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RESEARCH ARTICLE

Pattern of metastasis with breast cancer in Egyptian cancer patients: A single center retrospective study

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ABSTRACT

Background: An increasing body of research indicates that the molecular subtype of breast cancer can forecast the onset, course, and prognosis of metastatic. **Aim:** The aim of this retrospective study was to examine the distribution pattern of metastases, progression free survival, and overall survival of cancer patients with skeletal, visceral, and non-visceral metastases **Patients and Method:** Patients diagnosed with breast cancer who visited the Clinical Oncology Department at Suez Canal University Hospitals in Egypt between January 2013 and December 2014, with follow-up until July 2023, comprised the study population. **Results:** For every patient (n = 242), the metastatic pattern varies between therapy groups. Visceral and bone metastases were the most common sites of metastasis in Luminal A group, with 17.2% developing metastasis with a mean ± SD of 6.96 ± 2.97 years. 36% of group 2 experienced metastases, with a mean ± standard deviation of 5.25 ± 1.55 years. Within Luminal B tumor subgroup, bone-only metastasis was the most frequent pattern of metastasis. In HER2 enriched, lung metastasis affected many patients, while bone and visceral metastases were the most frequent metastatic patterns. In triple negative subtype, most patients had a visceral exclusively metastatic pattern, with lung metastasis being the most prevalent location. There was a statistically significant difference (P<0.001) in the 5-year PFS between the groups under investigation. There was a statistically significant difference (P<0.001) in overall survival between the groups under investigation. **Conclusion:** Breast cancer exhibits a systematic and predictable dissemination, where visceral and bone metastases were the most common sites in luminal A , bone-only metastasis in luminal B , both bone and visceral metastases in HER2+ subtype. , and a visceral exclusively metastases in triple negative subtype. .

Keywords: Breast cancer, Molecular types, Bone metastasis, Visceral metastasis

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INTRODUCTION

Despite differences in incidence rates between urbanized and developing nations, breast cancer remains the most frequent kind of female cancer in Egypt, with an age-specific incidence rate of 48.8/105. Approximately 46,000 cases are expected by 2050. Although Egypt's incidence rate is lower than worldwide estimates, mortality is higher at an age-standardized rate of 20.4/100,0004 compared to the US rate of 12.3/105 and the developed nations' rate of 12.8/105 (Azim et al. 2023).

With a projected 46,000 cases in 2050, breast cancer will be the most common disease among Egyptian women, accounting for 38.8% of all cancers in this age group (Ibrahim et al. 2014). After hepatocellular carcinoma, breast cancer is the second most common cause of cancer-related death with a mortality rate of about 11% (International Cancer Control Partnership 2020).

Over 90% of these deaths are attributable to metastasis (Jin et al. 2015). Treatment for metastatic breast cancer is still palliative despite recent advancements, and patient survival rates differ greatly. The skeleton is the most common metastatic site in breast cancer, which exhibits a distinct metastatic pattern (Jin X, et al. 2015, Chiang AC. et al. 2008). Bone metastases are seen in 65-75% patients with metastatic breast cancer (Galasko CSB. 2004 and Coleman RE. 2006).

A significant histopathological characteristic of breast cancer that is linked to patient outcome is the expression of estrogen, progesterone, and Human Epidermal Growth Factor Receptors 2 (HER2) in the tumor; this receptor expression forms the basis of the new molecular taxonomy of breast cancer. Perou et al. found that the molecular profile of breast cancer influences

the timing, pattern, and prognosis of metastatic disease (Perou et al. 2000).

Furthermore, the receptor expression profile of metastatic lesions may differ from that of the original tumor. Because of this, the standard of care for treating patients with breast cancer is now breast cancer molecular phenotyping (estrogen, progesterone, and HER2) (Sørlie et al. 2001, Cancer Genome Atlas Network. 2012).

Recent research on metastatic breast cancer subtypes suggests that risk stratification by subtype may provide more customized care with a focus on. Risk stratification by subtype may offer more specialized, individualized care, with an emphasis on targeted follow-up for individuals at increased risk of metastatic illness, according to recent metastatic breast cancer subtype research. Metabolic relapse rates were lowest in Luminal A ER-positive tumors. The median survival period for individuals with luminal A is around 2.2 years following the first metastasis, which is significantly longer than that of any other subtype, including luminal B (Perou. et al. 2000).

