Clinical analysis of sentinel lymph node identification in patients with cervical cancer

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Summary

Objective: To study the accuracy and feasibility of identifying sentinel lymph nodes (SLN) using methylene blue dye in patients with cervical cancer. *Materials and Methods:* Fifty-six cases with early-stage cervical cancer patients were studied using methylene blue injection into the cervix 90~120 minutes before abdominal pelvic lymph node dissection and extensive hysterectomy. The lymph nodes that resulted from staining were removed and pathohistology was performed. *Results:* A total of 106 SLN were identified in 49 patients (49/56). The detection rate of SLN was 87.5%. Sensitivity of the SLN was 90.91%, and specificity of the sentinel lymph nodes was 86.67%. Eleven patients (19.64%) were diagnosed with lymph node metastases and ten of them were in the group of SLN. Eight patients had positive SLN only. Two patients had both positive SLN and pelvic lymph nodes. None of the patients had positive pelvic lymph nodes and negative SLN. *Conclusion:* The use of methylene blue injection for cervical cancer SLN biopsy has a higher detection rate of SLN. SLN detection can accurately predict the pathological status of pelvic lymph nodes in patients with cervical cancer.

Key words: Endometrial cancer; Brachytherapy; Radiotherapy; Toxicity.

Introduction

Cervical cancer is the most common gynecologic malignant tumor. The incidence is second in women with a malignant tumor, that is, after breast cancer [1]. There are about 500,000 new cases in the world each year, approximately 85% concentrated in developing countries [2]. Cervical cancer metastasis occurs through the lymph nodes. Since abdominal radical hysterectomy was first carried out by Wertheim in 1898, pelvic lymph node dissection has been an indispensable part of the surgical treatment of cervical cancer. Pelvic lymph node metastasis is an important factor affecting the cervical cancer prognosis, which is also an important basis for follow-up treatment after surgery. The pelvic lymph node metastasis rate of cervical cancer is 0~4.8% in Stage IA, 0~17% in Stage IB, 12~27% in Stage II A, and 25~39% in Stage II B [3-5]. If detection and evaluation of pelvic lymph node metastasis state can be achieved, pelvic lymph node negative patients do not require a wide range of pelvic lymph node dissection to reduce the chance of trauma and postoperative complications. It is extremely necessary to improve the quality of life of patients, that is, to retain reproductive function in women of childbearing age. Personalized treatment programs for cervical cancer enable unnecessary overtreatment. It is also the purpose of this study: to improve the quality of life of patients.

Sentinel lymph node (SLN) is the first lymph node which is affected by primary tumor metastasis. SLN is an effective screening method for cancer metastasis prevention [6]. In theory, if the lymph node is negative, this signifies that other lymph nodes will also have no metastasis. Cervical cancer metastasis pathway is based in lymph node, and it is suitable for the introduction of the SLN detection method because of pelvic lymph drainage with certain regularity. SLN biopsy was first used in cervical cancer research by Echt *et al.* in 1999 [7]. It is expected to improve the reproductive function and hence the quality of life of the patients because it more accurately predicts the pelvic lymph node involvment [8]. SLN is the first to most likely be affected by metastasis. It has a higher grade of precision and low false negative rate and can accurately predict early cervical cancer patients with pelvic lymph node involvement. Therefore, lymph node dissection can be prevented. This research uses methylene blue dye as tracer and the present authors analyzed the pathological result of non-sentinel lymph node (NSLN) and SLN. To study the accuracy and feasibility for SLN treatment for cervical cancer, the authors needed to achieve a base for individualized treatment for cervical cancer.

Materials and Methods

Patients

Between June 2009 and December 2010, 56 patients with FIGO Stage IA2-IIA cervical cancer were scheduled to undergo fertility-sparing surgery at the Affiliated Hospital in Ningxia Medical University and Institute participated in this study. All patients underwent radical hysterectomy and total pelvic lymphadenectomy. This study was conducted in accordance with the Declaration of Helsinki. This study was also conducted with approval from the Ethics Committee of Affiliated Hospital of Ningxia Medical University. Written informed consent was obtained from all participants. The median age was 45.5 years (range 23 to 67). All patients in this study had no surgical contraindication, without severe disease, and no obstetric complica-

