

# Sentinel Lymph Node Detection by Dye Method in Patients with Cervical Cancer

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**Abstract Objective** To investigate the feasibility of detecting intraoperatively blue sentinel lymph node (BSLN) in patients with cervical cancer and to evaluate the accuracy of predicting pelvic lymph node metastases. **Methods** Between May 2002 and Jun 2003, 29 patients with cervical cancer in FIGO stage Ib (n=3), stage IIa (n=21) and stage IIb (n=5) underwent BSLNs detection. During operation 4 ml of methylene blue was injected into the cervical tissue around the tumor or at 3, 6, 9, and 12 o'clock of normal appearance of cervix for about 0.5 cm deep. Blue lymph vessels and BSLNs were observed and located carefully for 10 minutes. Tumor characteristics, surgical findings, and location and number of BSLNs were recorded and correlated with the pathologic results to get the accuracy and false-negative rate. **Results** Among 29 patients underwent this technique, BSLNs were seen in 24 patients. Total detection rate was 83% (24/29). Location of BSLNs was mainly in obturator and internal iliac region. 11 patients had BSLNs located in left internal iliac region and 13 patients in right internal iliac region, and 10 patients in left obturator region, 14 patients in right obturator region, separately. 3 patients had BSLNs in both common iliac and internal iliac region. Among 24 patients with BSLNs, there were 6 patients with lymph node metastases. 5 patients had only SLN metastases and 1 patient had both SLN and other lymph node metastases. 18 patients had neither SLNs nor other pelvic lymph nodes metastases. The false-negative rate was 0. **Conclusions** Intraoperatively BSLN detection was feasible and safe. Sentinel lymph node can predict the status of pelvic lymph node accurately.

**Key Words** Radical hysterectomy; blue sentinel lymph node(BSLN); dye method

Since Wertheim first performed radical abdominal hysterectomy in 1898, radical hysterectomy and pelvic lymph node dissection has become the routine surgery for patients with cervical cancer in stage Ib and IIa<sup>[1]</sup>. The status of pelvic lymph nodes is an important factor influencing prognosis and determining the necessity of adjuvant treatment. It had been reported that the rate of lymph node metastases in stage Ib and IIa cervical cancer was 19.3% and 26%, respectively<sup>[2]</sup>, that is to say, over 70% patients were free of lymph nodes metastases. In addition, pelvic lymphadenectomy may cause many complications, such as the traumas of vessels and nerves and lymphoid cyst etc. Therefore, the routine lymph node dissection has been questioned by some scholars<sup>[3,4]</sup>. Since there is no accurate technique to assess the pelvic lymph node metastases up to now, the concept of sentinel

lymph node (SLN)<sup>[5,6]</sup> is introduced into cervical cancer. In breast cancer, the accuracy of predicting the axillary lymph node involvement by SLNs biopsy was 95%~98%<sup>[7,8]</sup>. Since May 2002, we conducted the research of SLN detection and localization using blue dye in cervical cancer.

## MATERIAL AND METHODS

### Patient Selection

There were two different stages in the research. In the first stage (from May 2002 to Jan 2003), Patients who were to undergo a radical abdominal hysterectomy and pelvic lymph node dissection in our surgery group were asked to participate in our trial. In the second stage (since Feb 2003), the procedure was abandoned in those who were found enlarged and fixed lymph node during operation and had lymph node involvement confirmed by frozen section.

### Clinicopathologic Characters

Altogether 29 patients with cervical cancer un-

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derwent intraoperatively SLNs detection by dye method. 3 cases were in FIGO stage I b, 21 cases in stage II a and 5 cases in stage II b. The median age was 45 years old (ranged 28~67 years old). The diameter of cervical tumor was  $\geq 4$  cm in 21 cases and  $< 4$  cm in 8 cases. 20 patients had intervening treatment or afterloading radiation before the operation, while 9 patients had no pre-operative treatment. The histological type was squamous carcinoma in 28 cases and adenocarcinoma in 1 case.

### Technique

At the time of surgery, patients were placed in the lithotomy position. Laparotomy was performed using a vertical incision. After thorough exploration, the bowel loops were cleared from the pelvis and retracted into the upper abdomen. Then vesicoperitoneal fold and the anterior leaf of bilateral broad ligaments were opened. A large speculum was placed in the vagina and 4 ml 1% Methylene was injected into the cervical stroma around the cervical cancer at 2~3 locations or into the normal-appearing cervical tissues at 3, 6, 9, and 12 o'clock. The pelvis was examined carefully and once dye uptake was observed in parametrial lymphatic channels, obturator, internal and external iliac, inguinal and common iliac nodal regions were carefully inspected for blue-stained lymph nodes. Up to 10 minutes was allowed for inspection. The lymph node with obvious dye uptake was designated the "blue sentinel lymph node (BSLN)". The location and number of BSLNs were recorded on the research diagram. Then routine pelvic lymphadenectomy and radical hysterectomy was performed. BSLNs and other specimens were sent for pathological examination separately. After the operation, high risk factors were found in 9 cases. 3 cases had only pelvic radiation and 6 cases both chemotherapy and radiotherapy postoperatively.

