Predictive Factors for Site of Local and Systemic Recurrence in Breast Cancer Patients

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Abstract:

Background and aim of the work: Breast cancer is the most common type of female cancer in Egypt with high morbidity and mortality. The purpose of this study is to assess whether clinical characteristics can predict the most probable site of recurrence

Methods: We retrospectively studied clinic-pathological characteristics of 134 female patients had breast cancer who presented at South Egypt Cancer Institute (SECI) from January 2015 to December 2022 for association with certain metastatic sites.

Results: Our data analysis revealed that premenopausal status, low Body Mass Index (BMI) and high Ki67 can predict higher incidence of bone metastasis. Nodal involvement and Progesterone Receptor (PR) negativity can predict higher incidence of lung metastasis. Age younger than 50 years, premenopausal status and presence of Ductal Carcinoma in Situ (DCIS) component can predict higher incidence of liver metastasis. Tumor size ≥T3 can predict higher incidence of brain metastasis. Lastly, larger tumor size ≥ T3, low BMI, ER negativity, PR negativity and high Ki67 can predict higher chance for recurrence. Grade III differentiation and PR negativity led to increase of lymph node metastasis.

Conclusion: Certain clinicopathological characteristics are associated with specific sites of metastasis, which direct health care providers for meticulous follow up.

Keywords: breast cancer, recurrence, metastasis, South Egypt Cancer Institute.

Introduction:

Breast cancer (BC) is the most commonly diagnosed cancer worldwide, with estimated new cases exceeding 2 million in 2020. In addition, it is the leading cause of female cancer deaths forming up to 680,000. [1] Breast cancer is the most common type of female cancer in Egypt with an age-specific incidence rate of 48.8 patients for each 100,000. [2] At this time, it is the second most common cause of Egyptian cancer mortality after hepatocellular carcinoma with estimated mortality rate around 11%. [3]

Higher incidence and mortality in Egypt than other countries due to delayed diagnosis. In Egypt, most of the cases discovered at locally advanced or metastatic stages. [4, 5]

Breast cancer metastasis to distant organs accused for the majority of breast cancer-related deaths. This caused by higher cancer burden and absence of effective drugs to use for the treatment of metastatic breast cancer. Thus, it is essential to identify prognostic markers that can accurately predict potential risks of metastasis and therapeutic targets to use for treating patients with metastatic breast cancer. Although there are discrepancies among reports regarding the preferred metastatic sites of breast cancer subtypes, it is adopted that diverse subtypes exhibit distinct behavior regarding the sites of distant metastasis. [6]

The metastasis is highly challenging problem in breast cancer patients that affect survival outcome and quality of life. There is paucity of studies that titled the prediction of metastases. So, we decided to study whether patients' and tumor characteristics can predict the site of recurrence in breast cancer.

Patients and Methods:

Study design and patients:

We conducted this retrospective study on 134 female non-metastatic breast cancer at the initial presentation according to American Joint committee on cancer's staging system for breast cancer, Eighth Edition. [7] All patients were treated at the Medical Oncology Department, South Egypt Cancer Institute, Assiut University during the period from January 2015 to December 2022. The inclusion criteria were histologically or cytologically proven breast carcinoma, age of 18 yrs or older. Patient with incomplete data and double malignancy were excluded. Ethical approval was obtained from our institutional ethical committee SECI-IRB with number IORG000563-601.

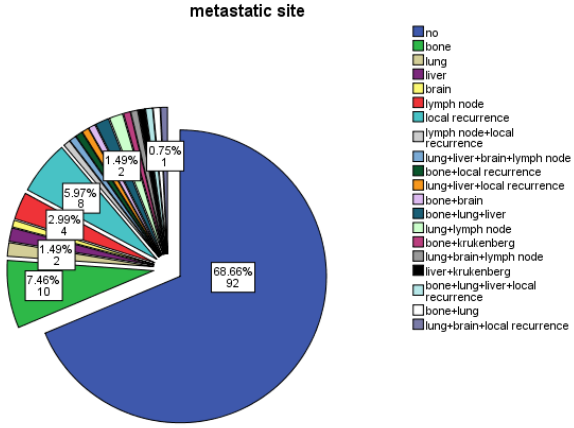
Assessment and treatment:

