Sentinel Lymph Node Biopsy in Early Breast Cancer: An Institutional Experience from GCRI for the Year 2018-19

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Summary

Sentinel lymph node biopsy is the standard of care for management of node negative axilla in early breast cancer. Objectives of present study were to share our institutional experience, to analyze factors predicting presence of positive non sentinel axillary nodes, to analyze factors predicting axillary node metastasis. This was an observational study of prospectively managed data of sentinel lymph node biopsy in early breast cancer for the year 2018-2019. Total 168 procedures were performed. SPSS statistics version 25 was utilized for statistical analysis. Overall sentinel node identification rate was 95.2% (160/168). There was no statistically significant difference between blue dye method alone or dual technique (p=0.736). Sentinel lymph node biopsy after lumpectomy (n=40, success rate=92.5%) did not affect sentinel node identification (p=0.352). Median of sentinel nodes was four (1–13). Only 35.7% patients had positive non sentinel axillary nodes after having positive sentinel nodes. Presence of three or more positive sentinel nodes (80% vs. 29.7%), positive non blue non-radioactive node (suspicious enlarged node) (66.7% vs. 30.6%) were associated with high chance of finding positive non sentinel axillary nodes. Hence it may be concluded that dual method is standard of care for sentinel lymph node biopsy, but in resource constraint center blue dye technique can be utilized. In selected patients axilla may be preserved even after positive one or two sentinel nodes. Factors like hormone receptor negative status, tumor biology other than IDC, age>50 years, grade 1 tumor and T1 tumor size are associated with high chance of negative SLNs.

Keywords: Sentinel lymph node biopsy, Axillary lymph node dissection, Early breast cancer, Radiocolloid, Methylene blue

Introduction

Sentinel lymph node biopsy (SLNB) is the standard of care for management of node negative early breast cancer. It prevents morbidities like lymphedema, sensory neuropathy, shoulder dysfunction, and seroma formation associated with axillary lymph node dissection (ALND). Main objectives of present study were to audit and share our institutional experience of SLNB, to study factors associated with extra positive nodes (other than SLNs) in ALND, to study factors associated with axillary nodal involvement in present patients' cohort.

Materials and Methods

Patients

This study presents the experience of SLNB in early breast cancer from February 2018 to July 2019 from a prospectively managed data in The Gujarat Cancer & Research Institute. SLNB was done in all clinicoradiologically node negative axilla. In those patients who had clinicoradiologically suspicious N1 node, ultrasound guided fine needle aspiration cytology (FNAC) was done and SLNB was done only if FNAC came negative or FNAC was not possible due to very small size of node. Total 168 SLNBs were performed during the study period, 117(69.6%) by dual technique (radiocolloid + methylene blue dye) and 51(30.4%) by only blue dye technique (methylene blue dye). Only blue dye technique was done only when radiocolloid was not available in nuclear medicine department or due to other logistic issues. Out of 168 patients, SLNs were identified in 160 patients. From this 160 patients, sentinel lymph nodes were sent for frozen section analysis in 154 patients and in 6 patients nodes were sent directly for final histology examination.

Blue dye method

Two to five ml of one percent W/V methylene blue dye was injected aseptically after painting and draping in periareolar region intradermally or subdermally based on surgeon's preference. The injection site was massaged for five minutes. Then first, an axillary incision (in breast conservative surgery) or superior flap incision at its lateral aspect (in case of mastectomy) was put and dissection was done towards the axilla. Once the blue lymphatic got identified, it was traced to reach blue axillary node. (Figure 1) After removing first blue node, other blue nodes were searched in nearby area and were removed. Utmost care was taken not to injure intercostobrachial nerve. The whole procedure was completed by 15 to 20 minutes after putting skin incision; as more delay may cause blue dye to reach second echelon lymph nodes which increases unnecessary more lymph node removal.

