AN OBSERVATIONAL STUDY OF SLN MAPPING IN PATIENTS OF LOCALLY ADVANCED BREAST CANCER FOLLOWING NCT

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Abstract

Background: Locally advanced breast carcinoma (LABC) includes a wide range of clinical scenarios- advanced primary tumors (T4), advanced nodal disease and inflammatory carcinomas⁽¹⁾. Traditionally, treatment of LABC included a combination of Chemotherapy, Radiation and Surgery⁽²⁾. However, there has been a shift to Neoadjuvant Chemotherapy in recent times.⁽³⁾

Histological status and the number of axillary lymph nodes with metastasis is one of the most important prognostic factors and most powerful predictor of recurrence and survival in patients of breast carcinoma and remains so, even after neo-adjuvant chemotherapy.⁽³⁾ Information derived from the sentinel lymph node is considered valuable, with less discomfort to the patient when compared with axillary dissection.⁽⁴⁾ However, its role in detecting nodal metastasis after neo-adjuvant chemotherapy in LABC is still debatable and definitive studies to evaluate its role are still evolving.⁽⁵⁾

Materials and Methods: Patients of LABC were evaluated using ultrasonography (USG) of axilla. Neo-adjuvant chemotherapy (NACT) was administered and patients were reassessed by USG of axilla. Thirty patients with node negative axillary status were subjected to Sentinel lymph node mapping using isosulfan blue followed by Modified Radical Mastectomy and Axillary Lymph Node Dissection. Histopathological evaluation of stained and unstained lymph nodes done and the data, thus obtained, was statistically analysed.

Results: Sentinel lymph node biopsy performed using Isosulfan Blue dye alone, after neo-adjuvant chemotherapy predicts the status of axillary lymph nodes with low accuracy.

Conclusions: Further studies would be required to establish the role of sentinel lymph node biopsy in patients with LABC after NACT.

Keywords: Sentinel lymph node, locally advanced breast carcinoma, Neoadjuvant chemotherapy

Introduction

Neoadjuvant chemotherapy (NCT) has been established as a standard therapeutic modality for patients with locally advanced or early stage breast cancer. The presence of axillary lymph node (ALN) metastasis is important for decision making regarding the use of chemotherapy and NCT is considered an effective and safe treatment option for node-positive breast cancers at presentation. Sentinel lymph node biopsy (SLNB) has replaced axillary lymph node dissection (ALND) in patients with clinically node negative disease and is now considered a standard procedure.⁽⁵⁾ In patients with biopsy-proven ALN metastasis at diagnosis, the current standard surgical procedure for axilla is completion ALND at definitive surgery after NCT.⁽⁵⁾ However, 20-70 % of node-positive patients experience pathologic complete remission (pCR) of ALNs after NCT depending on the chemotherapeutic

implemented.⁽⁵⁾ Thus, it is debatable whether ALND is optimal for all patients receiving NCT for management of locally advanced breast cancer (LABC).

Our study aims to evaluate the role of sentinel lymph node mapping in patients with locally advanced breast cancer receiving anthracycline based neo-adjuvant chemotherapy.

Materials and Method

Our Study was an Observational study of thirty patients, which was conducted over a period of one and half year between November 2015 and March 2017.

Patients with LABC (i.e. Stage IIb and stage III) were evaluated after taking informed consent for enrolment in the study.

Ultrasonography (USG) of axilla was done for accurate measurement of the lymph node size in order to stage the

disease accurately. FNAC was not done for assessing the nodal metastases in the study.

The patients were then subjected to blood and radiological investigations including an echocardiogram before initiation of neo-adjuvant chemotherapy (NACT) that was administered in standard doses at three weekly intervals [Cyclophosphamide 500 mg/m², Adriamycin 50 mg/m² with or without 5-FU 500 mg/m²]. All cases were re-assessed clinically and with ultrasonography of the axilla for response after each cycle.

After 3 weeks of the last cycle of NACT, only those thirty patients who became clinically and ultrasonologically node negative, were included in the study. They were taken up for surgery i.e. modified radical mastectomy (MRM) with a standardized technique by the same surgical team.

Pre-operatively peri-tumoral injections of 2-3 ml of isosulfan blue dye was given followed by breast massage for five minutes before the patient was draped and prepared for surgery.

The sentinel node/s (i.e. blue node/s – as shown in figures 1 and 2) were mapped and isolated after raising the flaps and before the standard axillary lymph node dissection.

Figure 1: Blue stained sentinel lymph node

Figure 2: Blue stained lymphatics in axilla

The sentinel lymph node/s was sent in a separate container and were assessed for the presence of metastatic deposits and compared with the rest of the

axillary lymph nodes. Stained lymph nodes testing positive and negative for tumor on histopathology vs those unstained testing positive and negative were analysed statistically using SPSS version 20. Chi square was applied as the sample size was 30. Flowchart depicting the method of research shown in figure 3.

