

Combined Methylene Blue Dye and Radioactive Tracer Technique for Sentinel Lymph Node Localization in Early Breast Cancer

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Abstract

Background: Sentinel lymph node biopsy is a technique used to identify the axillary node most likely to contain tumor cells that have metastasized from a primary carcinoma of the breast. This technique provides accurate staging with fewer complications than axillary dissection and may result in decreased costs. We designed the present study to determine the accuracy and success rate of a combined blue dye and radioactive tracer technique in sentinel node localization.

Methods: This prospective study included 70 patients with early stage (tumor >5 cm; T¹, T²) operable breast cancer and nonpalpable axillary lymphadenopathy seen between 2005 and 2009. Patients underwent sentinel lymph node localization using 4 mL of blue dye combined with radioactive colloid. After identification and removal of the sentinel node(s), the axilla was checked for any residual radioactivity. A sentinel node was defined as any node that was hot, hot and blue or only blue.

Results: The sentinel node was identified in 66 patients with a detection rate of 94.2%, and a mean of 1.5 sentinel nodes were identified and harvested (range of 1-4). In 23 cases, the sentinel lymph node contained metastatic disease on pathological assessment. There was no pathological evidence of any metastases in the sentinel node in the remaining 43 patients. All sentinel lymph nodes were located in level I of the axillary region. In four patients, no sentinel lymph node was found, so axillary dissection was performed. The sensitivity of the procedure in predicting further axillary disease was 95.6% with a specificity of 97.6%.

Conclusion: The present study describes the blue dye and radioisotope localization technique as successful in identifying the sentinel lymph node in early-stage breast cancer patients.

Keywords: Sentinel lymph node, Breast cancer, Tumor staging

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Introduction

The axillary node status is the single most important prognostic variable in the management of breast cancer.¹ It directs the need for further axillary and adjuvant systemic treatment in patients with early breast cancer.²⁻⁴ Axillary lymph node dissection, i.e., clearance levels I, II, and III, is the gold standard in axillary staging as it has a very low false-negative rate of less than 2%. However, the morbidity associated with the procedure, including lymphedema (15-30%),⁵ neuropathy including intercostobrachial nerve syndrome (78%),⁶ hematoma and seroma (10-52%),⁷ is well recognized, along with treatment costs associated with length of the operation and inpatient stay.

Sentinel lymph node (SLN) biopsy is a valuable new technique to assess the nodal status of patients with early breast cancer.⁸ Sentinel lymph node biopsy in breast cancer can accurately stage the axilla, is a safe and accurate minimally invasive procedure with less morbidity compared to axillary clearance.²⁻⁴ Initially used in penile cancers and melanoma, it was applied to breast cancer using a radioisotope by Krag et al. in 1993.⁹ Sentinel lymph node localization using blue dye was first used in breast cancer in 1994 by Giuliano et al., who reported a 93% success rate and 100% accuracy.^{10,11} A combination of blue dye and isotope introduced by Albertini et al. has gained widespread popularity because of the higher success rate.¹² Many variations to the blue dye techniques (alone and in combination) have since been used for SLN localization.¹³ We designed the present study to determine the accuracy and success rate with the use of a combined methylene blue and radioactive tracer technique to locate SLN.

Materials and Methods

Seventy patients with early stage operable breast cancer, seen between 2005 and 2009, were included in this prospective evaluation. Preoperative diagnosis included clinical examination, imaging (mammogram, ultrasound), cytology or core biopsy. Exclusion criteria were tumors >5 cm on ultrasound assessment, clinical

or radiological evidence of axillary lymph node involvement, previous operation in the breast or axilla, neoadjuvant chemotherapy and patient refusal. As part of an ethically approved prospective study, patients gave fully informed consent for SLN localization with immediate axillary clearance.

Our protocol was that early-stage tumors with negative axilla on clinical and ultrasound assessment underwent guided axillary sampling; tumors in higher stages underwent axillary clearance. Patients who had a positive axilla on guided axillary sampling usually proceeded to axillary clearance.

All patients underwent SLN localization using 4 mL of blue dye combined with radioactive colloid. The application methods for blue dye and radioactive tracer were subdermal and subareolar, with a 23G needle. We used ^{99m}Tc in patients who had lymphoscintigraphy on the same day or the night before surgery. Patients had preoperative lymphoscintigraphy and the location of SLN was marked on the skin. Four mL of blue dye was injected 10-15 min before the skin incision.

