Comparison of two procedures for sentinel lymph node detection in patients with endometrial cancer: A pilot study

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Summary

Objective: The purpose of this study was to assess the feasibility and contribution of two intraoperative procedures of lymphatic mapping and sentinel node detection using a blue dye in surgically-staged patients with early stage endometrial cancer.

Methods and Materials: In 25 cases of endometrial cancer, patent blue-V was injected into the subserosal myometrium (13 cases, SM group) or cervico-subserosal myometrium (12 cases, CSM group) during a surgical staging procedure. Laparoscopically-assisted vaginal hysterectomy and pelvic lymphadenectomy were completed successfully in 23 women out of 24 laparoscopically-staged patients (95.8%). One patient with FIGO stage IIa was indicated for a radical abdominal surgery.

Results: A deposition of the blue dye was found in at least one pelvic lymph node (LN) in eight out of 13 cases (61.5%) in the SM group compared with ten out of 12 cases (83.3%) in the CSM group ($p = 0.378$). The mean number of dye-colored LN (DCLN) was 1.15 (SM group) and 2.5 (CSM group), respectively ($p = 0.05$). The rate of DCLN/LN was 15/188 (SM group) versus 30/190, respectively ($p = 0.03$). An uptake of the blue bye was observed in a total of 45 out of 388 LN.

Conclusion: An intraoperative combination of cervico-subserosal myometrium application of the blue dye allows successful detection (83.3%) of sentinel LN in patients with endometrial cancer. Comparing SM and CSM groups the statistical significant difference was found in the DCLN/LN rate and mean number of sentinel lymph nodes ($p = 0.03$, $p = 0.05$, respectively). Clinical validity of this surgical procedure must be assessed prospectively.

Key words: Sentinel lymph node detection; Endometrial cancer.

Introduction

Endometrial cancer (EC) is the most frequently occurring malignant tumor of the female genital tract. Its incidence in developed countries is 45.8 cases per 100,000 women in the USA compared with 29.5/100,000 in the Czech Republic and 1.7/100,000 in Japan [1]. The presence of lymph node metastases has a major impact on the prognosis of women with endometrial cancer. One of the cornerstones of gynecologic cancer surgery is the assessment and removal of the regional lymph nodes. However, the most appropriate and reliable technique for assessing regional pelvic and paraaortic nodes remains uncertain [2]. The sentinel node (SN) is the first lymph node to receive cancer cells metastasizing from the primary tumor. Sentinel lymph node dissection (SLND) and intraoperative lymphatic mapping were, therefore, designed as a less invasive alternative to the routine elective lymph-node dissection in patients with early-stage cutaneous melanoma [3].

Only two reports of cases of sentinel lymph node dissection in endometrial cancer have been published [2, 4]. Burke and colleagues [2] demonstrated an open technique of intra-abdominal lymphatic mapping in 1996. A report on the preliminary results of laparoscopically-assisted sentinel dissections has been published by Holub *et al.* [4]. We report the results of a continuing study comparing the two operative procedures for lymphatic mapping and sentinel node dissection in surgically-staged patients with early-stage endometrial cancer.

