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Original Research

Laparoscopic near-infrared fluorescent imaging as an alternative option for sentinel lymph node mapping in endometrial cancer: A prospective study

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HIGHLIGHTS

- Laparoscopy is an alternative option for sentinel node mapping in endometrial cancer.
- Sentinel lymph node mapping with laparoscopic system has high accuracy.
- Laparoscopic platform can provide widespread use of sentinel node mapping.

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ABSTRACT

Background: To evaluate feasibility of sentinel lymph node (SLN) mapping by using near-infrared fluorescent imaging and indocyanine green (NIR/ICG) integrated laparoscopic system in clinically uterine-confined endometrial cancer.
Materials and methods: Patients with clinically early-stage endometrial cancer were included in this prospective study. ICG was injected to the uterine cervix and NIR/ICG integrated laparoscopic system (Spies Full HD D-Light P ICG technology, Karl Storz, Tuttlingen, Germany) was used during the operations. SLN and/or suspicious lymph nodes were resected. Side specific lymphadenectomy was performed when mapping was unsuccessful. Systematic lymphadenectomy was completed following SLN algorithm steps.
Results: Seventy-one eligible patients were analyzed. The overall, unilateral and bilateral SLN detection rates were 95.7%, 18.3%, 77.4%, respectively. There were 8 (11.2%) patients with lymph node metastasis. One of them was isolated para-aortic node metastasis. Negative predictive value, sensitivity and false negative rate for detecting lymphatic spread were 98.4%, 87.5% and 1.5%, respectively.
Conclusion: Sentinel lymph node mapping can easily be performed with high accuracy by using NIR/ICG integrated conventional laparoscopic system in endometrial cancer and almost all lymphatic spread can be detected.

1. Introduction

Uterine carcinomas are mostly diagnosed in early stages and extrauterine spread is relatively rare [1]. Although lymphadenectomy is a step of surgical staging in uterine cancer, it may not be necessary for all patients. Moreover, systematic lymphadenectomy has potential morbidities such as lymphedema [2]. However, lymph node metastasis (LNM) is the most important prognostic factor in clinically early-stage uterine carcinoma and if it is under-diagnosed, adjuvant treatment may not be tailored appropriately and survival may be affected adversely [3]. Although presence of uterine high risk factors (high grade, deep myometrial invasion, tumor dimension, etc.) may be used for decision of lymphadenectomy, many cases who have these features will not have lymph node metastasis. Nevertheless, there is no imaging tool to detect LNM accurately [4] and 18F-Fluorodeoxyglucose Positron Emission Tomography/

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Computed Tomography does not have enough success for detection of low volume metastases [4–6].

Sentinel lymph node (SLN) mapping is a promising option to assess lymph node status truly without surgical morbidities of systematic lymphadenectomy. There is a growing literature on SLN biopsy in uterine cancer [7–11], and an algorithm beyond mapping has been proposed by Memorial Sloan Kettering Cancer Center [7]. Recently, this algorithm has been adopted into the National Comprehensive Cancer Network (NCCN) staging guidelines for endometrial cancer [12]. SLN mapping with indocyanine green (ICG) has a high success rate in detection of SLN, however it requires near infrared (NIR) technology integrated system.

NIR/ICG integrated laparoscopic systems may provide widespread use of SLN mapping. In this study we aimed to evaluate feasibility of laparoscopy for SLN mapping in patients with clinically early-stage endometrial cancer.

2. Materials and methods

Patients with clinically early-stage endometrial cancer were included in this prospective study between July 1, 2016 and February 28, 2017. The study was registered at ClinicalTrials.gov (NCT02822833). Institutional Ethical Committee approval and informed consent of the patients were obtained. Transvaginal ultrasonography and chest X-ray were routine preoperative tests. Additional imaging studies (computed tomography, magnetic resonance imaging, or 18F-PET/CT) for high-risk tumors were performed to exclude extrauterine disease. All patients with clinically early-stage uterine cancer during the study period, except patients treated without lymphadenectomy due to morbid obesity and medical comorbidities, were included into the study. Clinically early-stage cancer was defined as the disease confined to the uterus.

Surgeons had at least 10 years of postgraduate experience of endoscopic surgery including lymphadenectomy and SLN mapping with blue dye in at least 50 endometrial and cervical cancer cases. Surgeries were performed under general anesthesia by laparoscopy and in the minority of the cases by laparotomy. Laparotomy was preferred when there was a contraindication for Trendelenburg position or increased intraabdominal pressure due to medical comorbidities.