### Judgment of results

Detection failure was defined as no BSLN being found during the operation, which includes minimal or no dye uptake by inadequate injection of dye, or with visible dye uptake but no apparent blue sentinel node. By co-analysis of surgical finding and post-operation pathology, false-negative was defined as the case in which all SLNs were free of metastases while non-SLNs in the same basin were involved.

### Statistical Analysis

Data were analyzed by  $\chi^2$  test.

## RESULTS

### Location and Number of BSLNs

Dye was observed in lymphatic channels within 5 minutes after dye injection. 27 out of 29 cases were observed blue-containing lymphatic vessels in a linear or bifurcate way within 5 minutes, and 24 cases were observed blue-stained lymph nodes in the basin within 10 minutes after dye injection (Fig.1, 2). BSLNs were most commonly located in

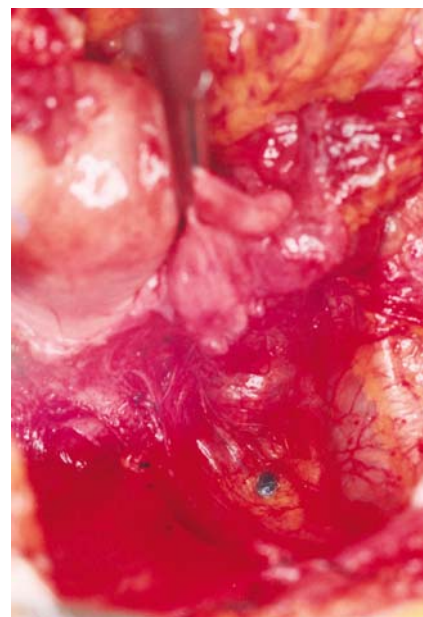


Fig1. Blue stained left internal iliac lymph node

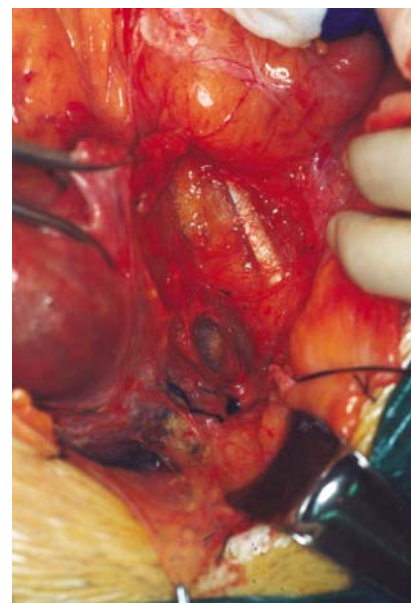


Fig2. Blue stained left obturator lymph node

obturator and internal iliac nodal region. There are 14 cases in the right obturator region, 10 in left obturator region, 13 in right internal iliac region, and 11 in the left internal iliac region, respectively. 3 cases (1 on the left and 2 on the right) were observed BSLNs in the common iliac region.

### Detection rate of SLNs

The total detection rate of SLNs in our research was 83% (24/29) with the different detection rate in the first and second stages. In the first stage, the detection rate was 78% (14/18) because of detection failure in 2 cases with enlarged and fixed pelvic lymph nodes and confirmed lymph node metastases by frozen section and 2 cases for inappropriate injection. In the second stage, the detection rate was 91% (10/11) which was higher than before because the procedure was abandoned in those who were found enlarged and fixed lymph node during operation and had lymph node involvement confirmed by frozen section.

### Coincidence of SLNs detection and Pathologic examination

Eight out of 29 cases (27.7%) were found lymph node metastases histologically, in which 5 had only SLNs involvement, 1 had both SLN and non-SLN involvement, and 2 had no SLN identified. 18 cases who had no SLN involvement were also free of pelvic lymph node metastases. Therefore, in 24 successfully detected cases, all SLNs had predicted the status of pelvic lymph nodes correctly. There was no patient with pelvic lymph node involvement when SLNs detection was negative. The false-negative rate was zero.

