Sentinel Node Mapping in Early Stage Endometrial Cancer: A Pilot Study

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Abstract

Introduction: We assessed the feasibility of sentinel node (SN) procedure based on the injection of patent blue dye in patients with endometrial cancer.

Methods: Twenty patients were included in this study. The median age of patients was 58 years (range 49-67 years). The median body mass index was 33.3 (range 28.1-38.8) and the mean was 31.5. All patient were diagnosed with histologically proved endometrial cancer of stage I. They all underwent sentinel lymph node (SLN) biopsy procedure based on patent blue injected in the fundal subserous myometrium. After the SN procedure, all patients underwent complete pelvic lymphadenectomy and either.

Results: In 17 cases blue colored lymph nodes were observed, while it wasn't identified in 3 patients. The detection rate for the SLN was 85%. Twenty-five SLN were detected in 17 cases, i.e. the mean number of SLN is 1.47 per case (range 1-3 lymph nodes). Three of the seventeen patients with colored SLNs showed metastasis; 2 cases in the obturator group of lymph nodes and 1 in the internal iliac lymph node group. Two out of these patients had other pelvic lymph nodes positive for metastasis, while the other patient had the SLN the only positive lymph node for metastasis.

Conclusions: SLN procedure based on injection of patent blue is feasible in patients with early endometrial cancer. It is a safe procedure, with minimal complications that may reduce the associated morbidity with the classical pelvic lymphadenectomy in selected cases of low grade early stage endometrial cancer. Further studies with larger number of patients should be done to standardize such procedure.

Key Words: Sentinel node – Patent blue – Endometrial cancer.

Introduction

ENDOMETRIAL carcinoma is the most common gynecologic malignancy in Western countries, with an overall annual incidence in the United States of 25 per 100,000, increasing to more than 85 per 100,000 in women 60 years or older. Because the majority of patients present with early-stage disease, the prognosis of endometrial carcinoma patients is generally good, with 5-year overall and cancer-specific survival rates of 80% to 85% and 90% to 95% [1,2]. However in Egypt it comes in the 13th rank among female cancer representing 1.6%. At Cairo National Cancer Institute (NCI), it is the third most common gynecological cancer after cancers of the ovary and cervix constituting 23%, and the median age is 60 years [3].

Since the Gynecologic Oncology Group (GOG)-33 staging study which reported an overall 9% risk of pelvic lymph node metastases in clinical stage I endometrial cancer (25% for cases with outer-third myometrial invasion and 18% for grade 3 disease), gynecologic oncologists have advocated standard lymphadenectomy or sampling procedures for all intermediate and low-risk endometrial cancer patients [4,5].

Surgical management of early-stage endometrial cancer includes peritoneal cytology, total hysterectomy with bilateral salpingo-ophorectomy, and lymph node sampling [6]. The main prognostic factors of endometrial cancer include histological grade, depth of myometrial invasion by tumor and lymph node status [7]. The International Federation of Obstetricians and Gynecologists recommends pelvic lymphadenectomy to assess lymph node status in this setting [8], whereas the Gynecological Oncology Group (GOG) recommends systematic pelvic and para-aortic lymphadenectomy. However, the later approach is associated with higher and significant morbidity. In addition, the proportion of women who have pelvic lymph node involvement ranges from 4.7% to 13% and from 18.8% to 44.8% in stage I and stage II endometrial cancer,
respectively. Thus, approximately 8 in 10 women with stage I endometrial cancer will not get benefit from lymphadenectomy; furthermore, morbidity will be increased in those patients who will need worse postoperative radiotherapy [9,10].

However, the therapeutic role of lymphadenectomy has not been well established, with two recent randomized trials in fact failing to show a survival benefit. There still exist debate regarding the extent of nodal dissection (lymphadenectomy versus lymph node sampling, removal of pelvic versus pelvic and para-aortic nodes with or without removal of “high” infrarenal nodes) and for whom the procedure is best suited. Groups at low, intermediate, and high risk for metastasis have been identified, with intraoperative frozen section being used to categorize patients at the time of surgery. However, due to the clinically significant discrepancies in preoperative and postoperative grade and final stage are not infrequent when relying on frozen section, some advocate full lymphadenectomy on all patients at the time of surgery.

The aim of this study is to evaluate the feasibility to identify the sentinel lymph node in endometrial cancer, to test the procedure in relation to site of injection and anatomical location of the sentinel node and finally, its relevance in relation with pelvic lymphadenectomy.

Patients and Methods

From July 2009 to May 2010, 20 selected consecutive patients with endometrial cancer were included in this prospective study.

The inclusion criteria were biopsy-confirmed endometrial cancer of Stage 1A and 1B FIGO staging (B) and they followed-up during the whole period of the study [11].

All patients underwent preoperative routine full laboratory investigations, chest radiography, transvaginal U/S and pelviabdominal MRI.

