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A study on uterine lymphatic anatomy for standardization of pelvic sentinel lymph node detection in endometrial cancer

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HIGHLIGHTS

- Two consistent pelvic uterine lymphatic drainage pathways exist.
- The external/obturator nodes drain the upper, the presacral the lower paracervical pathway.
- Ideally, at least one SLN should be identified in each pelvic pathway bilaterally.
- Cervical injection results in a higher technical success rate than fundal injection.
- Lymph node metastases were found in 8% of patients with low risk profile.

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ABSTRACT

Objective. To describe the anatomy of uterine lymphatic drainage following cervical or fundal tracer injection to enable standardization of a pelvic sentinel lymph node (SLN) concept in endometrial cancer (EC).

Methods. A prospective consecutive study of women with EC was conducted. A fluorescent dye (Indocyanine green) was injected into the cervix ($n = 60$) or the uterine fundus ($n = 30$). A systematic trans- and retroperitoneal mapping of uterine lymphatic drainage was performed. Positions of the pelvic SLNs, defined by afferent lymph vessels, and lymph node metastases were compared.

Results. Two consistent lymphatic pathways with pelvic SLNs were identified irrespective of injection site; an upper paracervical pathway (UPP) with draining medial external and/or obturator lymph nodes and a lower paracervical pathway (LPP) with draining internal iliac and/or presacral lymph nodes. Bilateral display of at least one pelvic pathway following cervical and fundal injection occurred in 98% and 80% respectively ($p = 0.005$). Bilateral display of both pelvic pathways occurred in 30% and 20% respectively ($p = 0.6$) as the LPP was less often displayed. Nearly one third of the 19% node positive patients had metastases along the LPP. No false negative SLNs were identified.

Conclusions. Based on uterine lymphatic anatomy a bilateral detection of at least one SLN in both the UPP and LPP should be aimed for. Absence of display of the LPP may warrant a full presacral lymphadenectomy. Although pelvic pathways and positions of SLNs are independent of the tracer injection site, cervical injection is preferable due to a higher technical success rate.

1. Introduction

Endometrial cancer (EC) is the most common cancer of the female reproductive organs in developed countries with a lifetime risk of 2.8% [1]. The most significant prognostic factors besides stage are histological type and grade. The initial management in early stage EC is usually surgical and the extent of the surgical procedure is determined by a preoperative risk assessment. In women with a high risk for lymph node metastases (LNM), a full pelvic and infrarenal paraaortic lymphadenectomy is recommended in addition to the hysterectomy and bilateral salpingooophorectomy [2,3]. A lymphadenectomy is associated with higher morbidity and it is still controversial whether it in addition to being a staging procedure for prognosis and choice of adjuvant treatment also has a curative intent [4–6]. LNM are detected in approximately 20% of women who belong to the high-risk group and in 3–9% of women in the low risk group [7–9]. A sentinel node (SLN) concept in all women with EC would allow for detection of LNM beyond a decreased morbidity in women regardless of preoperative risk factors and diminish erroneous preoperative subgrouping that may befall up to 15% of patients [10–13]. Lymphatic mapping including identification

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of SLNs in EC was first described in 1996 [14]. Logically an SLN algorithm must be based on lymphatic anatomy, clearly defined and surgically and clinically reproducible. Early anatomical studies identified two consistent pelvic lymphatic pathways: an upper paracervical (also called "external iliac pedicle", "preureteral pedicle" or "primary pedicle") with a course along the uterine artery with draining external iliac lymph nodes and a lower paracervical pathway (also called "posterior pedicle", "hypogastric pedicle" or "retroureteral pedicle") running along the uterine vein to the hypogastric area and/or presacral area [15–17]. In addition, a non-pelvic pathway runs along the Infundibulo-pelvic ligament to paraaortic lymph nodes [15–18].

The true potential of the SLN technique in EC has only been recognized during the last decade. A variety of dyes and radiotracers, alone or in combination have been described. SLNs are usually depicted as "radioactive/hot nodes" or "colored nodes" without reference to the lymphatic *anatomy* [19–23]. Only two available studies depict additional lymphatic dispersion of the tracer in lymphatic pathways [24,25].

Recent studies have shown a high bilateral pelvic detection rate following cervical injection although whether paraaortic SLNs can be identified remains unclear [26–30]. Concerns have been raised about whether a non-peritumoral injection will result in representative SLNs in EC patients [23,27,31,32].

The aim of this study was to describe the anatomy of uterine lymphatic drainage and the SLN detection rate following cervical or fundal injection of Indocyanine green (ICG) to enable standardization of an anatomically based, reproducible pelvic SLN concept in EC.

2. Material and methods

Between June 2014 and February 2016, consecutive patients with EC scheduled for robot-assisted surgery using the da Vinci® Surgical System (Intuitive Surgical Inc., Sunnyvale, Ca, USA) were included in this prospective clinical trial. The study complied with principles outlined in the Declaration of Helsinki, was approved by the institutional review board (2013/163) and registered at Clinical trials.gov (NCT02690259). All patients gave their written informed consent.

