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Feasibility of sentinel lymph node fluorescence detection during robotic laparoendoscopic single-site surgery in early endometrial cancer: a prospective case series

Liliana Mereu*, Alice Pellegrini, Roberta Carlin, Erica Terreno, Claudia Prasciolu and Saverio Tateo

Abstract

Background: In the last few decades, the introduction of technologies such as single-site surgery, robotics, and sentinel lymph node detection has reduced invasiveness in the treatment and staging of endometrial cancer patients. The goal of the present prospective cohort study is to evaluate the feasibility of lymph node fluorescence detection with robotic single-site approach in low-risk endometrial cancer.

Results: Fifteen non consecutive low-risk endometrial atypical hyperplasia (EAH) patients underwent sentinel lymph node (SLN) biopsy and total hysterectomy utilizing the Da Vinci Si Single-Site Surgical. System and Firefly 3D imaging. Indications for surgery included eight (53.3%) IA FIGO stage G1 EC, three (20%) IA FIGO stage G2 EC, and four (26.6%) EAH. Mean operative time was 155 min (range 112–175). One vaginal laceration was the only perioperative complication encountered, and all patients were discharged within 48 h of surgery.
SLN was detected in 86.6% of cases; 1/29 (3.4%) SLN results were positive for isolated tumor cells (ITCs) at immunohistochemical analysis.

Conclusions: The present study demonstrates the feasibility and applicability of robotic single-site approach with SLN fluorescence detection for the staging of low-risk endometrial cancer.

Keywords: Single-site surgery, Robotic, Fluorescence, Sentinel lymph node, Low-risk endometrial cancer, Minimal invasive surgery

Background

Surgery is considered the gold standard for staging and treating women with endometrial carcinoma (EC). The surgical treatment of endometrial cancer has quickly evolved since the late 1980s with the introduction of laparoscopy. In 2005, the US Food and Drug Administration approved the da Vinci robotic platform (Intuitive Surgical Inc., Sunnyvale, CA, USA) for gynecology, adding another tool for the management of EC.

Even if robotic surgery shows some disadvantages, such as size, number of port sites, and costs, it has obtained an important role in gynecologic surgery, due to its short learning curve, comfortable ergonomics, and improved intra- and postoperative outcomes.

The laparoendoscopic single-site surgery (LESS) is an alternative to conventional laparoscopic or robotic surgery, as it provides the improved cosmetic benefits of minimally invasive surgery while avoiding the potential morbidity related to multiple incisions. Although LESS is innovative, it nevertheless presents some challenges, requiring specific laparoscopic skills. The combination of robotics and single-site surgery appears to be the perfect fusion between the two techniques, enhancing the advantages and reducing the limitations.

* Correspondence: liliana_mereu@yahoo.com
Department of Obstetrics and Gynecology, Santa Chiara Hospital, Largo Medaglie d'Oro 9, 38122 Trento, Italy

Recent studies demonstrate that the robotic single-site (RSS) technique applied to total extra-fascial hysterectomy and even pelvic lymphadenectomy is a feasible and reproducible technique for the staging of endometrial cancer without the need of additional ports or conversion to laparoscopy [1–8]. Since 2015, the development of a fluorescence robotic camera for the RSS console makes it possible to apply the sentinel lymph node (SLN) protocol with RSS approach as described by Sinno et al. [9–11] and Silva E Silva [12].

SLN mapping may be an acceptable surgical strategy placed in between lymphadenectomy and no nodal evaluation in patients with endometrial cancer [13, 14]. As underlined by Abu-Rustum, the main point of SLN mapping is to reduce the number of nodes removed for staging, by targeting those most likely to contain metastasis and still maintaining the ability to find microscopic nodal disease [13]. Despite the low incidence of nodal disease in low-risk EC, omitting extra-peritoneal evaluation would result in an inadequate staging precluding adjuvant therapy when necessary; SLN can be an efficient alternative to the selection of patients to be surgically staged based on the intrauterine risk factor identification by means of frozen sections [15, 16].

The aim of this study is to evaluate the feasibility of robotic single-site hysterectomy (RSSH) plus sentinel node biopsy for the staging of endometrial endometrioid cancer.

Methods

This is a prospective, cohort study on nonconsecutive low-risk endometrial cancer patients treated with RSS hysterectomy plus bilateral salpingo-oophorectomy and SLN detection with the da Vinci Si Surgical System. All 15 patients were operated at the Gynecological Unit in S. Chiara Hospital by two senior surgeons (ST and LM) using the same surgical team. The main inclusion criteria were a clinical diagnosis of low-risk endometrial cancer (IA FIGO stage, G1–G2) or atypical endometrial hyperplasia revealed by the preoperative exams (endometrial biopsy, pelvic ultrasound, and/or MRI). We excluded patients with anesthesiological contraindications for the minimally invasive approach, body mass index > 30, and large uterus.