We provide data on patients with visceral, non-visceral, and bone metastases. A post-mortem investigation of breast cancer patients who had a metastatic trend throughout their illness was used to gather data. In addition, we discuss the differences in overall survival (OS) among patients.

METHODOLOGY & DESIGN

Study Design

The aim of this retrospective study was to examine the distribution pattern of metastases, treatment options, and overall survival of cancer patients with skeletal, visceral, and non-visceral metastases.

Study Population

The experiment comprised breast cancer patients who visited the Clinical Oncology Department at Suez Canal University Hospitals in Egypt from January 2013 to December 2014, with an extra follow-up period scheduled until July 2023.

Inclusion Criteria

- Females only
- Age is greater than 18 but less than 65 years.
- Histologically proved breast cancer patients.
- Patients who develop metastases while undergoing treatment.
- Radiologically verified skeletal, visceral, and non-visceral metastases.

Exclusion criteria

- Multiple primary tumors or dual pathological lesions
- Bone primary tumors.
- Patients with isolated epidural or intradural spinal metastases.

Participant Enrollment

A list of all eligible patients was collected from the patient's records, and the list was followed up with over the necessary period (from January 2013 to December 2014, with a follow-up period until July 2023) to record the sickness result and clinico-pathological characteristics. This analysis used data from the Clinical Oncology Department's file recording system. The system stored patient information such as personal, clinical, laboratory, radiographic, and pathological data, as well as therapy received and follow-up.

Sample size

The following equation was used to calculate sample size: (Charan et al. 2013)

$$\mathbf{n} = \frac{(\mathbf{Z}_{\mathbf{1-\frac{\alpha}{2}}})^2 * \mathbf{p(1-p)}}{\mathbf{d^2}}$$

Where

n = the sample size.
$Z_{1-\alpha/2}$ = the confidence interval which equals to 1.96 when type 1 error is 5%.
P= prevalence of breast cancer in Egypt is 38.8%.
d=Absolute error or precision, usually equals 10%.

The calculated sample size is 100 participants; however, after adding the expected (drop-out) rate (10%), the final sample size was 242 participants

Ethical consideration

The research ethics committee of the Faculty of Medicine Suez Canal University (FOMSCU) accepted the final protocol. Clinical data was collected with the agreement of the FOMSCU study ethics committee. The data for the study

came from the patients' medical records. To ensure patient privacy and information confidentiality, no personal information was revealed. Only one study used data, and patient interaction was required to reduce the possibility of inaccurate recording and follow-up. The data analysis was kept private and did not divulge the patients' identities. Ethic committee Number (Research 5447).

Statistical analysis

Progression-free survival (PFS) is defined as the time from random assignment to disease progression. The OS is the period elapsed between the initiation of first-line therapy and the date of death from any cause. At the time of last contact, the number of patients who were alive or lost to follow-up at the data cut was calculated. Descriptive statistics for categorical variables are reported as frequencies and percentages. The mean and standard deviation are used to illustrate numerical variables with normal distribution. The Chi square test compares categorical variables. A one-way ANOVA was used to compare numerical factors. The log-rank test was used to compare survival rates among groups. Cox regression analysis was used to determine the impact of different variables on survival over a certain period. The statistical study was carried out using IBM SPSS 28 software, which runs on Windows. The P-value of 0.05 is commonly used and considered statistically significant.

RESULTS

Patient and tumor characteristics

A retrospective analysis was performed using data from 242 breast cancer patients. The average age of the patients was 47.5 years (SD = 11.12), and their BMI was 31.77 kg/m² (SD = 6.09). In terms of residency, 146 patients (60.3%) lived in cities, and 96 patients (39.7%) lived in rural areas. Of the patients, 112 (46.3%) were premenopausal, 52 (21.5%) were perimenopausal, and 78 (32.2%) were postmenopausal. A positive family history of breast cancer was reported in 60 patients (24.8%). In terms of comorbidities, 84 patients (34.7%) had chronic illness, 54 (22.3%) had hypertension, 50 (20.7%) had diabetes, 8 (3.3%) had chronic liver disease, and 11 (4.5%) had hepatitis C virus infection. The clinical and demographic characteristics of breast cancer patients are shown in Table 1.