### The size of cervical tumor and the detection rate of SLNs

In the 8 cases with the diameter of cervical tumor < 4 cm, SLNs were successfully detected in 7 cases with the detection rate of 87%. While in the 21 cases with the diameter of cervical tumor  $\geq$  4 cm, SLNs were failed to be detected in 4 cases with the detection rate of 81%. Therefore, the detection rate was lower in those whose tumor diameter was  $\geq$  4 cm.

### Adverse Effect

Apart from blue urine for 24 hours after operation, no other adverse reactions and complications due to the procedure were observed. All operations

were performed by the same group of surgeons. The time of operation was longer for 10~15 minutes in the research group than those without this procedure, while the blood loss was almost the same.

## DISCUSSION

Lymphatic mapping and SLNs detection can be used to predict the status of lymph nodes intraoperatively in many kinds of tumors. For example, the SLNs detection has already been widely applied in cutaneous melanoma and breast cancer, which can predict the lymph node metastases at the accuracy of 95%~98%. And the complications were reduced<sup>[7,8]</sup> by allowing omission of the local lymphadenectomy in the patients with negative SLNs. It has been reported that the detection rate is related with operator skill, the drainage pattern of tumor lymphatic vessels, and the accessibility of SLNs. Lymphatic mapping and SLNs detection in patients with cervical cancer undergoing radical hysterectomy is a brand-new topic in china with no report on it till now. In our study, we intended to explore the feasibility of this technique and to evaluate the accuracy of predicting pelvic lymph node metastases.

Over the course of this study, we found that opening the abdominal cavity and retroperitoneum before dye injection is very important. In the first stage of our study, 2 cases were failed to be detected because the time of dye injection was too earlier. From the 3rd case, all 25 cases had dye uptake in the lymphatic vessels. 5~10 minutes window from dye injection, which is absorbed into the lymphatic capillaries and then passes through the cervical lymphatics to the pelvic lymph nodes. Therefore, opening the retroperitoneum before the dye injection is helpful for observing lymphatic mapping and SLNs detection.

The total detection rate in our study is 83% (24/29), which is similar to the report by dargent et al. (89%, 35 cases)<sup>[9]</sup>. They performed SLNs detection via laparoscopy by injecting Patent blue into the cervical tissues, and the predictive accuracy was 100%. In our research, the detection rate was different in the first and second stages with a higher detection rate in the second stage (91%), and in the first stage it was 78%, which may be due to patient selection and technique factors. In the second stage, firstly, the procedure was abandoned in

those who were found enlarged and fixed lymph node during operation and had lymph node involvement confirmed by frozen section; secondly, the technique of SLNs detection need to be learned and practiced. At the beginning of the research, 2 cases lost the opportunity to be found BSLNs because of too early dye injection. Besides that, the size of cervical tumor is also a factor which can influence the SLNs detection. In our research, the detection rate was lower in those whose tumor diameter was  $\geq 4$  cm than those whose tumor diameter was  $< 4$  cm., which is similar to what O'boyle et al<sup>[10]</sup> reported. In the cases with large size tumor, O'boyle reported that the detection rate might be elevated by using a Potocky needle which is used for parametrial nerve block. And it had also been reported that the dose of tracer should be increased in such cases. In our study, 4 ml Methlene was injected in each case. But it was difficult to estimate the actual amount of infiltrated dye because of dye spilling from the injection point or from the pelvic peritoneal side. 2 out of 4 detection failure cases were due to larger tumor size or less amount of injected dye. It is been suggested that the tumor diameter  $\geq 4$  cm should also be a exclusive criteria. But we think more cases needed to draw this conclusion. To avoid the dye spillage from the injection point, care must be taken to control the depth of needle penetration within 0.5 cm. Then the injection site should be pressed for 5~10 minutes to elevate the detection rate.

In our study, 14 cases BSLNs were located in the right obturator region, 10 in left obturator region, 13 in right internal iliac region, and 11 in the left internal iliac region, respectively. 3 cases were observed BSLNs in the common iliac region and internal iliac region at the same time. The result was correlated with the character of lymphatic metastases in cervical cancer. In as early as 60's in 20th century, Henrikson had classified the lymph nodes in cervical cancer metastases into two groups. Parametrial, obturator, internal and external iliac lymph nodes belong to the first group, and common iliac, presacral and inguinal lymph nodes belong to the second group. In our study, most BSLNs were the first group lymph nodes. Only 3

cases had common iliac nodes positive besides the first group nodes, which may be due to jumping or multiple lymphatic pathway. BSLNs in 24 cases were all located in the internal iliac and obturator nodal region, and the parametrial nodes were failed to be detected because of tissue dye staining.

In our research, apart from blue urine for 24 hours after operation, no other adverse reactions and complications due to the procedure were observed. Therefore, the technique of SLNs detection in cervical cancer is safe and feasible.

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