Radiocolloid method

Aseptically prepared filtered 99mTc sulfur colloid (filtered with 0.22μ Millipore filter) (total 0.4

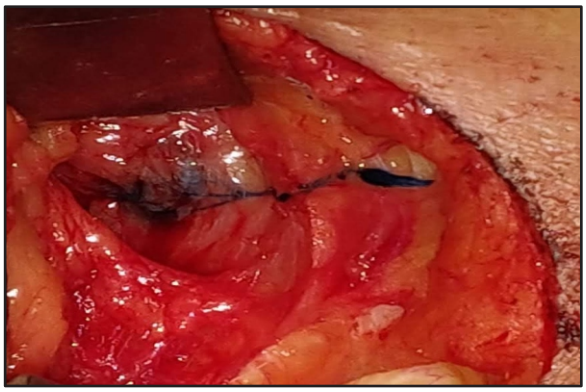

Figure 1: Blue lymphatic draining towards blue sentinel lymph node

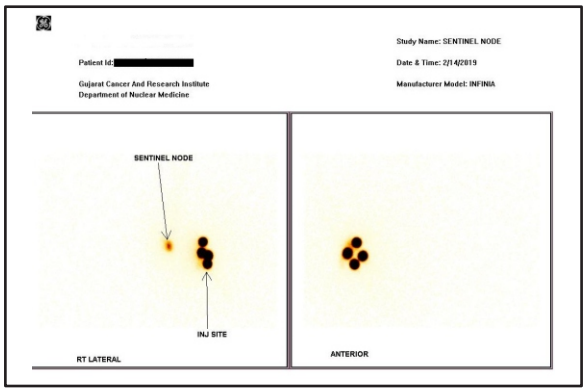

Figure 2 : Static nuclear scan image after injection of radiocolloid

Figure 3: Ex vivo radioactivity counting by gamma probe of highest active node

ml) was injected in periareolar region intradermally. The total injected dose was 400-500 uCi for the same day surgery (2-3 hours before surgery) and approximately 800-1200uCi, if the surgery was planned next day (16-24 hours before surgery). Usual precautions like gentle shaking of the syringe prior to injection were taken to avoid the clumping of colloidal particles together. After injecting, each site was massaged for one to two minutes to facilitate lymphatic flow. Bleb formation at the injected site confirms the proper injection technique. Sequential dynamic or static images were taken to identify the sentinel node by gamma imaging. (Figure 2) Sentinel node localization by probe and surface marking was done after proper identification of sentinel node by gamma probe in the department of nuclear medicine. During surgery, the highest radioactive (hot) sentinel lymph node removed first. Other radioactive nodes were searched by gamma probe and removed till the radioactivity of the axillary bed was less than ten percent of the highest radioactive sentinel lymph node. (Figure 3)

Any enlarged hard suspicious non blue non-radioactive nodes were also removed, as diseased node might not take dye or radiocolloid if it was studded with disease or lymphatics were blocked by the tumor cells.

For patients who presented after lumpectomy from outside our institute and had scar at upper outer quadrant, blue dye and radiocolloid were injected at upper and outer side of the scar. In such cases to prevent obscuring of the radioactive sentinel lymph nodes by background radioactivity of injection site, the skin of radiocolloid injection site were excised if required.

Intraoperative frozen section evaluation

Frozen section analysis was done as per the recommendation provided by the College of American Pathologist. All sentinel lymph nodes sent for frozen section were submitted entirely. Sentinel lymph nodes were bisected along the longitudinal axis and 2mm thick multiple slices were submitted. Imprint smears were also taken in all large lymph nodes. Two slides were prepared from each slice of tissue. Sections were stained with Hematoxylin and Eosin. The entire procedure took 15-20 minutes.

Statistical Analysis:

SPSS Statistics for Windows, version 25 (IBM Corp, Armonk, NY) was utilized for statistical analysis. Frequencies in descriptive statistics was used to calculate mean, median and range. Pearson Chi-square test was applied as a test of significance. Multivariate analysis was done by logistic regression method. P value <0.05 was considered significant.