Hormonal receptor status

According to the major tumor receptor status assessment, 155 patients (64.0%) had positive estrogen receptor status (ER+), 145 patients (59 .9%) had positive progesterone receptor status (PR+), and 78 patients (32.2%) had positive Human Epidermal Growth Factor Receptor 2 status (HER2+). The study population was divided into four groups, and each group was further investigated based on the receptors present at the main diagnostic.

Group 1 included 29 patients (12%) with luminal A subtype (HR positive HER2neu negative KI 67 < 14). **Group 2** included 75 patients (31%) with luminal B subtype (HR positive HER2neu negative KI 67 greater than 14). **Group 3** included 78 patients (32.2%) with the HER2neu positive subtype. **Group 4** had 60 patients (24.8%) with the Triple negative subtype.

Table 1. Descriptive data of all patients (N=242)

	Mean	SD
Age (years)	47.5	11.12
BMI (kg/m^2)	31.77	6.09
	N	**%**
Residency		
Urban	146	60.3
Rural	96	39.7
Menopause		
Pre-menopausal	112	46.3
Peri-menopausal	52	21.5
Postmenopausal	78	32.2
Family history	60	24.8
Chronic illness	84	34.7
HTN	54	22.3
DM	50	20.7
CLD	8	3.3
HCV	11	4.5
ER		
Negative	87	36.0
Positive	155	64.0
PR		
Negative	97	40.1
Positive	145	59.9
HER2		
Negative	164	67.8
Positive	78	32.2

BMI: Body mass index, HTN: Hypertension, DM: Diabetes mellitus, CLD: Chronic liver disease, HCV: Hepatitis C virus, ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2.

There was a significant difference (p<0.001) in the Ki 67 expression across the groups. Groups 2, 3, and 4 exhibited greater mean Ki 67 expressions (32.86±16.13, 32.31±17.8, and 21.50±14.65, respectively), while Group 1 had a lower mean expression (8.31±6.67).

Pathological tumor characteristics

There was no discernible difference between the groups in the distribution of the tumor location (left or right) (p = 0.596). In all groups, most patients had right-sided tumors. The type of surgery performed did not significantly differ across the groups (p = 0.405). Across all groups, modified radical mastectomy was the most prevalent surgical treatment, with the highest proportion occurring in Group 2. There was a significant difference between the groups in staging (p<0.001). There was a substantial variation in tumor size (T) between the groups (p<0.001). The proportion of T2 tumors was largest in Group 2, while the proportion of T1 tumors was greatest in Group 1. There was a significant difference (p<0.001) in the groups' lymph node involvement (N). Group 1 had the highest rate of N1 participation, whereas Group 3 had the highest percentage of N4 involvement. There was a substantial variation in the quantity of positive lymph nodes between the groups (p<0.001). In comparison to Group 1, the mean number of positive lymph nodes was larger in Groups 2, 3, and 4. There was a significant difference between the groups when additional nodal extension was present (p=0.006). Groups 2 and 3 had a higher percentage of patients with extra nodal extension.

There was a noteworthy variation in lymph vascular invasion between the groups (p<0.001). The percentage of individuals with lymph vascular invasion was greater in Groups 2 and 3. There was a significant variation in perineural invasion between the groups (p = 0.009). Group 3 had the highest frequency of patients with perineural invasion. There was no discernible difference between the groups' histopathology (p = 0.159). Across all groups, the most prevalent histological subtype was invasive ductal carcinoma. Differentiation revealed a significant difference between the groups (p=0.027). The proportion of undifferentiated tumors was highest in Group 3, while the proportion of well-differentiated tumors was highest in Group 4. There was no discernible difference in the surgical margins between the groups (p = 0.550). In every group, most patients had surgical margins that were negative. Regarding tumor grading, there was a statistically significant difference (p<0.001) between the four groups (Table 3).

