VALIDATION OF METHYLENE BLUE IN SENTINEL LYMPH NODE IDENTIFICATION IN BREAST CANCER

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ABSTRACT

Background: Sentinel lymph node biopsy (SLNB) is now considered a standard of care in early breast cancers with N0 axillae; however, its role in locally advanced breast cancer (LABC) after neo-adjuvant chemotherapy (NACT) is still being debated. The present study assessed the feasibility, efficacy and accuracy of sentinel lymph node biopsy (SLNB) using "dye alone" (methylene blue) method in patients with LABC following NACT.

Objective: To validate methylene blue dye in sentinel lymph node identification in breast cancer.

Methodology: 179, biopsy proven cases of LABC that had received three cycles of neo-adjuvant chemotherapy (cyclophosphamide, adriamycin, 5-fluorouracil) were subjected to SLNB (using methylene blue dye) followed by complete axillary lymph node dissection (levels I-III). The sentinel node(s) were/were and the axilla were individually assessed histologically. The SLN accuracy parameters were calculated employing standard definitions. The SLN identification rate in the present study were 100%. The sensitivity of SLNB were 86.6% while the accuracy were 93.3%, which were comparable with other studies done using dual lymphatic mapping method. The SLN were found at level I in all cases and no untoward reaction to methylene blue dye was observed.

Results: The SLN identification rate in the present study were 100%. The sensitivity of SLNB were 86.6% while the accuracy were 93.3%, which were comparable with other studies done using dual lymphatic mapping method. The SLN were found at level I in all cases and no untoward reaction to methylene blue dye was observed.

Conclusions: This study confirms that SLNB using methylene blue dye as a sole mapping agent is reasonably safe and almost as accurate as dual agent mapping method. It is likely that in the near future, SLNB may become the standard of care and provide a less morbid alternative to routine axillary lymph node dissection even in patients with LABC that have received NACT.

Key Words: Methylene Blue, Sentinel Lymph Node, Breast Cancer

INTRODUCTION

Breast cancer is the most common site specific cancer in women and represents 20% of all female malignancies. In developing countries like India, 25-30% patients still present with locally advanced breast cancers (LABC). The current treatment guidelines for LABC focus upon multimodality approach i.e. neo-adjuvant chemotherapy (NACT) followed by surgery and adjuvant therapies in the form of chemotherapy, radiotherapy, hormone therapy etc. The well known advantages of NACT include, down staging and downsizing of the tumor to make it amenable to breast conservation surgery, as well as serving as an *in-vivo* test of sensitivity to the chemotherapy regimen used[1,2,3]. The histological status of axillary lymph nodes is one of the most important prognostic factors in patients with breast carcinoma and remains so, even after NACT[1,2]. NACT, initially introduced to downstage LABC to facilitate optimum surgery, results in an improved disease free survival and overall survival, which is comparable with the effects of adjuvant chemotherapy[4,5,6,7]. More recently, the indications for NACT have also been extended to selected patients with an early staged disease to allow breast conserving surgery[8,9]. Another potential advantage of NACT is the opportunity to observe chemosenstivity *in vivo*, providing prognostic information[10].

This regard, the current study were designed and the rationale of this study were to evaluate the effectiveness of methylene blue dye in identification of sentinel lymph node in breast cancer at our local population. Various studies have been carried by authors belonging to different schools of thought. They differ in their approach. Keeping in mind these discrepancies and difference of approach I have opted to conduct this study based on local practices in our setting.

METHODOLOGY

This was a Cross Sectional (Descriptive) study conducted in the department of Surgery, Khyber Teaching Hospital, and Peshawar from September 2014 to December 2015. A total sample size were 179 using 65% efficacy of methylene blue dye, 95% confidence level and 7% margin of error, with the help of WHO software for sample size determination. All case were selected through non probability consecutive sampling using

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the following selection criteria;

Patients having age 20 – 55 years, patients with early breast cancer detected on triple assessment and patients of breast cancer with no palpable lymph nodes and Patients with clinically palpable axillary metastatic lymph nodes, Patients allergic to methylene blue dye and Patients with inflammatory cancer were excluded.

