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The role of staging Computed Tomography on detection of occult metastasis in asymptomatic breast cancer patients

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Abstract

Background: The use of advanced imaging in staging of breast cancer is on the rise. In countries with limited resources, appropriate patient selection for advanced imaging is mandatory.

Aims: We sought to evaluate the number of asymptomatic breast cancer patients with normal staging Chest X-ray and ultrasound scan of abdomen but were found to have occult metastasis on CT scan of chest, abdomen, and pelvis and to identify predictive factors for occult distant metastasis to guide selection of patients for advanced imaging in resource constrained settings.

Methods and Results: This was a descriptive cross-sectional study carried out in Jaffna, Sri Lanka between March 1, 2012 and March 31, 2019. Statistical analysis was done using SPSS software version 21. The prevalence of occult metastasis was calculated. Bivariate and multivariate analysis was done to identify predictive factors for occult metastasis. There were 233 eligible patients. Only 13% (n = 30) had stage I disease. T1 disease was reported in 21% (n = 50) and axillary nodal metastasis in 48% (n = 135). A total of 15% (n = 34) had occult metastasis on CT scan. Bone (n = 25) was the commonest site of metastasis, followed by lung (n = 10) and liver (n = 06). On bivariate analysis, tumor (P = .019), nodal (P = .001), and overall stage (P = .001) were significant predictors for occult metastasis. On multivariate analysis, nodal metastasis (P = .045) was the only significant predictor.

Conclusion: In unscreened population with limited resources, staging of breast cancer with CT scan should be considered for at least patients with axillary lymph nodal metastasis.

KEYWORDS

breast cancer, CT scan, occult metastasis, staging

1 | INTRODUCTION

Staging of breast cancer is mandatory to make appropriate treatment decisions. Current staging system involves clinical and pathological staging. Imaging requirements for staging differs between early and advanced stage disease. The National Comprehensive Cancer Network (NCCN) recommends Chest X-ray (CXR) and Ultrasound scan (USS) of the abdomen for early stage patients who are asymptomatic for metastatic disease with normal blood tests.[1] Advanced imaging modalities used to stage breast cancer include Computed Tomography (CT), Positron emission tomography (PET), Magnetic Resonance Imaging (MRI), and Bone Scintigraphy. These are recommended in newly diagnosed early stage patients only if they elicit symptoms of metastatic disease or if blood tests were

suggestive of metastasis or in patients with advanced disease inclusive of stage IIIA and above.

According to published literature, 2% to 10% of breast cancers are metastatic at diagnosis and majority of them will have signs and symptoms of metastatic disease.[2,3] The rate of occult metastasis in asymptomatic patients varies between 1% and 14%.[3,4]

Breast cancer is the commonest cancer among women in Sri Lanka. It accounts for 25% of all newly diagnosed cancers among females each year.[5] Most patients present with a palpable lump as there is no established screening program in Sri Lanka. A previous study by Thanikai et al[6] among the breast cancer patients of Northern Sri Lanka revealed that majority of patients present at least 3 months after detecting a palpable lump. This delay may result in radiologically detectable distant metastases at the time of presentation, even though clinically occult. The true incidence of occult metastatic disease at diagnosis in this unscreened population is unknown.

As Sri Lanka is a developing country, majority of breast cancer patients with advanced disease have limited access to advanced imaging such as CT, MRI, PET, and Bone Scintigraphy. In the Northern province of Sri Lanka where this study was carried out, there are only two diagnostic CT scanners for a population of 1.2 million. Other advanced imaging modalities are not available in the province. Hence, asymptomatic newly diagnosed breast cancer patients irrespective of stage at diagnosis, are staged using CXR and USS of the abdomen.

To assess the utility of this current policy we sought to evaluate the number of asymptomatic breast cancer patients who had a normal CXR and USS of abdomen but were later upstaged to stage IV by performing a CT scan of chest, abdomen, and pelvis. We also sought to identify predictive factors for occult distant metastasis in asymptomatic patients to guide selection of patients for advanced imaging in resource constrained settings.

2 | MATERIALS AND METHODS

2.1 | Patient selection criteria

This was a descriptive cross-sectional study carried out at the Teaching Hospital, Jaffna and the Tellipalai Trail Cancer Hospital, Jaffna, Sri Lanka between March 1, 2012 and March 31, 2019. Patients with newly diagnosed breast cancers who were asymptomatic for metastatic disease at diagnosis with a normal CXR and USS of abdomen were included. Patients with ductal carcinoma in situ, malignant Phyllodes tumor, male breast cancer, symptoms of metastatic disease, suspicious lesions on CXR or USS of abdomen and indeterminate lesions on CT scans were excluded. All patients were above the age of 18.

