

Metastatic Workup of Locally Advanced Breast Cancer Cases in Resource Constrained Setting: Experience of High Volume Tertiary Centre

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ABSTRACT

BACKGROUND

In developing countries, majority of breast cancer patients present in advanced stage with poor outcomes. In rural parts of India, 50% to 60% of all breast cancer patients have locally advanced disease or distant metastasis at presentation. It is recommended to include CECT abdomen and CECT thorax for metastatic work up of locally advanced breast cancer (LABC). This study was done to compare CECT abdomen versus USG abdomen and CECT thorax versus Chest X-Ray respectively in LABC patients for detecting visceral metastasis.

METHODS

Medical records of patients referred to State Cancer Institute, GMC, from July 2017 to March 2019 were retrieved for analysis. From this data investigations performed for metastatic work up, results, and costs were recorded. Sensitivity and specificity of CECT thorax and abdomen were calculated and compared to those of Chest X-Ray (CXR) and Ultrasound abdomen (USG) respectively. Fischer's exact test and Pearson chi square test were used for univariate analysis. McNemar test was used to compare the sensitivities.

RESULTS

CECT abdomen and USG abdomen had sensitivity rates of 80% and 85.7% respectively. The sensitivity of CECT thorax and CXR was found to be 88.9% and 66.6% respectively, however specificity of both the modalities was comparable at 91.6% and 95.6% respectively. Patients having tumour size ≥ 8 cm, oral tobacco chewers and having N2, N3 disease were at significantly high risk for developing visceral mets. On comparing the sensitivities, it was found there is no significant difference between USG and CECT abdomen, CXR and CECT thorax.

CONCLUSIONS

More than 80% of patients with visceral mets could be diagnosed combining CECT thorax and USG abdomen. Hence, it is recommended to further subgroup LABC patients into low and high risk, based on presence of any one of the features which are significantly associated with visceral mets (≥ 8 cm tumour size, N2, N3 disease and tobacco chewer). We can consider using CECT thorax and CECT abdomen for high risk patients.

KEYWORDS

Contrast Enhanced Computed Tomography (CECT), Chest X-Ray (CXR), Ultrasonography (USG), Visceral Metastasis (Mets), Locally Advanced Breast Cancer (LABC)

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BACKGROUND

Locally Advanced Breast Cancer (LABC) is a heterogeneous clinical entity that includes advanced stage non-metastatic breast cancers.¹ It includes TNM stages T3N1, N2-N3 with any T and T4 with any N. In Rural parts of India, 50%-60% patients present with LABC or distant metastasis.² However, situation in urban India has significantly changed due to increasing awareness and screening facilities.³ Incidence of distant metastasis on initial staging in clinical LABC is 13.2%.⁴ Mortality rates are particularly high in low income populations due to delayed presentation and advanced disease at time of diagnosis. Late stage disease presentation leads to poor outcome when combined with limited capacity for correct diagnosis and adequate therapy in low and middle resource countries. Many patients in middle resource countries have little personal finances which is a substantial barrier to care. Out of pocket payments can push families into poverty, adversely affecting otherwise desirable health seeking behaviour of women with few financial resources who have breast complaints.

It is recommended to include CECT abdomen and CECT thorax for metastatic work up of LABC patients.⁵ This study was done to compare CECT abdomen and thorax to USG abdomen and Chest X-ray respectively in LABC patients for detecting visceral metastasis.

METHODS

Medical records of breast cancer patients referred to our institute from July 2017 to march 2019 were retrieved. Out of 140 patient records initially reviewed, 38 were excluded due to insufficient data. Only those patients who had undergone USG abdomen, CECT abdomen, CECT thorax and CXR were taken up for final analysis. 102 patients were included in the final analysis. Sensitivity and specificity were calculated for all the four tests and compared by McNemar test. Demographic data are presented as totals and means, with ranges and standard deviations displayed where appropriate. Categorical variables were analysed using Fisher's exact test or Chi-square test and. $P < 0.05$ was considered as a statistically significant result.