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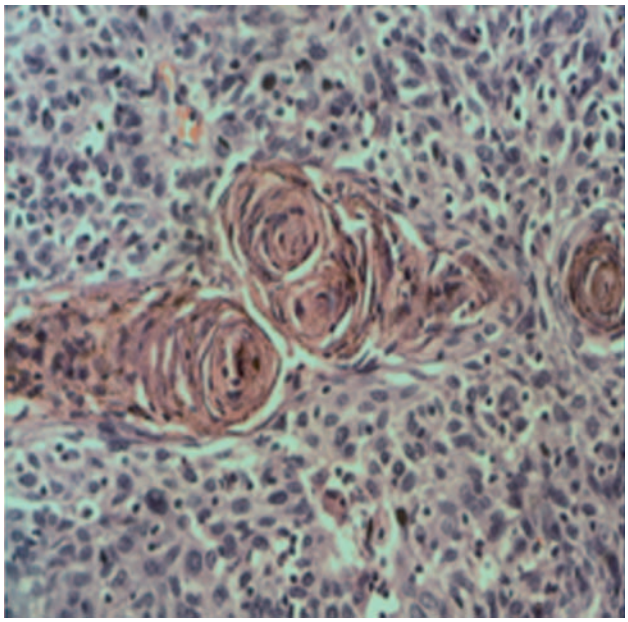

Figure 1. — Successful detection of SLN.

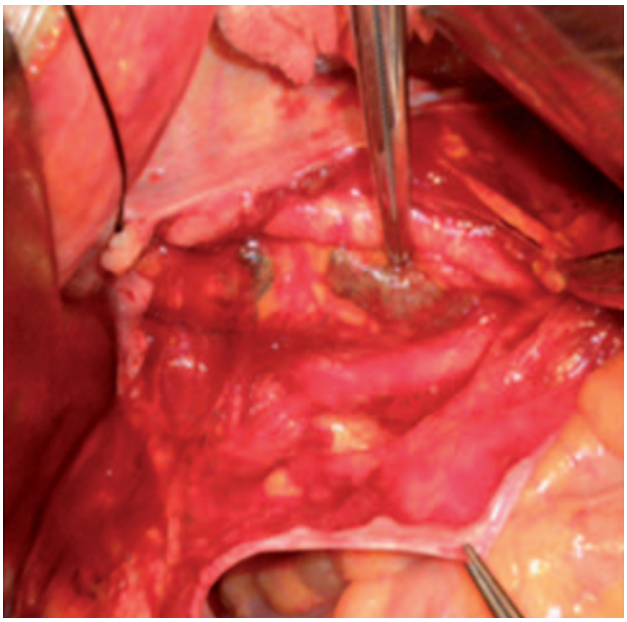

Figure 2. — Cervical cancer (HE x200).

tions. All patients had previous biopsy and histology with no neoadjuvant radio-chemotherapy. Iconographical examinations and physical examinations before surgery showed no lymph node intumescence and the patients had no cancer histories in other system and organs. The criteria for staging included FIGO 2008 classification; of the 56 patients, six were in Stage IA2, 24 in Stage IB, and 26 in Stage IIA. Histological assessment confirmed that 50 patients had squamous cell carcinoma, five had adenocarcinoma, and one had other type. Fourteen patients were well-differentiated, 18 were moderately-differentiated, and 16 were poorly-differentiated.

SLN injection

SLNs were detected with an isotope injection technique into the uterine cervix. On surgery day 90~120 minutes postoperatively, the authors injected fluid containing two ml (20 mg) of methylene blue into four quadrants (three, six, nine, and 12 o'-clock positions) of the cervix, each quadrants one ml, and total was four ml. The diameter of particle ranged from five mm. The SLNs were identified by methylene blue staining during surgery. The authors then sent all of the lymph nodes and other tissues to biopsy after the surgery to confirm whether there was cancer metastasis or not (Figure 1). Through scanning the pelvic sidewall, presacral area, and para-aortic lymph node area, hypercaptive nodes were detected on the basis of counts that were more than ten-fold above background level, and were defined as SLNs. Then the SLNs were excised with safety margins and submitted to fast frozen section. The radioactivity of the tissue was measured in vivo and after excision; as well, the radioactivity of the surgical bed was also analyzed to confirm whether the marked lesion had been fully excised. After removal of the SLNs, bilateral pelvic lymphadenectomy was routinely performed.