Metastasis pattern & PFS according to tumor subtype

Every patient has a different metastatic pattern depending on the treatment group. When patients were tracked from diagnosis to July 2023, they showed diverse patterns of metastasis.

Table 2. Baseline characteristics and comorbidities of the studied groups

	Receptors at primary diagnosis								P-value
	Group 1		Group 2		Group 3		Group 4		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age	49.00	13	46.76	12	47.10	10	48.22	11	0.753
BMI	33.2	5.8	30.9	6.5	32.6	5.9	31.2	5.8	0.158
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Residency									0.503
Urban	17	58.6%	41	54.7%	52	66.7%	36	60.0%	
Rural	12	41.4%	34	45.3%	26	33.3%	24	40.0%	
Menopause									0.067
Pre-menopausal	12	41.4%	39	52.0%	37	47.4%	24	40.0%	
Peri-menopausal	7	24.1%	9	12.0%	24	30.8%	12	20.0%	
Postmenopausal	10	34.5%	27	36.0%	17	21.8%	24	40.0%	
Family history	4	13.8%	20	26.7%	18	23.1%	18	30.0%	0.389
Chronic illness	8	27.6%	24	32.0%	30	38.5%	22	36.7%	0.687
HTN	5	17.2%	15	20.0%	19	24.4%	15	25.0%	0.777
DM	3	10.3%	14	18.7%	19	24.4%	14	23.3%	0.395
CLD	1	3.4%	5	6.7%	1	1.3%	1	1.7%	0.244
HCV	2	6.9%	4	5.3%	3	3.8%	2	3.3%	0.810

Visceral and bone metastases were the most common sites of metastasis in group 1, with 17.2% developing metastasis with a mean ± SD of 6.96 ± 2.97 years. In group 1, 82.8% did not experience metastases. 36% of group 2 experienced metastases, with a mean ± standard deviation of 5.25 ± 1.55 years. In group 2, the second metastatic site developed in 37% of metastatic patients. Within this tumor subgroup, bone-only metastasis was the most frequent pattern of metastasis. In group 3, 65.4% of patients developed a first metastatic site within a mean ± SD of 5.59 ± 1.78 years. 34.6% of cases had no metastases. In this cohort, lung metastasis affected most patients, while bone and visceral metastases were the most frequent metastatic patterns. 48.3% of patients in group 4 experienced metastases, with a mean ± standard deviation of 3.39 ± 1.73 years.

Most patients had a visceral exclusively metastatic pattern, with lung metastasis being the most prevalent location. The study groups exhibited substantial differences in time to first metastasis ($p<0.001$), with group 1 having the longest duration at 6.96 ± 2.97 years, followed by group 3 at 5.59 ± 1.78 years, group 2 at 5.25 ± 1.55 years, and group 4 at 3.39 ± 1.73 years. There was a significant difference ($p<0.001$) in the incidence of first metastasis between the four groups. Among the patients with metastases, Group 4 had the largest percentage (48.3%) of patients with lung metastases, followed by Group 1 (40%), Group 3 (27.5%), and Group 2 (11.1%), with a statistically significant difference between the four groups ($p = 0.022$).

Metastasis to the brain, liver, bone, lymph nodes, and other organs: There were no statistically significant differences between the four groups in terms of metastasis to these locations ($p > 0.05$). Table 4 provides comprehensive facts. For Second Metastasis: There was no discernible difference in the frequency of a second metastasis between the groups ($p = 0.746$). Patients in Group 1 had the highest percentage of second metastases (60.00%), followed by those in Groups 3 (47.1%), 4 (44.8%), and 2 (37.0%). There was a significant difference in the metastatic pattern between the groups ($p = 0.004$). The most prevalent kind of metastasis was "vascular only," accounting for 6.9% in Group 1, 10.7% in Group 2, 21.8% in Group 3, and 25% in Group 4. The proportion of patients lost to follow-up was similar in all four groups ($p = 0.322$).