Sentinel nodes were localized with a hand-held gamma probe to look for hot nodes and to trace the afferent lymph vessels leading to the blue node. After the SLN were identified and removed, the axilla was checked for any residual radioactivity. An SLN was defined as any node that was hot, hot and only blue or blue.

Patients underwent breast conservation surgery or mastectomy. All nodes were sent for frozen section, permanent pathologic evaluation and assessed histologically hematoxylin and eosin-stained sections at nominal 2-mm intervals.

The data were analyzed with the Fisher exact test and Pearson chi-squared test. A P value <0.05 was considered statistically significant.

Results

Seventy patients who fulfilled the entry criteria participated in the study. We used a combined blue dye and radioactive colloid tracer in all 70 patients. An experienced surgeon performed the

procedure. The SLN was identified in 66 patients with a detection rate of 94.2%. A mean of 1.5 sentinel nodes were identified and harvested (range of 1-4). The SLN contained metastatic disease on pathological assessment in 23 cases. There was no pathological evidence of any metastases in the SLN in the remaining 43 patients. All SLN were located in level I of the axillary region.

In four patients, no SLN was found, so axillary dissection was performed.

There were 23 cases with positive sentinel nodes seen in the frozen section specimens, but there was 1 case with a negative sentinel node in the permanent specimens, therefore we had a false positive rate of 4.2%. There were 43 cases with negative sentinel nodes. If we had identified this patient she would have benefited from avoiding further axillary surgery. The sensitivity of the procedure in predicting further axillary disease was 95.6%; specificity was 97.6% and the detection rate of 94.2%.

On further examination of the axillary contents, one patient was found to have metastatic disease in the sample or clearance material, for a false negative rate of 2.3%. This patient underwent axillary clearance in a second operation.

Use of the combined methylene blue and radioactive tracer helped us to localize the SLN quicker with better accuracy.

Discussion

Sentinel lymph node biopsy is a technique used to identify the axillary node most likely to contain tumor cells metastasizing from a primary carcinoma of the breast. This technique provides accurate staging with fewer complications than axillary dissection, and may result in decreased cost.¹⁻³ Our results yielded an overall success rate of 94.2% in identifying the SLN with the combined methylene blue dye and radioactive tracer technique. Various studies have demonstrated that dual-agent mapping with blue dye and ^{99m}Tc yields optimal identification rates compared with either identification method alone.¹⁴

In our study, among the subset of patients for whom radioisotope status was recorded, a 94.9% concordance existed in terms of identification of the SLN with both methylene blue and ^{99m}Tc. We had four patients with no SLN, each of whom underwent axillary dissection. Further pathologic evaluation of one of these patients showed no malignancy. The other three patients had lymph nodes that were positive for malignancy. One was stage N3, which may explain why we did not find this lymph node as those at higher stages of metastasis usually have a disturbed lymphatic pathway. Another patient underwent surgery 22 hours after injection of the radioactive tracer, possibly because the SLN could not be identified.

The final patient with a positive SLN who underwent axillary dissection had a negative result in the permanent biopsy. Additionally, upon further evaluation, one patient with a negative SLN had a positive axillary lymph node and underwent additional surgery.

The tumor status of the SLN should accurately predict the histopathologic status of the regional lymphatic basin draining the tumor; in particular, a SLN free from tumor metastasis would exclude tumor spread to the at-risk regional lymphatic basin. Although an SLN with metastatic involvement of a second-tier node may be negative, this occurrence is very rare, especially when the primary tumor is in an early stage of growth. Therefore, in most patients the SLN concept remains valid.¹⁷

Comparison of the data in this study with data from studies that evaluated the success of the radioactive tracer technique in localizing the SLN demonstrates that the combined use of methylene blue and the radioisotope is an effective technique to accurately identify sentinel nodes in patients with breast cancer. The high rate of concordant identification of the SLN further supports its efficacy. The greatest benefit of using the combined technique was quicker localization of the SLN and hence an overall reduction in operative time. In the literature, the combined technique has been reported to be significantly better than blue dye alone with increased

sensitivity (77%-87%), accuracy (91.5%-95.5%) and success rate (86%-100%).¹⁵⁻¹⁹

The findings to date suggest that SLN biopsy is a safe alternative to axillary node dissection in women with early-stage breast cancer, but additional data are required to assess the significance of micrometastases in this patient population with regard to long-term survival and local/regional recurrence patterns.

Conclusion

In conclusion, the present study describes the methylene blue dye and radioisotope localization technique as a successful technique to identify SLN in patients with T1 and T2 breast cancer. We suggest that a larger prospective study be undertaken to confirm the accuracy of the combined methylene blue dye and radioisotope method to validate these findings and compare this combined technique with methylene blue dye or ^{99m}Tc isotope, alone.