Criteria standard

According to the SLN criteria standard [9], the state of the SLN was judged with the naked eye by the surgeons. SLN showing blue staining was defined as successful and SLN that remained unstained was considered as failure.

Relevance ratio indicated SLN positive cases/total cases *100%. Sensitive ratio indicated SLN positive cases/pelvic lymph nodes positive cases *100%. Accurate ratio indicated [(SLN positive cases + SLN negative ratios)] /SLN identification cases *100%. Specificity ratio indicated SLN negative cases/non lymph nodes metastasis cases *100%. False negative ratio indicated: false negative cases/ pelvic lymph nodes metastatic cases *100%. Predictive value of negative indicated: SLN negative patients had non-pelvic lymph nodes metastasis cases / SLN negative cases *100%.

Statistical analysis

Multiplicity was compared with unconditioned logistic regression analysis. Statistical significance was defined at a level of $p < 0.05$. All analyses were performed using SPSS version 13.0.

Results

Detected ratio of SLN

A total of 1,052 lymph nodes were detected as SLNs in 49 of 56 patients (Figure 2) and the relevance rate was 87.5% (49/56). A total of 106 SLN were cut (10.08% in total: 106 / 1,052). The number of SLNs identified per patient was one in 15 cases (30.61%), two in 19 cases (38.78%), three in eight cases (16.32%), and four in seven cases (14.29%). The number of SLNs identified per patient was six in six Stage IA2 cases (100%), 22 in 24 Stage IB cases (91.67%), and 21 in 26 Stage IIA cases (80.77%).

Pathological result of detected SLNs

Eleven cases had pelvic lymph node metastasis in total 56 cases: the transfer ratio was 19.64% (11/56), 15 SLN had cancer cells metastasis in a total of 28 (53.57%), and NSLN in 13 cases in total 28 (46.43%). Ten had cancer cell metastasis in 49 SLN identified as successful cases, which is

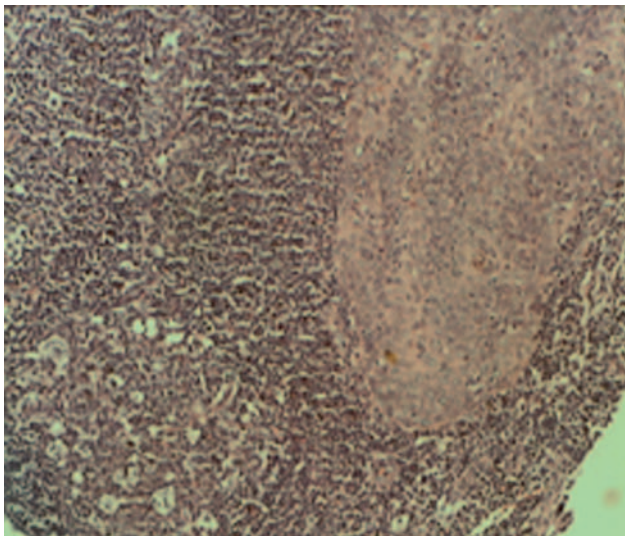

Figure 3. — SLN (HE negative x100).

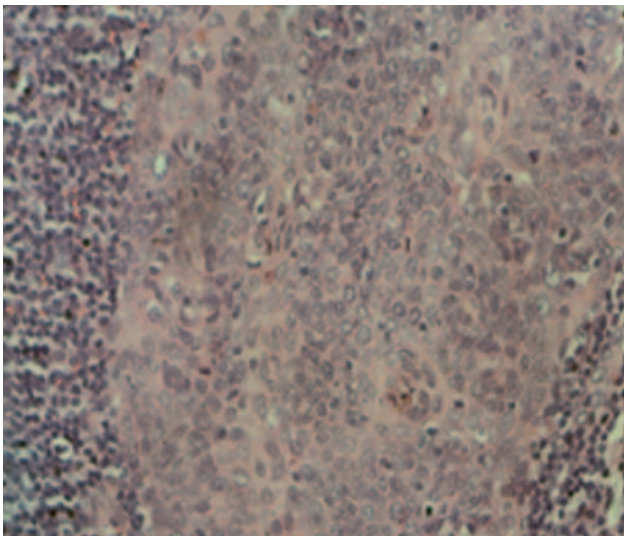

Figure 4. — SLN (HE negative x200).