Five-year survival analysis of breast cancer patients according to receptors at primary diagnosis

Figure 1 illustrates that there was a statistically significant difference ($p<0.001$) in the DFS between the groups under study. While all patients in groups 1 and 2 did not experience a local recurrence until their last follow-up, group 4 had a higher risk of recurrence, with a shorter median survival time than group 3 (HR=2.298, 95%CI: 0.538 to 9.816).

Overall survival

Group 1 had the highest mean survival time of 9.788 years, followed by group 2 with a mean survival time of 9.607 years (HR = 2.652 compared to group 1), group 3 with a slightly lower mean survival time of 8.826 years (HR = 7.428), and group 4 with the lowest mean survival time of 8.319 years (HR = 8.803), according to Kaplan-Meier survival analysis, which showed a statistically significant difference between the studied groups regarding overall survival ($p<0.001$) (Figure 2). Univariate analysis revealed that ER and HER2 receptor positive patients had significantly higher mortality probabilities than negative HER2 patients (HR = 1.87, 95% CI: 1.17 to 3, P=0.009) and lower mortality probabilities than negative ER patients (HR = 0.5, 95% CI: 0.32 to 0.8, P=0.004).

Patients with T3 and T4 tumors, in comparison to those with T1 tumors, had a significantly increased chance of dying (HR = 3.22, 95% CI: 1.39 to 7.47, P = 0.007) and (HR = 3.7, 95% CI: 1.11 to 12.31, P = 0.033), respectively, in terms of tumor size. Patients' hazard of death was considerably lower in patients with N1 and N2 lymph nodes involved than in patients without any lymph node involvement (HR = 0.18, 95% CI: 0.07 to 0.51, P = 0.001) and (HR = 0.41, 95% CI: 0.19 to 0.9, P = 0.026), respectively.

