

Sentinel Node Lymphoscintigraphy: An Update

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INTRODUCTION

The first lymph node in the lymphatic basin draining the primary tumor called the sentinel node (SN). The concept of the sentinel node as the first node to drain lymphatic flow from the tumor site and the best biopsy indicator of the presence or absence of tumor in lymph node was first described by Morton and his colleagues⁽¹⁾. This concept states that the SN will always contain tumor cells if lymphatic spread of the tumor has occurred, so that pathology of the sentinel node will reflect the histopathology of the entire nodal bed. In breast cancer, axillary lymph node involvement is still the most important prognostic factor, on which adjuvant therapy is based. Selective biopsy of the SN may be an alternative for axillary lymph node dissection in staging breast cancer patients and extensive surgery can be avoided.

Lymphoscintigraphy is not a new procedure, but one which has been in clinical use for decades without getting much attention and enthusiasm from surgeons and nuclear medicine clinicians. Though it is now a part of standard management for melanoma, lymphoscintigraphy for detection of SN is underutilized. Lymphoscintigraphy has previously been used to identify metastasis in the axillary lymph nodes (LN)⁽²⁾ or to locate internal mammary nodes for radiation treatment planning⁽³⁾.

In the last 5 years, there has been revolutionary development in the immunohistologic techniques with the development of newer radiopharmaceuticals, which leads to early mapping of SN to avoid unnecessary axillary node dissection. SN can be detected by vital blue dye injected around the tumor at the time of surgery and by radiocolloid mapping separately or simul-

taneously with the blue dye method. Radiocolloid diagnosis of SN was found to be more convenient with more and more success rate, though it is slightly costlier than blue dye method.

Prognosis of breast cancer depends on several factors, such as patients characteristics (age and menstrual status), tumor differentiation (histologic variables, estrogen and progesterone receptors, DNA ploidy status), proliferative rate and tumor invasiveness or metastatic potential⁽⁴⁾. For breast cancer, the presence of regional metastasis decreases 5-years survival rate by approximately 28%-40%^(5,6). Therefore, the current management of breast cancer includes ipsilateral axillary lymph node dissection for staging invasive breast cancer with no clinically evident nodes. However with complete axillary node dissection, the complication rates of the procedure after a mean follow-up time of six

months are 40% lymphedema, 5% chronic lymphedema, 40% parasthesis of the arm and 10% seroma formation⁷. Patients with intraductal carcinoma in situ with no palpable mass is likely to have LN metastasis but smaller invasive cancers may have axillary nodal metastasis^(8,9).

Current interest in this procedure reflects the growing popularity of intra-operative lymphatic mapping with selective lymphadenectomy as a minimally invasive operative technique to determine the tumor status of the draining lymph node basin⁽¹⁰⁻¹⁴⁾. In this small review article, we tried to reviewed the utility of lymphoscintigraphy in breast cancer patients to detect SN, its advantages & disadvantages, experience in different laboratories and further possibilities of this technique.

EVOLUTION OF SENTINEL NODE CONCEPT:

A MAJOR BREAKTHROUGH IN SURGICAL ONCOLOGY

The first lymph node (SN) receiving lymphatic drainage from a tumor will always contain tumor cells, if lymphatic spread of the tumor occurs. This concept was first published by Cabanas and his colleagues⁽¹⁵⁾ back in 1977. Before that, in 1970 Kett and his coworkers first identified a draining lymph node using some contrast media⁽¹⁶⁾. From this concept of their study, idea of blue dye method of lymphatic channel mapping evolves. In 1995, some researchers from MD Anderson Cancer Center, Houston, Texas, USA first introduced this blue dye method⁽¹⁷⁾ for mapping lymphatic channel in a patient with penile carcinoma. But major revolution in this SN concept was done by Morton and his team⁽¹⁸⁾. They used this

concept to delineate the lymphatic drainage pathways between the SN and cutaneous melanoma using vital blue dye. But in this method, there were some difficulties about the timing of operation between the intradermal injection of the blue dye and skin incision made to find out the blue stained SN. If the incision is made too early, the lymphatic channels can be cut off before the blue dye could make its passage through it. Whereas if the incision is delayed, surgeons may face considerable difficulty finding a small blue lesion. To overcome this problems, some researchers introduced radionuclide lymphoscintigraphy in 1993 and then introduced gamma detector probe to find out SN during operation in melanoma patients^(19, 20).