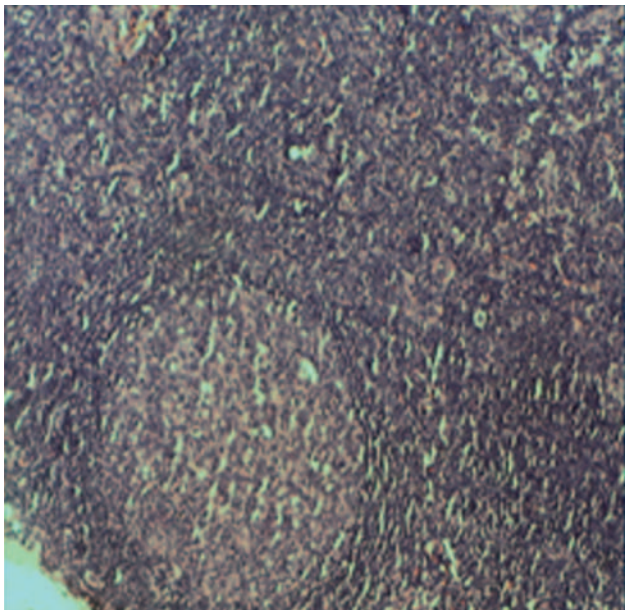

Figure 5. — SLE (HE positive x100).

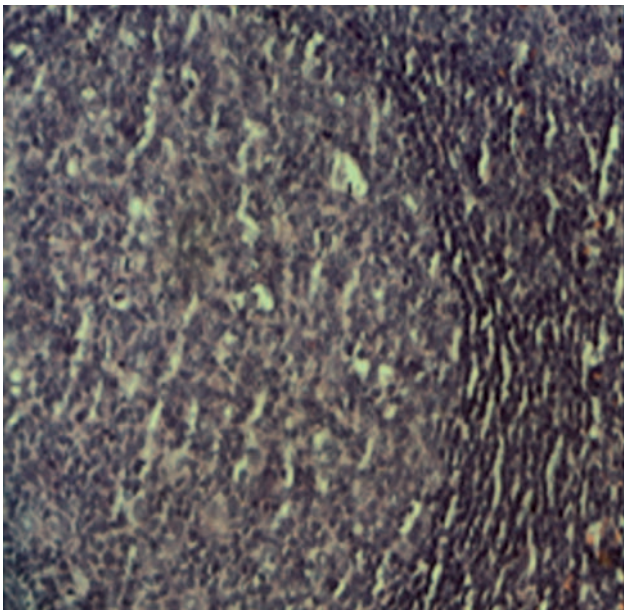

Figure 6. — (SLN HE positive x200).

shown in Figures 3 and 4. The metastasis ratio was 20.41%. One cancer cell metastatic case failed in SLN identification. No cases of SLN negative and NSLN positive (false negative cases) resulted, as shown in Figures 5 and 6. Both SLN and NSLN were negative in 39 cases. According to the aforementioned criteria standard, sensitive ratio was 90.91 (10/11), specificity ratio was 86.67% (39/45), accurate ratio was 100% (49/49), false ratio was 0, and predictive value of negativity was 100% (39/39).

Distribution of SLN

Eighteen unilateral SLNs were detected in 49 SLN detected successful cases (36.73%) and 31 bilateral SLNs were detected (63.27%). The distribution of 106 SLNs is shown in Table 1. The distribution of 15 positive SLNs is shown in Table 2. As shown in Table 1, SLN was concentrated on obturator, external iliac, and internal iliac; the detected rate was 92.45% in total (98/106).

As shown in Table 2, positive SLNs were concentrated on the obturator and occupied more than 50%.

The influential factor of SLN detected ratio

The study took into consideration the age of the patients, the diameter of the tumor, the clinical stage, and the detected ratio to formulate an unconditioned logistic regression analysis. The results showed that the ratio was

Table 1. — *The distribution of 106 SLNs.*

The distribution of SLN	No. of patients	No. of cases with SLNs detected (%)
Obturator	42	39.62
External illiac	30	28.30
Internal illiac	26	24.53
Deep inquinal lymph nodes	5	4.72
Common illiac	3	2.83
Total	106	100.00