Data Collection Procedure

This study was conducted after approval from hospital ethical and research committee. All patients presented to emergency department or admitted through O.P.D meeting the inclusion criteria were included in the study. The purpose and benefits of the study were explained to all the patients and informed consents were obtained. All the patients were subjected to detailed history and clinical examination. Routine investigations were done from all the patients.

All patients were operated under the supervision of a senior, who were the fellow of CPSP and have extensive experience in his field. Routine skin preparation were performed in all patients preoperatively and in all patients 1ml of sterilized solution of 1% methylene blue

Table 1. Group Wise Age Distribution

Age (years)	No. of patients	Percentage
20-30	102	57%
31-40	44	24%
41-55	33	19%
Total	100	100%

Table 2. Pre NACT vs. Post NACT tumor Size

		Mean	N	Std. Deviation
	Pre NACT	6.31	30	2.4
Tumor	Post NACT	3.44	30	1.9

Table 3. Efficacy of sentinel lymph node biopsy and axillary status

Sentinel lymph node	Axilla(n = 179)	
	Positive	Negative
Positive	76(43.3%)	0(0%)
Negative	12(6.6%)	89(50%)

was infiltrated with a 23G needle attached to the syringe, in the sub-dermal region of areola in the diseased breast(s). A gentle massage was done for about 1-2 minutes and then with in five to ten minutes a transverse or vertical incision was made in the axilla and search was started for blue node or blue lymphatics.

RESULTS

DISCUSSION

The histological status of axillary lymph nodes is one of the most important prognostic factors in patients with breast carcinoma and remains so, even after NACT[1,2]. NACT, initially introduced to downstage LABC to facilitate optimum surgery, also results in an improved disease free survival and overall survival, which is comparable with the effects of adjuvant chemotherapy[4,5,6,7]. More recently, the indications for NACT have also been extended to selected patients with an early staged disease to allow breast conserving surgery[8,9]. Another potential advantage of NACT is the opportunity to observe chemosenstivity in vivo, providing vital prognostic information[10]. Following NACT, traditionally ALND is performed as a part of optimum breast surgery. This however is associated with considerable morbidity[11,12]. A less aggressive approach is therefore sought for, making SLNB after NACT an attractive strategy as the axilla is down staged to N0 in a number of patients (20-40%)[8,13]. In concordance with the established data, the nodal down staging in the present study was about 50%. Thus considerable number of patients could be spared the morbidity of ALND, once the SLNB gets established as a standard of care in patients with LABC after NACT. Theoretically, NACT could have several negative effects on the accuracy of the SLN biopsy. Firstly, both primary tumor and metastatic lymph nodes respond by yielding reactive changes like fibrosis affecting the lymphatic drainage patterns. Secondly, chemotherapy can induce an uneven tumor response in axilla. These effects are likely to result in decreased SLNB accuracy after NACT. It has been observed in various studies that there could be a reduction in the identification rates without a significant drop in the predictive value of SLNB even after NACT[14]. The accuracy and false negative rates of sentinel lymph node biopsy after NACT were found to be comparable with those of other multicenter trials of SNB (without NACT) and the present study also highlights the same[15] The false negative rates in the present study were 13.3%, favorably comparable with those of (7-13%) in SNB studies before NACT, suggesting that the apprehension regarding skip nodal metastasis could be over-rated and that the SLNB remains almost equally reliable.

CONCLUSIONS

The present study confirms the observations of various other studies in the literature that sentinel lymph node biopsy is feasible and reliable even in locally advanced carcinoma after NACT. The possibility of skip metastasis is perhaps an exaggerated apprehension. There is a high likelihood in near future of SLNB becoming the standard of care even in post NACT-N0 axillae in LABC. SLNB with methylene blue "dye alone" method used in the present study was found to be a cost effective, reliable and almost as accurate as dual

agent mapping method to assess the status of axilla. Should SNB become established as the standard method for staging axilla, it will be reasonable to utilize this technique in LABC patients also that have received NACT, expanding the utility of both interventions.