Baseline and subsequent assessments were according to local guidelines. These included history taking, clinical examination, radiological diagnosis (CT/MRI, PET/CT scan, and/or bone scan; when indicated), and pathological data. Patients were subjected to different lines of systemic treatment, including adjuvant chemotherapy with various protocols including Anthracyclines, Taxenes, Trustuzumab (for HER2 positive tumors), capecitabine for triple negative disease (when indicated), and hormonal treatment. Hormonal therapy includes Tamoxifen or Aromatase inhibitor ± Goserline.

Statistical analysis:

Data were described in terms of mean ± standard deviation (±SD), or median and range for normally distributed and not normally distributed variable; respectively. Frequencies and percentages were used when appropriate. For comparing categorical data, Chi square ($\chi 2$) or Fisher Exact test (when appropriate) was performed. P-value is always 2 tailed set, and considered significant if less than 0.05 level. All statistical calculations was done using SPSS (statistical package for the social science; SPSS Inc., Chicago, IL, USA) version 22.

Results:



In this study, patients with age range of 24 to 80 (median, 50 years). Patients was subcategorized into patients aged below 50 yrs (61; 45.5%) and patients aged 50 yrs or above (73; 54.5%). At diagnosis, seventy-eight (58.2%) patients were postmenopausal. Regarding BMI, fifty-nine patients (44%) were obese. The most common pathology was invasive ductal carcinoma (97.01%). Grade II differentiation recorded in 92.5% of patients. About two thirds of patients (94, 70.1%) had tumor size less than 5 cm, also about two thirds (92, 68.7%) of patients had nodal involvement. Luminal A, luminal B, HER2 overexpression and triple negative patients was distributed as follows 34, 43, 22 and 35, respectively.

The four most common sites of recurrences were bone (14.1%), lung (9.7%), local breast (8.9%), and lymph node (7.5%).

Bone metastasis was found to be associated with premenopausal status as 21.4% of premenopausal patients developed bone metastasis compared to only 9% of postmenopausal patients (P= 0.042). Also, BMI less than 30 associated with higher incidence of bone metastasis as 20.0% of the patients that had BMI below 30 developed bone metastases, while only 9% of patients that had BMI above or equal 30 developed bone metastasis (P= 0.029). In addition, patients with high Ki67 level had 5-fold increase incidence of bone metastases when compared to the rate in patients with low Ki67 level (23.5% versus 4.5%, respectively; P= 0.002), (Table.1).

Lung metastasis showed significant association with nodal involvement and PR negativity. Node positive patients has incidence of 14.1% compared to zero percent in node negative group (P= 0.009). Ten patients (14.9%) with PR negative had lung metastasis compared to only three patients with PR positive disease (P= 0.041) as shown in Table 2.

The younger the patient, the more common liver incidence as age younger than 50 years was associated liver metastasis of 13.1%, while patients aged of 50 years or older had not developed liver metastasis (P= 0.001). In a similar manner, higher incidence of liver metastasis in premenopausal patients, as 14.3% of premenopausal patients developed liver metastasis

while no one of postmenopausal patients developed liver metastasis (P= 0.001). Liver metastases were 10% in DCIS group and absence of event in absence of DCIS (P= 0.021) (Table 3).

There is association for developing brain metastasis with tumor size ≥ T3 breast cancer patients, as 12.5% of patients that had tumor size ≥ T3 developed brain metastasis while only 1.1% of patients with tumor size <T3 developed brain metastasis (P= 0.009) as shown in Table 4.

Local recurrence showed clear association with ER negativity as 15.5% of ER negative patients developed local recurrence, while only 3.9% of ER positive patients developed local recurrence (P= 0.020). PR negativity led to higher local recurrence (14.9% vs. 3%, P= 0.016). Tumor size ≥ T3 associated with higher incidence of local recurrence (17.5% vs. 5.3%, P= 0.042). High Ki67 also increased incidence of local recurrence (14.7%) compared to only 3.0% with low Ki67 (P= 0.018). Low BMI also associated with increased recurrence rate (13.3% vs. 3.4%, P= 0.045) Table 5.

