

Incidence of Internal Mammary Nodes in Locally Advanced Breast Cancer and Its Prognostic Significance

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Abstract :

Objective: (1) To determine the incidence of internal mammary nodal disease on computed tomography (CT) in patients with locally advanced breast cancer (LABC). (2) To determine the prognostic significance of internal mammary nodal disease in patients with LABC. **Materials and Methods:** We retrospectively reviewed our database of all locally advanced breast cancer patients coming at our centre from 1st January 2015 to 31st December 2015. The inclusion criteria for this study included all patients with clinical staging of locally advanced breast cancer with their baseline CECT of thorax available on our hospital Picture Archiving and Communication System (PACS). All patients whose images were not available on our PACS or those with metastatic disease on baseline imaging were excluded from the study. These patients were followed up for one year at our centre, GCRI. **Results:** A total of 405 cases of LABC were registered at our centre during this period. Of this, a total of 148 patients had undergone baseline CT at our centre. Of these, 21 patients had metastatic disease on baseline study and hence, these were excluded. A total of 127 patients were hence enrolled in the study. Of the 127 patients, internal mammary nodes were identified in a total of 53 patients. No nodes were seen in remaining 74 patients. In this study, the incidence of internal mammary nodes (IMNs) on LABC was calculated to be 41.73%. Incidence of metastatic disease in LABC patients on follow up were 19.68 %. Incidence of metastatic disease in LABC patients with IMNs on baseline imaging on follow up was 27.3%. Incidence of metastatic disease in LABC patients, without internal mammary nodes on baseline imaging, on follow up was 14.8 %. **Conclusion:** We conclude that internal mammary nodes are important prognostic factor in LABC and these should be reported in all cases of breast cancer undergoing cross sectional imaging.

Key words : Internal mammary node, Locally advanced breast cancer

Introduction:

Breast malignancies constitute one of the most common malignancies in women worldwide. The average global incidence of breast malignancies was 1,676,633 in the year 2012 according to GLOBOCAN;⁽¹⁾ breast malignancies constituting about 25.2% of malignancies in women all over the world. Same report stated mortality of about 14.7% in and 5 year survival rate of 36% worldwide. In India, the incidence of breast cancer is about 1,44,937; with incidence of about 27% of all female malignancies.⁽¹⁾ The mortality of breast cancer patients is about 21.5% and their 5 year survival rate is about 35.3%, so now it has become the most common malignancy in Indian females.⁽¹⁾ The lifetime risk of developing breast cancer in Indian women is 1 in 28 women. There is a significant increased lifetime risk in urban women, i.e., 1 in 22. The increased lifetime risk in rural women is 1 in 60.⁽²⁾ The high risk age group of breast cancer in India is 43-46 years, which is

significantly lower than that of our western counterparts, standing at 53-57 years.⁽²⁾

CT scan has become more helpful in advanced breast cancers as a part of routine workup. It serves as a useful modality to assess the regional extent of the disease and enlarged internal mammary nodes. It is a sensitive tool to look for any distant metastases involving lung, liver, adrenals or bones. Internal mammary nodes lie along the internal mammary artery. Internal mammary artery arises from first part of subclavian artery. It gives rise to anterior intercostal arteries from first to sixth intercostal space, and terminates by dividing into superior epigastric and musculophrenic arteries. Internal mammary nodes get involved in the disease process, when there is an obstruction in the lymphatics drainage by tumor cells. It is very rare to find isolated internal mammary node metastases in the absence of enlarged axillary nodes.⁽³⁾ This pathway is important in cases of breast cancer and also in surgery with axillary node clearance. The surgical procedures result in blockage of axillary lymphatic drainage and therefore internal mammary nodes provide important alternative

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drainage pathway; hence metastasis in operated breast cancer patients in internal mammary nodes holds significance.⁽⁴⁾

According to American Joint Committee on Cancer (AJCC) TNM classification, the grading for metastases in clinically detected ipsilateral internal mammary lymph nodes, and in the absence of clinically evident axillary nodes is given as N2b and for clinically detected ipsilateral internal mammary nodes in the presence of clinically evident axillary level I, and II lymph nodes, is given as N3b.

Following characteristics will be considered as locally advanced breast cancer:

Any tumor more than 5 cm in maximum size, tumor involving chest wall, tumor with skin involvement like skin edema, peau d' orange, ulceration of overlying skin and satellite nodules, clinically extensive nodal involvement-N2 or N3 and inflammatory breast cancer.⁽⁵⁾

Advanced tumors are being offered breast conservation surgery after instituting neoadjuvant chemotherapy, worldwide. For this, staging of breast cancer is needed in order to design management plan for each patient. The imaging modalities employed in breast cancers include chest radiograph, USG examination of abdomen and pelvis, Technetium-99 bone scan, CECT scan of thorax, abdomen and pelvis, and in some cases PET for skeletal metastases. Locally advanced tumors have a greater probability of distant metastases. Hence, these require a comprehensive work up. The management of suspicious internal mammary nodes is controversial.