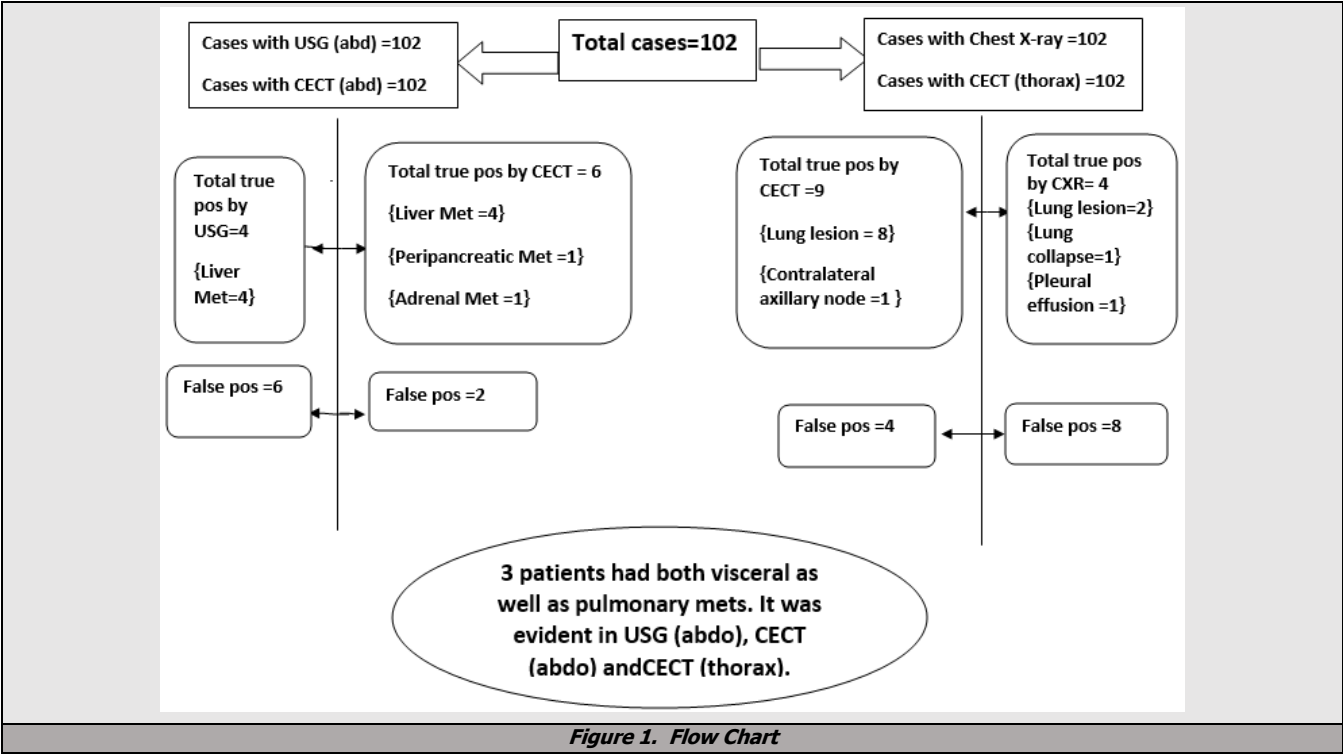
The patients are referred from peripheral hospitals where initial workup of USG whole abdomen and chest X-ray are invariably done. After coming to tertiary centre, CECT abdomen and thorax was ordered for them. Hence, for this group of patients, investigation reports of CECT abdomen and thorax, USG and CXR were available for study. We recorded the basic clinicopathologic data and results of all CECT abdomen and thorax. Any patient who had suspicious findings in CECT abdomen or thorax, underwent PET-CT scan to confirm the presence of metastasis, if any.

RESULTS

Out of 102 evaluable patient's majority of them (98) were females while 4 males. Most clinicopathologic features of patients were not found to be significantly associated with presence of visceral mets except three. (Table 1 shows incidence of visceral mets according to clinicopathologic characteristics of the study population). Mean age of the group was 45.7 years (range, 32-63 years). Mean tumour size in cases with mets was 7.93 ± 2.98 cm whereas, in cases without mets was 6.88 ± 2.02 cms. The mean tumour size was larger in cases with visceral mets and this difference was statistically significant (p value < 0.05). 55% of the study population was oral tobacco chewer and it was also significantly associated (p value < 0.05) with presence of visceral mets. Highest (66%) number of patients in T4bN3 stage were found to have mets followed by 18.8% in T4cN2, 16.6% in T3N2, 11.1% in T4bN2, 9% in T4cN1, 4% in T4bN1. There was significant association (p value < 0.05) between N1 vs N2, N3 stage and presence of visceral mets. None of the other known factors examined, ER, PR and HER2 receptor status, type of histopathology or grade, betel nut consuming had statistically significant association with visceral mets.