Table 2. — *The distribution of 15 positive SLNs.*

The distribution of 15 positive SLNs	No. of patients	No. of cases with positive SLNs detected (%)
Obturator	8	53.33
External illiac	4	26.67
Internal illiac	2	13.33
Common illiac	1	6.67
Deep inquinal lymph nodes	0	0.00
Total	15	100.00

Table 3. — *An unconditioned logistic regression analysis of SLN detected ration.*

Character	β	SE	Wald	Sig	OR
Age	0.570	0.681	0.701	0.403	1.768
The diameter of tumor	1.882	1.229	2.345	0.126	6.565
Clinical stage	1.975	1.122	3.101	0.078	7.210

independent from the age of the patients, from the diameter of the tumor, from the clinical stage, and from the detected ratio; the difference had no statistical significance ($p > 0.05$, Table 3).

Discussion

Cervical cancer is the most common gynecologic malignant tumor and it is the first female malignant tumor in China [10]. It tends to occur at a younger age and is a serious threat to women's health and lives in recent years. The main route of metastasis is via the pelvic lymph node, and lymph node metastasis is also the key factor that influences treatment and cure. Therefore, it is very important to assess the accuracy of treatment in order to determine whether the lymph nodes are metastasizing or not. Currently, the standard treatment of cervical cancer is generally still hysterectomy and bilateral pelvic lymphadenectomy. There is no tumor metastasis of the conventional resection of pelvic lymph nodes in the vast majority during surgery. Excessive pelvic lymph node dissection has not only failed to be beneficial to patients, but will also cause them unnecessary vice damage, such as urinary retention, lymph cyst, peripheral vascular nerve damage, pelvic adhesion, infections, immunity problems, etc. Therefore the present authors adopted an individual treatment that prevented over-treatment, which is an area of great concern when studying cervical cancer. SLN detection can assist to further study the treatment of cervical cancer.

SLN detection rate

As early as the 1990s, the study of SLN detection began, and the ratio was only 15% [7]. Along with the developed skills, the ratio was improved. The studies in recent days showed that the ratio was nearly 100% [11]. There is a varying detection rate according to different testing methods. Cervical cancer SLN detection rate is 62.5% ~ 87% with the dye method [12], the detection rate is 70% ~ 100% with the nuclide method [13], and the detection rate is 88.8% ~ 100% with the joint method [11, 14]. Different detection methods with detection rate differences may be associated with the surgeon's technological experience. Dargent *et al.* used methylene blue as a tracer, completed the laparoscopic lymphadenectomy, and achieved 89% SLN detection ratio [15]. Di Stefano *et al.* used methylene blue as a tracer to study 50 cases, and achieved a 90% SLN detection ratio [16]. In their study, 49 cases were successfully detected and the ratio was 87.5% (49/56). One hundred six SLNs were detected in total and 2.16 on average; this is in accordance with the present report. Therefore, the present authors believe that methylene blue used as a tracer in SLN detection is reliable.

Accuracy and false-negative rate of SLN

The accurate ratio and the false negative ratio of SLN are the important index to predict whether the tumor has metastasized or not and false negative ratio is the key to accurately predict SLN. False negative results can lead to mistaken results and therefore lead to incorrect treatments. Cervical cancer SLN biopsy accuracy and false-negative rate reported in the literature are not consistent; the false-negative rate is between 0% to 25%. There are five summaries of the reason [17]: 1) technical proficiency of the operator, including the surgeon, cannot adequately identify and remove all of the SLNs; 2) the later tumor metastatic tumor thrombus blocking nor diverting lymphatic drainage which does not recognize the true SLN; 3) there is about one percent of the lymph node metastasis jumping; 4) there is error and omission micrometastases in SLN biopsy; 5) detecting the number of cases is too small. Malur *et al.* [18] reported 50 cases SLN predictive value of negative was 97.1%, and sensitive ratio was 83.3%. Niikura *et al.* [19] reported 295 cases; the detected ratio of SLN was 85%, sensitive ratio was 93%, and predictive value of negative ratio was 99%. This study showed the sensitive ratio was 90.91 (10/11), specificity ratio was 86.67% (39/45), accurate ratio was 100% (49/49), false ratio was 0, and predictive value of negative was 100% (39/39). The results suggest that SLNs and pelvic lymph node metastasis are consistent.