The internal mammary lymph node (IMLN) chain is the first lymphatic drainage site in breast cancer. Historically, between the 1940s and 1960s, the surgery of IMLN was performed during the classical Halsted radical mastectomy with extra pleural resection of the internal mammary chain (extended radical mastectomy).⁽⁶⁻⁸⁾ Some studies have reported a high metastatic rate of IMLNs (44%-65%) in breast cancers with medial tumors and positive axillary nodes.⁽⁹⁻¹¹⁾ However, a multicentric randomized clinical trial, which started in 1962, did not show any survival benefit for radical dissection of IMLNs,^(12,13) and hence extended radical mastectomy (ERM) has since been abandoned. Currently, the TNM staging of the 6th American Joint Committee on Cancer is determined by metastatic status of IMLNs; and the National Comprehensive Cancer Network Clinical

Practice Guidelines recommended considering radiotherapy for patients with suspected IMLN metastasis. However, for determining the direction of treatment and prognosis for these patients, an accurate assessment of IMLN metastasis is the most important consideration.⁽¹⁴⁾ The presence of metastatic IMLNs can change the tumor stage and can determine the direction of treatment.

Materials and Methods:

This was a retrospective study performed at our institute, Gujarat Cancer Research Institute. We retrospectively reviewed our database of all locally advanced breast cancer patients coming at our centre from 1st January 2015 to 31st December 2015. The inclusion criteria for this study included all patients with clinical staging of locally advanced breast cancer with their baseline CECT of thorax available on our hospital Picture Archiving and Communication System (PACS). All patients whose images were not available on our PACS or those with metastatic disease on baseline imaging were excluded from the study. The patients underwent CT scan using a 6 slice multi detector CT scanner after administration of contrast medium. The parameters employed were 150kvp, 150-300 ma, 25 mm collimation and 70 cm display FOV. The patients were scanned in supine position and soft copy of the data was stored. All patients having distant metastases were excluded from the study. The following CT findings were noted: age, sex, laterality of primary tumor, tumor quadrant, histological diagnosis and grading, internal mammary nodes, number of nodes if present, size of largest node, unilateral /bilateral internal mammary nodes and specific location of the node. These patients were followed up for one year at our centre, GCRI. The incidence of these patients developing metastases was calculated and incidence of patients having distant metastases with internal mammary nodes was also calculated.

Results:

A total of 405 cases of LABC were registered at our centre during this period. Of this, a total of 148 patients had undergone baseline CT at our centre. Of these, 21 patients had metastatic disease on baseline study and hence, these were excluded. A total of 127 patients were hence enrolled in the study.

Incidence of internal mammary nodes:

Of the 127 patients, internal mammary nodes were identified in a total Of 53 patients. No nodes were seen in remaining 74 patients. In this study, the incidence of internal mammary nodes on LABC was calculated to be 41.73%.

Size of internal mammary nodes:

Total 82 nodes were identified in these 53 patients. Size of all the nodes were measured in short axis. The distribution of IMNs in LABC according to size is as follows (Table 1):

Table 1: Distribution of IMNs according to their size

Size	Number of nodes	Percentage* (n=82)
<4 mm	19	23.2%
4-6 mm	17	20.7%
6-8 mm	20	24.4%
8-10 mm	12	14.6%
>10 mm	14	17.1%

*- Rounded off to the nearest decimal.

Distribution of internal mammary nodes:

All identified internal mammary nodes were localized along the intercostal mammary vessels, and their location with respective intercostal spaces was described (Table 2).

Table 2: Location of IMNs with respect to the intercostals spaces

Intercostals space	Number of nodes	Percentage* (n=82)
1st intercostal space	30	36.6%
2nd intercostal space	35	42.7%
3rd intercostal space	13	15.8%
4th intercostal space	4	4.9%

*- Rounded off to the nearest decimal.

Laterality of internal mammary nodes:

Internal mammary nodes were analyzed for the laterality with respect to primary tumor and also as per individual

location. Incidences of ipsilateral side nodes were more common than contra lateral side, as described in Table 3.

Table 3: Incidences of location of IMNs with respect to the tumor location

Location of nodes	Number of cases	Percentage* (n=53)
IMN on ipsilateral side	45	84.9%
IMN on contralateral side	1	1.9%
IMN present bilaterally	7	13.2%

*- Rounded off to the nearest decimal.

Internal mammary nodes incidence and laterality of primary breast tumor:

Incidence of internal mammary nodes was calculated in relation with location of primary breast tumor. It was found that incidence of IMNs was higher in upper outer quadrant tumor as described in Table 4.