Figure 3: Flowchart depicting method of the research

Results

We studied 30 female patients with biopsy proven locally advanced breast cancer and who were node negative after receiving 3 cycles of anthracycline based neo-adjuvant chemotherapy. The mean age of patients in our study was 46.43 with a standard deviation of 8.908. Out of 30 patients, 8 were pre-menopausal and 22 were post-menopausal. Among these 30 patients, 18 belonged to stage IIIa, 6 to stage IIIb and 6 to stage IIIc.

Out of 30 patients, 12 had lump in upper outer quadrant, 6 in upper inner quadrant, 4 in lower outer and 8 in lower inner quadrant. Sentinel lymph nodes were successfully identified in 24 patients. Identification rate was 80%. Comparison of histopathology report of sentinel lymph nodes with axillary lymph nodes dissected was done, as shown in Table 1.

Table 1: Comparison of histopathology report of sentinel lymph nodes with ALND (excluding sentinel lymph node)

	ALND Positive (n=20)	ALND Negative (n=4)
Sentinel lymph node positive (n=14)	12	2
Sentinel lymph node negative (n=10)	8	2

Since positive sentinel lymph nodes also constitutes a "Positive Axilla" irrespective of ALND, the summarized results for comparison of histopathology report of sentinel lymph nodes with status of axilla are slightly different from above (Table 2).

Table 2: Comparison of histopathology report of sentinel lymph nodes with status of axilla

	Axilla Positive (n=22)	Axilla Negative (n=2)
Sentinel lymph node positive (n=14)	14	0
Sentinel lymph node negative (n=10)	8	2

Out of 24 patients in whom sentinel lymph node was successfully identified, 14 patients had disease in both sentinel lymph nodes and axillary lymph nodes. In 8 patients, sentinel lymph nodes were negative for disease while disease was present in other axillary lymph nodes. In 2 patients, both sentinel lymph nodes and other axillary lymph nodes showed no evidence of disease.

Out of 6 patients in whom sentinel lymph nodes were not identified, 5 showed presence of disease in other axillary lymph nodes.

Sentinel lymph node accuracy parameters were calculated according to standard definitions, used in various studies on sentinel lymph nodes and they were as follows-

The **Identification Rate** was defined as the number of patients in whom blue node/lymphatics could be identified divided by the total number of patients in whom the sentinel lymph node biopsy was attempted. The identification rate in present study was 80%, i.e. sentinel lymph node could be identified in 24 patients out of 30 in whom sentinel node mapping was done.

The results from each successfully identified sentinel lymph node were categorized as true positive, true negative or false negative, taking the outcome of complete status of axilla as the "reference standard".

A **True Negative** SLN was defined in this study as a negative SLN and a negative axilla after ALND. True negative SLN in the present study is 2 out of 24 patients.

A **True Positive** SLN was defined as a positive SLN with or without a positive axilla and in this study 14 cases were true positive.

A **False Negative** SLN was defined as negative SLN with positive lymph nodes on ALND. There were 8 false negative cases in this study out of a total of 24 cases.

From the previously mentioned definitions, following statistics have been calculated-

True Positive= 14 out of 24

True negative= 2 out of 24

False Negative- 8 out of 24

Negative Predictive Value= True negative/(True negative+ False negative)= 2/10= 20%

Positive Predictive Value= 14/14= 100% (implying that when sentinel lymph node is reported positive, the status of axilla is also considered positive)

Sensitivity of SLN = True positive/(True positive + False negative) = 14/22 = 63.6%

Accuracy = (True positive + True negative)/ Total number of patients in whom sentinel lymph node was successfully identified = 16/24 = 66.7%

Statistical Analysis

Null hypothesis - SLNB is not a procedure of choice in patients following anthracycline based neo-adjuvant chemotherapy as compared to ALND (Table 3).

Table 3: Table for testing null hypothesis that SLNB is not a procedure of choice in patients following anthracycline based neo-adjuvant chemotherapy as compared to ALND.

	ALND Positive (n=20)	ALND Negative (n=4)
Sentinel lymph node positive (n=14)	O =12 E = 20X14/24 = 11.67	O = 2 E = 4X14/24 = 2.33
Sentinel lymph node negative (n=10)	O = 8 E = 20X10/24 = 8.33	O = 2 E = 4X10/24 = 1.67

Chi square= Sum of [(O-E)^2/E]=
0.0093+0.0467+0.0131+0.0652= 0.1343

Degree of freedom=1

From probability table, the value of chi square for degree of freedom 1 with a probability of 0.05 (significant level=95%) is 3.84

Since the value of chi square calculated from our data is much below the level so the null hypothesis is true. According to our study, SLNB is not a superior method in the management of axilla of patients who have received neo-adjuvant chemotherapy as compared to ALND.

Discussion

In this study, we found that in the patients who have undergone neo-adjuvant chemotherapy, once sentinel lymph nodes have been identified they can predict the status of axilla with an accuracy of 66.7%. In the study, the histopathological reports of sentinel lymph nodes and the rest of the axillary lymph nodes in the mastectomy specimen were compared.

