

## Sentinel Node Biopsy as an Indicator for Pelvic Nodes Dissection in Early Stage Cervical Cancer

The purpose of this study was to investigate the feasibility of sentinel node frozen biopsy to minimize the extensive pelvic lymph nodes dissection in early stage cervical cancer patients on the basis that the risk of skip metastasis to the para-aortic area is negligible. Twenty-six patients with early stage cervical cancer were enrolled in this study. Technetium-99m colloid albumin (Tc<sup>99m</sup>) was injected intradermally around the tumor for allowing preoperative lymphoscintigraphy and intraoperative hand-held gamma probe detection of sentinel nodes. For visual detection, isosulfan blue dye was injected into the peritumoral sites before peritoneal opening. Postoperative morbidity and negative predictive value were the endpoints of this study. The 26 patients, ranging in age from 32 to 71 yr, underwent intraoperative sentinel nodes mapping. All the patients underwent complete pelvic lymph nodes dissection including para-aortic nodes. There was one case with positive non-sentinel nodes despite the negative sentinel node by frozen biopsy (negative predictive value, 95.2%). This new technique of sentinel node mapping is safe and simple to perform. Further clinical trials using the combination of Tc<sup>99m</sup> and isosulfan blue dye are warranted and this technique will make a true advance for less aggressive management of patients with early stage cervical cancer.

**Key Words :** Sentinel Lymph Node Biopsy; Cervix Neoplasms

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## INTRODUCTION

Radical hysterectomy with pelvic lymphadenectomy is considered the standard surgical treatment for early stage cervical cancer. The term radical hysterectomy has been widely used to define operations with striking variation in radicality among surgeons. It is known that the risk of skip metastasis to the para-aortic area is negligible in early stage cervical cancer (1). The proper indications for radical hysterectomy and the role of extreme radicality in effectiveness of cure in patients with cervical cancer still remain debatable, and attempts have been made to identify a subset of patients with early stage cervical cancer eligible for less extensive radical surgery (2). The sentinel lymph node is defined as the first node of a regional lymphatic basin that receives the lymphatic drainage from a tumor (3), thus representing an elective site of lymph node metastasis (4). According to the sentinel lymph node hypothesis, histologically negative sentinel lymph nodes can guarantee the histological negativity of the remaining regional lymph nodes (5). It has been demonstrated that there is an orderly and predictable pattern of lymphatic flow in cervical cancers, and there is a sequential progression of tumor cells passing by means of lymphatic vessels to the primary draining lymph node; the first lymph node filters the afferent lymph, whereby the tumor cells become entrapped. The evolution of the tumor cells is influenced by the immunologic response

generated within the lymph node. These assumptions suggest that the sentinel node can be a suitable marker of regional lymph node status. Thus sentinel node biopsy may be a reasonable alternative to unnecessary pelvic lymph nodes dissection and a suitable method for limited control of early stage cervical cancer. To improve the sentinel node detection in surgical procedures, we investigated lymphatic mapping of sentinel lymph nodes with isosulfan blue dye (lymphazur 1%) and technetium-99m colloid albumin. The sentinel lymph node frozen biopsy for early stage cervical cancer is gaining a widespread interest due to its accurate prediction of the regional lymph node status (95-100%) that could safely avoid extensive dissection of the regional lymph nodes.

The concept of the sentinel lymph node was introduced by Cabanas in 1977 with regard to the management of penile carcinoma (6). He proposed that the lymph nodes that first receive lymphatic drainage from a tumor could be removed by limited surgery and examined to determine whether more extensive lymph node dissection should be performed (7). The technique of intraoperative lymphatic mapping for early stage melanoma was described by Morton and others and has been freely adapted to the cervical cancer with different routes of injection, such as intradermal, subdermal, intraparenchymal, or intratumoral, for marking the sentinel nodes (7-9).

This study was aimed to evaluate the feasibility of lymphatic mapping with a combined approach -isosulfan blue dye

and technetium 99m colloid albumin- and the correlation between the sentinel node and non-sentinel nodes status and their statistical significance in early stage cervical cancer.