Table 4: Relation of IMNs with location of the primary breast tumor

Quadrant	Incidence of IMNs in tumors	Percentage (n=53)
Upper outer	25	47.16%
Upper inner	7	13.20%
Lower outer	8	15.09%
Lower inner	7	13.20%
Multicentric/ tumors involving all quadrants	6	11.32%

All patients were screened for one year in our study. The incidence rates of distant metastases in all these LABC patients were calculated. Incidence rate of metastases on follow up in patients with identifiable IMNs was calculated.

Incidence of metastatic disease in LABC patients on follow up was 19.68%.

Number of patients showing distant metastases on follow up study was 25 out of 127(19.68%) patients. Number of patients without any obvious distant metastases on follow up study of 1 year was 102 out of 127(80.31%) patients. Incidence of metastatic disease

in LABC patients with IMNs on baseline imaging on follow up was 26.41%. Number of patients with internal mammary nodes on baseline imaging showing distant metastases on follow up was 14 out of 53(26.41%) patients. Number of patients showing no distant metastases on follow up 1 year was 39 out of 53(73.58%) patients. Incidence of metastatic disease in LABC patients without internal mammary nodes on baseline imaging on follow up was 14.86 %. Number of patients without IMN on baseline imaging showing distant metastasis on follow up was 11 out 74(14.86%) patients. Number of patients showing no distant metastasis on 1 year follow up was 63 out of 74(85.13%) patients.

Discussion:

Our study shows that incidence of distant metastases was higher in cases with IMNs than those without any identifiable internal mammary node on baseline imaging. The incidence of internal mammary nodes was highest in second intercostal space, followed by first intercostal space. Most of the internal mammary nodes were identified on the same side of primary. In our study, incidence of IMNs was higher in upper quadrant tumors; it may be because the incidence of upper outer quadrant tumors in general, is highest. The limitation of our study was less sample size and that not all patients presenting with LABC had undergone CECT for baseline imaging.

Internal mammary nodes are important pathway of lymphatic drainage in breast tumor. Many studies show association of metastatic internal mammary nodes with poor prognosis in breast cancer. Some other studies have validated IMNs as an independent prognostic factor in breast cancer.⁽¹⁵⁾ These studies show decreased survivals and increased rates of metastases in these patients. The study published by university of Chicago demonstrating that the survivability was significantly lower in patients presenting with internal mammary nodal metastasis as compared to those presenting with axillary nodal metastasis. The gold standard for ascertaining the metastatic status of the internal mammary nodes is surgical sampling. However, majority surgeons do not practice sampling of IMNs during breast surgery. Two large studies performed by European group have reported overall improved survival in these patients – due to realization of more tailored therapy and more accurate staging.^(16,17) Numerous studies were

performed in later 19th century, wherein the result of Halsted mastectomies with those of extended mastectomies were compared.⁽¹⁸⁾ These studies did not show any significant change in overall survival in patients undergoing IMNs sampling. It has been shown that undetected metastatic IMNs specifically in inner quadrant tumor have worse prognosis.⁽¹⁹⁾ Hence, imaging has come to play an important role in detection of suspicious internal mammary nodes. In imaging, numerous studies have shown that PET CT has a higher sensitivity as compared to CECT scan in detection of internal mammary nodes.

In early 19th century, internal mammary nodes were routinely sampled along with radical breast surgeries. However, subsequently, according to randomized controlled trails, no significant difference was noted in survival rates of patients undergoing internal mammary nodes sampling versus those undergoing no sampling of these nodes. Also sampling of internal mammary nodes resulted in considerable morbidity to these patients. Hence, the sampling of internal mammary nodes fell out of favour among surgeons.

Breast cancer is an important cancer amongst women which is amenable to early diagnosis and treatment due to availability of good screening methods. In India, breast cancer is diagnosed early as compared to the western world. Locally advanced breast cancers are those in which primary tumor is larger than 5 cm, involving skin, chest wall or both. Our study shows that incidence of distant metastases was higher in patients with internal mammary nodes than those without any identifiable internal mammary node on baseline imaging. The incidence of internal mammary nodes was highest in second intercostal space, followed by first intercostal space. Most of internal mammary nodes were identified on the same side of primary tumor. In our study, incidence of internal mammary nodes was higher in upper quadrant tumors. The limitation of our study was less sample size and not all patients presenting with locally advanced breast cancer had undergone CECT for baseline imaging.

Conclusion:

Internal mammary nodes are significant prognostic factors for long term survival in breast cancer patients. CT scan has become more helpful in advanced breast cancers as a part of routine workup, so CT scan is a

useful modality to assess the regional extent of the disease and tool to look for any distant metastases involving nodes, lung, liver, adrenals or bones. Presence of internal mammary nodes in locally advanced breast cancer cases is associated with poor prognosis.

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