Results

In present series, 99.4 % (167/168) patients were female and one patient was male. Median age of patients was 52 years (range: 28 -82 years).(Figure 4) Out of 168 SLNB procedures; 111 patients got spared of any radical axillary treatment [ALND or radiotherapy(RT)], 50 patients underwent ALND and 7 patients received radiotherapy to axilla [Figure 5]. Breast conservative surgery was done in 43.5 %(73/168) patients. Median node yield was four (range-1 to 13) in SLNB and 15(range- 8 to 27) in ALND. (Figure 6)

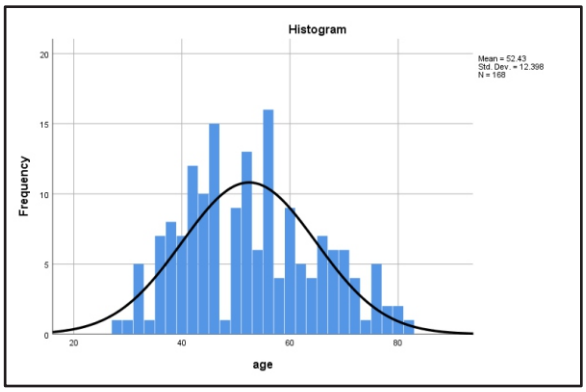

Figure 4: Histogram showing age distribution of present study cohort

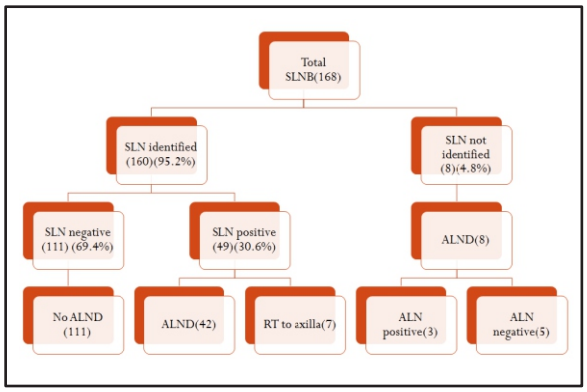

Figure 5: A Hierarchy graph showing the result of SLNB procedures and final axillary treatment received by present study cohort

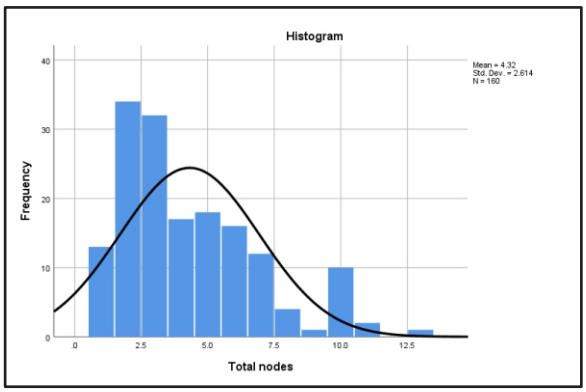

Figure 6A : Histogram showing node yield in SLNB

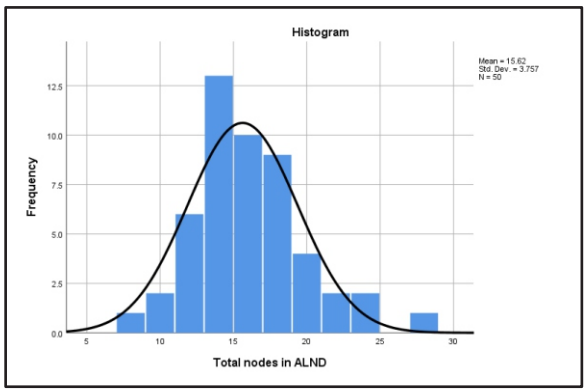

Figure 6B: Histogram showing node yield in ALND

Node identification rate

Total 117 cases were done by dual technique and 51 cases were done by blue dye technique only. Overall node identification rate in our study was 95.2% (160/168). In blue dye only technique the SLN identification rate was 96.1 %(49/51) while by dual technique it was 94.9%(111/117; p=0.736). Although this was not quantified in present study, it was experienced that in dual technique it was easier and faster to identify sentinel nodes (blue and hot nodes), which took more time and more dissection in blue dye technique alone.