Our institutional review board approved the protocol. All patients gave their written consent after receiving relevant information, including the potential adverse effects of patent blue, general anesthesia, and surgical procedure.

All patients received intravenous prophylactic third generation cephalosporin antibiotic and subcutaneous injection of low molecular weight heparin (0.4ml) was started the day before surgery and was continued until day of discharge.

The patients were placed supine and under general anesthesia. Midline incision was done and peritoneal cavity was explored for any peritoneal deposits or metastasis.

Pelvic peritoneal wash was done with 200 c.c warm saline and sent for cytological examination.

Then patent blue dye (Bleu Patenté V; Guerbet Laboratory, Issy les Moulineaux, France) was injected subserously at the fundus of the uterus at 3,6,9 and 12 o’clock sites (0.5mL per injection; 1.5cm deep).

After patent blue injection, the pelvic and lower para-aortic regions were carefully inspected for lymph ducts and specific dye uptake by lymph nodes.

After location of the SN, the peritoneum was opened above the external iliac vessels to the round ligament. Each blue node was removed separately and labeled according to its anatomical location.

Bilateral pelvic lymphadenectomy was performed systematically after the SN procedure. All node tissue along the obturator fossa and the external vessels, up to the iliac bifurcation, was dissected and sent for pathological examination. Then completion to radical hysterectomy procedure was performed. The para-aortic region was palpated for the presence of any suspicious para-aortic lymph nodes and was resected and sent for pathology.

Analysis:

SNs were recorded as blue-stained. The false-negative rate was defined as the number of procedures with a negative SN and one or more positive non-SNs divided by the number of procedures with any positive pelvic lymph nodes.

Results

The median age of patients was 58 years (range 49-67 years). The median body mass index was 33.3 (range 28.1-38.8) and the mean was 31.5.

All patients underwent intraoperative sentinel lymph node mapping using the blue dye.

There were no intraoperative complications and all patients had smooth postoperative period. Median time of discharge was 3 days (Range 2-6 days).

In 17 cases blue colored lymph nodes were observed, while it wasn't identified in 3 patients. The detection rate for the SLN was 85%.
Table (1) shows all 20 cases with corresponding pathology, anatomical site of SLN, number and histopathological type and grading.

**Site of SLN was as follows:**
- Eight patients had SLN at the obturator group.
- Five patients showed SLN in the internal iliac lymph node group.
- Four patients showed SLN in the external iliac lymph node group, towards the site of its origin from the bifurcation of the common iliac vessels.

Twenty-five SLN were detected in 17 cases, i.e. the mean number of SLN is 1.47 per case.

**Histopathology of the SLN:**
- Fourteen of the seventeen patients with colored SLNs were negative for metastasis and other dissected pelvic lymph nodes were also negative.
- Three of the seventeen patients with colored SLNs showed metastasis; 2 cases in the obturator group of lymph nodes and 1 in the internal iliac lymph node group. Two out of these patients had other pelvic lymph nodes positive for metastasis, while the other patient had the SLN the only positive lymph node for metastasis.

**Histopathology of the endometrial carcinoma:**
Seventeen patients had endometrioid adenocarcinoma, two patients had papillary serous adenocarcinoma and one patient had mucinous adenocarcinoma. There were no changes in the histopathology between preoperative and postoperative pathological classification.

Concerning grading, only 2 cases were upgraded in the postoperative pathology to grade 2 instead of grade 1 in the preoperative pathology.

Table (2) shows the relation between sentinel node involvement and histopathological characteristics of the 20 cases.

**Discussion**

Lymph node status remains the most important prognostic factor and the sentinel lymph node mapping (SLNM) could help to find women in whom adjuvant therapy could be omitted, more oven, the detection rate for SLNM in endometrial cancer varies from 45 to 100% [12].

Lymph node removal for the purpose of staging is intended to detect microscopic disease that may guide the need for adjuvant therapy [13].
Evaluation of lymph node metastasis in endometrial cancer has important prognostic and therapeutic implications. Complete pelvic and para-aortic lymphadenectomy provides accurate information on lymph node status. Nevertheless, the majority of patients with stage I disease (90%) will not have any metastasis and will be subjected to the side effects of lymphadenectomy.

The purpose of lymphatic mapping is to identify a sentinel lymph node (SLN) that would be representative of the rest of the lymph nodes draining the tumor. The results of the pathologic examination of the SLN would be indicative of the status of the rest of the nodes, obviating the need for a full lymphadenectomy and avoiding its potential complications, without losing the information on the degree of spread of the cancer.

Because many studies revealed that grade 1 early stage endometrial carcinoma has very low risk of lymph node metastasis several publications suggested that lymphadenectomy could be omitted in this group of patients to avoid its complications like leg lymphedema, lymphocycle in women with endometrial carcinoma who often have comorbidities such as obesity, hypertension and diabetes.

