

## Clinical study of sentinel lymph node biopsy in early uterine cervical carcinoma

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### Abstract

**Background:** Radical hysterectomy and complete pelvic lymphadenectomy is the standard treatment for early cervical carcinoma. But the rate of pelvic and paraaortic nodal metastasis is found to be low, pointing that most of the patients possibly undergo unnecessary nodal dissection.

**Aim:** To study the value of sentinel lymph nodes (SLNs) in prediction of the pelvic lymph node status and to determine the significance of SLN detection in pelvic lymph node dissection in patients with early stage cervical carcinoma.

**Settings and design:** Retrospective study.

**Methods:** From August 2002 to August 2004, 20 patients with early stage cervical carcinoma, planned to undergo radical hysterectomy and extensive pelvic lymph node dissection received an intracervical injection of a blue dye to identify and perform resection of SLN. The SLNs were pathologically compared with non-SLNs with frozen section, paraffin section, and anti-cytokeratin immunohistochemical staining.

**Results:** Out of 20 patients, SLNs were detected in 15 patients. A total of 46 SLNs were identified and the mean was 3 per patient. The detection rate of SLN was 75%. Sensitivity, specificity and accuracy of the SLN biopsy were 75%, 100% and 95%, respectively.

**Conclusion:** SLN detection can predict the pelvic lymph node status in early stage cervical carcinoma, but the feasibility and safety of this technique to substitute conventional surgical modality should be evaluated by large series of prospective studies.

**Keywords:** Cervical cancer; Sentinel lymph node biopsy; Lymph node excision

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Radical hysterectomy and pelvic lymph node dissection is the standard treatment for early uterine cervical carcinoma. The rate of pelvic and para aortic lymph node metastasis is found to be 0-31% and 0-22%, respectively in patients with early uterine cervical carcinoma.<sup>1</sup> Therefore, it appears that most of the patients with early uterine cervical carcinoma undergo unnecessary pelvic lymph node dissection. Sentinel lymph node (SLN) is the first station for lymphatic drainage and it is also the most probable site for lymphatic metastasis.<sup>2</sup> Sentinel lymph node biopsy may give us the foresight into lymphatic metastasis and save patients from undergoing unnecessary pelvic lymph node dissection if it comes to be negative. It can also help in shortening the operative time, decrease postoperative complication and improve the quality of life of the patient. However, far fewer studies have been conducted with cervical cancer than with other malignancies, such as, melanoma, breast cancer and vulvar cancer.<sup>3-5</sup> Our study aims at the accuracy of SLN mapping, its pathological diagnosis and its value and safety in surgery for early uterine cervical carcinoma.

### Methods and Materials

During year 2002-2004, 20 consecutive patients with the diagnosis of carcinoma of cervix and FIGO stage I-IIa were selected for radical surgery and SLN biopsy at Hebei Provincial Xingtai County Hospital. A written consent was taken from all patients. Cervical punch biopsy was used to diagnose carcinoma. Thorough general and radiological examinations were used to ascertain the absence of pelvic and para aortic nodal metastasis.

One percent Methylthionium solution (methylene blue) produced in Beijing Yong Kang Pharmaceutical was used for mapping. After anaesthesia 4ml dye was

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injected at 3, 6, 9 and 12 o'clock of submucosa of cervix followed by immediate laparotomy or after laparotomy 4ml dye was injected immediately at posterior region of uterus (1 ml per injection site).

Blue lymph nodes were identified, and excised. Then bilateral iliac lymph node were dissected followed by inguinal and obturator lymph node dissection. Radical hysterectomy was done after lymph nodes dissection. Excised SLN was sent for frozen section biopsy where as rest of the specimen was sent for routine biopsy. A senior pathologist performed H & E staining followed by Immunohistochemistry (IHC) examination of SLN. IHC examination was done using anti-cytokeratin immunohistochemistry Kit bought from Beijing Zhong Shang Bio Tech Company. Same pathologist performed routine biopsy procedure for rest of the radical hysterectomy specimen. All patients were in follow up for a period of 1-12 months.

### Results

Twenty consecutive patients between the ages of 24-65 years (mean age 42.4 years) were studied. Seventeen patients had squamous cell carcinoma, two patients had adenocarcinoma, and one patient had clear cell carcinoma. Seventeen patients had not undergone any prior treatment entering this study group. Two patients (one of adenocarcinoma and one of clear cell carcinoma) underwent chemotherapy with cisplatin, vincristine and bleomycin (PVB) regimen, whereas one patient with adenocarcinoma underwent cisplatin, doxorubin and cyclophosphamide (PAC) regimen chemotherapy for 2 cycles prior to surgery.

