Original Article

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Need for Staging Investigations in Newly Diagnosed Breast Cancer: Establishing Local Guidelines for Radiological Staging in Bahrain

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ABSTRACT

Objective: Staging workup and detection of distant metastases is important in newly diagnosed breast cancer in order to make treatment decisions and establish the prognosis. There is wide variation in current recommendations for staging investigations in breast cancer. Routine staging is performed for all patients in Bahrain because of lack of consistent guidelines. Optimization of the criteria for staging is important for identification of metastases, while minimizing harm and costs. The aim of this study was to evaluate factors associated with distant metastases in newly diagnosed patients with breast cancer, in order to establish local guidelines for proper selection of patients for systemic staging.

Materials and Methods: Patients with newly diagnosed breast cancer at Salmaniya Medical Complex in Bahrain who underwent staging investigations between January 2016 and December 2022 were identified from a pathology database. Patients with previous history of cancer, synchronous tumors, bilateral breast cancer and ductal carcinoma *in situ* were excluded. Clinical, radiological and pathological data were retrospectively analyzed.

Results: A total of 593 patients underwent staging computed tomography and bone scans or a PET scan. Distant metastases were identified in 20.7% of cases. M1 disease was significantly associated with multifocality/multicentricity, high grade tumors, hormone receptor-negative cancers, high Ki67 index, advanced tumor stage, node-positive disease, triple-negative breast cancer, use of PET scans and those who underwent neoadjuvant chemotherapy. Age was not associated with identification of distant metastases.

Conclusion: The prevalence of distant metastases in this population of newly diagnosed patients with breast cancer was higher than previously reported. Routine staging of all patients at presentation was not indicated, especially for asymptomatic patients with early breast cancer. This study identified certain groups of patients with a higher risk of distant metastasis, in whom metastatic workup should be performed. These findings may allow for the development of a local guideline that addresses the question of which breast cancer patients need staging investigations for distant metastases.

Keywords: Body image; breast cancer; breast carcinoma; early breast cancer; metastasis

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Key Points

- Identification of distant metastases in breast cancer is important for decision-making when considering treatment options and establishing the prognosis.
- Routine baseline imaging of all patients with breast cancer at presentation is not indicated, especially asymptomatic cases with early breast cancer.
- Metastatic workup in patients with locally advanced breast cancer and those with symptoms of metastases is appropriate, with consideration to be given to those with abnormal axillary lymph nodes, aggressive molecular subtypes and before starting neoadjuvant chemotherapy.
- This study allows for the development of a local guideline for staging investigations of patients with newly diagnosed breast cancer.

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Introduction

Breast cancer is the second most common cancer worldwide and the most frequent among females. In Bahrain, it accounts for 37.2% of all female cancers and 20% of all new cancer cases, which is considered the highest in all Gulf Cooperation Council countries and among the highest in the world (1). Staging and identification of distant metastases in breast cancer is important, both in decision-making when considering treatment options and establishing the prognosis. The presence of metastatic disease at the time of breast cancer diagnosis is very low, with a reported incidence of 4% (2).

Many guidelines advise against baseline imaging of asymptomatic patients with early breast cancer, however, these recommendations are quite disparate and lack consistency (3). For example, the National Comprehensive Cancer Network (NCCN) guidelines advocate the use of imaging only in patients with signs and symptoms suggestive of distant metastases, locally advanced disease, significant axillary nodal burden or workup prior to neoadjuvant systemic therapy (4). Other European guidelines include T3 disease and tumors with aggressive biology as justification for staging investigations, due to higher prevalence of occult distant metastases in these patients (5).

Despite there being no clear evidence to support routine universal staging in all patients, many patients undergo extensive imaging at the time of diagnosis (6). In Bahrain, all patients newly diagnosed with breast cancer are screened for distant metastases using computed tomography (CT) and bone scans or positron emission tomography (PET) scans. However, overuse of staging investigations can lead to inappropriate use of resources, increased healthcare costs, patient anxiety and psychological distress and delay in treatment (7). Nevertheless, the failure to identify distant metastases during initial workup may also lead to increased morbidity including unnecessary treatment, such as inappropriate breast surgery, radiation therapy and systemic treatment (3). The aim of this study was to assess the necessity for staging imaging investigations by evaluating factors predictive of distant metastases at presentation, in order to establish local guidelines and identify appropriate patients for systemic staging in breast cancer in Bahrain.

