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Research Article

## Detection of sentinel lymph nodes in patients with endometrial cancer using patent blue injection in the uterine cervix-a study of 58 cases

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**Abstract:** Endometrial cancer is the second most common malignancy in women after breast cancer. The staging of the disease is solely surgical so the information concerning the lymph node status is crucial for the postoperative treatment and prognosis.

**Aim.** The aim of the study was to determine the feasibility of sentinel lymph node detection in patients with endometrial cancer stage I, via injecting patent blue in the uterine cervix.

**Materials and methods.** The study includes 58 patients with endometrial cancer. The technique includes 4 ml of blue dye administered intracervical at two sites-3 and 9 o'clock. After 20 min sentinel lymph nodes were detected.

**Results.** Lymph nodes were detected in 52 patients and in only 6 patients the method was unsuccessful thus leaving the detection rate at 89.65 %

**Conclusion.** This method for detection of sentinel lymph nodes in patients with endometrial cancer is promising, fast and easy to implement, but additional studies must be done for it to become part of the standard for surgical treatment of endometrial cancer.

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**Key words:** endometrial cancer, sentinel lymph node, patent blue.

### INTRODUCTION:

Endometrial cancer is the second most common malignant disease in women after breast cancer. It is usually diagnosed in women between the ages of 60-65 but in one third of all cases patients are younger. The staging of this neoplasm is surgical and the radical removal of the pelvic lymph nodes is crucial because of this. The status of regional lymph nodes is the most important prognostic factor for patients with endometrial cancer and it determines the need of postoperative treatment.<sup>1</sup>

According to the FIGO stage I the risk of LNM occurrence is 10-12% and the risk for para-aortic LNM is 4-6%.<sup>2</sup> The LN dissection could be either selective or total- for example selective LN dissection is performed in Europe, whereas in the USA the method of choice is total LN dissection. Because of this the idea of sentinel LN biopsy is so convenient. The first report about SLN detection was done by Burke et al in 1996.<sup>3</sup>

**AIM:** The aim of the study was to determine the feasibility of sentinel lymph node detection in patients with endometrial cancer stage I, via injecting patent blue in the uterine cervix.

### MATERIALS AND METHODS:

58 patients were included in this study for the period September 2014-august 2016 (23 months). Criteria for inclusion were stage I endometrial cancer and informed

concern of the patients. Criteria for exclusion were medical history for allergies (patent blue V could lead to various allergic reactions), previous surgery that could change the uterine lymphatic drainage and patient refusal. After the induction of anesthesia the color agent was injected intracervical with 25 gauge spinal needle at 3 and 9 o'clock positions (2 ml per injection). The SLN are detected after 20 minutes and total LN dissection is performed by an open (28 cases) or robotic (30 cases) approach. We inspected the pelvic and paraaortic regions for colored LNs and lymph channels. Dissection of all blue colored LNs and LNs connected to blue colored lymph channels was made. We recorded the position of all SLNs to the major pelvic vessels. We did not find any SLNs in the para-aortic region. Total hysterectomy with different type of LN dissection was performed on all patients. The risk of LN metastasis is determined from the preoperative clinical data and the intraoperative findings. According to this system either total or selective LN dissection was done.

### RESULTS

58 patients with endometrial cancer stage I were treated in our clinic. 28 patients were treated by open approach with success rate 100%. 30 patients were treated by robotic approach, 6 of which were unsuccessful (success rate 80%). Demographic

characteristics of the studied population are presented in

table 1: Patients' demographic characteristics

Characteristics	Open approach	Robotic approach
Age (years)	64.28 (49-76)	59.2 (36-76)
BMI	30.3	36.2
Preoperative histology		
endometrioid	23 (82.14%)	30 (100%)
non-endometrioid	5(17.86%)	0 (0%)

visualization of SLN was not possible in 6 cases. All 6 cases were operated by robotic surgical approach. The detection rate was 100% for the open approach and 80% for the robotic approach. The detection rate in the right and left hemipelvis was the same for the robotic approach and 100% and 96.3% for the open approach-there was one patient with undetected SLN in the left hemipelvis. For the 6 unsuccessful cases the SLN was not detected on both sides. There was no detection of para-aortic SLNs in any of the cases. All of the dissected LNs are from the pelvic area. Table 2 shows the number of all removed LNs as well as the number of removed SLNs (the total number and separately for the left and right hemipelvis, respectively).