Out of 102 pts, 4 patients had liver mets evident in CECT abdomen, 1 patient had adrenal met and 1 had peripancreatic mets. True positive cases were total 6 and 2 patients had false positive lesions. Whereas Ultrasound abdomen revealed 4 patients with true positive liver mets. Ultrasound could not pick up adrenal and peripancreatic mets. In 6 cases false positive results were obtained in Ultrasound results. (Figure 1). Sensitivity of CECT abdomen and USG abdomen was comparable at 85.7% and 80% respectively, similar was the case with specificity at 97.8% and 93.8% respectively. On comparing the sensitivities, it was found that there is no significant difference between these two tests (P value = 0.683).

In metastatic work up of thorax, CECT thorax results revealed that 8 patients had lung mets and 1 case had metastatic contralateral axillary lymph nodes. Therefore total 9 patients had true positive findings. Chest X-ray could pick up 4 patients with lung metastasis while 8 patients had false positive findings. Although CECT thorax had sensitivity rate of 88.9% as against that of CXR, 66.6%. On comparing the sensitivities by McNemar test, it was found that there is no significant difference between CXR and CECT thorax (P value = 0.507). The specificity of CECT thorax and CXR was comparable at 95.6% and 91.6%. 12 patients in total had visceral and pulmonary mets and 4 patients were finally upstaged leading to change in their management. The overall yield of positive results in USG, CECT (abdomen), CXR, CECT (thorax) was 3.92%, 5.88%, 3.92% and 8.82% respectively.



Parameters	Visceral Mets (+)	Visceral Mets (-)	p
Age (Yrs.)			0.11
<50 (n=69)	7	62	
≥50 (n=33)	5	28	
Sex			0.23
M (n=4)	0	4	
F (n=98)	12	86	
Tobacco			<0.05
No (n=55)	2	53	
Yes (n=47)	10	37	
Size			<0.05
<8 (n=70)	5	65	
≥8 (n=32)	7	25	
Betel nut			0.15
No (n=22)	1	21	
Yes (n=80)	11	69	
Biopsy			0.19
IDC (n=97)	11	86	
ILC (n=2)	0	2	
Others (n=3)	1	2	
Grade			0.088
1 (n=1)	0	1	
2 (n=54)	6	48	
3 (n=47)	6	41	
Oestrogen and Progesterone Receptor			0.05
Positive (n=48)	8	40	
Negative (n=54)	4	50	
HER2 neu			0.71
Negative (n=62)	8	54	
Positive (n=40)	4	36	
N Stage			<0.05
N1 (n=58)	3	55	
N2, N3 (n=44)	9	35	

Table 1. Incidence of Visceral Mets According to Clinicopathologic Characteristics

Cost Estimates

The cost of CECT thorax and abdomen were obtained from State Cancer Institute, Radiology Department Patients are charged Rs. 4700 (\$68) for one such imaging. This total included costs for staging imaging only. No follow-up scans, other diagnostic interventions like PET-CT were included in these costs. Patients who were diagnosed to have inconclusive findings in CECT thorax or abdomen had to undergo PET-CT (2 patients) for confirmation of presence of metastasis.

DISCUSSION

European guidelines for quality assurance in breast cancer screening and diagnosis stated, that a complete diagnostic workup to detect metastases is unnecessary in the majority of patients with newly diagnosed breast cancer whereas it may be indicated for patients with advanced disease.² As we know distant metastases in a patient with breast cancer upgrades the stage of disease, with concomitant prognostic and therapeutic implications. The location and extent of metastases are also of key importance, with the most common sites being the lung, liver and bone.⁶ Minimal workup of LABC includes a chest X-ray, ultrasound of the abdomen, and a bone scan, if available.^{7,8} In countries with enhanced and maximal resources, bilateral mammography and bone scan, as well as chest and abdominal tomography scans are recommended for LABC.⁵

In this study, we found significant association between tumour size (≥8 cm) and presence of visceral mets, it is in accordance with the findings of Rungnapa et al⁹ and Andy et al.¹⁰ Greater the clinical volume, the higher the proportion of metastases at diagnosis (M1) and of metastases appearing later during the course of the disease, it was the finding of Kosciely et al.¹¹ Andy et al¹⁰ concluded that unabated tumour growth can contribute to metastasis by selecting for metastatically competent cells. Also, there is a significant association between clinical stage of the disease and visceral metastasis. The association is clearly evident with N2 and N3 disease. Stages T3N2, T4bN2, T4cN2 and T4cN3 combinedly had 9 (75%) cases of metastatic diseases. Axillary node involvement and fixed matted nodes (stage N2 and N3) were significantly associated with presence of lung and liver mets, this finding is in accordance with Satoru Tanaka et al,⁶ Rungapu et al,⁹ Ravioli et al,¹² Gangadharan et al.¹³