References

1. Fisher B, Bauer M, Wickerham L, Redmond CK, Fisher ER, Cruz AB, et al. Relation of number of positive nodes to the prognosis of patients with primary breast cancer. An NSABP update. *Cancer* 1983; 52(9):1551-7.
2. Carter CL, Allen C, Henson DE. Relation of tumour size, lymph node status and survival in 24,740 breast cancer cases. *Cancer* 1989; 63(1):181-7.
3. Fisher ER, Anderson S, Redmond C, Fisher B. Pathologic findings from the national Adjuvant Breast Project protocol B-06: 10 year pathological and clinical prognostic discriminants. *Cancer* 1993; 71(8):2507-14.
4. Canavese G, Gipponi M, Catturich A, Di Somma C, Vecchio C, Rosato F, et al. Sentinel lymph node mapping in early stage breast cancer: technical issues and results with vital blue dye mapping and radioguided surgery. *J Surg Oncol* 2000;74(1):61-8.
5. Keramopoulos A, Tsionou C, Minaretzis D, Michalas S, Aravantinos D. Arm morbidity following treatment of breast cancer with total axillary dissection: A multivariate approach. *Oncology* 1993;50(6):445-9.
6. Lin PP, Allison D, Wainstock J, Miller KD, Dooley WC, Friedman N, et al. Impact of axillary lymph node dissection on the therapy of breast cancer. *J Clin Oncol* 1993;11(8):1536-44.
7. Tadych K, Donegan WL. Postmastectomy seromas and wound drainage. *Surg Gynecol Obstet* 1987;165(6):483-7.
8. Veronesi U, Paganelli G, Viale G, Galimberti V, Luini A, Zurrada S, et al. Sentinel lymph node biopsy and axillary dissection in breast cancer: Results in a large series. *J Natl Cancer Inst.* 1999;91:368-73.
9. Krag DN, Weaver OJ, Alex JC, Fairbank JT. Surgical resection and radiolocalisation of the sentinel node in breast cancer using a gamma probe. *Surg Oncol* 1993;2(6):335-9.
10. Giuliano AE, Jones RC, Brennan M, Statman R. Sentinel lymphadenectomy in breast cancer. *J Clin Oncol* 1997;15(6):2345-50.
11. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenopathy for breast cancer. *Ann Surg* 1994;220(3):391-401.
12. Albertini JJ, Lyman GH, Cox C, Yeatman T, Balducci L, Ku N, et al. Lymphatic mapping and sentinel node biopsy in patients with breast cancer. *JAMA* 1996;276(22):1818-22.
13. Sym DB, Collins JP, Mann GB. Comparison of blue dye and isotope with blue dye alone in breast sentinel node biopsy. *ANZ J Surg* 2005;75(9):817-21.
14. Kissin MW, Querci Della Rovere G, Easton D, Westbury G. Risk of lymphedema following the treatment of breast cancer. *Br J Surg* 1986;73(7):580-4.
15. Varghese P, Mostafa A, Abdel-Rahman AT, Akberali S, Gattuso J, Canizales A, et al. Methylene blue dye versus combined dye-radioactive tracer technique for sentinel lymph node localisation in early breast cancer. *Eur J Surg Oncol* 2007;33(2):147-52.
16. Radovanovic Z, Golubovic A, Plzak A, Stojiljkovic B, Radovanovic D. Blue dye versus combined blue dye-radioactive tracer technique in detection of sentinel lymph node in breast cancer. *Eur J Surg Oncol* 2004;30(9):913-7.
17. Mariani G, Moresco L, Viale G, Villa G, Bagnasco M, Canavese G, et al. Radioguided sentinel lymph node biopsy in breast cancer surgery. *J Nucl Med* 2001;42(8):1198-215.
18. Schijven MP, Vingerhoets AJ, Rutten HJ, Nieuwenhuijzen GA, Roumen RM, Van Bussel ME, et al. Comparison of morbidity between axillary lymph node dissection and sentinel node biopsy. *Eur J Surg Oncol* 2003;29(4):341-50.
19. Cody HS 3rd, Fey J, Akhurst T, Fazzari M, Mazumdar M, Yeung H, et al. Complementarity of blue dye and isotope in sentinel node localisation for breast cancer: Univariate and multivariate analysis of 966 procedures. *Ann Surg Oncol* 2001; 8(1):13-9.