Table 2-number removed lymph nodes

Number of removed LN	Open approach	Robotic approach
All lymph nodes		
Total (median)	364 (13)	97 (3.28)
In left hemipelvis (median)	208 (7.42)	52 (1.73)
In right hemipelvis (median)	156(5.58)	45 (1.5)
Sentinel lymph nodes		
Total (median)	78 (2.78)	54 (1.8)
In left hemipelvis (median)	38 (1.36)	27 (0.9)
In right hemipelvis (median)	40 (1.42)	27 (0.9)

There are four cases with metastatic SLN detection with further metastatic LNs for the open approach. For the robotic approach there is one case with metastatic SLN detection with further metastatic LNs.

In two cases- one from each group- the metastatic SLNs were detected from both sides and the following non SLNs were also metastatic. In one case from the open approach there were metastatic SLNs from both sides but the metastatic non SLN were only from the right side. The forth case is with metastatic SLNs only from the right hemipelvis and with no metastatic SLNs from either side. In all other 48 cases neither the SLNs,

nor the non SLNs were non-metastatic from both sides. After the histological results, the patients were grouped by the following criteria: grading, myometrial invasion (MI) and tumor diameter (TD)-figure 4

Table 3-Classification of patients by histopathological results

Histopathological features	Open approach	Robotic approach
Grading-n (%)		
G1	11 (39.3%)	20 (66.7%)
G2	10(35.7%)	7(23.3%)
G3	7 (25%)	3(10%)
MI-n (%)		
<50%	18 (66.7%)	19 (63.3%)
>50%	9 (33.3%)	11 (36.7%)
TD-n (%)		
<2 cm	8 (29.6%)	16 (53.3%)
>2 cm	19 (70.4%)	14 (46.7%)

One patient had preoperative histologic diagnosis - endometrial cancer in polyp. After the open surgery the final specimen was clear of any malignant process-thus lowering the number of cases with MI and TD to 27.

As a result of the histological findings (type of cancer, grading, MI, TD)- the risk for LN metastasis was divided in three groups according to ESMO 2013 criteria : 1. Low risk- 1A G1-2 , endometrioid cancer; 2. Intermediate risk- 1A, G3 endometrioid cancer; 1B G1-2 endometrioid cancer; 3. High risk-1B G3 endometrioid cancer and all non-endometrioid types.

The results are shown in Table 5

Table 4-Risk of LN metastasis

Risk of LN metastasis	Open approach	Robotic approach
Low-n (%)	14 (59%)	18 (60%)
Intermediate -n (%)	8 (28.6%)	10 (33.3%)
High -n (%)	6 (21.4%)	2 (6.7%)

Most of the patients are in the low risk group, followed by intermediate risk group.

## DISCUSSION

SLN detection in endometrial carcinoma is not a standard procedure, as it is in the melanoma, breast and vulvar cancer. The method has developed by many authors for the needs of endometrial localization since 1996. As a result several injection sites and localisations (subserosal endometrium,

endocervical and in the endometrium-nearby the tumor via hysteroscopy) were exploited, as well as the single or combined application of blue dye and radiocolloid. The different teams of researchers reported detection rate 45-94% and false negative rates 0.33% (4) The success rate improves when it is done by more experienced researchers. Unlike the SLN biopsy in melanoma and breast cancer, there is no standard rate for the number of removed SLN in endometrial cancer. Selman et al (5) reported that SLN biopsy technique is more accurate than MRI and CT scan. This conclusion is made after a meta-analysis of various techniques that assess LN status in endometrial cancer.

Six of the cases (10.34%) were unsuccessful. All of them were in the group of the robotic approach. This could be due to the lack of experience because all six unsuccessful operations were done in the beginning of this study. The results of our study suggest that SLN biopsy by use of cervical injection of patent blue V could take place between systemic lymphnodectomy and no dissection at all in patients with low and intermediate risk for endometrial cancer. Our results are in accordance with the previous publications, concerning this topic-detection rate 83-84%. (6, 7) The cervical injection of radiocolloid improves the success rate, as cited in literature-91-100% (8, 9). Some authors suggest the injection of patent blue V in the subserosal myometrium because of the direct drainage of the uterine fundus via the gonadal vessels. (3) The risk of para-aortic LNM is very low in first stage endometrial cancer. (3) We used cervical injection of patent blue V because it is an easy method to learn and we had previous experience in detection SLN in patients with cervical cancer. In this research no false negative cases were found, sensitivity and negative predictive value (NPV) were 100%. Metastatic LNs were diagnosed in 7.7% (n=4) of all cases. Two cases were from the high risk group and two from the intermediate risk group.

Our results propose that SLN biopsy alone can diagnose LN metastasis in patients with first stage endometrial cancer. The need of adjuvant therapy in low and intermediate risk patients can be decided later according to the results of SLN biopsy. The patients from the high risk group should undergo systematic lymphnodectomy and further therapy in any case. (10) The main benefit of SLN concept in patients with first stage endometrial cancer is to avoid the risk of morbidity in surgical staging. The method provides the LNs needed for the LN status and the histological diagnosis.