## MATERIALS AND METHODS

### Patients selection

Between April 2001 and January 2002, 26 patients with early stage cervical cancer successfully underwent sentinel lymph node frozen biopsy. Lymphoscintigraphy was performed in 24 of 26 cases and 2 of 26 cases received only isosulfan blue dye injection during this period. Informed consents about lymphatic mapping and sentinel lymph node biopsy were obtained before surgical procedures. We performed a prospective study on 26 consecutive patients undergoing sentinel node frozen biopsy by isosulfan blue dye and technetium-99m colloid albumin. In all patients, the sentinel lymph node frozen biopsies were followed by extensive pelvic lymph nodes dissection, regardless of the sentinel lymph nodes status.

### The lymphatic system of uterine cervix

There are two sets of lymphatic systems in the uterus (10, 11). One is the superficial lymphatic system and the other is the deep one. The superficial lymphatic system is placed beneath the peritoneum, and the deep one in the parenchyme of the organ. The lymphatic vessels of the uterine cervix run

in three directions: transversely to the external iliac glands, postero-laterally to the hypogastric glands, and posteriorly to the common iliac glands. The majority of the vessels of the body and fundus of the uterus pass lateralward through the broad ligaments, and continue up with the ovarian vessels to the lateral and para-aortic glands. A few, however, run to the external iliac glands, and one or two run to the superficial inguinal glands.

### Lymphoscintigraphy and isosulfan blue dye administration

Technetium-99m colloid albumin was used for lymphatic mapping. The procedure was as follows; about 3 hr before surgery, the patients were transported to the nuclear medicine unit and subjected to large field scintillation camera-guided peritumoral injection of 10-20 MBq technetium-99m colloid albumin at 2 or 3 sites around the primary tumor (Fig. 1). Dynamic scintigraphy was commenced immediately using a large field scintillation camera. Static scintigraphy was prolonged for 20 to 40 min based on the visualization of sentinel lymph node (Fig. 2). The scintigraphic hot spots *in vivo* were detected using a hand-held gamma probe (Neoprobe 1500® Neoprobe Corp, Dublin, OH, U.S.A.). About 3 hr after tracer injection, the patients were sent to the operation room and radical hysterectomy with pelvic lymphadenectomy was performed following sentinel lymph node frozen biopsy. After induction of general anesthesia, isosulfan blue dye was injected in the peritumoral area with a 20-gauge needle (Fig. 3). The sentinel lymph node identification was always followed

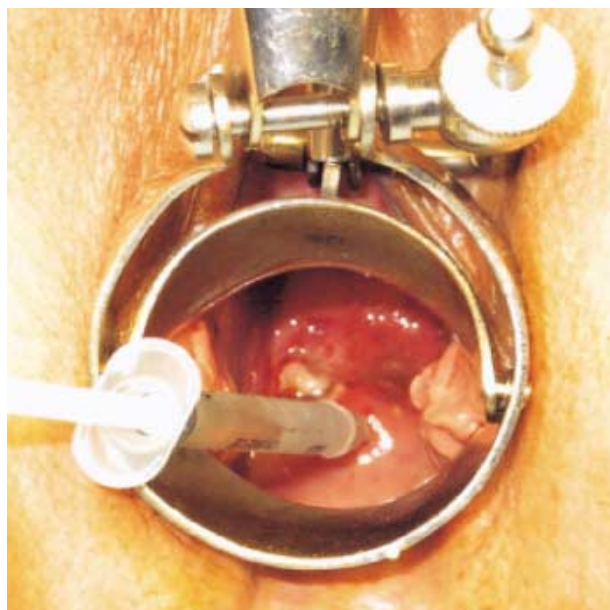


Fig. 1. Intradermal technetium-99m colloid albumin injection in an early stage cervical cancer.