2.2 | Staging

All patients were staged using the Tumor, Node, and Metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC), 7th edition.[7] The patients who underwent primary surgery had pathological staging. Those who underwent neoadjuvant chemotherapy were staged clinically. A CXR and USS of the abdomen were the imaging modalities used for initial staging. The CT scan of chest, abdomen, and pelvis were done for all eligible patients. Bone Scintigraphy scans were done for patients with advanced disease at the National Hospital of Sri Lanka which is 425 km away. Bone Scintigraphy was performed mostly after the commencement of treatment due to practical reasons and the findings were not considered for this study. Patients who had definitive evidence of metastasis on CT scan were upstaged to stage IV.

2.3 | Predictive factors examined

We analyzed the influence of age, tumor (T) stage, nodal (N) stage, overall stage, grade, lymphovascular space invasion (LVSI), estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) on increasing the risk of upstaging through advanced imaging.

2.4 | Statistical methods

Statistical analysis was done using SPSS software version 21. The prevalence of occult metastasis was calculated. The tumor and patient related factors predictive of detecting occult metastasis were analyzed. Categorical variables were analyzed by using chi-square test. *P* value at .05 level was considered as statistically significant. Multivariable analysis was done by including the tumor related factors which were significant in bivariable analysis.

3 | RESULTS

A total of 233 patients were included in the study and the demographic and tumor characteristics are shown in Table 1. Median age was 55 years ranging from 26 to 82 years. Ductal carcinoma was the commonest histology accounting for 94% of cancers. Only 13% of patients had stage I disease. Almost half the cohort had grade 2 tumor and one-third had LVSI.

Among the 233 patients, 34 (15%) had occult metastasis on CT scan. There were 44 abnormalities detected on CT. The details of stage and sites of occult metastasis have been shown in Table 2. Among the patients who had occult metastasis, none had stage I disease. A total of 11 (32%) patients had stage II disease and 24 (68%) had stage III disease. Of these patients, 5% (n = 3/56) of stage IIA, 17% (n = 8/48) of stage IIB, and 23% (n = 23/100) of stage III patients had occult metastasis on CT scan. Bone (n = 25) was the commonest site of metastasis, followed by lung (n = 10), liver (n = 6), and others (n = 3) such as ovary, muscle, and mediastinal lymph nodes. Nine (4%) patients had indeterminate findings on CT scan and were excluded from the analysis. Unfortunately, we could not perform other

TABLE 1 Patients and tumor characteristics

Variables	Levels	No. of patients (%) 233 (100%)
Age	Median (range)	55 (26-82)
Stage	I	30 (13)
	II	103 (44)
	III	100 (43)
T stage	Tx	02 (01)
	T1	49 (21)
	T2	112 (48)
	T3	39 (17)
	T4	31 (13)
Lymph node status	N0	98 (42)
	N1	63 (27)
	N2	38 (16)
	N3	34 (15)
Histology	Ductal	219 (94)
	Lobular	06 (03)
	Others	08 (03)
Grade	I	44 (19)
	II	**121 (52)**
	III	58 (25)
	NA	10 (4)
LVSI	**Yes**	**69 (30)**
	No	140 (60)
	NA	24 (10)
Estrogen receptor	**Positive**	**89 (38)**
	Negative	95 (41)
	NA	*49 (21)*
Progesterone receptor	**Positive**	**80 (34)**
	Negative	103 (44)
	NA	*50 (22)*
Her-2 receptor	**Positive**	**63 (27)**
	Negative	102 (44)
	Equivocal	*13 (05)*
	NA	*55 (24)*

Abbreviation: LVSI, lymphovascular space invasion.

advanced imaging to assess the nature of the indeterminate lesion due to resource constraints.

3.1 | Predictive factors

Bivariable analysis was done to see the association of selected patient and tumor factors such as age, overall stage, tumor (T) stage, nodal stage (N), histology, grade, LVSI and ER, PR and HER-2 status in upstaging of the disease. In bivariate analysis, overall stage IIB or above (P = .001), tumor size more than 2 cm (P = .019), and lymph node involvement (P = .001) were significant predictors of occult metastasis (Table 3). Age (P = .925) and grade (P = .926) were not predictive. The correlation with LVSI and ER, PR and Her-2 status could not be elicited due to insufficient data. On multivariable analysis only lymph node positivity (P = .045, 95% confidence interval of 1.025-9.396) predicted occult metastasis (Table 4).