Grade III differentiation and PR negativity led to increase in development of lymph node metastasis with 30% versus 5.6%, respectively; P = 0.028, for grade category and 11.9% versus 3%, respectively; P = 0.049, for PR status.

Table 1. Correlation of bone metastasis with Patient and disease characteristics

Patient and disease characteristics		**Bone metastasis**				**P- value**
		No (N=115)		**Yes (N=19)**		
		N	**%**	**N**	**%**	
Age	< 50 yrs	50	82.0%	11	18.0%	0.242
	≥ 50 yrs	65	89.0%	8	11.0%	
Menopausal status	pre	44	78.6%	12	21.4%	**0.042**
	post	71	91.0%	7	9.0%	
BMI	< 30	60	80.0%	15	20.0%	**0.029**
	>/= 30	55	93.2%	4	6.8%	
Grade	I, II	107	86.3%	17	13.7%	0.634
	III	8	80.0%	2	20.0%	
Tumor size	< T3	82	87.2%	12	12.8%	0.472
	≥ T3	33	82.5%	7	17.5%	
Nodal involvement	Node negative	39	92.9%	3	7.1%	0.115
	Node positive	76	82.6%	16	17.4%	
ER	Negative	50	86.2%	8	13.8%	0.911
	Positive	65	85.5%	11	14.5%	
PR	Negative	57	85.1%	10	14.9%	0.804
	Positive	58	86.6%	9	13.4%	
HER2 neu	Negative	88	85.4%	15	14.6%	1.000
	Positive	27	87.1%	4	12.9%	
Ki67	Low	63	95.5%	3	4.5%	**0.002**
	High	52	76.5%	16	23.5%	
Biological subtype	Luminal A	31	91.2%	3	8.8%	0.410
	Luminal B	34	79.1%	9	20.9%	
	HER2 overexpression	20	90.9%	2	9.1%	
	Triple negative	30	85.7%	5	14.3%	
DCIS	No	48	88.9%	6	11.1%	0.403
	Yes	67	83.8%	13	16.3%	
LVI	No	39	88.6%	5	11.4%	0.514
	Yes	76	84.4%	14	15.6%	
PNI	No	80	87.0%	12	13.0%	0.577
	Yes	35	83.3%	7	16.7%	
TILs	less than 50 %	103	84.4%	19	15.6%	
	more than 50 %	12	100.0%	0	0.0%	

Abbreviations: BMI, body mass index; ER, Estrogen Receptor; PR, Progesterone Receptor; DCIS, Ductal Carcinoma In Situ; LVI, Lymphovascular Invasion; PNI, Perineural Invasion; TILs, Tumor Infiltrating Lymphocytes.

Table 2. Correlation of lung metastasis with Patient and disease characteristics

Patient and disease characteristics		**Lung metastasis**				**P- value**
		No (N=121)		**Yes (N=13)**		
		N	**%**	**N**	**%**	
Age	< 50 yrs	53	86.9%	8	13.1%	0.222
	≥ 50 yrs	68	93.2%	5	6.8%	
Menopausal status	pre	48	85.7%	8	14.3%	0.129
	post	73	93.6%	5	6.4%	
BMI	< 30	68	90.7%	7	9.3%	0.871
	≥ 30	53	89.8%	6	10.2%	
Grade	I, II	113	91.1%	11	8.9%	0.250
	III	8	80.0%	2	20.0%	
Tumor size	< T3	88	93.6%	6	6.4%	0.059
	≥ T3	33	82.5%	7	17.5%	
Nodal involvement	Node negative	42	100.0%	0	0.0%	**0.009**
	Node positive	79	85.9%	13	14.1%	
ER	Negative	49	84.5%	9	15.5%	0.075
	Positive	72	94.7%	4	5.3%	
PR	Negative	57	85.1%	10	14.9%	**0.041**
	Positive	64	95.5%	3	4.5%	
HER2 neu	Negative	95	92.2%	8	7.8%	0.178
	Positive	26	83.9%	5	16.1%	
Ki67	Low	61	92.4%	5	7.6%	0.413
	High	60	88.2%	8	11.8%	
Biological subtype	Luminal A	32	94.1%	2	5.9%	0.540
	Luminal B	40	93.0%	3	7.0%	
	HER2 overexpression	19	86.4%	3	13.6%	
	Triple negative	30	85.7%	5	14.3%	
DCIS	No	49	90.7%	5	9.3%	0.887
	Yes	72	90.0%	8	10.0%	
LVI	No	41	93.2%	3	6.8%	0.545
	Yes	80	88.9%	10	11.1%	
PNI	No	83	90.2%	9	9.8%	1.000
	Yes	38	90.5%	4	9.5%	
TILs	less than 50 %	109	89.3%	13	10.7%	0.606
	more than 50 %	12	100.0%	0	0.0%	