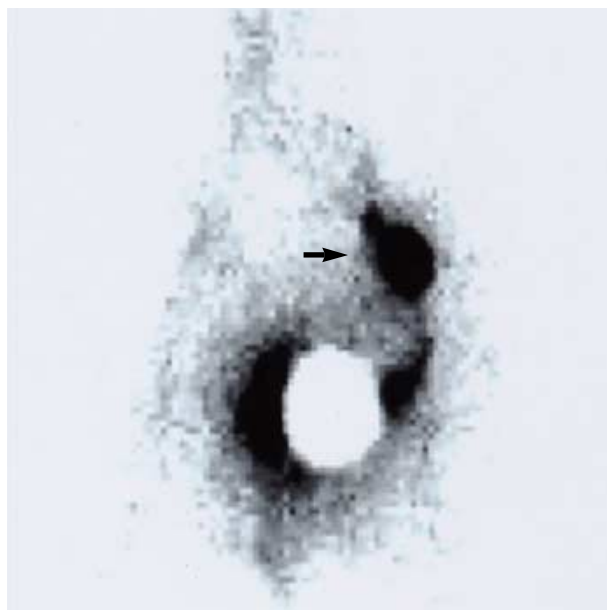
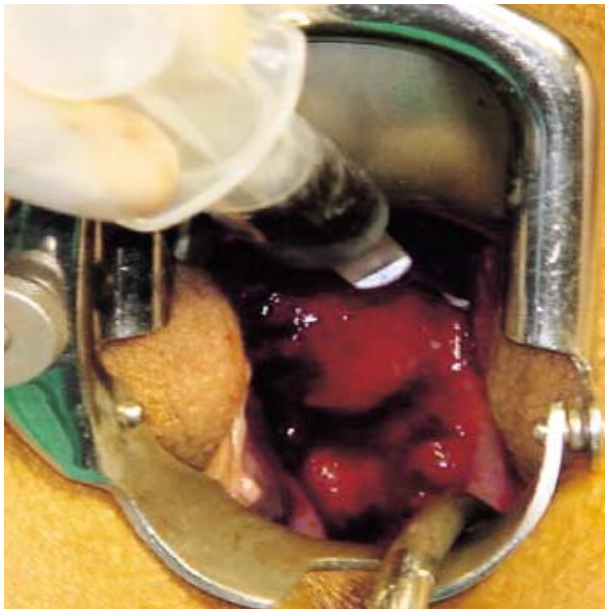


Fig. 2. Lymphoscintigraphy using a scintillation camera (arrow indicates scintigraphic hot spot and shows the location of lymph node).



**Fig. 3.** Peritumoral injection of isosulfan blue dye around the cervical lesion.

by radical hysterectomy. The probe was used before making the abdominal skin incision to identify the area of greatest activity. Background activity was obtained in four areas of abdomen. Usually, sentinel lymph nodes had 6-to 8- fold radioactivity compared to non-sentinel lymph nodes as the background. Careful dissection was performed to identify the blue stained afferent lymphatic vessels, and they were followed up to the first blue-stained lymph node. The hand-held gamma probe was used to confirm the location of the sentinel lymph nodes, as well as to guide the dissection whenever the afferent lymphatic channels were not detectable (Fig. 4).

#### Removal of sentinel nodes and pathologic examination

The sentinel node was excised together with a rim of surrounding tissue and sent as a separate specimen for intraoperative histologic examination. A pathologist examined all the surgically removed sentinel node specimens using a standard technique. The nodes were isolated fresh from the fat tissue. One section was taken per 5 mm of the greatest dimension. Nodes greater than 5 mm in diameter were divided into two parts along the longitudinal axis. Nodes less than 5 mm in the major axis were totally embedded. Three histological sections were obtained from each specimen at different cut levels and were stained with hematoxylin and eosin.

## RESULTS

The 26 patients who underwent radical hysterectomy with



**Fig. 4.** Detection of sentinel lymph node using an isosulfan blue dye and hand-held gamma probe (A: hand-held gamma probe. Arrow indicates the sentinel lymph node).

pelvic lymph nodes dissection using preoperative technetium-99m colloid albumin and intraoperative isosulfan blue dye injection were analyzed for the location of sentinel lymph nodes and for the sensitivity and negative predictive value for the purpose of clinical application of only sentinel lymph node frozen biopsy for less extensive pelvic lymph nodes dissection in early stage cervical cancer. The order of sentinel

**Table 1.** Distribution of locations of sentinel lymph node in 26 cervical cancer patients

Locations of sentinel lymph node	Number of detected sentinel lymph node
External iliac	18
Obturator	12
Internal iliac	8
Parametrium	8
Common iliac	2
Inguinal	1