The distribution of the sentinel lymph node

In 1971, Plentl, Friendman [20] formulated the cervical cancer of the lymphatic drainage system description. It is interstitium → subserosal lymphatic → parametrial lymph nodes in the cervical → obturator → internal iliac and common iliac lymph nodes outside → perirectal lymph nodes → abdominal aortic lymph node. In this lymphatic drainage pathway, is not difficult to see that parametrial lymph nodes should be the first to arrive at the lymph nodes of the cervical lymph circulation. The transfer rate reached up to 30% in some reports [21]; however most of the local literature home and abroad is not found parametrial the SLN or very low recognition rate. The reason may be due that cervical cancer SLN identification method is injection of tracer from the cervical part of parametrial lymph nodes which is the closest to the cervical tissue, while parametrial lymph nodes smaller tracer injection cause the entire cervical blue dye. This will affect the recognition of parametrial SLN. In addition, during surgery, the parametrial lymph nodes are removed with extensive hysterectomy. This is easily ignored by both pathologists and clinicians. No parametrial SLN was found in this study.

Foreign literature reports that the most cervical cancer SLN identification occurs in iliac external lymph nodes. SLN is identified in methylene blue tracer method by Di Stefano *et al.* [16], 50 cases of patients with cervical cancer early detection SLN of the communist party of 86, which accounts for 55% of them located in the iliac outer area and the obturator foramen area in 38%. In this study, 106 SLNs were detected in a total of 56 patients. The most common site for SLN detection was the obturator (42SLNs), detected in 39.62% (42/106); followed by the external iliac (30SLNs), detected in 28.30% (30/106); the internal iliac (26SLNs) in 24.53% (26/106); inguinal deep five, accounted for 4.72%, and the common iliac (3SLNs) in 2.83% (3/106). There were 15 positive SLNs in total, eight were in the obturator fossa, accounting for 53.33%, four were in iliaca extenal region, accounting for 26.67%, two were in iliaca internal region, accounting for 13.33%, one was in iliac area, accounting for 6.67%; obturator, external iliac, and internal iliac together were 92.45, and this is in accordance with Kushner *et al.* [22], who reported that these three areas can evaluate more than 80% SLNs. This result shows that recognition of SLN can indicate a certain area for lymph drainage, avoiding excessive lymphadenectomy.

The influencing factors of sentinel lymph node

Whether the SLN could be detected successfully depended on the next step. According to O'Boyle *at al.* [23], SLN detection is in relation to the diameter of the tumor. Some studies showed the stage could influence SLN detection. According to Darai *et al.* and Coutant *et al.* [24, 25], early-stage SLN detection ratio was higher than in a later one. When tracer was injected, osmosis was not good or deleted due to osmosis. In this study, the authors found except the factors mentioned above, that the depth and the angle when they injected the trace, the distance from the tumor, and the doctor's skill are also the factors. This study showed that 49 cases of SLN detection was successful in all 56 cases, whereas seven cases failed. In these latter seven cases, two were in Stage IB and five were in Stage IIA; the detected ratio was lower with the increasing of the stage, but the difference has no statistical significance. In theseseven failed cases, three with a diameter > four cm, the left obturator lymph node became enlarged (3 x 4 x 3cm) firm and fixed in one case, the pathological result after the surgery confirmed lymph node metastasis. This indicates that the SLN detection in the diameter of tumor > four cm is lower than it ≤ four cm, ($p > 0.05$); the difference has no statistical significance. At the beginning of this study, due to blue dye effluence after cervical injection of tracer, the recognition of SLN failed in two cases.

Problems and prospects

In conclusion, the current study indicated that SLN procedure using methylene blue, as a tracer is minimally invasive, and an accurate technique to assess pelvic lymph node status in patients with cervical cancer. Lymph node mapping using SLN biopsy may help predict the metastatic status of cervical cancer patients. It can provide a new perspective in the treatment for cervical cancer, but still the following questions remain: 1) How to improve the sentinel lymph node with to predict pelvic lymph node detection rate, sensitivity, and accuracy? 2) How to reduce the SLN identification of false negative rate? 3) SLN detection method for patients whether relapse, follow-up treatment, and survival rate influence existence? Cervical cancer SLN research is still in the primary stage whether to use SLN biopsy replace traditional pelvic lymph node dissections remains to be further researched. The sample quantity of this study is less, if to want to this technique is applied to clinical guidance operation scope, it still needs to large sample, multicenter, prospective case study.

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