Table 3. Correlation of liver metastasis with Patient and disease characteristics

Patient and disease characteristics		Liver metastasis				P- value
		No (N=126)		Yes (N=8)		
		N	%	N	%	
Age	< 50 yrs	53	86.9%	8	13.1%	**0.001**
	≥ 50 yrs	73	100.0%	0	0.0%	
Menopausal status	pre	48	85.7%	8	14.3%	**0.001**
	post	78	100.0%	0	0.0%	
BMI	< 30	70	93.3%	5	6.7%	1.000
	≥ 30	56	94.9%	3	5.1%	
Grade	I, II	118	95.2%	6	4.8%	0.110
	III	8	80.0%	2	20.0%	
Tumor size	< T3	91	96.8%	3	3.2%	0.051
	≥ T3	35	87.5%	5	12.5%	
Nodal involvement	Node negative	42	100.0%	0	0.0%	0.056
	Node positive	84	91.3%	8	8.7%	
ER	Negative	56	96.6%	2	3.4%	0.465
	Positive	70	92.1%	6	7.9%	
PR	Negative	64	95.5%	3	4.5%	0.718
	Positive	62	92.5%	5	7.5%	
HER2 neu	Negative	97	94.2%	6	5.8%	1.000
	Positive	29	93.5%	2	6.5%	
Ki67	Low	61	92.4%	5	7.6%	0.489
	High	65	95.6%	3	4.4%	
Biological subtype	Luminal A	32	94.1%	2	5.9%	0.674
	Luminal B	39	90.7%	4	9.3%	
	HER2 overexpression	21	95.5%	1	4.5%	
	Triple negative	34	97.1%	1	2.9%	
DCIS	No	54	100.0%	0	0.0%	**0.021**
	Yes	72	90.0%	8	10.0%	
LVI	No	42	95.5%	2	4.5%	1.000
	Yes	84	93.3%	6	6.7%	
PNI	No	88	95.7%	4	4.3%	0.258
	Yes	38	90.5%	4	9.5%	
TILs	less than 50 %	114	93.4%	8	6.6%	1.000
	more than 50 %	12	100.0%	0	0.0%	

Table 4. Correlation of brain metastasis with Patient and disease characteristics