RADIOPHARMACEUTICALS

Since the introduction of lymphoscintigraphy, numerous radiopharmaceuticals have been employed for this purpose. With the growing popularity of lymphoscintigraphy, the search is on for better radiopharmaceutical agents designed specifically for SN imaging. These includes:

- 99m Tc labeled dextran⁽²¹⁾
- 99m Tc hydroxyethyl starch⁽²²⁾
- 99m Tc human serum albumin^(23, 24)
- 99m Tc Stanous phytate⁽²⁵⁾
- 99m Tc Sulphur colloid^(26,27)
- 99m Tc antimony sulphur colloid⁽²⁸⁾
- 99m Tc albumin colloid⁽²⁹⁾
- 198 Au colloid⁽³⁰⁾

Among these radiopharmaceuticals, few are in use presently. Due to some drawback properties, which influences the lymphoscintigraphy, many of the above mentioned isotopes are now not in use. The characteristics of ideal radiopharmaceuticals for lymphoscintigraphy should be:

- Rapid clearance from the injection site
- Rapid, complete and sustained uptake by the sentinel node
- Short half life (preferably ^{99m}Tc labeled)
- Low energy
- Low cost
- Stable for long hours
- Small particle size as to penetrate the capillary membrane.

Among these agents, for their ideal characteristics, only Tc-^{99m} Albumin colloid, Tc-^{99m} human serum albumin and Tc-^{99m} sulfur colloid are presently used for lymphoscintigraphy. The most preferred radiopharmaceutical is Tc-^{99m} antimony colloid with particle size 3-30 nm. The next best is Tc-^{99m} SC (particle size 10-1000 nm), which is filtered to remove the larger particles, creating a nearly ideal particle size⁽³¹⁾.

INSTRUMENTATION AND METHODOLOGY

There is still no consensus regarding the optimal methods for lymphoscintigraphy. A total dose of around 1 mCi of Tc-^{99m} labeled lymphoscintigraphic agent is administered subcutaneously around the tumor site using a tuberculin syringe. Tracer is deposited subcutaneously and images are obtained immediately (15-30 sec.) which demonstrate the injection site, the regional draining lymphatics and the closest lymph node. Dynamic images are important to identify the first node the tracer goes with the draining channel⁽³²⁾.

Images are obtained using a gamma camera with low energy high resolution collimators immediately and again after 2-4 hours after injection, if there is any LN collects tracer lately.

TECHNIQUE

Vital blue dye

Usually 3 to 5ml of 1% isosulfan blue dye is injected into the breast parenchyma surrounding the primary tumor or into the wall of the biopsy cavity. Three to 7 minutes after the injection a standard transverse axillary dissection incision is made just inferior to the hair-bearing region of the axilla, as there is no clue to the approximate location of the sentinel node before incision by this method. Blunt dissection is performed to identify a blue-impregnated lymphatic channel. The blue lymphatic channel then is followed proximally and distally until the (first) sentinel node is identified. Sometimes two and rarely more than two blue-stained sentinel node can be identified along the lymphatic tract. All blue stained LNs are excised and labeled as sentinel node and sent for pathological examination.

Lymphoscintigraphy (Radionuclide study)

The following are the steps of patient preparation for sentinel node lymphoscintigraphy and intra-operative localization by portable gamma probe:

A) Imaging

The patient is positioned supine with arm raised above the head.