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Subjects and Method

Between February 2000 and September 2001, 25 patients withe endometrial cancer FIGO stage I were subjected to sentinel lymph node dissection and lymphatic mapping during the primary laparoscopically-assisted surgical staging (LASS) procedure or to the open surgical staging procedure. Ages of the patients ranged from 46 to 78 years, with a mean of 60.5. The patients' weight ranged from 54 kg to 110 kg (BMI 18.2-38.7), with a mean of 79.7 kg (BMI 27.1). Before the surgery, all patients underwent a complete history and physical examination, and a routine laboratory investigation included biopsy, ultrasound, computed tomography or magnetic resonance. The patients were subsequently selected and criteria for the laparoscopic approach included clinician's suspicion of early-stage endometrial cancer (grade 2 or 3) and myoinvasion as well as a mobile uterus amenable to the laparovaginal approach to hysterectomy. The first 13 patients were selected subsequently for the intraoperative laparoscopically-assisted procedure of the blue dye injection into the subserosal myometrium at three sites (SM group) and a further 12 patients subsequently underwent a combined vaginally-laparoscopic (11 cases) or vaginally-abdominal (1 case) injection of the blue dye into the cervix and into the cervico subserosal myometrium (CSM group). Sentinel node biopsy and lymphatic mapping were performed in two patients during laparotomy and in 23 patients during laparoscopy. In one patient (SM group), LASS was started laparoscopically and the approach was changed to the open procedure due to extensive fibrotic adhesions. This patient had a history of three laparotomies. Radical abdominal hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy were primarily indicated in another patient (CSM group) with endometrial cancer FIGO stage IIa.

The decision concerning the extent of laparoscopic surgery was based on guidelines suggested by Childers [5]. The laparo-

scopic technique for pelvic lymphadenectomy (PLN) and laparoscopically-assisted vaginal hysterectomy (LAVH) has been described in a previous study [4]. The study protocol was approved by the Regional Committee on Human Research at the Kladno Hospital and participants gave their informed consent up on enrollment. This study was supported by a Grant Fund from the Minister of Health.

Subserosal myometrium (SM) application procedure

The intraoperative mapping technique for an open procedure described by Burke *et al.* [2] was modified for laparoscopy. Two millilitres of Paten-blue V (2.5% in aqueous solution containing 0.6% of sodium chloride and 0.05% of disodium hydrogen phosphate - Laboratoire Guerbet, Aulney-Sous-Bois, France) were injected into the subserosal myometrium at three midline sites using a 5 mm laparoscopic puncture needle with a 1.2 mm wide needle bore on the end (Karl Storz Endoscope, Tuttlingen, Germany). The injection sites were located at the most superior portion of the uterine fundus, the anterior midline 2 cm below the superior injection site, and the posterior midline 2 cm below the superior injection site. The injection sites were selected to mimic a location of endometrial cancer arising in any part of the uterine corpus. The midline injections were used to maximize chances of observing bilateral pelvic lymphatic drainage.

Cervical and subserosal myometrium (CSM) application procedure

Two millilitres of Paten-blue were diluted in 5 ml of isotonic solution of sodium chloride and 4 ml of this solution were applied to the cervix at 3, 6, 9 and 12 o'clock positions. The remaining 3 ml of solution were injected into the subserosal myometrium at the midline site of the uterine fundus.

Surgical technique

Dye uptake was monitored transperitoneally for five minutes after laparoscopically- or open-assisted injection and then, the pelvic retroperitoneal space was opened. The upper limit for pelvic lymph node dissection was situated at the level of bifurcation of the common iliac vessel while the lower limit for PLN was the femoral ring and pelvic floor. Pelvic groups included the common iliac, external iliac, obturator, internal iliac and presacral nodes. The sentinel nodes were removed during complete lymphadenectomy. Blue lymphatic channels were dissected in an effort to identify dye-containing lymph nodes in the pelvic region. When identified, these nodes were removed as biopsies and forwarded to the pathology lab as individual specimens. The nodal package was removed from the operative field through the upper 10 mm trocar. After the pelvic lymph node dissection, laparoscopically-assisted vaginal hysterectomy and bilateral salpingo-oophorectomy were carried out.

A harmonic scalpel and laparosonic coagulating shears (LCS-K5), (Ultracision, Ethicon Endo Surgery, Johnson & Johnson Ltd, Cincinnati, Ohio, USA) were used in most cases, whereas bipolar electrocauters (Karl Storz Edoscope, Tuttlingen, Germany) were applied in some cases only.