Table 3. Clinical characteristics of the studied groups

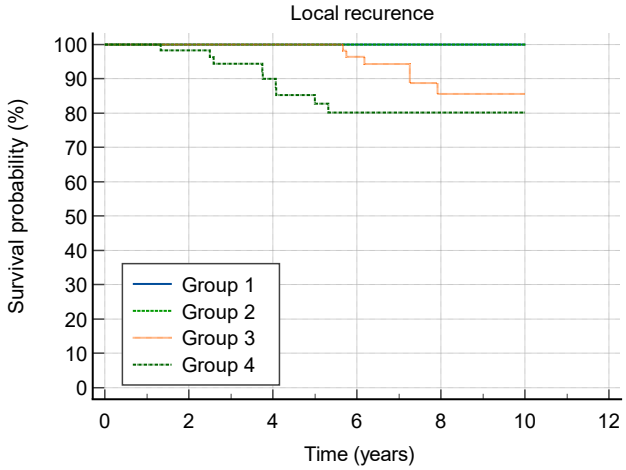
	Receptors at primary diagnosis				P-value
	Group 1	Group 2	Group 3	Group 4	
Ki 67 (mean± SD)	8.31±6.67	32.86+16.13	32.31±17.8	21.50±14.65	**<0.001**
Site					0.596
Right	17 (60.7%)	38 (50.7%)	47 (60.3%)	31 (51.7%)	
Left	11 (39.3%)	37 (49.3%)	30 (38.5%)	29 (48.3%)	
Bilateral	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	
Type of surgery					0.405
Modified radical mastectomy	23 (79.3%)	68 (90.7%)	68 (87.2%)	50(83.3%)	
Conservative breast surgery	6 (20.7%)	7 (9.3%)	10 (12.8%)	10 (16.7%)	
Staging					**<0.001**
Stage 1A	10 (34.5%)	0 (0.0%)	4 (5.1%)	3 (5.0%)	
STAGE 1B	2 (6.9%)	0 (0.0%)	2 (2.6%)	1 (1.7%)	
STAGE 2A	14 (48.3%)	12 (16.0%)	11 (14.1%)	20 (33.3%)	
STAGE 2B	2 (6.9%)	17 (22.7%)	13 (16.7%)	12 (20.0%)	
STAGE 3A	0 (0.0%)	26 (34.7%)	24 (30.8%)	11 (18.3%)	
STAGE 3B	0 (0.0%)	2 (2.7%)	4 (5.1%)	6 (10.0%)	
STAGE 3C	1 (3.4%)	18 (24.0%)	20 (25.6%)	7 (11.7%)	
T					**<0.001**
T1	17 (58.6%)	5 (6.7%)	15 (19.2%)	7 (11.7%)	
T2	11 (37.9%)	54 (72.0%)	45 (57.7%)	43 (71.7%)	
T3	1 (3.4%)	15 (20.0%)	16 (20.5%)	6 (10.0%)	
T4	0 (0.0%)	1 (1.3%)	2 (2.6%)	4 (6.7%)	
N					**<0.001**
N1	18 (62.1%)	12 (16.0%)	13 (16.7%)	26 (43.3%)	
N2	10 (34.5%)	21 (28.0%)	23 (29.5%)	15 (25.0%)	
N3	0 (0.0%)	24 (32.0%)	20 (25.6%)	11 (18.3%)	
N4	1 (3.4%)	18 (24.0%)	22 (28.2%)	8 (13.3%)	
Number					0.265
Unicentric	23 (12.7%)	50 (27.6%)	62 (34.3%)	46 (25.4%)	
Multicentric	6 (9.8%)	25 (41.0%)	16 (26.2%)	14 (23.0%)	
No. of positive lymph nodes (mean± SD)	1.24±2.86	7.91 ±7.25	7.65 ±7.91	4.53 ±7.11	**<0.001**
Total lymph nodes dissected (mean± SD)	14.41±3.60	17.83±5.87	16.96 ±6.49	14.93±5.26	**0.006**
Extra nodal extension	5 (17.20%)	34 (45.30%)	36 (46.20%)	16 (26.70%)	**0.006**
Lymph vascular invasion	0 (0.0%)	22 (29.3%)	26 (33.3%)	7 (11.7%)	**<0.001**
PNI	1 (3.4%)	7 (9.3%)	12 (15.4%)	0 (0.0%)	**0.009**
Histopathology					0.159
Invasive ductal carcinoma	26 (89.7%)	64 (85.3%)	65 (83.3%)	57 (95.0%)	
Invasive lobular carcinoma	3 (10.3%)	8 (10.7%)	7 (9.0%)	2 (3.3%)	
Mixed subtype	0 (0.0%)	0 (0.0%)	4 (5.1%)	0 (0.0%)	
Others	0 (0.0%)	3 (4.0%)	2 (2.6%)	1 (1.7%)	
Differentiation					**0.027**
Well differentiated	19 (65.5%)	43 (57.3%)	41 (52.6%)	46 (76.7%)	
Undifferentiated	10 (34.5%)	32 (42.7%)	37 (47.4%)	14(23.3%)	
Margins	0 (0%)	0 (0%)	1 (1.3%)	0 (0%)	0.550
Grade					
Grade 1	3 (10.3%)	2 (2.7%)	0 (0%)	11 (18.3%)	**<0.001**
Grade 2	25 (86.2%)	65 (86.7%)	59 (75.6%)	34 (56.7%)	
Grade 3	1 (3.4%)	8 (10.7%)	18 (23.1%)	15 (25%)	

Data are presented as frequency (%) unless otherwise mentioned, Statistical significance at P value<0.05, PNI: Perineural invasion

Table 4. Metastasis Distribution and Site-Specific Occurrence among the studied Groups