It was also found that there is a significant relation between consumption of tobacco and metastasis. The population in North East India consume tobacco in the form of oral chewable powder. Susan Murin et al¹⁴ and Franciscopaulo Di Cello et al¹⁵ both observed adverse effects of smoking on metastatic process, however in both these studies their population was tobacco smoker. Cigarette smoke exposure is associated with an increase in the total pulmonary metastatic burden in the murine model of metastatic mammary cell cancer.¹⁴

Current study presents the most recent cohort of North Eastern Indian patients suffering from locally advanced breast cancer. Staging investigations were performed on 102 patients. We found 15 true positive metastatic lesions in 12 patients. The sensitivity and specificity of USG abdomen in our study is 80% and 93.8%. Gangadaran et al¹³ reported that sensitivity and specificity of USG abdomen is 100% and 99%. Sensitivity and specificity of CECT thorax in detecting distant metastasis is 88.9% and 95.6%, it is comparable to Gangadaran et al¹³ in which sensitivity and specificity were 92% and 99% respectively. However, the difference in sensitivity of CXR was remarkable to be 66.6% and 21% respectively. The specificity of CXR is again comparable at 91.6% and 94%. The difference between two studies with respect to sensitivity and specificity can be attributed to the fact that our cohort is of LABC patients strictly whereas Gangadaran et al studied patients of stage I to III. The overall yield of positive results from CECT thorax in our study is 8.89% which is comparable to those from Justin James et al¹⁶ (9%), from Piatek et al¹⁷ (5%) and Kim et al¹⁸ (6%). The most common cause for a false-positive result in CECT thorax was an indeterminate pulmonary nodule and most common cause for false positive liver lesion in CECT abdomen was liver haemangioma. These false-positive results required further PET-CT to confirm metastatic lesion, which incurred further expense and cause anxiety to the patients.¹⁹

The 31.98% of Assam population is below poverty line (BPL), i.e. the total household monthly income of this population is approx. Rs. 2250 (\$33). It means that cost of CECT thorax and abdomen (Rs. 4700) will be equal to 2 months household income for BPL population. This cost did not include follow up scans or PET- CT in case of false positive or suspicious lesions. A cost effective analysis of breast cancer interventions in Ghana revealed that mammographic screening of women aged 40-69 yr old would cost \$12908 per disability life year(DALY) averted. In contrast, biennial CBE and mass media awareness campaigns would cost \$1200 and \$1365 DALY averted, respectively.²⁰ Distrust of the medical system and myths about breast cancer persist, leading women to rely on traditional healers in lieu of health centres to their detriment. Financial resources are likely better invested in public awareness campaigns and training community health workers to educate the public and perform clinical breast exams. It is particularly important to address this disease in developing nations, where over 70% of all cancer cases will occur by 2020.²⁰ There is an overwhelming need for

systematic studies that pinpoint areas of need within the context of each developing nation and also within regions in a developing nation. Previous studies mentioned demographic, pathological characteristics, hormone receptors, and types of treatment as the main prognostic factors for recurrence and survival of patients with breast cancer and most studies were done in developed countries. Whether these characteristics would be similar in poor developing countries is still inconclusive.⁹

The study has the limitation, being a retrospective one. Number of patients with eligibility criteria are less, hence our cohort is smaller. Another limitation was that, not all suspected lesions had confirmed pathology laboratory results. Also, for the calculation of sensitivity and specificity, a person-based approach was used instead of lesion based. This procedure reflects that treatment decisions are generally made based on the presence of recurrent or metastatic disease, rather than on the number of lesions involved. Consequently, it is clinically more relevant to consider the patient-based data rather than the lesion-based analyses.

CONCLUSIONS

Locally advanced breast cancer cases can be further grouped and routine use of CECT (thorax and abdomen) may be avoided in low risk groups for better treatment resource allocation. Patients having high risk (tumour size $\geq$ 8 cm, tobacco chewer, N2, N3 disease) may undergo CECT thorax and abdomen whereas remaining could undergo CECT thorax and USG abdomen.

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