Patient and disease characteristics		Brain metastasis				P- value
		No (N=128)		Yes (N=6)		
		N	%	N	%	
Age	< 50 yrs	57	93.4%	4	6.6%	0.411
	≥ 50 yrs	71	97.3%	2	2.7%	
Menopausal status	pre	52	92.9%	4	7.1%	0.235
	post	76	97.4%	2	2.6%	
BMI	< 30	70	93.3%	5	6.7%	0.229
	≥ 30	58	98.3%	1	1.7%	
Grade	I, II	119	96.0%	5	4.0%	0.378
	III	9	90.0%	1	10.0%	
Tumor size	< T3	93	98.9%	1	1.1%	**0.009**
	≥ T3	35	87.5%	5	12.5%	
Nodal involvement	Node negative	42	100.0%	0	0.0%	0.176
	Node positive	86	93.5%	6	6.5%	
ER	Negative	53	91.4%	5	8.6%	0.085
	Positive	75	98.7%	1	1.3%	
PR	Negative	62	92.5%	5	7.5%	0.208
	Positive	66	98.5%	1	1.5%	
HER2 neu	Negative	99	96.1%	4	3.9%	0.622
	Positive	29	93.5%	2	6.5%	
Ki67	Low	65	98.5%	1	1.5%	0.208
	High	63	92.6%	5	7.4%	
Biological subtype	Luminal A	34	100.0%	0	0.0%	0.210
	Luminal B	42	97.7%	1	2.3%	
	HER2 overexpression	20	90.9%	2	9.1%	
	Triple negative	32	91.4%	3	8.6%	
DCIS	No	51	94.4%	3	5.6%	0.685
	Yes	77	96.3%	3	3.8%	
LVI	No	41	93.2%	3	6.8%	0.394
	Yes	87	96.7%	3	3.3%	
PNI	No	88	95.7%	4	4.3%	1.000
	Yes	40	95.2%	2	4.8%	
TILs	less than 50 %	116	97.5%	6	2.5%	1.000
	more than 50 %	12	100.0%	0	0.0%	

Table 5. Correlation of local recurrence with Patient and disease characteristics

Patient and disease characteristics		**Local recurrence**				**P- value**
		No (N=122)		**Yes (N=12)**		
		N	%	N	%	
Age	< 50 yrs	55	90.2%	6	9.8%	0.744
	≥ 50 yrs	67	91.8%	6	8.2%	
Menopausal status	pre	50	89.3%	6	10.7%	0.546
	post	72	92.3%	6	7.7%	
BMI	< 30	65	86.7%	10	13.3%	**0.045**
	≥ 30	57	96.6%	2	3.4%	
Grade	I, II	114	91.9%	10	8.1%	0.221
	III	8	80.0%	2	20.0%	
Tumor size	< T3	89	94.7%	5	5.3%	**0.042**
	≥ T3	33	82.5%	7	17.5%	
Nodal involvement	Node negative	41	97.6%	1	2.4%	0.103
	Node positive	81	88.0%	11	12.0%	
ER	Negative	49	84.5%	9	15.5%	**0.020**
	Positive	73	96.1%	3	3.9%	
PR	Negative	57	85.1%	10	14.9%	**0.016**
	Positive	65	97.0%	2	3.0%	
HER2 neu	Negative	94	91.3%	9	8.7%	1.000
	Positive	28	90.3%	3	9.7%	
Ki67	Low	64	97.0%	2	3.0%	**0.018**
	High	58	85.3%	10	14.7%	
Biological subtype	Luminal A	33	97.1%	1	2.9%	0.114
	Luminal B	41	95.3%	2	4.7%	
	HER2 overexpression	19	86.4%	3	13.6%	
	Triple negative	29	82.9%	6	17.1%	
DCIS	No	50	92.6%	4	7.4%	0.762
	Yes	72	90.0%	8	10.0%	
LVI	No	41	93.2%	3	6.8%	0.750
	Yes	81	90.0%	9	10.0%	
PNI	No	83	90.2%	9	9.8%	0.753
	Yes	39	92.9%	3	7.1%	
TILs	less than 50 %	110	90.2%	12	9.8%	0.600
	more than 50 %	12	100.0%	0	0.0%	

Table 6. Correlation of lymph node metastasis with Patient and disease characteristics