Statistical analysis

We evaluated and compared differences in the perioperative and postoperative outcomes of the two groups of surgically-staged patients with endometrial cancer. The results for the sentinel lymph node detection in the subserosal-myometrium application procedure group were compared with the outcomes for SLND in the cervico-subserosal myometrium group. Data were collected on a number of dye-colored sentinel lymph nodes (DCLN), the total number of removed lymph nodes (LN) and detection rate of patients. We used a non-parametric Chi-square test and non-parametric Fisher's exact probability test due to a non-Gaussian distribution of our data and low values in one cell of the table. Statistical data were checked using the Wilcoxon unpaired test and also the Spearman coefficient of rank correlation. A p-value of less than 0.05 was considered significant.

Results

The laparoscopic procedure was completed successfully in 23 women out of 24 laparoscopically-staged patients (95.8%). One patient with FIGO stage IIa was indicated for radical abdominal surgery. There were no statistically significant differences between the studied groups with regard to age, weight, previous pelvic surgery or type of surgery (Table 1).

Complete pelvic lymph node dissection was performed in 24 patients and laparoscopic pelvic lymph node sampling in one patient with oxygen hypoventilation during anesthesia. A deposition of the dye in at least one lymph node was found in eight out of 13 cases (61.5%) in the SM group, compared with ten out of 12 cases (83.3%) in the CSM group (p = 0.378). The blue dye uptake was observed in a total of 45 out of 377 lymph nodes. Uterine lymphatic vessels with bilateral drainage to the broad and infundibulopelvic ligaments were seen in all cases within 30-60 seconds. The dye within the lymphatic channels was easily seen after the round ligaments were divided and lateral pelvic incisions were made to expose retrope-

Table 1. — *Types of surgery and patient characteristics.*

Type of surgery	SM group	CSM group	Total
LAVH, BSO, PLND	11	11	22
LAVH, BSO, PLNS	1	0	1
TAH, BSO, PLND	1	0	1
RAH, BSO, PLND	0	1	1
Totals	13	12	25
Patient characteristics			
Weight (kg)	81.2	77.3	NS
Range	54-110	54-101	
Age (yrs.)	59.8	61.3	NS
Range	46-72	48-78	

Values are mean and range. LAVH = laparoscopic-assisted vaginal hysterectomy; BSO = bilateral salpingo-oophorectomy; PLND = pelvic lymph node dissection; PLNS = pelvic lymph node sampling; RAH = radical abdominal hysterectomy; NS = not significant.

Table 2. — *Results of sentinel lymph node detection.*

Technique of procedure	SM application	CSM application	p value
Number of patients	13	12	NS
Detection rate (patients) (%)	8/13 (61.5)	10/12 (83.3)	NS (0.378)
Mean number of removed LN	15.2	15.8	NS
Range	5-22	6-27	
Mean number of DCLN	1.2	2.5	p 0.05
Range	0-3	0-5	
Number of removed DCLN	15	30	
Number of removed LN	188	190	
DCLN/LN rate (%)	15/188 (7.9)	30/190 (15.7)	p 0.03

Abbrevations: LN = lymph node; DCLN = dye containing lymph node; NS = not significant.

ritoneal structures. A prominent blue-stained lymphatic channel to one or more pelvic sentinel nodes could be identified in all but four patients, indicating an identification rate of 77.8% (14 of 18 patients). In these 14 cases, dissection along the sprayed larger lymphatic vessels led to an evident blue-stained lymph node. Even in cases of uncolored nodes, dissection along colored lymphatic vessels allowed for identification of a range of lymphatic pelvic nodes. The mean number of blue-colored sentinel nodes was 1.15 (SM group) and 2.5 (CSM group), respectively ($p = 0.05$) and the average number of removed lymph nodes was 15.2 and 15.8 in both groups. Other results are summarized in Table 2. Evaluation using the Spearman coefficient of rank correlation showed a statistically significant negative dependency ($r = -0.520$, $p < 0.02$) between the total number of removed nodes and the number of unstained nodes.