All SLNs were examined histologically and with immunohistochemistry. This double examination prevents the risk of sporadically missed micro metastasis and isolated tumor cells (ITC). (11) All metastasis in our study were diagnosed histologically. This is the reason we cannot say whether or not the immunohistochemically examination is needed.

The limitations of our study are: 1. Only a small number of patients, especially the ones with non-endometroid cancer were included in this research. 2. Para-aortic LN biopsy is not

a standard procedure according to Bulgarian guideline. 3.The use of this technique (cervical injection of patent blue V alone) might have given lower rate of SLN detection. Because of this some authors prefer to combine the cervical application with subserosal or subendometrial injection of blue dye. (12)

The positive aspects of this study can be summarized as: 1.The method is easy to learn and use. 2. The detection rate is high although it does not mark LNs in the para-aortic area. 3. It is a good alternative for patients who will not benefit from systematic lymphnodectomy, which is associated with increased morbidity. (13-15) 4. The method is a cost-effective way to diagnose ITCs and micro metastasis in endometrial cancer.

**CONCLUSION:** SLN biopsy using cervical injection of patent blue V is a safe method for collecting information about the LN status. It is especially useful for low and intermediate risk patients thus avoiding systematic LN dissection and the following complications. Using this technique lowers the possibility of patients not receiving postoperative treatment when needed.

#### **Reference:**

1. Bogani G, Dowdy S., Cliby W, Ghezzi F, Rossetti D, Mariani A. Role of pelvic and para-aortic lymphadenectomy in endometrial cancer: Current evidence. *J Obstet Gynaecol Res.* 2014 February ; 40(2): 301–311
2. Creasman WT, Morrow CP, Bundy BN et al. Surgical pathologic spread patterns of endometrial cancer (a GOG study). *Cancer* 1987; 60: 2035–2041.
3. Burke TW, Levenback C, Tornos C, Morris M, Wharton JT, Gershenson DM. Intraabdominal lymphatic mapping to direct selective pelvic and paraaortic lymphadenectomy in women with high-risk endometrial cancer:results of a pilot study. *Gynecol Oncol* 1996;62(2):169–73.
4. Altgassen C, Pagenstecher J, Hornung D, Diedrich K, Hornemann A. A new approach to label sentinel nodes in endometrial cancer. *Gynecol Oncol* 2007; 105: 457–61.
5. Selman TJ, Mann CH, Zamora J, Khan KS. A systematic review of tests for lymph node status in primary endometrial cancer. *BMC Womens Health* 2008; 8: 8.
6. Holub Z, Jabor A, Lukac J, Kliment L. Laparoscopic detection of sentinel lymph nodes using blue dye in women with cervical and endometrial cancer. *Med Sci Monit* 2004;10:587-91.
7. Holub Z, Jabor A, Kliment L. Comparison of two procedures for sentinel lymph node detection in patients with endometrial cancer: a pilot study. *Eur J Gynaecol Oncol* 2002;23:53-7.
8. Pelosi E, Arena V, Baudino B, Bello M, Giusti M, Gargiulo T, Palladin D, Bisi G.Pre-operative lymphatic mapping and intra-operative sentinel lymph node detection in early stage endometrial cancer. *Nucl Med Commun* 2003;24:971-5.

9. Gargiulo T, Giusti M, Bottero A, Leo L, Brokaj L, Armellino F, Palladin L. Sentinel lymph node (SLN) laparoscopic assessment early stage in endometrial cancer. *Minerva Ginecol* 2003;55:259-62.
10. Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. *Lancet* 2010; 375: 1165–72.
11. Gonzalez Bosquet J, Keeney GL, Mariani A, Webb MJ, Cliby WA. Cytokeratin staging of resected lymph nodes may improve the sensitivity of surgical staging for endometrial cancer. *GynecolOncol* 2003;91:518-25
12. Delpech Y, Coutant C, Darai E, Barranger E. Sentinel lymph node evaluation in endometrial cancer and the importance of micrometastases. *Surg Oncol* 2008; 17: 237–45.
13. Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet* 2009; 373: 125–36.
14. Benedetti Panici P, Basile S, Maneschi F, et al. Systematic pelvic lymphadenectomy vs no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. *J Natl Cancer Inst* 2008; 100: 1707–16.
15. May K, Bryant A, Dickinson HO, Kehoe S, Morrison J. Lymphadenectomy for the management of endometrial cancer. *Cochrane Database Syst Rev* 2010; 1: CD007585