Materials and Methods

The study protocol was approved by the Research Ethics Committee of Government Hospitals Bahrain (approval no: 129261223; date: 26.12.2022). All female patients who were newly diagnosed with breast cancer and underwent staging investigations at Salmaniya Medical Complex between January 2016 and December 2022 were included and retrospectively reviewed. Patients with a previous history of extramammary malignancy, synchronous cancers, bilateral breast cancer, ductal carcinoma *in situ*, male patients and those treated for local recurrence were excluded. The following data were collected from electronic medical records of the clinical notes, radiology and pathology reports: age at diagnosis, tumor laterality, tumor type, histological grade, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor 2 (HER2) receptor status, Ki67 index, lymphovascular invasion (LVI), history of neoadjuvant therapy, tumor size, T-stage, nodal status, presence of distant metastases, site of metastasis and type of imaging modalities used for detection of metastases.

All patients with breast cancer were evaluated by triple assessment. All patients were investigated with breast ultrasound, mammogram and tru-cut biopsy. For the T-stage, the largest tumor size (on radiological imaging or after surgical excision) was considered for the analysis. On axillary ultrasonography, if abnormal or suspicious lymph nodes were identified, standard practice was to perform ultrasound-guided biopsy of the nodes. Biopsy- proven metastatic lymph nodes or patients with positive sentinel lymph node biopsy (SLNB) were considered node-positive (N+), whereas benign appearing or absence of suspicious lymph nodes on imaging and negative SLNB were considered node-negative (N0). For patients who underwent axillary dissection, the pathological nodal status was considered for the analysis. For patients who underwent neoadjuvant therapy, the most advanced T and N stages (clinical or pathological) were used for the analysis.

The imaging modalities that were used for staging included CT and bone scan or a PET scan. Results of staging investigations were classified as: no distant metastases (M0), presence of distant metastases (M1) or indeterminate findings (Mx). Patients with indeterminate lesions underwent a follow-up CT scan within three months or further investigations, such as magnetic resonance imaging (MRI) or PET scans. Patients with indeterminate lung or liver nodules that were later found to be unchanged on follow-up CT or not metastatic on MRI or PET scans were classified as M0, whereas those indeterminate features later proven to be distant metastases were labelled as M1. Staging was determined according to the eighth edition of the tumor, node, metastasis system of the American Joint Committee on Cancer staging manual (8).

Statistical Analysis

Descriptive analyses were used to summarize the data and evaluate rates of distant metastases. The chi-square or Fisher's exact test was performed to test for an association between clinicopathological characteristics and the presence of distant metastases. A $p<0.05$ was considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences, version 29.0 (SPSS, IBM Corp, Chicago, IL, USA).

Results

In total, 593 patients with newly-diagnosed invasive breast cancer who fulfilled the inclusion criteria were identified and retrospectively reviewed. Clinicopathological characteristics of the study population are summarized in Table 1. The mean age at diagnosis was 54 (range 23–94) years. Just over half of patients had left- sided breast cancer (51.1%). Most had unifocal disease (78.6%) and only 9.84% of patients had multicentric disease. Invasive ductal carcinoma was the most common histological tumor subtype (84.3%). Most tumors were reported as grade 2 (54.1%). The majority of patients had T2 tumors (46.7%).

LVI was present in 22.1%. Of the cohort, the majority of cases were node-positive (59.2%). Most cases were ER and PR positive (78.6% and 68.6%, respectively). Moreover, 29.2% of tumors were found to be HER2 positive and 62.3% of patients had a Ki67 index >20%. Of the molecular subtypes, the most common tumor biology was Luminal B breast cancer (62.1%). Out of all the patients, 33.6% underwent neoadjuvant systemic therapy.

CT scan of the chest, abdomen, and pelvis along with a bone scan were the imaging modalities of choice (77.1%) for staging, compared to 22.9% of patients who underwent a PET scan. Distant metastases were detected in 20.7% of all patients, with bones being the most frequent site of metastases (47.9%). When univariate and multivariate analysis were performed, the following variables were identified as

predictors for distant metastases: multifocality/multicentricity, high grade tumors (grade 2–3), ER/PR-negative tumors, Ki67 index >20%, neoadjuvant therapy, advanced T stage (T3/T4 tumors), node-positive tumors, triple-negative breast cancer and use of PET scans (Table 2). Although metastatic disease tended to be more frequent in younger (<50 years) individuals and patients with HER2-positive tumors, these findings were not significant.