Among 25 patients with endometrial cancer, two patients (8%) were found to have cancer within three resected obturator nodes, but only two lymph nodes were stained by the blue dye. The pelvic sentinel node ($n = 45$) was localized in 55.5% (25 of 45 lymph nodes) at the fossa obturatoria and internal iliac sites, in 17.7% (8 of 45 lymph nodes) at the division of the common iliac artery. In 26.8%, sentinel lymph nodes were located at other pelvic areas. Adenocarcinoma was the most common histology found in the study groups (Table 3).

Perioperative parameters (blood loss, total operating time, hospital time) were comparable in both groups (Table 4). There were no incidences of major perioperative complications. Only for one patient in the SM group, was the laparoscopic procedure of lymph node dissection changed to lymph node sampling due to oxygen hypoventilation during anesthesia. The group of CSSM patients showed green coloring of skin and mucous tissue up to the first day after surgery. Also during the vaginal stage of LAVH, we detected distinctive coloring of tissues in the pericervical areas in these patients.

Table 3. — *Surgical stating and histology results.*

Surgical staging	SM group	CSM group
Stage Ia, no myoinvasion	2	0
Stage Ib, myoinvasion to 50%	6	4
Stage Ic, myoinvasion over 50%	4	6
Stage IIa	0	1
Stage IIIc	1	1
Histology		
Adenocarcinoma	10	10
Adenoacanthoma	2	0
Papillary carcinoma	1	0
Adenosquamous carcinoma	0	1
Clear-cell carcinoma	0	1

Table 4. — *Surgical and recovery outcomes.*

Outcome parameters	SM group	CSM group	p value
Estimated blood loss (ml, range)	170 (50-300)	205 (50-400)	NS
Duration of surgery (min.)	139	153	NS
Hospital stay (days, range)	3.2 (3-4)	3.5 (3-7)	NS
Complication total	1	0	
Conversion to laparotomy	1	0	

Discussion

Surgical staging of endometrial cancer is an operative technique recommended by FIGO 1988 [5]. Identification of lymph node metastases is an integral part of surgical staging. The presence of regional lymph node metastases is an important prognostic factor for most solid neoplasms. Complete lymph node dissection is considered the gold standard technique for staging patients. However, this technique is of questionable therapeutic value and is associated with considerable morbidity [6]. In 1990, Morton *et al.* [3] introduced intraoperative lymphatic mapping and sentinel node dissection as an alternative to the complete lymph node dissection in patients with early-stage melanoma. The concept of injecting the blue dye into the genital organ to study lymphatic anatomy is not new. In 1963, Parry-Jones [7] demonstrated that vulvar lymphatics do not cross the labial crural fold by intraoperatively injecting a patent blue and following its uptake into lymphatic channels. After establishing SLND using the blue dye alone in melanoma patients, the technique has been applied to breast cancer and to other tumors such as thryoid cancer, Merkel cell tumors, gastrointestinal cancers and squamous cell carcinoma of the head and neck [8-11].

Dye-directed SLND has recently been reported for gynaecological malignancies [12-16]. In a small study, Medl *et al.* [13] demonstrated that preoperative lymphatic mapping is an easily performed technique to visualize SLND in cervical cancer. O'Boyle *et al.* [14] identified SLND in cervix cancer patients in 60% and concluded that the sentinel LN identification was likely in patients with tumors larger than 4 cm. Also, the number of reports on the use of laparoscopy in cervical cancer remains scant. Two institutions, however, join the few who have done research in this area: Dargent *et al.* [15] in France and Malur *et al.* [17] in Jena, Germany. Dargent *et al.* [16] described a minimally invasive technique to identify the sentinel nodes in patients affected by early-stage cervical cancer and reported that one or more blue-dyed lymph nodes were evidenced in 59 out of 69 sentinel nodes dyed. The rate of failure depends on the quantity of injected dye. In Jena, Germany, Malur *et al.* [17] investigated the validity of SLN detection after radioactive isotope and/or blue dye injection in patients with cervical cancer. The detection rate of SLN was 78%. After the combined injection of radioactively-labeled albumin with the blue dye, the detection rate, sensitivity and negative predictive values were 100%.

