

The role of sentinel node mapping with indocyanine green and endoscopic near-infrared fluorescence imaging in endometrial and cervical cancer

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Summary

Introduction: Endometrial and cervical carcinoma are common neoplasms in gynecological oncology. The prognosis and treatment depend on the stage of the cancer according to the FIGO staging system. Stage IA1 may be treated by hysterectomy or even local surgical procedures. For Stage IA2, radical hysterectomy and lymphadenectomy must be performed. Lymph node metastasis is an important prognostic factor in both cancers, however lymphadenectomy is associated with long-term complications. Thanks to the sentinel lymph node biopsy (SLNB), we can more accurately discover the staging of the primary tumor, and in case of sentinel lymph node (SLN) negative patients, can resign regional lymphadenectomy. Some researchers claim that new techniques such as indocyanine green (ICG) and endoscopic near-infrared fluorescence imaging for sentinel node mapping can be used instead of the traditional techniques. **Aim:** To establish the role of sentinel node mapping technique in endometrial and cervical cancer. **Material and Methods:** A retrospective study of medical records of five patients with cervical cancer (first group) Stage I and nine patients (second group) who underwent laparoscopic radical hysterectomy and SLNB or group of lymph nodes. These procedures were performed at Gynecology Department of the District Hospital in Garwolin. **Results:** All lymph nodes were clear of metastases. All patients after histopathological diagnosis were finally referred to the Cancer Centre and Institute of Oncology due to consultation or for further treatment. **Conclusion:** Based on the present first results and literature review, intracervical ICG injection with fluorescence imaging seems to be the best SLN mapping technique, because of its simplicity, safety, and overall lower cost. More data is required to determine if the nodes identified with this technique are able to predict metastatic disease.

Key words: Fluorescence imaging; Lymph node metastasis; Sentinel node mapping; Endometrial and cervical carcinoma.

Introduction

Worldwide, cervical cancer is both the fourth most common cause of cancer and deaths from cancer in women [1]. In 2012, it was estimated that there were 528,000 cases of cervical cancer and 266,000 deaths [1]. It is the second most common cause of female specific cancer after breast cancer, accounting for around 8% of both total cancer cases and total cancer deaths in women [1]. Approximately 80% of cervical cancers occur in developing countries [2]. The prognosis and treatment depends on the stage of cancer according to the FIGO staging system. Stage IA1 may be treated by hysterectomy or even local surgical procedures such as a loop electrical excision procedure (LEEP) or cone biopsy [3]. For Stage IA2, radical hysterectomy and para-aortic and pelvic lymphadenectomy has to be done.

As of 2014, approximately 320,000 women are diagnosed with endometrial cancer worldwide each year and 76,000 die, making it the sixth most common cancer in women [1]. It is more common in developed countries, where the lifetime risk of endometrial cancer in people born with uteri is 1.6%, com-

pared to 0.6% in developing countries. It occurs in 12.9 out of 100,000 women annually in developed countries. The prognosis for patients depends on the stage of cancer according to the FIGO staging system. There is a good prognosis in FIGO Stage I, when the tumor is limited to the uterus. The overall five-year survival rate for these patients is estimated to be about 80% [4-6]. The main surgical approach in the treatment of endometrial cancer in FIGO Stage I is a hysterectomy with bilateral salpingo-oophorectomy. This procedure should be extended to additional pelvic lymphadenectomy in some specific cases. They are as follows: moderately or poorly differentiated (Grade G2 or G3 cancer), clear cell or serous cancer, and when the infiltration through the myometrium is over 50%, although accurate indications for these procedures are not clear and are still controversial [4, 7, 8].

Minimally invasive surgery like laparoscopy radical hysterectomy, thanks to short duration of hospitalization, less blood loss, less febrile morbidity, and wound-related complications, may be a better and safe option for surgical treatment of cervical and endometrial cancer [9-11].

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Lymph node metastasis, together with parametrial infiltration and positive surgical margins, is an important prognostic factor in both cancers, however lymphadenectomy is associated with long-term complications such as lymphedema, nerve injury, and lymphocyst formation [12–14]. In early stage of cervical cancer (Ib), the incidence of lymph node metastasis is 12–22% [15] and in endometrial cancer lymphadenectomy is still controversial [7].

Sentinel lymph node biopsy (SLNB) holds promise of more accurate staging of the primary tumor, fewer wound complications, and lymphedema compared to lymphadenectomy. Regional lymphadenectomy may no longer be a requirement in SLNB-negative patients if the sentinel lymph node (SLN) procedure is adequately validated in prospective clinical trials for gynecologic malignancies. [16]

The concept of SLN mapping is gaining interest and credibility in the management of endometrial cancer as a valuable compromise between complete lymphadenectomy and no lymph node dissection at all [17].