REFFRENCE

1. Cure H, Amat S, Penault-Llorca F, le Bouëdec G, Ferrière JP, Mouret-Reynier MA, Kwiatkowski F, Feillel V, Dauplat J, Chollet P: Prognostic value of residual node involvement in operable breast cancer after induction chemotherapy. Breast Cancer res Treat. 2012, 76: 37-45. 10.1023/A:1020274709327.View ArticlePubMedGoogle Scholar

2. Kuerer HM, Newman LA, Buzdar AU, Hunt KK, Dhingra K, Buchholz TA, Binkley SM, Ames FC, Feig BW, Ross MI, Hortobagyi GN, Singletary SE: Residual metastatic axillary lymph nodes following neoadjuvant chemotherapy predict disease free survival in patients with locally advanced breast cancer. Am J Surg. 2009, 176: 502-9. 10.1016/S0002-9610(98)00253-0.View

3. Rouzier R, Extra JM, Klijanienko J, Falcou MC, Asselain B, Vincent-Salomon A, Vielh P, Bourstyn E: Incidence and prognostic signioficance of complete axillary downstaging after primary chemotherapy in breast cancer patients with T1 to T3 tumors and cytologically proven axillary metastatic lymph nodes. J Clin Oncol. 2012, 20: 1304-10.

4. Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, Wickerham DL, Begovic M, DeCillis A, Robidoux A, Margolese RG, Cruz AB, Hoehn JL, Lees AW, Dimitrov NV, Bear HD: Effect of pre-operative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol. 1998, 16: 2672-2685.PubMedGoogle Scholar

5. Van der Hage JA, Van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L, van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L: Preoperative chemotherapy in primary operable breast cancer: results from the European Organisation for Research and Treatment of Cancer trial 10902. J Clin Oncol. 2010, 19: 4224-37.

6. Mauri D, Pavlisdis N, Ioannidis JP: Neoadjuvant vs adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst. 2005, 97: 188-94.

7. Mieog JS, Van der Hage JA, Van de Velde CJ: Neoadjuvant chemotherapy for operable breast cancer. Br J Surg. 2007, 94: 1189-2000.

8. Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG, Cruz AB, Fisher ER, Wickerham DL, Wolmark N, DeCillis A, Hoehn JL, Lees AW, Dimitrov NV: Effect of preoperative chemotherapy on loco-regional disease in women with operable breast cancer: findings from NSABP B-18. J Clin Oncol. 2007, 15: 2483-93.

9. Bonadonna G, Veronesi U, Brambilla C, Ferrari L, Luini A, Greco M, Bartoli C, Coopmans de Yoldi G, Zucali R, Rilke F: Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters or more. J Natl Cancer Inst. 2008, 82: 1539-45.

10. Fisher B, Mamounas EP: Preoperative chemotherapy: a model for studying the biology and therapy of primary breast cancer. J Clin Oncol. 2009, 13: 537-40.

11. JS, Dijkstra PU, Geertzen JH, Baas P, de Vries J, Dolsma WV, Groothoff JW, Eisma WH, Hoekstra HJI: Treatment related upper limb morbidity 1 year after sentinel node biopsy or axillary lymph node dissection for stage I or II breast cancer. Ann Surg Oncol. 2004, 11: 1018-24.

12. Schrenk P, Rieger R, Shamiyeh A, Wayand W: Morbidity following sentinel lymph node biopsy versus axillary lymph node dissection for patients with breast carcinoma. Cancer. 2010, 88: 608-14.

13. Kuerer HM, Sahin AA, Hunt KK, Newman LA, Breslin TM, Ames FC, Ross MI, Buzdar AU, Hortobagyi GN, Singletary SE: Incidence and impact of documented eradication of breast cancer axillary lymph node metastases before surgery in patients treated with neoadjuvant chemotherapy. Ann Surg. 2001, 230: 72-8.

14. Mamounas EP, Brown A, Anderson S, Smith R, Julian T, Miller B, Bear HD, Caldwell CB, Walker AP, Mikkelson WM, Stauffer JS, Robidoux A, Theoret H, Soran A, Fisher B, Wickerham DL, Wolmark N: Sentinel node biopsy after neo-adjuvant chemotherapy in chemotherapy in breast cancer: results from NSABP protocol B-27. J Clin Oncol. 2013, 23: 2694-702.

15. Xing Y, Foy M, Cox DD: Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer. Br J Surg. 2006, 93: 539-46.