The ICG injection site was cervical or fundal in a 2:1 ratio. All women underwent a hysterectomy and bilateral salpingooophorectomy. A full pelvic and infrarenal paraaortic nodal staging following removal of the SLNs was considered in all high-risk EC patients (with at least one of following risk factors: FIGO grade 3, FIGO stage IB-II, non-diploid flow cytometry or non-endometrioid histology). In the presence of extensive comorbidity or advanced age and in low-risk patients the procedure was restricted to SLN removal. For the injection, 25 mg ICG powder (Pulsion Medical Systems, PICG0025SE, Feldkirchen, Germany) was diluted in 10 mL sterile water to achieve a 2.5 mg/mL solution. The ICG was injected either in the cervix during vaginal preparation or transabdominally in the fundus. For the cervical injection 0.25 mL (0.625 mg) ICG was slowly injected into the cervix at each injection site (2-4-8-10 o'clock respectively) using a 0.6 × 38 mm 23G × 1 1/2 needle and a 1 mL syringe. Half the volume was administered submucosally and the remaining half 3 cm into the cervical stroma. For the transabdominal fundal injection an equal amount of ICG was injected subserosally at four injection sites (two centimeters below the round ligament anteriorly and posteriorly on each side) using a "Williams Cystoscopic Injection Needle" 23G × 45 cm with an 8 mm long tip (Cook Incorporated, Bloomington, USA). For the first injection 0.3 mL ICG solution was added to compensate for the volume of the 45 cm long needle. ICG will when illuminated with a near infrared (803 nm) light emit fluorescence of 830 nm. The integrated fluorescence imaging capability of the da Vinci system (Firefly technology) enables the identification of "firefly green" draining lymph vessels and lymph nodes in contrast to the surrounding tissue which appears grey. The system allows a swift change between Firefly imaging and normal white light.

The injection of ICG was performed under visual observation with the robot set in the Firefly mode. The lymphatic drainage was observed for at least 15 min through an intact peritoneum and the lymphatic mapping was recorded at an anatomical chart. The avascular planes of the presacral, paravesical and pararectal spaces were opened keeping the upper parametrial tissue intact for later removal following the completion of the SLN procedure. For identification of the presacral SLNs, the peritoneum was opened medial to the right common iliac artery just below the aortic bifurcation and the common iliac arteries and veins, ureters and the hypogastric nerve fibers were identified prior to lymph node removal. The Firefly mode was used intermittently to avoid division of the lymphatic vessels and allow for a second evaluation of the lymphatic anatomy. Video recordings were obtained of all procedures for later review. The SLN was defined as the first (juxtauterine) ICG positive node with a clear afferent lymphatic vessel in each separate lymphatic compartment/pathway (for anatomical definition see Table S1). The positions of the SLNs were marked on an anatomical chart. All SLNs and the separately removed upper parametria were assessed pathologically by ultrastaging with five sections at three different levels using both hematoxylin and eosin staining and immunohistochemistry.

For statistical analyses we used Fisher's exact test and Mann-Whitney's test. A value of $p < 0.05$ was considered statistically significant. An intention to treat policy was used for the analyses.

3. Results

A total of 90 women were included; ICG was injected in the cervix in 60 women and in the fundus in 30 women. Clinicopathologic characteristics are presented in Table 1.

Two consistent lymphatic pathways with pelvic SLNs were identified irrespective of injection site; an upper paracervical pathway (UPP) running along the uterine artery to draining medial external and/or obturator lymph nodes before crossing the external iliac artery with a continued course lateral to the common iliac artery to the lateral precaval and paraaortic areas (Figs.s 1, 2). A lower paracervical pathway (LPP) with a course along the upper rim of the sacrouterine ligament to the presacral area medial of the internal iliac artery with internal iliac and/or presacral draining nodes before continuing medial to the common iliac artery to the medial paraaortic and precaval areas. A network of small interwoven lymphatic vessels often adjoin the right and left LPP just cranial to the promontory, but otherwise the injections resulted in side specific display of the UPP and LPP.

In addition, an Infundibulo-pelvic pathway (IPP) with a course along the fallopian tube and upper broad ligament via the Infundibulo-pelvic ligament to its origin (Figs.s 1, 2) was identified mainly following fundal injection. The UPP and LPP seemed to communicate with finer lymphatics at the level of the cardinal ligament, thereafter dividing into separate non-communicating courses lateral and medial to the common iliac artery respectively up to a level 1–2 cm cranial of the aortic bifurcation. Communicating lymph vessels in the medial broad ligament from the mesosalpinx merging the juxtauterine IPP and the UPP and/or LPP distal to the sacral promontory were rarely seen.

The technical success rate differed between the two injection sites (Table 2). The overall (at least one SLN) detection rate was 100% after a cervical and 93% after a fundal injection ($p = 0.11$) and the bilateral detection rate was 98% and 80% respectively ($p = 0.005$). Bilateral display of both pelvic pathways occurred in 30% and 20% respectively ($p = 0.6$) as the LPP was less often displayed (Table 2). Bilateral display of the UPP occurred more often after a cervical injection (95% vs 70%, $p = 0.002$) whereas a bilateral display of the IPP occurred more often after a fundal injection (30% vs 2%, $p = 0.01$) (Table 2). The UPP was displayed more rapidly (usually ≤ 1 min) than the LPP and the absorption rate was longer following a fundal injection compared with a cervical injection. A fundal injection was technically more challenging and intraabdominal leakage of the ICG frequently occurred.

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