As study institute is a tertiary cancer care institute, many patients came after undergoing breast lump excision outside the institute. SLNB was also done in such cases if axilla was node negative. In present study 23.8 %(40/168) such cases underwent SLNB. SLN identification rate in these patients was 92.5 %(37/40) [p = 0.35{when comparing with SLN identification rate of non-lumpectomy patients which was 96.1 %(123/128)}].

Rate of positive non sentinel nodes in ALND specimen and factors affecting it

Out of 42 patients who underwent ALND for positive SLN, only 15 patients (35.7%) had extra positive nodes in ALND specimen, which means that 64.3% patients had undergone unnecessary ALND. Factors like more than two positive SLNs, positive non blue non radioactive suspicious node, extranodal extension in SLNs, LVI in primary tumor and their effect on presence of extra positive nodes in ALND was analyzed. Presence of more than two positive SLNs was significantly associated with high chance of presence of extra positive nodes in ALND and positive non blue non radioactive SLN was showing trend towards it (Table 1).

Analysis of various factors and axillary lymph node involvement

Total 52 patients (31%) had positive axillary node in present study in final histology. On comparing ultrasonography findings with final axillary node status, overall accuracy of sonography was 65.9% with sensitivity of 21.2% and specificity of 86.1% (Table 2).

In total 154 patients, frozen section analysis of SLNs was done. In 153 patients there was concordance between frozen report and final histology report of SLNs, while in one patient frozen report of SLNs was negative but final histology report of SLNs came out to be positive, so this patient was given axillary radiotherapy. Accuracy of frozen section analysis was 99.4%(153/154) and sensitivity was 97.8%(44/45).

Table 1: Factors associated with presence of positive non sentinel nodes in ALND specimen

Factor	% of cases with extra positive nodes	p value
Number of positive SLNs: >2 SLNs positive <=2 SLNs positive	 80% (4/5) 29.7% (11/37)	0.028
Status of non blue non radioactive SLN: Positive Negative/not identified	 66.7% (4/6) 30.6% (11/36)	0.087
ENE in SLN: Present Absent	 37.5% (6/16) 34.6% (9/26)	0.850
LVI in primary Present Absent	 30% (6/20) 40.9% (9/22)	0.461

Table 2: Comparison of ultrasonography finding of axilla and final (histological) axillary status

USG status of axilla	Final histological status of axilla	
	Positive	Negative
Pathological/ metastatic node	11 (True Positive)	16 (False Positive)
Benign node	41 (False Negative)	99 (True Negative)

Patient and tumor characteristics and their effect on positive axillary status was analyzed.(Table3 and 4) On univariate analysis, factors like age<=50, higher T stage, invasive ductal carcinoma biology, high grade, and positive hormone receptor status were significantly associated with more chance of positive axillary lymph node, while lymphovascular invasion showed trend towards positive axillary status. On multivariate analysis, hormone receptor positive status was significantly associated with positive axillary node, while age <50 and high T stage showed trend towards positive axillary status.

Discussion

Median age of breast cancer in U.S. is 62 years, while in present study it was 52 years.[1] This suggests that there is an unmet need to identify those factors which put Indian women at a risk to get breast cancer ten years earlier.

Axillary lymph node status is one of the most important prognostic factors in breast cancer. Sentinel lymph node biopsy has replaced axillary lymph node dissection in node negative early breast cancer, as lower morbidity with comparable survival can be achieved with SLNB.[2-4]

Nonsurgical assessment of the axilla is not promising, different imaging modalities like

Table 3: Univariate analysis of various factors and their impact on final axillary status