Discussion and Conclusion

It is important to optimize the criteria for radiological staging in breast cancer in order to identify distant metastases, while avoiding potential harm, such as unnecessary radiation exposure, patient anxiety, false-positives, increased healthcare costs and delay in starting treatment (5). Although guidelines do exist, which address the question of staging investigations for distant metastases, breast cancer patients in Bahrain undergo intensive staging by radiological imaging modalities. One study found that most patients with early breast cancer would prefer having staging imaging investigations, even though this is against the current guidelines (9). This, as well as the demand by our local oncologists and tumor board for comprehensive staging, may explain why all patients in Bahrain undergo routine metastatic workup for newly diagnosed breast cancer.

Table 1. Clinicopathological characteristics of the study population

Age		**ER status**	
Mean	54	Positive	466 (78.6%)
Median	53	Negative	127 (21.4%)
Range	23-94		
Tumour laterality		**PR status**	
Right breast	290 (48.9%)	Positive	407 (68.6%)
Left breast	303 (51.1%)	Negative	186 (31.4%)
Disease focality		**HER2 status**	
Unifocal	466 (78.6%)	Positive	173 (29.2%)
Multifocal	69 (11.6%)	Negative	420 (70.8%)
Multicentric	58 (9.8%)		
Tumour type		**Ki67 index**	
Invasive ductal carcinoma	500 (84.3%)	≤20%	224 (37.8%)
Invasive lobular carcinoma	61 (10.3%)	>20%	369 (62.2%)
Other	32 (5.4%)		
Tumour grade		**Imaging modality**	
Grade 1	116 (19.6%)	CT and bone scan	457 (77.1%)
Grade 2	321 (54.1%)	PET scan	136 (22.9%)
Grade 3	156 (26.3%)		
Tumour stage		**Molecular subtype**	
T1	133 (22.4%)	Luminal A	108 (18.2%)
T2	277 (46.7%)	Luminal B	368 (62.1%)
T3	118 (19.9%)	HER2-enriched	64 (10.8%)
T4	65 (11.0%)	Basal-like	53 (8.9%)
Lymph node status		**Site of metastasis**	
N0	242 (40.8%)	Bone	59 (48.0%)
N1	247 (41.7%)	Lung	15 (12.2%)
N2	73 (12.3%)	Liver	11 (8.9%)
N3	31 (5.2%)	Multiple sites	38 (30.9%)
LVI		**Neoadjuvant therapy**	
Yes	131 (22.1%)	Yes	199 (33.6%)
No	462 (77.9%)	No	394 (66.4%)

ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor 2; CT: Computed tomography; PET: Positron emission tomography

Table 2. Association of clinicopathological risk factors and distant metastases

Age	Distant metastases	*p*-value (univariate)	*p*-value (multivariate)
≤50 years	24.3%	0.116	
>50 years	18.6%		
Disease focality			
Unifocal	18.1%	**0.023**	**0.005**
Multifocal/ multicentric	33.9%		
Tumour type			
Ductal	21.6%		
Lobular	21.3%	0.115	
Other	6.25%		
Tumour grade			
Grade 1	7.76%		
Grade 2	24.1%	**<0.001**	**<0.001**
Grade 3	22.7%		
Tumour stage			
T1	1.78%		
T2	8.72%	**<0.001**	**<0.001**
T3	30.7%		
T4	63.5%		
Lymph node status			
N0	8.94%	**0.031**	**0.027**
N+	28.1%		
LVI			
Present	21.5%	0.807	
Absent	20.4%		
ER status			
Positive	18.4%	**0.013**	**0.001**
Negative	29.3%		
PR status			
Positive	17.9%	**0.016**	**0.010**
Negative	26.8%		
HER2 status			
Positive	23.2%	0.371	
Negative	19.6%		
Ki67 index			
≤20%	15.2%	**0.006**	**0.003**
>20%	24.2%		
Imaging modality			
CT and bone scan	17.7%	**0.002**	**<0.001**
PET scan	30.8%		
Molecular subtype			
Luminal A	11.1%		
Luminal B	20.9%	**0.009**	**<0.001**
HER2-enriched	26.5%		
Basal-like	32.1%		
Neoadjuvant therapy			
Yes	28.3%	**0.002**	**<0.001**
No	17.2%		

ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor 2; LVI: Lymphovascular invasion; CT: Computed tomography; PET: Positron emission tomography