A rare pilot study was performed by Burke *et al.* [2] in 1996. The authors explored the possibility of using open intra-abdominal lymphatic mapping as a method to visualize the lymphatic drainage of the uterus. A deposition of isosuflan blue dye into at least one of the lymph nodes was only observed in 67% of cases. In our previous laparoscopic pilot study, we used the identical technique of blue dye application [4]. Contrary to the study of Burke *et al.* [2], we used a different type of dye (patent blue-V) and an application needle with a wider diameter (1.2 mm). We confirmed that the use of a minimally invasive

technique is feasible in patients with endometrical cancer. A deposition of dye into laparoscopically identifiable lymph nodes was seen in 62.5% of cases.

We found in our present comparative study a higher detection rate of patients (83.3%) using a combined cervical and subserosal myometrium application technique than when using the subserosal myometrium application (61.5%) only. The difference between the detection rate was not statistically significant. The value of the DCLN/LN rate and mean number of DCLN are shown in Table 2. There was a significant statistical difference between the compared groups ($p = 0.03$, $p = 0.05$, respectively). The difference in the detection patient rate and statistically significant increased DCLN/LN rate in the compared groups can be influenced not only by the site of application of the blue dye but the amount of applied solution. We also found a statistically significant negative relationship between the total number of removed nodes and the number of collected unstained nodes.

Pelvic sentinel lymph nodes were mostly located in the interiliac area or at the division of the common iliac artery. In the two patients with metastases in the three nodes located in the fossa obturatoria region, only two lymph nodes were contaminated with the dye. It is not entirely clear whether the penetration of dye into other afflicted nodes took place during a metastatic or hyperplastic affliction of a sentinel node.

Lymphatic channels in pelvic areas were observed in every laparoscopically-staged patient. A prominent blue-stained lymph channel to one or more pelvic SLN was identified in 14 patients (identification rate 77.8%). However, we believe that laparoscopically-assisted lymphatic mapping of the uterine corpus can improve the accuracy of surgical staging in patients with uterine malignancy. It is a fundamental question whether the concept of sentinel lymph node dissection proposed by Morton *et al.* [2] can be applied without exception to endometrial cancer. Joosten *et al.* [18] assessed the feasibility of sentinel node biopsy in colorectal cancer. These authors concluded that the concept of lymphatic mapping and sentinel node identification is not valid for colorectal cancer. On the other hand, Esser *et al.* [19] and Wood *et al.* [20] believe that the application of the sentinel lymph node technique to colon cancer may make it easier to identify lymph nodes most likely to contain metastatic disease, potentially "down-staging" more patients.

Future detection of micrometastases in the SLN using molecular biological methods must be performed [17]. Cote and colleagues [21] showed that occult metastases detected by immunohistochemistry have a substantial impact on prognosis and on the indication of the subsequent adjuvant therapy in breast cancer. Bembenek *et al.* [22] found additional occult micrometastases in 7% patients with breast cancer, who had undergone successful sentinel lymph node detection and biopsy. Adding novel techniques such as histopathology ultrastaging, immunohistochemistry staining and reverse transcriptase polymerase chain reaction assays will help increase the accuracy and rate of detection of disease [23].

We suppose, judging from the outcome of our study on women with endometrial cancer, that further extensive prospective studies need to be carried out. It needs to be confirmed whether the described minimally invasive technique or open technique (which we used) and the selected dye and cervico-subserosal myometrium application procedures and sites reflect the true lymphatic drainage of endometrial cancer or whether spreading the blue dye into the pelvic lymphatic stream will make identification and removal of sentinel lymph nodes easier.

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