4 | DISCUSSION

The use of advanced imaging in the staging of breast cancer is on the rise and adherence to guidelines is not known.[8] The increasing use of advanced imaging may be due to clinicians relying on imaging with better anatomical resolution for initial work up as detection of metastasis will have a profound effect on patient management and prognosis. This could also be due to patient preference.

CT scans have better sensitivity and specificity, lower false positivity, and better anatomical resolution compared to CXR, USS, and Bone Scintigraphy.[9]

The conventional staging of a high-risk patient will warrant a CXR, USS of liver, and Bone Scintigraphy. This may lead to three visits to the hospital. In addition, Bone Scintigraphy takes around 5 hours to be completed. Whereas, the acquisition time for CT scan of the chest, abdomen and pelvis can be less than 1 second and could be done with one visit to the hospital. In addition, CT scan of the chest, abdomen, and pelvis has the potential to screen most of the viscera, soft tissue and major portions of the skeleton. Groves et al[10] and Bristow et al[11] have reported that bone scan could be omitted if CT scan of chest, abdomen, and pelvis could be done as major portion of the skeleton gets scanned.

However, CT scanning involves, false positive scans leading to invasive procedures and emotional distress to patients, increased work load and huge cost per patient.[12] Clinicians should be mindful of the balance between the benefits and risks and be selective in ordering CT scans for staging.

In the present series, 15% (n = 34) of patients got upstaged to stage IV due to occult metastasis on CT scan, in a cohort where 43% consisted of stage III patients. Similar upstaging rate of 13.6% among asymptomatic patients had been reported by Gangadaran et al[4] in an Indian study where greater proportion of patients had stage III disease. A Japanese study by Tanaka et al[13] has reported 5.4% of occult metastasis on CT scans among stage I-III asymptomatic patients. This cohort consisted only 14% of stage III disease in contrast to 43% in the present series. James et al[3] reported upstaging rate of 1% among the Australians with only 10% of the cohort consisting of stage III patients.

In developed countries with established screening programs, majority of patients are diagnosed in early stages and the detection rates of occult metastasis is very low unlike in developing countries like Sri Lanka and India, where majority of patients have stage III disease at diagnosis with higher rates of occult metastasis.

TABLE 2 Sites of distant metastasis in relation to stage

Stages	No. of abnormal lesions	Bone metastasis	Lung metastasis	Liver metastasis	Other sites
All (n = 203)	44	25	10	06	3
I	0	0	0	0	0
II	13	9	3	1	0
III	31	16	7	5	3

TABLE 3 Factors predictive of occult metastasis on bivariate analysis

		Tumor upstage						
		Yes		No		Statistics		
Predictive factor	Category	Number	%	Number	%	Odds ratio	95% CI	*P* value
Tumor stage	T_1	2	4.1	47	95.9	4.95	1.18-43.97	0.019
	$T_2/T_3/T_4$	32	17.4	152	82.6			
Nodal stage	N_0	5	5.2	91	94.8	4.89	1.76-9.95	0.001
	N_{1-3}	29	21.2	108	78.8			
Overall stage	I/IIA	3	3.8	75	96.2	6.25	1.84-32.85	0.001
	IIB/III	31	20.0	124	80.0			

TABLE 4 Factors predictive of occult metastasis on multivariate analysis

Predictive factors	Significance (*P* value)	Odds ratio	95% CI for odds ratio
Tumor status	0.248	2.597	0.513-13.135
Nodal stage	0.045	3.103	1.025-9.396
Overall stage	0.259	2.333	0.536-10.155

In the present series, none of the stage I patients had occult metastasis. However, 32% (n = 11) of stage II and 68% (n = 24) of stage III patients had occult metastatic disease. Among the stage II patients who got upstaged, two-thirds had stage IIB disease. The Japanese study reported 0%, 1.9%, and 31.3% of upstaging for stages I, II, and III, respectively.[13] An American study by Merrill et al[12] found no cases of metastatic disease in stage I and II asymptomatic patients but found 22% of metastatic disease in patients with stage III disease or symptomatic for metastatic disease irrespective of stage. A study in the United Kingdom revealed no cases of upstaging in stage I.[9] It appears that for stage I patients, advanced imaging could be safely avoided. Studies done in developed countries either report no or very low rates of upstaging among stage II patients and guidelines recommend avoiding advanced imaging for these patients. It is not the same for our patients where 32% of patients with occult metastasis had stage II disease. This finding needs to be interpreted cautiously, as only 11 out of 34 patients with occult metastases had stage II disease. Further, stage was not a significant predictor on multivariate analysis.