2.1. SLN mapping technique with laparoscopic system

ICG was used at a concentration of 1.25 mg/mL (Pulsion Medical Systems, Feldkirchen, Germany) and injected by the same author (S.T.) in all cases. A 25-mg vial of ICG powder was diluted in 20 mL of aqueous sterile water and a total of 4 mL of this solution was injected into the cervix at 3 and 9 o'clock locations, 1 mL deep (1 cm) and 1 mL superficial (3–4 mm). The dye was injected slowly, at a rate of 10 s, in each site.

NIR/ICG compatible laparoscopic system (Spies Full HD D-Light P ICG technology, Karl Storz, Tuttlingen, Germany) was used in all surgeries. All of the cases were managed according to the SLN algorithm steps [7,12] and then systematic lymphadenectomy was performed. Briefly, after observing peritoneal cavity, pelvic and abdominal structures, we accessed retroperitoneum. Bilateral hemipelvises were prepared for SLN algorithm steps and systematic lymphadenectomy. Loose tissue was dissected carefully to avoid detrimental effect on SLN detection rate by preventing disruption or obstruction of lymphatic channels. Anatomical spaces were created and then SLN mapping was visualized by using a foot switched pedal and by this pedal surgeon could pass from white light-high definition view to NIR function and vice versa. Laparoscopic system has a special camera that is able to visualize NIR light as it is invisible to the naked eye. SPECTRA visualization option of the camera was used while using NIR mode. SLN ICG fluorescence images appeared blue under NIR mode, while all other tissues appeared black. In the event of ICG extravasation, SLN was seen as bright blue focus and this enabled discrimination of the SLN from surrounding tissue. Possible SLN localization was checked with NIR mode, however further dissection was performed under white light. Intermittent switching to NIR mode during resection of SLN was done to determine exact borders of SLN (Supplementary Item). During the laparotomic operations laparoscopic endoscope or an endoscope developed for open surgery (Vitom II ICG Exoscope) was used in the same manner.

Mapped SLNs were resected and any suspicious lymph node was removed regardless of mapping. When SLN mapping could not achieved in the first hemipelvis, the contralateral side was checked and before systematic lymphadenectomy the first hemipelvis was checked again. In addition to the algorithm steps, if bilateral mapping was unsuccessful, presacral area and para-aortic area at least up to the inferior mesenteric artery were always explored for any SLN or suspicious node.

Afterwards, bilateral systematic pelvic lymphadenectomy was performed in all cases as our clinic's policy. Preoperative non-endometrioid histology, grade 3 endometrioid cancer, positive lymph nodes on intraoperative frozen section, or enlarged para-aortic nodes suspicious for malignancy were indications of para-aortic lymphadenectomy. Hysterectomy with bilateral salpingo-oophorectomy was performed at the end of the operation. Operations were recorded and these records were reviewed when necessary.

2.2. Pathologic evaluation and ultrastaging

SLNs were routinely sectioned and stained with hematoxylin and eosin (H&E). Ultrastaging protocol for SLNs was implemented if the SLN was negative on initial H&E staining. Serial sections were performed at intervals of 100–200 μm until the lymph node was exhausted. At each level two slides were created, one stained with H&E and one stained with the cytokeratin (clone AE1/AE3, Neomarkers) for immunohistochemistry analysis. Non-SLNs were evaluated only by H&E staining. Tumor foci larger than 2 mm in lymph node was considered as macrometastasis. Micrometastasis was defined as tumor foci in size from 0.2 mm to 2 mm. Isolated tumor cells were defined as tumor deposits less than 0.2 mm.

2.3. Statistical analyses

Performance of the algorithm was assessed by calculating sensitivity, false negative rate, and negative predictive value (NPV). Specificity and positive predictive value and false positive rate could not be reported because all positive SLNs have to be positive for LNM. True positivity was defined as a positive SLN or algorithm in a patient with LNM. Categorical variables were compared with Chi-square test. Descriptive data were presented as median (min-max) for continuous variables and as frequency (percentage) for categorical variables. A P value of <0.05 was considered statistically significant. All statistical analyses were performed using Stata version 9.0 (StataCorp, College Station, TX).

3. Results

Seventy-one patients were found to be eligible for the analyses after excluding 2 cases treated by vaginal hysterectomy alone due to morbid obesity and medical comorbidities. Characteristics of the patients were shown in Table 1 and Table 2. Median duration from ICG injection to detection of SLN was 21 min (range: 15–48 min).