	Receptors at primary diagnosis								P-value
	Group 1		Group 2		Group 3		Group 4		
	N	%	N	%	N	%	N	%	
1st metastasis	(n=29)		(n=75)		(n=78)		(n=60)		**<0.001**
Absent	24	82.8%	48	64%	27	34.6%	31	51.7%	
Present	5	17.2%	27	36%	51	65.4%	29	48.3%	
Time to 1st metastasis (years) (mean ± SD)	6.96 ± 2.97		5.25 ± 1.55		5.59 ± 1.78				**<0.001**
	(n=5)		(n=27)		(n=51)		(n=29)		
Lung	2	40%	3	11.1%	14	27.5%	14	48.3%	**0.022**
Brain	0	0%	1	3.7%	5	9.8%	5	17.2%	0.322
Liver	1	20%	12	44.4%	18	35.3%	9	31.0%	0.634
Bone	2	40%	14	51.9%	19	37.3%	8	27.6%	0.317
Lymph nodes	0	0.0%	0	0.0%	7	13.7%	2	6.9%	0.166
Other	0	0.0%	2	7.4%	2	3.9%	2	6.9%	0.838
2nd metastasis									0.746
Absent	2	40.0%	17	63.0%	27	52.9%	16	55.2%	
Present	3	60.0%	10	37.0%	24	47.1%	13	44.8%	
	(n=3)		(n=10)		(n=24)		(n=13)		
Lung	1	33.3%	3	30.0%	11	45.8%	1	7.7%	0.129
Brain	1	33.3%	3	30.0%	7	29.2%	4	30.8%	0.999
Liver	1	33.3%	3	30.0%	8	33.3%	6	46.2%	0.844
Bone	1	33.3%	5	50.0%	10	41.7%	4	30.8%	0.811
Lymph nodes	0	0.0%	0	0.0%	1	4.2%	1	7.7%	0.8
Metastasis group	(n=29)		(n=75)		(n=78)		(n=60)		**0.004**
Bone only	1	3.4%	9	12.0%	8	10.3%	3	5.0%	
Bone and visceral	2	6.9%	8	10.7%	17	21.8%	7	11.7%	
Bone and non-visceral	0	0.0%	0	0.0%	1	1.3%	2	3.3%	
Visceral only	2	6.9%	8	10.7%	17	21.8%	15	25.0%	
Non-visceral only	0	0.0%	0	0.0%	3	3.8%	0	0.0%	
Visceral and non-visceral	0	0.0%	0	0.0%	2	2.6%	2	3.3%	
No metastasis developed	24	82.8%	48	64.0%	27	34.6%	31	51.7%	
Bone, visceral, non-visceral	0	0.0%	2	2.7%	3	3.8%	0	0.0%	
Loss to follow up	1	3.4%	2	2.7%	7	9%	5	8.3%	0.322

Statistical significance at P value<0.0



	No. event	No. censored	Mean survival time (years)	HR	95% Confidence Interval		P-value
					Lower Bound	Upper Bound	
Group 1	0 (0%)	29 (100%)	10.01	---			**<0.001**
Group 2	0 (0%)	75 (100%)	10.01	---			
Group 3	6 (7.69%)	72 (92.31%)	9.557	Ref			
Group 4	9 (15%)	51 (85%)	8.769	2.298	0.538	9.816	

HR: Hazard ratio, Statistical significance at P value<0.05.

Figure 1. Overall Progression-Free Survival Analysis of Breast Cancer Patients According to Receptors at Primary Diagnosis.

More positive lymph nodes were associated with a significantly higher mortality risk (HR = 1.03; 95% CI: 1 to 1.06; P = 0.041). Patients receiving neoadjuvant chemotherapy (HR = 1.62, 95% CI: 1.01 to 2.6, P = 0.047) and palliative chemotherapy (HR = 7.16, 95% CI: 4.45 to 11.52, P<0.001) had a significantly higher risk of death compared to those who did not get these therapies. (Table 5).

Multiple regression analysis revealed that patients with diabetes and positive PR receptors had significantly higher mortality risks than other patients (HR = 4.14, 95% CI: 1.14 to 15.11, P = 0.031), whereas patients with chronic illnesses had significantly lower mortality risks (HR = 0.18, 95% CI: 0.04 to 0.79, P = 0.023). Patients undergoing palliative chemotherapy had a significantly higher chance of dying than those not receiving the treatment (HR = 8.08, 95% CI: 4.35 to 15.04, P<0.001). In contrast, patients undergoing palliative hormonal treatment had a significantly lower chance of dying than those not receiving the treatment (HR = 0.03, 95% CI: 0.004 to 0.26, P = 0.001).