In general, the identification of the SLN is done through injection of a blue dye, or radioactive colloid (Tc99m), or both. There are three injection sites currently described in lymphatic mapping of endometrial cancer: The subserosal myometrium, the cervix, and the endometrium (hysteroscopically). In our study, we only used the blue dye, and we used the first injection site, which is the subserosal myometrium.

As in other solid tumors like breast cancer and melanomas, where lymphatic mapping has become accepted standard practice, lymphatic mapping in endometrial cancer should first have to be established as a feasible, and accurate technique in determining lymph node status, and i.e. it should have a consistently high detection rate and a low false-negative rate. The aim of our study was to test the feasibility of such technique and to see the rate of detection of SLNs and if there were any false negative results.

Regarding detection rate of SLN, the results of our study showed that the SLN procedure could reliably determine the lymph node status in women with endometrial carcinoma. Overall SLN detection rate was 85% compared to 62-100% in other studies. Holub et al., reported detection rate of SLN to be 84%, using blue dye alone in 25 cases while Holub Z. et al. and Altgassen et al., [15,16] reported a detection rate of 92% using blue dye alone.

Dealoye et al., [17] in their article used both blue dye and Tc99 in 60 cases with detection rate reported to be 82%.

Regarding the site of detection of SLN, the results of our study showed that all the sentinel lymph nodes were located in the pelvis and no para-aortic SLN were detected. Some studies reported the detection of SLNs in both the pelvis and para-aortic region, but the majority of cases were confined to the pelvis. Li et al. and Bats et al., reported finding all the SLNs in the pelvis, while Altgassen et al., found 94% of SLN in the pelvis and 6% of SLN in the para-aortic region. In addition, these studies did not report any false results, which is comparable to our results [15-18,19].

In 2005, the MSKCC Gynecology Service initiated a prospective study to evaluate the role of lymphatic mapping in endometrial cancer using both radioactive Tc99m and blue dye injected into the cervix, with some cases receiving an additional injection into the uterine fundus. Their published results showed that in grade 1 endometrial carcinoma; the overall detection rate was 86% and there were no false-negative cases at all [20].

Khoury-Collado and his colleagues, described that sentinel node identification was successful in 223 out of 266 (84%) patients with endometrial cancer and positive nodes were diagnosed in 32 out of 266 (12%) patients [21].

In women with early stage endometrial cancer, the procedure of sentinel lymph node (SLN) biopsy after lymphatic mapping has resulted in avoidance of complete systematic lymphadenectomy with its morbidity [22,23].

The false-negative rate in different studies will let surgeons decide whether lymphatic mapping, even if associated with high detection rates, is safe for the patient (a false-negative case means that one or more metastatic nodes would have been left behind if a concomitant lymphadenectomy would not have been performed). Owing to the relatively small number of patients included in published studies, in addition to the relatively low incidence of lymph node metastasis in endometrial cancer, a larger number of patients will be needed before clinically significant false-negative rates can be calculated [24].

We believe that site of injection is one of the key factors for successful SLN mapping in solid
tumors. We used the subserous myometrial injection approach, which lead to an identification rate of 85%. We did not have a single case of para-aortic SNL. Burke et al., found para-aortic SNs in 38% of cases but did not specify whether these para-aortic SNs were associated with external or common iliac SNs [26,27]. Para-aortic metastasis without pelvic lymph node involvement is found in only 1% to 2% of patients with endometrial cancer [26,27]. Although lymphatic spread from the uterine corpus to the para-aortic area is not frequent, the data reported by Burke et al., raise the issue of whether fundal injection of patent blue should be added to pericervical patent blue and radiocolloid injections [28]. However, It has not yet been shown whether subserosal myometrial injection of patent blue increases the SN detection rate relative to combined pericervical injections of patent blue and radiocolloid [28].

There is no technique that is definitively superior to any other with regard to surgical modality, material used for injection, injection site or pathological technique (H).

So it can be found that the results of our study and other studies using lymphatic mapping for SLN detection have high detection rate and most studies show no false negative rate in using SLN procedure for evaluation of the nodal status of the draining lymph nodes.

So the sentinel lymph node biopsy procedure could be an alternative to systematic lymphadenectomy in women with grade 1 early stage endometrial carcinoma in an attempt to reduce the morbidity of lymphadenectomy without compromising survival.

In conclusion, our results confirm the feasibility of SLN procedure based on injecting patent blue in patients with endometrial cancer. We are encouraged by our results and believe SLN mapping to be a promising technique in assessing lymph node status in endometrial cancer. This procedure can contribute to decreasing the morbidity in patients undergoing pelvic lymphadenectomy and its associated complications are rare and consist mainly of allergic reaction to the blue dye. Further studies are required to confirm that this SN procedure is a valid alternative to systematic lymphadenectomy in patients with endometrial cancer.

References