In recent times, breast cancer has become a disease that is amenable to a wide variety of elective therapeutic options thereby enabling encouraging chances of survival for the patient.⁽⁶⁾ Traditionally, surgical management in the form of modified radical mastectomy has been the standard treatment for complete removal of the disease.⁽⁷⁾

Neo-adjuvant chemotherapy had originally been introduced to down stage LABC to facilitate optimum surgery, also results in an improved disease free survival and overall survival, which is comparable with the results of adjuvant chemotherapy. (8)

Nowadays, the benefit of neo-adjuvant chemotherapy is to downstage the disease, in order to enable selected patients with an early stage disease to undergo breast conservation surgery.⁽⁹⁾ Another advantage of NACT is the opportunity to assess chemo sensitivity in vivo, thereby providing vital information for planning adjuvant chemotherapy for the patient.⁽¹⁰⁾

Nowadays, taxanes are also considered first line drugs for neo-adjuvant chemotherapy. Data from few studies shown advantage of choosing taxane based chemotherapy in tumors positive for HER2neu receptor.⁽¹¹⁾

The histological status of axillary lymph nodes is one of the most important prognostic factor in patients with breast carcinoma.⁽¹²⁾

In our study, due to patient demographics, family setup and lack of awareness, all patients in the study had stage III disease.

Following NACT, a complete axillary dissection upto level II is usually performed as a part of modified radical mastectomy.⁽¹³⁾ This, however, is associated with considerable morbidity. Sentinel lymph node biopsy, thus serves as a useful and less radical modality for accurately assessing the axillary nodes and then tailoring the management.⁽¹⁴⁾ This is encouraged by available data regarding downstaging of nodal disease to N0 after NACT as seen in 20-40% of the patients. Thus, theoretically, considerable number of patients could be spared the morbidity of ALND, once the SLNB gets established as a standard of cure in patients with LABC after NACT.⁽¹⁵⁾

The accuracy of sentinel lymph node biopsy after neo-adjuvant chemotherapy, may always remain uncertain due to a number of reasons. Firstly, both primary tumor and metastatic lymph node respond by yielding reactive changes like fibrosis.⁽¹⁶⁾ This alters the architecture of lymphatics. Normal lymphatic drainage channels may get obliterated leading to opening up of alternate channels for drainage, theoretically accounting for skip metastasis. Secondly, chemotherapy can induce uneven tumor response in axilla. These effects are responsible for decreased accuracy of SLNB after NACT.⁽¹⁶⁾

There is also some difference in identification rate of sentinel lymph nodes after neo-adjuvant chemotherapy based on the technique used for SLNB. Data from meta-analysis by Xing-et al. shows the mean identification rate to be 93%, 95% and 92% for dye alone, radio-isotope alone and combination, respectively.⁽⁵⁾ In this meta-analysis,

there were 2 studies assessing sentinel lymph node biopsy using blue dye alone in which a total of 41 patients underwent the procedure out of which sentinel lymph node was identified in 38 patients. The identification rate in one of the study was found to be 80% and in the other study it was found to be 98%. Mean identification rate was identified to be 93%.⁽⁵⁾

The identification rate in our study was 80%, which is even below the lower limits of the data from previous studies. The reason for this may be that all patients included in the study had stage III disease, presumably having extensive involvement and blockage of lymphatics draining the tumor. Out of the 6 patients in whom sentinel lymph node could not be identified, 5 eventually had axillary nodes positive for lymph nodal metastasis. Another reason for lower identification rate in this study, that only blue dye was used for the procedure. According to the data from the meta-analysis by Xing et al., identification rate may also be improved by using radio-isotope either alone or in combination with blue dye, with identification rate as high as 98%.⁽⁵⁾

In our study, the sensitivity of the procedure was found to be 63.6% which is out of concordance with previous data where sensitivity was found to be 80% (60-90%).⁽⁵⁾

Negative predictive value and overall accuracy for the procedure from the pooled data was found to be 90% (range 56-100%) and 94% (range 77-100%), respectively.⁽⁵⁾ In our study, the negative predictive value was 20% and accuracy was 66.7% which is out on concordance with the data obtained from Xing et al. the reason for such differences could be explained by the selection of patients in the study, which included all patients with stage III disease.⁽⁵⁾

In the previous studies, the false negative rates have varied from 0% to as high as 33%.⁽⁵⁾ In a large multi-centre trial conducted by Mamounas et al as a part of NSABP B-27 trial, studied SLNB after neo-adjuvant chemotherapy, 428 patients underwent lymphatic mapping and the false negative rate was 11%. In our study the false negative rate was 33.3%.

A drawback of this study was the small sample size.

From the study, we can see that sentinel lymph node biopsy using isosulfan blue dye alone after neo-adjuvant chemotherapy cannot accurately predict the status of axillary lymph nodes.⁽⁵⁾ However, studies with a larger sample size would be required to validate these findings before it cannot be applied to potentially avoid axillary lymph node dissection.

Conclusion

From the results of our cross-sectional study we can conclude that-

1. Sentinel lymph node biopsy performed using isosulfan blue dye alone has low identification rates in patients after neo-adjuvant chemotherapy and when sentinel lymph node is identified, the accuracy of predicting the status of axilla is also low.

2. Since the sample size of the study was quite small, based on this, sentinel lymph node biopsy cannot be ruled out as a standard of care. For validating, the procedure as a standard of care, larger studies including larger number of patients is required.

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