A total of 532 lymph nodes (median 26 lymph nodes per patient) were excised. Fifteen patients (75%) had positive SLN. A total of 46 SLNs were detected pathologically, which accounted for 3 lymph nodes per patient. Sensitivity and specificity of SLN biopsy was 75% and of 100%, respectively. Prediction of pelvic lymph nodes status according to SLN and pathologic report was correlated in 95% cases. SLN distribution was most commonly found in obturator (59%), external iliac (30%), internal iliac (4%) group of lymph nodes. Unilaterally SLN was detected in 30% and bilaterally in 70% cases.

### Discussion

Pelvic lymph node metastasis is an important prognostic factor in early uterine cervical carcinoma. Recent studies have shown that in stages I and II, incidence of pelvic lymph node metastasis is only 0-16% and 24-31%, where as incidence of para aortic metastasis is only 0-22% and 11-19% respectively.<sup>1</sup>

When the diameter of local tumour is less than 2cm, probability of lymph node metastasis is 0-16%.<sup>6,7</sup> Detection of lymph node metastasis after surgery is above 90%.<sup>8</sup> Pelvic Lymph node dissection can bring complications such as trauma to blood vessels and nerves, lymphedema, lymphatic cyst, infections, adhesions, urologic disorders and decrease patients quality of life. Therefore as to how to correctly predict the pelvic lymph node involvement, bring individuality in treatment of the patients, decrease and avoid complication brought by unnecessary lymph node dissection are questions that need serious thoughts and discussions.

SLN is the primary site or the first station during the metastasis of primary tumour. SLN biopsy is already a standard procedure for malignant melanoma, vulvar carcinoma and breast carcinoma.<sup>3-5,9,10</sup> Main route for spread of cervical carcinoma is also lymphatic, which favours SLN detection to be applied.

There are 3 methods for SLN detection: bioreactive dyes, radioactive nucleotides and combined. Bioreactive dyes are easy to use and cost effective with no radioactive contaminations. Mostly Isosulfan blue and patent blue V are used in developed countries which have shown better detection rate. But because of limited resources, we used Methylthionium dye, which we believe, has lower detection rates in comparison to the standard dyes. The combined use of <sup>99m</sup>Tc sulphate and blue dye can increase the detection rate up to 94%.

The conventional way of radical hysterectomy and SLN biopsy is open, but recently there have been a number of series showing equally good results with the laparoscopic approach.<sup>11,12</sup>

Malur et al<sup>13</sup> believe that late stage disease or disease already with lymph node metastasis can decrease the detection of SLN. They report that the detection rate in stage I and stage II disease is 78.6% and 70.6%, respectively. Histopathologic confirmation of those cases suggested that 60% had lymph nodes metastasis and 82% did not have lymph node metastasis. This suggested that large local lesion (diameter>3 cm) and radiologically lymph node positive cases should be considered as exclusion criteria for SLN mapping. Especially in late stage disease, due to the tumour thrombosis of the lymphatics, the dissemination of the dye is blocked, which may lead to false negative finding in SLN detection; or due to the thrombosis of the lymphatics the direction of the lymphatic drainage may be changed which may lead to SLN detection in the false site, leading to false positive mapping. Pre operative radiation and chemotherapy

may lead to disappearance of metastasis in SLN lymph nodes, which again may lead to false negative results. So, generally these cases should be excluded as well.

The accuracy of SLN detection is the main factor for the usage of this technique, whether SLN can predict the status of lymph node metastasis is very important for the safety of the whole surgery. Wrong diagnosis can lead to wrong mode of surgery and planning of the adjuvant treatment. Besides, frozen section biopsy of the SLN can extend the operative time, and the authenticity of the frozen section biopsy and whether there is skip metastasis is equally important. Niikura et al summarized results of ten reports (including their own as well) concerning SLN in cervical carcinoma. A total of 295 patients were analysed with SLN detection rate of 85%. Sensitivity, specificity, and negative predictive value were 93%, 100%, and 99%, respectively.<sup>14</sup>

Carcinoma of cervix is an epidermal malignant tumour, therefore antikeratin IHC staining comes to be positive. Lymph nodes are non epidermal tissue; therefore antikeratin IHC staining comes to be negative unless they are metastatically involved. This method can decrease false negative detection rate. IHC has been found to be positive in up to 9-33% cases of breast carcinoma, where conventional H & E staining of SLNs was negative for metastasis.<sup>13</sup> We performed antikeratin IHC staining of all the SLNs that had undergone frozen section biopsy and HE staining. This combined method had 100% accuracy rate in the detection of metastasis in SLN. We are still in search for other easier method to minimize false negative rate of micro metastasis, and give a better base for the usage of SLN biopsy in early carcinoma of cervix. In conclusion, our study, though the sample size is small, very well shows that SLN detection can predict the pelvic lymph node status in early stage cervical carcinoma. The lower sensitivity rate of 75% in our study in comparison to the most recent series could be because of use of the blue dye alone. Moreover, as earlier mentioned, Methylthionium is, perhaps, inferior to the standard dye (isosulfan blue). Larger prospective trials are needed to prove the feasibility and safety of this technique and to prove whether it can substitute conventional surgical modality.

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