The pre-treatment evaluation included medical history collection, physical examination, vaginal pelvic examination, chest X-ray, pelvic ultrasound scan, or pelvic magnetic resonance imaging scan. Informed consent to RSSH and SLN fluorescence detection was obtained from all patients in accordance with the local and international legislation (Declaration of Helsinki) [17]. Approval to conduct the study was obtained independently from the Azienda Provinciale Servizi Sanitari (APSS) Ethics Committee (reference number RGCS-I-2016).

Clinical patient characteristics including age, body mass index (BMI), pre-surgical clinical staging, comorbidity, prior abdominal surgery, and intraoperative parameters including operative time, blood loss, conversion rate, and complications were recorded.

The operating time was measured from the beginning of the skin incision to the completion of skin closure. The estimated blood loss was calculated using the difference between washed and suctioned solution. Postoperative parameters included short-term (within 30 days of the procedure) and long-term (more than 30 days after the procedure) complications and length of hospital stay. Complications were measured by the Clavien-Dindo scale [18].

All patients were administered antibiotic prophylaxis (cefoxitin 2 g intravenously) and postoperative low molecular weight enoxaparin (40 mg/day subcutaneously). During the procedure, the patient was placed in the lithotomy position and underwent general anesthesia. The vaginal cavity was cleaned with a povidone-iodine solution and a Foley catheter was placed in the bladder. A speculum was placed for cervical visualization, and 4 ml of indocyanine green (ICG) was diluted to 1.25 mg/mL and was injected 1 ml superficially and 1 ml deeply into the cervical stroma at 3 and 9 o'clock position. A 2.5-cm incision was made using all the umbilical scar length, opening the peritoneal cavity. The single-site port was inserted into the abdominal cavity using an atraumatic forceps. The pneumoperitoneum was induced at a pressure of 12 mmHg. Four specific cannulae were introduced in the port: two 250-mm-long curved 5-mm cannulae for robotic instruments, one 8.5-mm cannula for the high-definition three-dimensional endoscope, and one 5-mm assistant surgeon cannula. The patient was moved to the Trendelenburg position, and the bowel was placed above the pelvic brim with a laparoscopic grasper. After adhesiolysis, if necessary, cytologic fluid aspiration and coagulation of both tubes with standard laparoscopic instruments were performed, and a Hohl uterine manipulator (Karl Storz GmbH & Co. KG, Tuttlingen, Germany) was placed using a video guidance. The da Vinci® Si System (Intuitive Surgical, Sunnyvale, CA) was docked between the patient's legs. A 3D 8.5-mm Firefly endoscope was used in the camera arm, and a unipolar hook and bipolar Maryland forceps were used on the right and left hands respectively. Fluorescence imaging was used to visualize the ICG tracer in the lymphatic system (Fig. 1). A successful mapping was defined as finding a channel leading from the cervix directly to one lymph node in at least one hemi-pelvis. The identified sentinel lymph nodes were then retrieved, labeled for a location with a clip, and inserted in an EndoBag. Extra-fascial total hysterectomy and bilateral salpingo-oophorectomy were then performed following the technique previously described [8]. The uterus and SLNs were extracted from the abdominal cavity through the

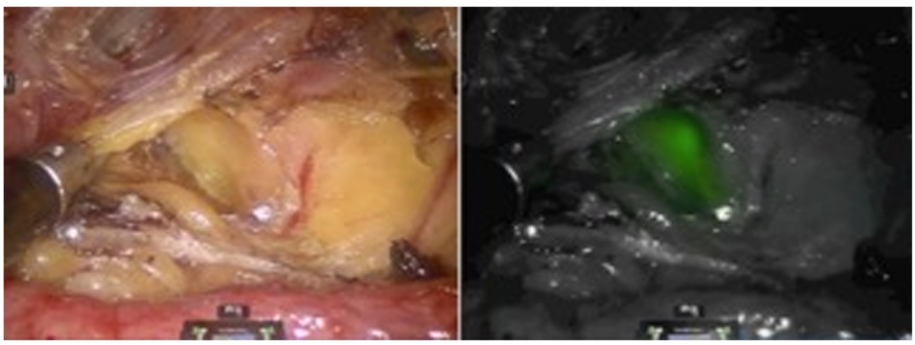

Fig. 1 Right external iliac SLN fluorescence detection

vagina. The vaginal cuff closure was performed internally with snaked single-port robotic needle holder and 0/0 barbed suture V-loc (Covidien Dublin, Ireland). The robot was undocked, and the single-site port was taken out. The umbilical incision was sutured in planes with number 1 Vicryl (Johnson & Johnson International, Belgium) on the aponeurosis, and Monocryl 3–0 (Johnson & Johnson International, Belgium) under the skin.

