases.

In 12 patients the SLN was not identified from one or both hemipelvis. Of these, 11 (91.7%) had a cervical diameter $\geq$ 30 mm.

Considering both hemipelvis, a median of 2 (range 0–4) sentinel lymph nodes were identified by pathological analysis (one for hemipelvis).

In the 49 patients in whom SLN was identified, 4 Isolated Tumor Cells (ITC), 5 micrometastases, and one macrometastasis were diagnosed.

Both on the right and left side the external iliac SLN was the most frequently encountered nodal localization (the other SLN localizations are summarized in Table 2).

In 23 cases SLN was identified after 20 min and in 26 cases within 20 min from the dye injection.

Discussion

Our study shows a unilateral and bilateral sentinel node uptake of 98% and 92% respectively due to small tricks during dye infiltration.

The first choice we made was the selection of the type of dye used.

Different retrospective and prospective studies analyzing the isosulfan blue, methylene blue, and ICG, are in favor of the latter [9,15,16].

ICG nodal tropism is probably due to the close link between the dye and the lymphatic lipoproteins. In addition, the dye reaches the lymph nodes phagocytized by macrophages [17]. Anyway, ICG quickly reaches the nearest lymph node stations [18].

The site of the injection has been extensively discussed in various works, and although the uterine fundus may be a valid alternative and has better aortic uptake, the cervix remains the site with better nodal uptake.

The reason lies in an anatomical explanation. The uterine cervix and the body of the uterus through the deep and superficial lymphatic pathways, respectively below and above the ureter, drain into the external iliac, obturator and internal iliac lymph nodes [19,20]. The fundus of the uterus, in 70% of cases, follows the lymphatic drainage pathway of the infundibulopelvic ligament which drains into the aortic stations [21]. Considering that the body of the uterus is the site most frequently involved in endometrial cancer, we have chosen the cervical site as the injection site.

Different techniques have been described with double infiltration sites, both cervical and fundal injection [21,22].

Nevertheless, the double infiltration site doesn't improve pelvic uptake with a more invasive procedure. Furthermore, in early stage endometrial cancer, aortic metastasis remains a rare event [23]. For these reasons, we have decided to infiltrate only one uterine site.

To our knowledge, no study in the literature analyzes the role of stapling the cervix during dye injection. Using vaginal valves and

Table 2
Sentinel lymph node features.

	Right	Left	Total (n)
Localization			95
Parametrial	1	0	1
Internal Iliac	2	3	5
External Iliac	28	29	57
Common Iliac	8	3	11
Paraaortic	0	2	2
Paracaval	2	0	2
Interaortocaval	0	0	0
Presacral	1	0	1
Obturator	8	8	16
Detection			
Bilateral	–	–	46
Monolateral	2	1	3
None	–	–	1
Dye Used (mL)	–	–	
4	–	–	38
5	–	–	9
6	–	–	3
Time of Detection (min)			
≤20 min	–	–	26
≤30 min	–	–	23
>30 min	–	–	1
Sentinel pathology			
ITC	3	1	4
Micrometastasis	3	2	5
Macrometastasis	0	1	1
Absent lymphatic tissue	0	1	1
Cervical Diameter (mm)			
<30 mm	–	–	34
≥30 mm	–	–	16

claw forceps on the anterior cervical lip greatly improve cervix exposure and infiltration accuracy.

The depth of dye infiltration described in the Abu-Rustum algorithm is based on an anatomical rationale [10]. Infiltrating both in-depth and on the surface ensures the infiltration of the dye in both uterine lymphatic drainage pathways. In our opinion, being precise in the depth of needle penetration is fundamental for correct nodal detection. Infiltrating too deeply could lead to injecting the dye directly into the venous vascular uterine void. In this way, the dye can be washed away from the venous system without reaching the lymphatic channels, and the needle could reach the parametrium causing vascular and nerve damage. For these reasons, we used a Steri-Strip to mark the point of maximum penetration of the needle (Fig. 1).