Characteristics	Sub characteristics	Axilla positivity rate	p value
Age (years)	<=50 >50	40.3% (31/77) 23.1% (21/91)	0.016
T stage	Tis T1 T2 T3 Tx	0% (0/1) 14.3% (5/35) 37.5% (42/112) 11.8% (2/17) 100% (3/3)	0.007 (excluding Tis and Tx)
Multicentric disease	Present Absent	33.3% (4/12) 30.8% (48/156)	0.853
Disease histology	Favorable (medullary, mucinous, papillary, DCIS, tubular) Metaplastic carcinoma ILC IDC	 0% (0/11) 0% (0/3) 16.7% (1/6) 34.5% (51/148)	0.007 (for IDC vs. other histology)
Grade	1 2 3 Unknown	18.8% (3/16) 46.7% (28/60) 30% (21/71) 0% (0/21)	0.042 (excluding unknown)
Lymphovascular Invasion	Present Absent	38.6% (27/70) 25.5% (25/98)	0.071
Perineural invasion (PNI)	Present Absent	42.9% (6/14) 29.9% (46/154)	0.314
Hormone/Her 2 receptor status	HR+Her2- HR+Her2+ HR-Her2+ HR-Her2- Unknown	37.1% (23/62) 45.9% (17/37) 13.8% (4/29) 16% (4/25) 30% (4/15)	0.009 (excluding unknown)

Table 4: Multivariate analysis of factors affecting axillary lymph node status

Variable	Odds ratio	95% Confidence Interval of odds ratio	p value
Age groups			
>50 years	1		
<=50 year	2.264	0.983-5.212	0.055
T stage			
T1	1		0.154
T2	2.986	0.904-9.864	0.073
T3	1.240	0.157-9.785	0.838
Histology			
Pathology other than IDC	1		
IDC	4.407	0.398-48.869	0.227
Grade			
G1	1		0.149
G2	2.315	0.498-10.753	0.284
G3	1.024	0.207-5.066	0.977
LVI			
Absent	1		
Present	1.551	0.666-3.613	0.309
PNI			
Absent	1		
Present	1.179	0.316-4.395	0.807
Receptor status			
HR negative	1		
HR positive	4.975	1.751-14.135	0.003

Table 5: Results of ultrasonography findings of present study and study by Hwang et al[5]

	Present study	Hwang et al study
Accuracy	65.9%	77.1%
Sensitivity	21.2%	44.6%
Specificity	86.1%	88.7%
Positive predictive value	40.7%	58.6%
Negative predictive value	70.7%	81.7%

ultrasonography, magnetic resonance imaging, and positron emission tomography/computed tomography have been proven to be of limited value in cN0 axilla.[5] In present study also, ultrasonography was of limited help with better specificity but poor sensitivity (Table 5).

In present study cohort, sentinel node identification rate was 95.2%. There was no significant difference with either blue dye alone method or dual tracer method. Combined use of both tracers appears to be complementary, minimizing the false negative rate (FNR) in most but not all studies.[6-9] In American college of Surgeons Oncology Group (ACOSOG) Z0010 trial also there was no significant differences in the rate of sentinel node identification with the use of blue dye alone, radiocolloid alone, or dual technique.[8] In systemic review by American Society of Clinical Oncology (ASCO), use of dual technique was associated with an almost significant trend toward fewer FNRs.[9] However in situations like surgeons with limited experience, prior breast or axillary surgery, obese patient, and after neoadjuvant therapy , dual technique should be used as there is high chance of low identification rate and high FNR with single technique.[7,8] Another important finding in present study was successful application of SLNB in patients who had undergone previous diagnostic excision biopsy of breast lump, there was no statistically significant difference of lymph node identification between patients who underwent lumpectomy vs. no lumpectomy prior to SLNB [92.5%(37/40) vs. 96.1% (123/128) respectively, p=0.35]. Other studies also have demonstrated similar findings and shown feasibility of SLNB for such patients.[10,11] One thing that should be taken care in such patients is that patients who had lump in upper outer quadrant of breast, should be injected tracer at outer expect of the excision scar as lymphatics might have been broken at the scar site which might hamper lymph flow if tracer injected at periareolar region or at inner site of the scar.