In the present study, bone (n = 25) was the commonest site of metastasis, followed by lung (n = 10), liver (n = 6), and others (n = 3) such as ovary, peritoneum, and mediastinal lymph nodes. None of the patients had brain metastasis at presentation. The Indian study also reported similar incidence of distant occult metastasis.[4] In contrary, the Japanese study reported lung to be the commonest site of metastasis followed by bone and liver.[13] This may be due to different biology of breast cancer in different ethnic groups but needs to be confirmed in future studies.

4.1 | Predictive factor analysis

A binomial logistic regression was performed to ascertain the effects of tumor, nodal, and overall stage on the likelihood of the participants having occult metastasis. Of the three predictors, only nodal stage was statistically significant. Nodal positivity had 3.1 times higher odds on upstaging than nodal negativity. Increasing tumor stage more than T_1, had 2.60 times increased likelihood of upstaging, but was not significant. Similarly, overall stage more than stage IIA had 2.33 times higher odds for upstaging than Stage IIB and III. This was also not significant. All the predicting variable included in the model showed wider confidence interval. The finding could be due to the limited number of subjects included in the study.

Gangadaran et al has shown significant association with larger tumor size and lymph node positivity in predicting occult metastasis. Tanaka et al[13] also have confirmed the predictive value of tumor and nodal stage on predicting occult metastasis.

A commonly accepted theory is that as the cancer grows, the cells acquire the ability to spread to regional and distant sites.[14-16] Many

older studies published in the literature showed a positive correlation between the tumor size and metastatic spread.[17-19] However, a recent Surveillance Epidemiology and End Results[SEER] database study including 819, 647 patients where the correlation between tumor size and lymph node and distant metastasis was studied and found that the correlation was not linear. This study questioned the conventional model that the capacity of primary breast tumor to metastasize increases as the tumor enlarges. The non-linear correlation of the SEER database study explains the lack of correlation for occult metastasis and tumor size in the present series.

Despite several new prognostic factors, axillary nodal metastasis remains the most important prognostic factor predictive of recurrence and survival.[20,21] Axillary nodal metastasis leads to 28%-40% reduction in overall survival.[22] The present study too confirmed that axillary lymph node metastasis remains the only predictive factor for occult metastasis. Hence it is reasonable to perform staging CT scans for patient with axillary lymph nodal metastasis.

We could not study the influence of LVSI, estrogen, progesterone, and HER-2 receptor due to insufficient data. The Japanese study by Tanaka et al[13] failed to show significance between estrogen, progesterone, and HER-2 receptors and the risk of occult metastasis. James et al[3] could not analyse the significance of predictive factors in an Australian cohort as only four patients were detected with occult metastasis. Gangadaran et al[4] showed significant influence of HER-2 positivity and triple negativity on upstaging of the disease.

This study has several limitations. This was a retrospective study with gaps in data. The total number of patients was small with only 34 patients with occult metastasis. Sri Lanka suffered a civil war for 30 years which ended in 2009. The Northern province of Sri Lanka where this study was done was badly affected. In the early post-war years, receptor studies were not available. Hence, important prognostic information such as the estrogen, progesterone, and Her-2 receptor status were not available for a significant number of patients and the correlation could not be studied.

5 | CONCLUSION

In unscreened population with limited resources, staging of breast cancer with CT scan of chest, abdomen, and pelvis should be considered for patients with axillary lymph node metastasis. A risk stratified staging protocol is beneficial to maximize the benefit of staging CT scans and to ensure judicial use of limited resources. Extended studies with larger number of patients are needed to develop such protocols. Clinicians should be mindful of a careful risk-benefit assessment before ordering CT scans for breast staging.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Chrishanthi Rajasooriyar: Conceptualization; data curation; methodology; project administration; writing-original draft; writing-review and editing. **Thamayanthy Sritharan:** Conceptualization; data curation; methodology; writing-original draft; writing-review and editing. **Suvithra Chenthuran:** Conceptualization; data curation; methodology; writing-original draft; writing-review and editing. **Kavitha Indranath:** Conceptualization; methodology; writing-original draft. **Surenthirakumaran Rajendra:** Conceptualization; formal analysis; methodology; writing-original draft; writing-review and editing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL STATEMENT

Ethical clearance was obtained from the "Ethics Review Committee," Faculty of Medicine, University of Jaffna, Jaffna, Sri Lanka; approval number: J/ERC/14/51/NDR/00800. The Committee decided to exempt the study from review since the project involved no risk to the participants and the participants were not identified directly or indirectly.

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