The injection was always performed by the same operator (BR), for years dedicated to oncological gynecology. We believe that a thorough knowledge of anatomy, a fair amount of surgical gestures, and a careful evaluation of uterine dimensions with a preoperative gynecological examination are essential requirements for good bilateral detection. Considering that the injection should be done after entering the abdominal cavity and after obtaining a correct exposure of the surgical field with adhesiolysis, the time of infiltration is often left to the resident in training, even in the early years, with little oncological experience.

In 24 cases (48%) the SLN was not detected after the classic 15–20 min of waiting. This aspect would suggest that each patient could have a different collection time than the other and therefore the simple waiting, as well as the reinjection, should both be analyzed as valid alternatives before decreeing the failure of the method. Persson et al. obtained excellent results with the reinjection alone, reporting a bilateral mapping rate of 95% [20]. Our data are in agreement with Harold et al., which describe a median SLN

Table 3
Summary of tricks.

	Commonly used	Our center
Cervix exposure	Speculum	Vaginal valves and anterior cervical lip clamping with hooked forceps
Needle (G)	21	19
ICG concentration (mg/ml)	1.25—2.5	5
Reinjection	No	Yes
Time Waiting (min)	20	>30
Amount of dye (ml)	4	4—6
Operator infiltrating	Not specified	Expert surgeon

G: gauge. Min: minutes.

identification time of 28 min [24]. To date, no study analyzes in detail whether there is an optimal waiting time before catching the target lymph node.

Furthermore, there is no standard ICG concentration to be used. In general, cases of ICG-toxicity have not been described in the literature, and different concentrations have been used in endometrial cancer ranged from 1.25 mg/ml to 2.5 mg/ml [4,25]. In our cases, a higher concentration of ICG 5 mg/ml has been used, without any adverse event. This concentration was considered safe and is recommended by the Food and Drug Administration (FDA) [26].

Even the gauge (G) of the needle used is devoid of a recommended standard. In an interesting review by Rocha et al. a range of 18—26 G needle is reported [27]. In our case study, a 19 G spinal needle was used with excellent infiltration comfort, to avoid excessive pressure to be exerted at the time of infiltration.

Finally, the same dose of dye is provided regardless of the cervical size. In our series, 91.7% of non-capturing cases had a cervical diameter ≥30 mm. These patients with greater cervical volume may require a greater amount of dye, and this is in line with the uptake after re-injection in 8 of 12 patients initially not capturing. The median cervical diameter is extremely variable and varies according to the age of the patient. In post-menopause women, the median cervical transverse diameter is ranged from 20 to 25 mm [28]. Several methods have been described in the literature on cervical volume measurement, from transvaginal ultrasound to magnetic resonance [29]. In our experience, a measurement with a simple forceps, in narcosis and after having exposed the cervix with the vaginal valves is an extremely simple and reproducible method. There is currently no study in the literature that modulates the amount of dye to be used in relation to cervical volume.

With our method, we have achieved a median of 2 removed SLNs, one for each hemipelvis, which results in very high precision of the technique used.

All our little tricks are summarized in Table 3.

Conclusions

Little tricks can increase the bilateral uptake of the SLN. The reinjection could be a key element for the success of the SLN technique both because it would lead to infiltrate a greater volume of tracer in the larger cervices and because it would give more time to the tracer to reach the SLN. The experienced surgeon could inevitably be a fundamental element in achieving percentages of collection beyond the average. Experienced surgeons could certainly play a fundamental role to raise bilateral SLN detection.

Further prospective randomized studies are needed to determine the best SLN infiltration strategy.

Author contribution

Capozzi VA, Berretta R, Chiantera V: Project development, manuscript writing/editing.

Cianciolo A, Gambino G, Armano G: Data collection.
Ceni V, Sozzi G: Data analysis.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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