Theoretically, DCIS (Ductal carcinoma in situ) is a noninvasive disease and it doesn't spread by lymphovascular route. However, according to one metaanalysis, up to 26% of the patients diagnosed by needle biopsy may harbor invasive or microinvasive disease on final histopathology.[12] Multiple factors like palpable mass, mammographic size>4 cm, high grade, age <55 years, diagnosis on smaller core biopsy needle, and muticentricity may predict an increased risk of invasive or microinvasive component in the final specimen.[13] Also patients who undergo mastectomy for DCIS should undergo SLNB, as chance of SLNB is lost if final histopathology suggest

invasive disease. In present series , four patients had cTis (three had DCIS and one had paget's disease) , out of which in final histological examination only one patient had DCIS, rest all had invasive or microinvasive disease. One reason for this finding is that, screening mammography is not common in our country, and majority of our patients with DCIS have a palpable mass, which put them into a high risk of having invasive or microinvasive disease.

Median sentinel node retrieval in present series was four (range 1-13). Wong et al[14] in their prospective multi institutional study, suggested that single sentinel node identification was associated with higher FNR (14.3%) as compared to multiple sentinel nodes retrieval (4.3%). In their study, use of blue dye injection alone was the only factor independently associated ($p<0.0001$) with identification of a single SLN. Chagpar et al[15] in their multi-institutional prospective study, retrieved median two SLNs (range 1-18), with more than three nodes removed in 17.9% patients. They suggested that FNR decreases with multiple SLNs identification, they also suggested that though most of the patients will have three or fewer SLNs identified, if more than three SLNs are identified, these SLNs should be removed because there is a significantly higher FNR associated with limiting SLN biopsy procedures to three SLNs. All blue, hot (more than ten percent radioactivity of the highest radioactive node), nodes at the end of blue lymphatics, and suspicious enlarged hard nodes should be sampled as sentinel nodes.

Multiple studies have shown that only approximately 40% of patients with a positive sentinel lymph node had residual disease in the axilla.[16,17] In present series, only 35.7% (15/42) patients had extra positive nodes in ALND specimen other that positive sentinel nodes. Presence of more than two positive SLNs was strongly associated with presence of extra positive nodes, while presence of positive non blue non-radioactive node was showing trend towards presence of extra positive nodes. Changsri et al[18] noticed that presence of extranodal extension (ENE) and size of the metastatic deposit in SLNs were associated with presence of residual disease in axilla. Turner et al[19] noticed presence of peritumoral lymphovascular invasion (LVI), size of primary tumor, ENE in SLNs as predictor of positive non sentinel lymph nodes.

Many trials studied avoidance of axillary dissection after positive SLNs. According to ACOSOG Z-0011 trial,[20] completion ALND can be avoided in patients with T1 or T2 breast cancer with one or two positive SLNs undergoing breast conservative surgery and SLNB followed by whole breast irradiation. In present series, total 49 patients have positive SLNs, out of which 16 (32.7%) patients were fulfilling Z0011 criteria and they could have been spared of further axillary treatment. After Mapping of the Axilla: Radiotherapy or Surgery (AMAROS) trial[21] compared axillary dissection vs. axillary radiotherapy after positive sentinel nodes by SLNB. There was no difference between disease free survival and overall survival. In present study, seven patients were given axillary radiotherapy instead of axillary dissection after positive sentinel nodes. The AMAROS trial showed axillary radiation to be an acceptable alternative to ALND in patients who have positive sentinel node(s) but do not meet the Z0011 criteria. For those who meet the Z0011 criteria, axillary radiation is likely to add morbidity without any added benefit. After the results of above mentioned trials on avoidance of completion ALND, many centers across the world have decreased the practice of completion ALND and intraoperative frozen section nodal assessment after SLNB.[22,23] In present series also we had started decreasing the use of intraoperative evaluation of sentinel nodes during last three months by not sending frozen section analysis in six cases, with the plan of giving axillary radiation if sentinel nodes comes positive, in accordance with AMAROS trial.