Our results suggest that the prevalence of occult metastases (20.7%) is approximately three times higher than in previous studies, as the overall prevalence of metastatic disease in newly diagnosed breast cancer is reported to be around 7% in other populations (10). In terms of tumor stage, our findings indicate that the rate of distant metastases T1-T2 cases is 10.5%, meaning that one in every 10 patients with early breast cancer will have metastases on staging workup. This rate is relatively high (around 2.5 times as high) compared to the low incidence (4%) previously reported (5). One explanation for higher rates of metastases in our cohort is heterogeneity between different populations with breast cancer and tumor characteristics, as a significant proportion of patients in Bahrain have aggressive tumors compared to Western countries (11). Another cause may be variations in the imaging modalities used for staging, which might affect the diagnostic ability of scans to identify small metastatic deposits. In the present study, PET scans had a significantly greater likelihood to detect distant metastases, but they are also more expensive and not readily available in all institutions (2). As reported in the present study, skeletal metastases represent the most common site of metastasis in patients undergoing baseline staging scans (12). It has been reported that more than 50% of patients with breast cancer in Bahrain have axillary lymph node metastasis at the time of presentation (1, 11). This finding was confirmed in the present study, as 59.2% of patients had positive nodes, and this high rate of nodal positivity is very likely associated with the high prevalence of distant metastases.

Our data indicated an increased likelihood of metastatic disease identification at presentation in those with multifocal or multicentric disease. This is because these cancers have larger tumor dimensions, greater metastatic rate to axillary lymph nodes and a high Ki67 proliferation index (13). As seen in the present study, a high Ki67 index is significantly correlated with a risk of distant metastases and adverse prognostic factors, since it is associated with high-grade and ER/PR-negative tumors (14).

Abnormal axillary lymph nodes on initial imaging have an increased risk of distant metastases, especially for larger tumors (15). In the present study, compared with N0 tumors, the risk of distant metastases was significantly greater for node-positive tumors. Triple-negative and HER2-positive cancers are typically more aggressive than tumors with hormone receptor-positive profiles (5). There is some controversy about the role of molecular subtypes in predicting

distant metastases, where some authors described a relationship (16), while others reported no association (2). Data from the present study, however, showed a significantly higher rate of distant metastases in patients with TNBC and HER2-enriched disease (26.5% and 32.1%, respectively). In the present study, patients who underwent neoadjuvant chemotherapy had an increased likelihood of metastatic disease identification at presentation. Although patient selection for neoadjuvant chemotherapy depends on several factors, such as tumor size, lymph node involvement and receptor status, consideration of CT staging in this group of patients seems reasonable (17).

On the basis of current NCCN guidelines, the accepted criteria for staging in newly diagnosed breast cancer with CT, bone scan or PET scan to detect distant metastatic disease in patients with signs and symptoms of possible metastases, ipsilateral recurrence and T4 disease continue to be appropriate (5). In addition, based on the results of the present study, consideration should also be given to patients with T3 tumors, abnormal axillary lymph nodes and aggressive tumor biology. Furthermore, CT staging is indicated prior to commencing neoadjuvant chemotherapy, in those not meeting the above criteria. However, routine metastatic workup should not be performed for patients with early breast cancer in the absence of symptoms.

Potential limitations of this study include its retrospective nature, patients enrolled from a single institution and a relatively small sample size compared to the literature. Some patients had a CT and bone scan, while others had a PET scan for systemic staging. Lack of standardization of the imaging modality used for detection of distant metastases might have affected our results. Nevertheless, to the best of our knowledge, this is the first study from the Middle East that evaluates the appropriateness of metastatic workup in newly diagnosed breast cancer in order to establish local guidelines for staging in Bahrain.

Although there was a higher prevalence of distant metastases in Bahrain than reported from elsewhere, the routine use of CT scans to screen for distant metastases does not appear to be indicated in all patients with newly diagnosed breast cancer. We identified subgroups of patients with a higher risk of distant metastases in whom a full metastatic workup could be indicated. Overall, our findings confirm that radiological staging of asymptomatic patients with early breast cancer is not warranted as a routine practice in Bahrain. Together with existing guidelines, our findings will help the adoption of a local policy in Bahrain for staging of patients with newly diagnosed breast cancer, with the hope of maximizing detection of metastases while minimizing harmful side effects and costs.

Ethics Committee Approval: The study protocol was approved by the Research Ethics Committee of Government Hospitals Bahrain (approval no: 129261223; date: 26.12.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: R.E., H.A.A.; Concept: R.E., H.A.A.; Design: A.A.A., N.F.A., A.Z.S.; Data Collection and/or Processing: A.A.A., S.A.A., T.H.A., W.Z.A., H.M.H., A.A.Als., N.A.A., F.A.A.; Analysis and/or Interpretation: A.A.A., N.F.A.; Literature Search: A.A.A., H.A.A.; Writing: A.A.A., N.F.A., A.Z.S., S.A.A., T.H.A., W.Z.A., H.M.H., A.A.Als., N.A.A., F.A.A., R.E., H.A.A.

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