1. Radiopharmaceutical, Dose, Volume and Route of injection: Tc-^{99m} labelled agents in a dose of 300 mCi-1 mCi is selected. The total volume of the solution varies according to the route of injection. For intradermal injection maximum of 0.3-0.4 ml solution is used. Whereas for intraparenchymal injection 4-8 ml of solution injected

- in 4-6 sites surrounding the lesion.
2. For non-palpable cancers the tumor is localized by guided ultrasound and the radiocolloid is injected through the localization needle or intradermally over the sector of the breast involved.
3. Dynamic images are obtained in the lateral projection (preferred over anterior projection for axillary node visualization) with a scintillation camera at 20-30 second intervals for 45 minutes.
4. Static images in the lateral and anterior views of 5 minutes each are obtained from 30 minutes with the patient in the supine position for visualizing the nodal uptake. Additional delayed images may be needed if the nodal uptake is not visualized at the end of the study.
5. Transmission images obtained with a cobalt-57 source are recommended for optimal anatomic localization first 2 frames of dynamic images and in static images; a Tc-99m flood source can also be used.
4. In vivo radioactivity is measured in counts per second with the sentinel node fully exposed.
5. An estimate of the background activity is obtained by measuring counts in four areas in the axilla equidistant from the injection site and away from the sentinel node.
6. Localization of the SN. Sentinel nodes are defined as nodes with a ratio to background activity of greater than 2.5.
7. After removal of the sentinel node the central bed is re-examined for activity and if the activity remains greater than 150% compared with background, the dissection is continued to search for additional sentinel node.
8. All sentinel nodes are labeled and sent for pathology.

B) Gamma Probe Guided Surgery

1. Usually a lumpectomy is done first with the area of injection to avoid high background activity.
2. A handheld gamma detector probe is used prior to making a skin incision to identify the area of greatest activity in the axilla in terms of CPS (counts per second).
3. A small incision is used over the maximum count area and the gamma probe is used to guide the dissection and finally localize the sentinel node.

DISCUSSION

There have been many previous studies reporting the use of lymphoscintigraphy in patients with breast cancer. These have included axillary lymphoscintigraphy, internal and mammary lymphoscintigraphy. Axillary lymphoscintigraphy has been used in the preoperative search for nodal metastases in the axilla^(3, 33) or to assess the completeness of axillary dissection postoperatively³⁴ or intraoperatively⁽³⁵⁾. Internal mammary lymphoscintigraphy has been used in attempts to diagnose nodal metastases⁽³⁶⁾ and to locate the internal mammary nodes for radiation treatment planning⁽³⁷⁾.

Many authors reported with variable success rate with blue dye in localize SN. Some results with different radiopharmaceuticals has been published.

But combine use of both blue dye and radiocolloid at the same time improves the result significantly. Giuliano et al⁽³⁸⁾ in 1994 reported a success rate of 66% using blue dye at the beginning of using this technique which later on increased to 88% and accuracy of 96% with gain of more experience as reported in 1997⁽³⁹⁾. Guenther et al⁽⁴⁰⁾ and Flett et al⁽⁴¹⁾ reported a success rate of 71% and 82% respectively by using blue dye alone and the accuracy was 97% and 95% respectively. Considering all the above studies with only blue dye the over all success rate is around 76% and an overall accuracy of 97%. Krag & his coworkers in 1993⁽⁴²⁾ reported a success rate of 82% with an accuracy of 100% using Tc-99mSulfur colloid only. Same group in 1998⁽⁴³⁾ reported success rate of 76% and accuracy of 100%. Others using Tc-99m Colloidal albumin showed a success rate varying from 69 to 99% with an accuracy varying from 97% to 100%^(44, 45). The over all success rate using radionuclide method alone is 90% and accuracy of 98%.

In 1996 Albertini et al⁽³²⁾ first reported to use both blue dye and Tc-99m sulfur colloid to improve the success rate and found a success rate of 92% and accuracy of 100%. Subsequently O'Hea et al in 1998⁽⁴⁶⁾ using the same combination reported a success rate of 93% and an accuracy of 95%. Borgstein et al⁽⁴⁷⁾ in 1997 and Barnwell et al⁽⁴⁸⁾ in 1998 used blue dye with Tc-99m colloidal albumin and reported success rate of 100% and 90% respectively. The overall success rate of combined method is 93% as compared to 76% by only blue dye and 90% by using the radionuclide method only.

The present evidence^(38, 42) strongly support the validity of the SN principle in breast cancer but there is a need for more data.