On univariate evaluation of factors affecting lymph node involvement, factors like young age<=50($p=0.016$), higher T stage ($p=0.007$), invasive ductal carcinoma (IDC) biology ($p=0.007$), high tumor grade($p=0.042$), and positive hormone receptor status($p=0.009$) were significantly associated with positive axilla, while lymphovascular invasion showed trend towards positive axillary status. Tumor biologies like medullary, mucinous, papillary, DCIS, tubular, metaplastic carcinoma, invasive lobular carcinoma have significantly less lymph node involvement ($p=0.007$). On multivariate evaluation, hormone receptor positive status was the only factor significantly ($p=0.003$) associated with positive axillary involvement, while young age (<50) and high T stage showed trend towards more axillary metastasis. In accordance to the present study, Oliveira Filho HR et al[24] reported that molecular subtype luminal A(ER and PR positive and Her-2 negative), larger tumors, younger patient's age, and the presence of LVI have the highest likelihood of axillary lymph node metastasis in early breast cancer, while triple negative subtype is predictive of a lower incidence of axillary lymph node metastasis regardless of patient's age or tumor size. They also reported in their results that patients with triple negative tumors had approximately a 90% lower chance of developing lymph node metastasis compared to those with luminal A tumors[OR=0.11; 95% CI 0.01-0.88; $p=0.01$). Ashturkar et al[25] also reported that ER and PR negative tumor, favorable histological type and grade I tumors have low probability of axillary involvement. From these

results, it appears that in invasive ductal carcinoma histology, hormone receptor positive disease has more propensity for locoregional spread while hormone receptor negative disease has more propensity for systemic spread.

Though in present series higher grade (grade 2 > grade 1) and higher T stage (T2 > T1) showed significant lymph node involvement in univariate analysis, grade 3 tumors and T3 stage tumors showed decreased lymph node involvement than grade 2 and T2 stage respectively. To find the reason, subgroup analysis was done. According to subgroup analysis of grade, there were significantly more hormone receptor positive tumors in grade 2 than in grade 3 subgroup (76.3% vs. 52.2% respectively; p=0.005) and in present series hormone receptor positive status was the only factor which was strongly associated with axillary lymph node involvement by both univariate and multivariate analysis. So this could be the reason of why grade 2 tumors had more lymph node involvement as compared to grade 3 tumors. On other hand, for T stage, the number of patients with T3 tumors (11.8%) was small in present series, it appears that T3 tumors only with low probability of lymph node metastasis might remain clinicoradiologically node negative and were able to undergo SLNB. Also 41.2%(7/17) of T3 tumors had biology other than invasive ductal carcinoma (biology other than IDC had low chance of lymph node metastasis) and other 41.2% (7/17) T3 tumors were grade 3 (grade 3 tumors showed low lymph node metastasis as compared to grade 2 tumors). Because of above mentioned reasons, there might be low lymph node involvement in T3 than T2 tumors in present series, but it is not justifiable to generalize this finding and to conclude that T3 tumors are associated with low chance of lymph node spread, a larger cohort needs to be analyzed to reach final conclusion.

Conclusion

Sentinel lymph node biopsy is standard of care for the management of node negative early breast cancer. Ultrasonography has good specificity but poor sensitivity to assess axillary status. SLNB can be performed after lumpectomy. Dual method is standard of care for SLNB, but in resource constraint centre, blue dye technique can be utilized. Role of intraoperative frozen section is decreasing after Z0011 and AMAROS trial results. Chances of extra positive axillary nodes(other than SLN) are high when 3 or more SLNs are positive or non blue non radioactive node is positive, so in selected patients axilla may be preserved even after positive one or two sentinel nodes. Factors like hormone receptor negative status, tumor biology other than IDC, age>50 years, grade 1 tumor and T1 tumor size are associated with high chance of negative SLNs.

Abbreviations:

ACOSOG- American College of Surgeons Oncology Group
ALND- Axillary lymph node dissection
AMAROS- After Mapping of the Axilla: Radiotherapy or Surgery
ASCO- American Society of Clinical Oncology
DCIS- Ductal carcinoma in situ
ENE- Extranodal extension
ER- Estrogen Receptor
FNAC- Fine needle aspiration cytology
FNR- False negative rate
HR- Hormone receptor
IDC- Invasive ductal carcinoma
LVI- Lymphovascular invasion
PNI- Perineural invasion
PR-Progesteron receptor
RT- Radiotherapy
SLN- Sentinel lymph node
SLNB- Sentinel lymph node biopsy
W/V- Weight by volume

Competing interests: None

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