Material and Methods

A retrospective study of medical records of five patients with cervical cancer (first group) Stage I and nine patients (second group) who underwent laparoscopic radical hysterectomy and biopsy of SLN or group of lymph nodes. These procedures were performed at Gynecology Department of the District Hospital in Garwolin from September 19th, 2014 to September 30th, 2015. The mean age of patients with cervical cancer was 44 ± 3 years; with endometrial cancer it was 69 ± 5 years. Prior to surgical treatment one pax of indocyanine green (ICG) was administrated intracervically 30 minutes before laparoscopic procedure. In laparoscopy, the access to the retroperitoneal space and to the obturator space was achieved by identifying the triangular between infundibulopelvic ligament, round ligament, and external iliac artery. Afterwards, the peritoneum overlaying the common iliac arteries was opened. The incision was extended to the bifurcation of the common iliac artery into the internal and external iliac artery towards the prevesical space. The round ligament was cut and lymph nodes pigmented by ICG were identified and removed in Endobags. The removal of lymph nodes was conducted by graspers, bipolar scissors or a harmonic knife. All the lymph nodes were histopathologically evaluated.

Results

In the first group, five women were diagnosed with plaeoepithelial carcinoma with no metastases to lymph nodes. In the second group, in four cases, the diagnosis was cancer of endometrioid type Grade 3, with no metastases to lymph nodes and in five cases, serous carcinoma was diagnosed also with no metastases to lymph nodes. The number of lymph nodes obtained in the first group was two to four and in the second group one to five. The average blood loss during laparoscopy was 225 ml. A short hospital stay of 2.6 days was achieved for patients in the first group and 3.2 days in the second group.

Histopathological examination of collected materials in-

cluded iliac and obturator SLN that revealed in the first group: three cases of inflammatory changes, and in the second group, seven cases of inflammatory changes. There were no pathological changes in the remaining lymph nodes. All lymph nodes were clear of metastases. All patients after histopathological diagnosis were finally referred to the Cancer Centre and Institute of Oncology due to consultation or further treatment.

Discussion

The authors report their first experience with SLN mapping using ICG and IMAGE1 SPIES ICG System.

Lymphadenectomy is an important component of the surgical management of cervical and endometrial cancer. Lymph node status is a major factor determining prognosis for early-stage cervical cancer [18]. While the role of lymphadenectomy for endometrial cancer is more controversial, American College of Obstetricians and Gynecologists (ACOG) recommends lymphadenectomy in patients with endometrial cancer [19]. Retroperitoneal lymphadenectomy is associated with a 3.4% to 7.2% risk of lower extremity lymphedema [13, 20]. The risk of genito-femoral nerve injury has been reported at 1.1% to 1.8% [21, 22]. Postoperative morbidity from lymphadenectomy is highest when a complete lymphadenectomy is paired with external beam radiation [14, 23].

Some practitioners may choose selective lymph node sampling rather than full dissection. Retrospective data suggest that patients who undergo multiple site sampling have improved survival rates over those who have limited sampling or no sampling performed [24, 25]. The caveat to nodal sampling rather than full dissection is that inspection or palpation of lymph nodes has not been shown to be a sensitive method for detecting positive lymph nodes, with fewer than 10% of patients with lymph node metastases having grossly enlarged lymph nodes [26]. To preserve the diagnostic and therapeutic benefits of lymphadenectomy, and at the same time minimize its side effects and morbidity, it is important to develop techniques for lymph node sampling.

Holloway *et al.* retrospectively compare results from lymphatic mapping of pelvic SLNs using fluorescence near-infrared (NIR) imaging of ICG and colorimetric imaging of isosulfan blue (ISB) dyes in women with endometrial cancer (35 patients) undergoing robotic-assisted lymphadenectomy. Fluorescence imaging with ICG detected bilateral SLN and SLN metastasis more often than ISB (97% vs. 77%, $p = 0.03$), and the combination resulted in 100% bilateral detection of SLN. [27] However combined use of ICG and blue dye appears unnecessary [28]. Sienna *et al.* also comered the ability to detect SLNs in women with endometrial cancer or complex atypical hyperplasia using fluorometric imaging with ICG vs. colorimetric imaging with ISB. SLN mapping success is

negatively associated with increasing patient BMI only when ISB is used, and confirmed that ICG is better than blue dye in obese women [29]. Rossi *et al.* proved that cervical ICG injection achieves a higher SLN detection rate and a similar anatomic nodal distribution as hysteroscopic endometrial injection for SLN mapping in patients with endometrial cancer (97% vs. 77%, $p = 0.03$) [30]. They published also initial pilot results of 20 patients with endometrial and cervical cancer and reported a detection rate of 88% [31].

In the present study, patients with cervical and endometrial cancer were included, however it was limited by the small number of cases. Based on these first results and literature review, intracervical ICG injection with fluorescence imaging seems to be the best sentinel node mapping technique, because of its simplicity, safety, and overall lower cost. More data is required to determine if the nodes identified with this technique are able to predict metastatic disease.

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