Patient and disease characteristics		Lymph node metastasis				P- value
		No (N=124)		Yes (N=10)		
		N	%	N	%	
Age	< 50 yrs	54	88.5%	7	11.5%	0.106
	≥ 50 yrs	70	95.9%	3	4.1%	
Menopausal status	pre	49	87.5%	7	12.5%	0.093
	post	75	96.2%	3	3.8%	
BMI	< 30	69	92.0%	6	8.0%	1.000
	≥ 30	55	93.2%	4	6.8%	
Grade	I, II	117	94.4%	7	5.6%	**0.028**
	III	7	70.0%	3	30.0%	
Tumor size	< T3	89	94.7%	5	5.3%	0.164
	≥ T3	35	87.5%	5	12.5%	
Nodal involvement	Node negative	41	97.6%	1	2.4%	0.171
	Node positive	83	90.2%	9	9.8%	
ER	Negative	51	87.9%	7	12.1%	0.101
	Positive	73	96.1%	3	3.9%	
PR	Negative	59	88.1%	8	11.9%	**0.049**
	Positive	65	97.0%	2	3.0%	
HER2 neu	Negative	98	95.1%	5	4.9%	0.051
	Positive	26	83.9%	5	16.1%	
Ki67	Low	62	93.9%	4	6.1%	0.745
	High	62	91.2%	6	8.8%	
Biological subtype	Luminal A	33	97.1%	1	2.9%	0.156
	Luminal B	41	95.3%	2	4.7%	
	HER2 overexpression	18	81.8%	4	18.2%	
	Triple negative	32	91.4%	3	8.6%	
DCIS	No	50	92.6%	4	7.4%	1.000
	Yes	74	92.5%	6	7.5%	
LVI	No	41	93.2%	3	6.8%	1.000
	Yes	83	92.2%	7	7.8%	
PNI	No	84	91.3%	8	8.7%	0.724
	Yes	40	95.2%	2	4.8%	
TILs	less than 50 %	113	92.6%	9	7.4%	1.000
	more than 50 %	11	91.7%	1	8.3%	

Discussion:

Breast cancer metastasis to distant organs accused for the majority of breast cancer-related deaths. This caused by higher cancer burden and absence of effective drugs to use for the treatment of metastatic breast cancer. Thus, it is essential to identify prognostic markers that can accurately predict potential risks of metastasis and therapeutic targets to use for treating patients with metastatic breast cancer. Although there are discrepancies among reports regarding the preferred metastatic sites of breast cancer subtypes, it is adopted that diverse subtypes exhibit distinct behavior regarding the sites of distant metastasis. [6]

On studying our patients clinic-pathological characteristics association with certain metastatic sites, we found that bone metastasis showed association with BMI <30 which may coincides with findings of Khalil Saleh et al. [8] who described that Low BMI was associated with the presence of visceral metastases and a higher number of metastatic sites. Although contradictory finding in the same study of Khalil et al. that the frequency of bone-only metastases increased with increasing BMI. [8]

In this study high Ki67 showed association with bone metastasis and local recurrence with significant P= 0.002, 0.017, respectively which Coincides with findings of several studies including that of Yuan P et al. [9]

Our study found that nodal involvement and PR negativity correlated with lung metastasis increased incidence which is in line with Qian Dong et al. [10] and Basim Ali et al. [11] who reported a significant association between nodal involvement and metastatic site in patients with stage IV breast cancer. While,

Spoik V et al. described a different data of a non-linear relationship between nodal involvement and distant metastases, Explanation may by a smaller proportion of cells accessible to the vascular or lymphatic system in larger tumors, a lack of stable blood supply leading to central necrosis, or a larger proportion of tumors with indolent phenotypes. [12]

Local recurrence positive correlation to tumor size in our study reported also in Pedersen RN et al. study who stated that recurrences continued to occur up to 32 years after primary diagnosis. Female patients with high lymph node burden, large tumor size, and estrogen receptor–positive tumors had increased risk of late recurrence according to Pedersen RN et al. study. The increased recurrence with hormonal receptor positivity finding of the same study of Pedersen RN et al. may contrast with our finding of increased local recurrence with PR negativity. [13] Low BMI was associated with increased local recurrence in our study, which coincides with the finding of Khalil et al. study that described increased risk of recurrence and number of metastatic sites with low BMI.

Association of liver metastasis with age below 50 yrs and premenopausal status supported by Ji L et al finding that breast cancer patients with young age have a high risk of developing liver metastases at initial diagnosis, and therefore deserve more attention during the follow-up. [14]

Conclusion:

In conclusion, some demographic and clinicopathological characteristics are associated with specific site of recurrence drawing our attention for meticulous investigations to detect these recurrences early. Further studies are recommended with larger sample size to confirm our results.

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