**Table 2.** Relationship between frozen biopsy of sentinel lymph node and permanent pathology of pelvic lymph node

	Permanent pathology (-) <sup>†</sup>	Permanent pathology (+) <sup>‡</sup>	Total
Frozen biopsy (-) <sup>*</sup>	20 cases	1 case	21 cases
Frozen biopsy (+) <sup>†</sup>	1 case	4 cases	5 cases
Total	21 cases	5 cases	26 cases

Frozen biopsy (-)<sup>\*</sup> denotes the benign sentinel lymph node. Frozen biopsy (+)<sup>†</sup> signifies the nodal status is malignant. <sup>†</sup>means there was no metastatic lesion in pelvic lymph nodes and <sup>‡</sup>implies there were metastatic nodes in pelvic cavity.

node detection sites were external iliac, obturator, and internal iliac areas (Table 1). The location of the primary cancer lesion had an influence on the detection sites of sentinel lymph nodes. The average number of sentinel lymph nodes per patient was two. Among 21 cases where sentinel lymph nodes were negative, pelvic lymph nodes were all negative except for in one case. Among 5 cases where sentinel lymph nodes were positive, 4 were positive in pelvic lymph nodes and 1 was negative. Sensitivity and specificity of sentinel lymph node frozen biopsy were 95.2% (20/21) and 80% (4/5), respectively. The negative predictive value of the technique was 95.2% (20/21) (Table 2).

## DISCUSSION

Sentinel lymph node biopsy in cervical cancer is a promising surgical technique to confirm nodal status and minimize postoperative morbidity (5, 9, 12). There are many different ideas concerning the site of injection of the isosulfan blue dye and radionuclides, the dose of radioactivity used, the interval between dye injection or lymphoscintigram and sentinel node frozen biopsy (13-15). Isosulfan blue dye is used for dye-guided sentinel lymph node biopsy in western countries for visual detection. According to the initial experience of only dye-guided sentinel node biopsy, the identification rates of sentinel lymph nodes ranged between 66% and 82% (12). Radionuclides for lymphatic mapping should be a few hundred nanometers in size, to permeate the lymphatic vessels and remain in the sentinel lymph nodes. However, technetium-99m HAS is too small ( $\leq 5$  nm) to be retained in the sentinel lymph nodes and technetium-99m TC is too big ( $\geq 500$  nm) to migrate through the lymphatic vessels compared with technetium-99m colloid albumin (16). These factors contributed to low success rate of sentinel node biopsy with the hand-held gamma probe detector. As for the relative contribution of each method to the detection of the sentinel node, it should be underlined that the detection rate was increased by means of combining isosulfan blue dye and technetium-99m colloid albumin. Hence, whenever it is affordable, isosulfan blue dye in combination with technetium-99m colloid albumin should be used for the lymphatic mapping. The combination of isosulfan blue dye and technetium-99m colloid albumin can improve the rate of identification of sentinel lymph nodes up to 100%, and seems to be the best way to accurately detect sentinel lymph nodes. If sentinel lymph nodes are histologically negative by immediate frozen section examination, extensive pelvic lymph nodes dissection can be omitted. However, it may be difficult to detect micrometastasis of cancer cells by the frozen section of sentinel lymph nodes. To compensate for this false negatives, it will be helpful to examine multiple sections of sentinel lymph nodes especially with immunohistochemical staining. In conclusion, sentinel node frozen biopsy with iso-

sulfan blue dye and radionuclide was found to be the best way to identify sentinel lymph nodes in early stage cervical cancer.

The acceptable false-negative rate remains unclear, but sentinel node biopsy in a multicenter validation study will prove feasible for predicting pelvic lymph nodes metastases. Our findings confirm that the detection rate of the sentinel node (49 of 53, 94%), the overall accuracy (48 of 49, 97%) and false negative rate (1 of 21, 4.76%) are satisfactory for clinical application. This prospective study provides evidence for the necessity of coupling lymphoscintigraphy and isosulfan blue dye and hand held gamma probe detector in order to enhance the identification rate of sentinel lymph node. Sentinel lymph node biopsy is less invasive than complete pelvic lymph nodes dissection and lowers both postoperative morbidity and cost. It is expected that sentinel node frozen biopsy in early stage cervical cancer will be performed as a standard practice for less extensive pelvic lymph nodes dissection in the near future.

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