For the pathologic evaluation of SLNs in EC, the procedure used was the ultra-staging described by Abu-Rustum et al. [13].

Normally distributed data are presented as mean SD and confidence interval while skewed data are presented as median and range. Categorical variables are reported as absolute values and percentages.

Results

Between September 2015 and September 2017, 15 women underwent RSSH plus SLN fluorescence detection at the Gynecological Department of Santa Chiara Hospital, Trento, Italy.

Indications for surgery included eight (53.3%) IA FIGO stage, grade 1 endometrial cancer; three (20%) IA FIGO stage, grade 2 endometrial cancer; and four (26.6%) endometrial atypical hyperplasia, diagnosed by preoperative curettage and instrumental exams. Median patients' age was 60 (range 55–69), and body mass index was 23 kg/m^2 (range 21–33). Six (40%) patients had had prior abdominal surgery. Mean uterine weight was 113 g (range 50–230). The mean operative time was 155 min (range 112–175). An intraoperative vaginal laceration occurred in one patient, and all patients were discharged within 48 h of surgery.

SLN was detected in 86.6% of cases (two cases of no detection, nine cases of bilateral detection, and four cases of mono-lateral detection). Uterine frozen section was done only in case of no SLN detection to confirm myometrial invasion and grading. No systematic pelvic lymphadenectomy was required. In one case of no SLN detection, a vaginal laceration with vaginal valve occurred soon after ICG intracervical injection (requiring vaginal suturing), and in one case, bilateral parametrial ICG diffusion has been observed. Twenty-nine SLNs were identified: 11 (37.9%) in the internal iliac region, 10 (34.5%) in the external iliac region, 5 (17.2%) in the obturator region, and 3 (10.4%) in the common iliac region (Table 1). 28/29 SLN proved negative at the final histological exam, in 1 (3.4%) SLN ITCs was detected by IHC. As shown in Table 2, upper staging occurred in 5/15 (33.3%) cases (3 endometrial atypical hyperplasia and 2 G1 endometrial cancer).

Discussion

The combination of robotic surgery, single umbilical access, and near-infrared fluorescence imaging makes it possible to minimize surgery and to apply SLN mapping at the same time, improving the intra- and postoperative outcome for the patients.

The technique used to perform a total hysterectomy and pelvic lymphadenectomy by RSS approach has already been described in our previous video article [8]. In the present case series, the closure of the vaginal cuff was performed internally with the utilization of robotic snaked needle holder. The 3D 8.5 mm Firefly™ fluorescence

Table 1 SLNs detection

Variable	*N*, frequency (%)
Mapping by pelvic	
Bilateral	9 (60.1)
Monolateral	4 (26.6)
None	2 (13.3)
SLN identified	29
Localization	
Internal iliac	11 (37.9)
External iliac	10 (34.5)
Obturator	5 (17.2)
Common iliac	3 (10.4)

Table 2 Pre- vs postsurgical staging

Variable	Preoperative, *N* (%)	Postoperative, *N* (%)
Endometrial atypical hyperplasia	4 (26.6)	1 (6.6)
Grading		
G1	8 (53.3)	8 (53.3)
G2	3 (20)	4 (26.6)
G3	0	2 (13.3)
Myometrial invasion		
M1	15 (100)	15 (100)
M2	0	0

endoscope (Intuitive Surgical) was utilized for the detection of SLN as already described by Sinno et al. [9–11].

The SLN detection rate was 86.6%, in line with the rate considered acceptable and reported to be from 80 to 90% or greater [19]. In two patients, SLN detection was not obtained in both hemi-pelvis: in one case, the vaginal laceration at the level of the right fornix could have promoted an IGC intraperitoneal diffusion, preventing the physiologic lymphatic spread of the dye; in the second case, bilateral parametrial diffusion probably obscured the visualization of the SLN.