Studies^(44, 49) suggest that SN localization using radiotracer performs better and is easier than dye-oriented techniques.

In the last five years there has been marked advancement in the techniques of serial sectioning of tissue, immunohistochemical staining, and reverse transcriptase polymerase chain reaction analysis in the detection of micrometastases^(50, 51). As a result, there was an increase in the number of micrometastases detected when the result of routine histologic examinations were negative in patients with melanoma, breast cancer, colon cancer, neuroblastoma, prostate cancer and stomach cancer^(52, 53). This micrometastases had proved to be clinically relevant. Thus, this technology may allow a more rational approach to the use of adjuvant chemotherapy.

To properly stage breast cancer and at the same time avoiding the more expensive and complicated axillary dissection, increasing number surgeons are practicing the SN technique. SN in the internal mammary could only be easily and non-invasively diagnosed by lymphoscintigraphy, which is not possible, by dye technique. Quite a number of centers when using both techniques together experiences that there were always few cases where SN localized by radiotracer not been localized by blue dye and vice-versa⁽⁵⁴⁾. The patients with outer quadrant breast tumors demonstrates internal mammary drainage and inner quadrant tumor demonstrate axillary drainage. One fifth of patients with upper quadrant tumors shows direct drainage to the supraclavicular and infraclavicular nodes⁽¹³⁾. Laterally placed breast tumors can drain primarily via the internal mammary lymphatic system, a system often ignored in treatment planning. This internal mammary spread explains the soli-

tary sternal metastases that can be identified on bone scan⁽⁵⁵⁾. So, to achieve maximum possible success rate and to exploit the advantage of the SN principle use of both techniques simultaneously is more justified rather than using any one procedure alone at this time point especially when the surgeon is still in his learning phase. There is still a 3-8% failure rate for SN localization using both methods simultaneously. Those patient should go for axillary dissection.

None of the radiopharmaceuticals used, were designed specifically for SN mapping. As a result imaging with any of these agents suffers from several deficiencies. Blue dye has problems, it only flows through the lymphatics does not bind or stay long, therefore, exact timing for axillary incision is not possible. In addition dye technique cannot give any idea before incision to the surgeon to plan the technique of incision ahead.

CONCLUSION

Lymphoscintigraphy in conjunction with the probe, used to facilitate surgical localization and excision of the sentinel node, is finding a niche in the surgical management of patients with early breast cancer.

Management based on the sentinel node concepts offers the following:

- It is cost-effective
- It has the potential to improve survival
- It provides a more rational approach to selecting patients for lymph node dissection as well as to defining the lymph node beds to be dissected.

Thus the rationality, cost effectiveness and potential for improving patients outcomes based on the lymphoscintigram and intraoperative gamma probe sentinel node localization and excision have converged to alter surgical management.

Combined with the use of intraoperative gamma probe to find the sentinel node and excise it, the impact on surgical management has been to save on cost, morbidity and perhaps improve therapeutic responses.

Quality and success of sentinel node localization will be enhanced by the image as a road map for using the probe. Breast lymphoscintigraphy is not difficult to perform but requires palpation of the tumor and correlation with the mammogram to estimate depth and localization of appropriate injection sites at four peripheral points that border and surround the tumor.

Certainly, good coordination among surgeon, pathologist, and the nuclear medicine physician will make the procedure more convenient and possibly will be incorporated into everyday practice of the management of early breast cancer. Lymphoscintigraphy performed the day prior to surgery can give the surgeon an idea about the location of the involved nodes and so he can plan the surgical incision. In the future, we hope and we do believe that the excision of SN can be done under local anesthesia as an outpatient procedure in properly selected patients saving the cost of hospital admission, anesthesia and will be more convenient to patient.

On summerizing this review, we can conclude that advantages of lymphoscintigraphic sentinel node identification in patients with breast cancer can be helpful for surgeon for mapping the lymphatic drainage. The sentinel node concept may

be an ideal approach for bypass the extensive axillary lymph node resection. However the sentinel node concept needs more extensive studies and further validation in breast cancer.

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