During the research of the fluorescent lymph node, the two surgeons noted a less brilliant green than in standard robotic surgery, which required a reduction of the distance between the camera and the target organ. This event could have been due to the reduced diameter of the endoscope, as compared with the 3D 10-mm camera utilized in multiport robotic laparoscopy. In a study performed on pigs to determinate the optimal dosage of ICG of the robotic single-site instrumentation, Levison et al. evidenced that the optimal concentration of ICG is 250–500 μg per 0.5 ml [20]. Probably, the utilization of a concentration of 2.5 mg/mL instead of 1.25 mg/mL could improve the intensity and the identification of SLNs from the surrounding tissue.

The removal of the identified sentinel lymph node was possible in all cases using a bipolar forceps and a unipolar hook. In the study by Creasman et al., pelvic nodal metastases were found in 5% of patients with superficial myometrial invasion [21]. On the basis of the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system, Chi et al. found that 5.5% of patients with endometrioid histology, all grades, and myometrial invasion < 50%, had nodal metastasis [22]. More recent studies on low-risk EC and SLN detection revealed an incidence of lymph nodal metastases between 6 and 10% [15, 23–25]. Similarly, the occurrence of metastatic lymph nodal EC in patients with a preoperative diagnosis of EAH has been widely described before [15, 26, 27]. In the present study in 1/29 (3.4%) SLN, isolated tumor cells were found at IHC. One patient, with endometrial cancer FIGO stage IA, grade 3, underwent adjuvant external beam radiotherapy.

Considering that classifying patients as EAH or low-risk EC based on pre- or intraoperative uterine factors alone may lead to an under-staging of 25–33% [23, 28, 29], in accordance with the previous studies we routinely performed SLN detection in EAH and low-risk EC. In this series of 15 patients, three cases of atypical hyperplasia became G1 and two cases of G1 endometrial cancer became G2 and G3 with the myometrial invasion of less than 50%.

Ten (66.6%) SLNs were detected in the internal iliac region, eight (53.3%) in the external iliac region, five (33.3%) in the obturator region, and three (20%) in the common iliac region; the present SLN mapping matches the SLN fluorescence detection with the Firefly system in stage I endometrial cancer reported by Abu-Rustum et al. [30]. The shortest single-port curve cannulae of 5 × 250 mm, 5-mm robotic single-site instruments (bipolar Maryland and monopolar hook), and standard docking made it possible to visualize and remove the SLNs also at the level of the common iliac vessels. The mean operative time of 155 min is longer than those reported by other studies, in which only a total hysterectomy without lymphadenectomy was performed [2, 3]. There is only one multicenter study on the feasibility of endometrial cancer by RSSL, where the mean time was 122 but pelvic lymphadenectomy was performed in only 17% of cases [7]. Following Sinno's algorithm [31], in two of 15 cases in which no SLNs were found, a frozen section analysis of the uterus was performed to confirm myometrial invasion and grading, without the need to perform systematic pelvic lymphadenectomy. In our institution, frozen section analysis of the SLN in EC patients is not routinely performed, because it may lead to high false-negative rates and may interfere with a proper ultra-staging at the permanent section.

As the technique did not require conversion, and as only one vaginal intraoperative laceration and no postoperative complications occurred, it may be considered safe for the patients and a valid and feasible alternative.

Conclusions

This preliminary study demonstrates the feasibility and applicability of robotic single-site approach with SLN fluorescence detection for the staging of low-risk endometrial cancer. A prospective multicenter case-control study is ongoing with the aim of comparing standard robotic vs single-site robotic approach for the treatment with SLN mapping of low-risk EC.

Further studies are needed to demonstrate the applicability of the SLN algorithm and to compare different minimally invasive approaches in higher risks endometrial cancer.

Abbreviations
APSS: Azienda Provinciale Servizi Sanitari; BMI: Body mass index; EAH: Endometrial atypical hyperplasia; EC: Endometrial cancer; ICG: Indocyanine green; IHC: Immunohistochemistry; ITC: Isolated tumor cell; LESS: Laparoendoscopic single-site surgery; RSS: Robotic single site; RSSH: Robotic single-site hysterectomy; SLN: Sentinel lymph node

Availability of data and materials
The datasets used and/or analyses during the current study are available from the corresponding author on reasonable request.

Authors' contributions
ML is a surgeon, and she designed and wrote the paper and interpreted the data. AP contributed to the data acquisition, analysis, and interpretation. RC and ET contributed to the acquisition of data and wrote the paper. CP contributed to the acquisition of data and drafting of the paper. ST is a surgeon, and he contributed to the interpretation and supervision. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Approval to conduct the study was obtained independently from the Azienda Provinciale Servizi Sanitari (APSS) Ethics Committee (reference number RGCS-I-2016).

Consent for publication
Not applicable

Competing interests
All authors declare that they have no competing interests.

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