DISCUSSION

Breast cancer is a heterogeneous disease with several subtypes exhibiting different cellular compositions, molecular changes, and clinical characteristics that depend on several factors such as size, grade, and hormone receptors, all of which affect the final prognosis and treatment response. Breast cancer can metastasis even in the early stages, and treatment methods that focus solely on shrinking the local tumor are ineffective, hence the condition is classified as systemic. It appears that tumor cells proliferate and circulate much in advance of the underlying tumor becoming visibly apparent. Certain patients experience long latency periods between initial treatment and recurrence, suggesting that tumor cells adapt to their host environment and respond to it to promote and sustain disease progression.

Patients with both local and distant metastases of breast cancer generally have poor overall prognosis and survival rates. Several factors, including age at diagnosis, lympho-vascular invasion, lymph node involvement, tumor size, and tumor grade, are predictive and prognostic markers for breast cancer. The general prognosis for these patients, for example, is based on their hormone receptor status; however, while prognostic and predictive indicators are well known, they are unable to pinpoint the exact locations that will be affected by metastasis (Niwinska et al. 2010, Park. et al. 2012). Patients ranged in age from 24 to 87 years old, with a mean age of 49.3 years, according to a study by Arpita J et al. The average age of presentation, according to Sandhu et al. (2010), was 47.8 years (Arpita et al. 2022, Sandhu et al. 2010).

The results of the current investigation supported the hypothesis that the patients' mean age was 47.5 years. There were 78 (32.2%) postmenopausal patients, 52 (21.5%) perimenopausal individuals, and 112 (46.3%) premenopausal patients (Sandhu D. S. et al. 2010). Wu Q et al. discovered that bone metastases are the most typical kind of breast cancer metastasis.

They found that the likelihood of bone metastases from HR-positive breast cancers was higher, which is consistent with other studies (Wu. et al. 2017). The key finding is that cancers expressing a lot of cyclooxygenases 2 (COX-2) are more likely to metastasize to the bone. Although it is not frequently the primary location of a distant recurrence in their current series, brain metastasis has been increasing recently (Da Silva et al. 2010, Ristimaki. et al. 2002). Previous studies have linked brain metastases to both the HER2 and Triple Negative subtypes (Kennecke. et al. 2010, Hess KR. et al. 2003, Solomayer. et al. 2000, Palmieri. et al. 2006). Smid et al. investigated whether any single organ was selected for relapse by the previously discovered molecular subtypes of breast cancer. They searched for molecular routes connected to this process of remote spread. They discovered that the basal subtype had the lowest bone relapse, whereas the luminal subtypes had the highest. The opposite was true for the incidence of brain and lung recurrence. They found that the four major genetic subtypes of breast cancer differ significantly in their ability to spread to distant organs and in the biological properties that they share with the target homing organs, hence encouraging metastasis to the targeted site (Smid. et al. 2008).

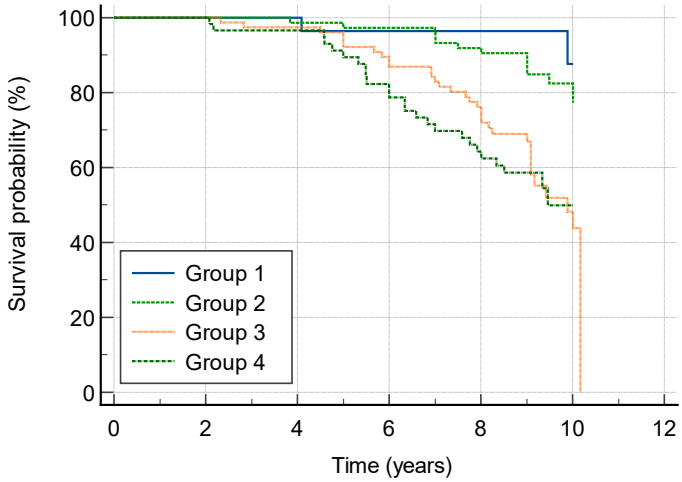
Table 5. Univariate and multivariable Cox regression analysis for factors associated with overall survival of breast cancer patients

	Univariate analysis			Multivariable analysis		
	HR	**95%CI**	**P value**	**HR**	**95%CI**	**P value**
Age	1	0.98 to 1.02	0.901	1.01	0.95 to 1.07	0.758
BMI	1.01	0.97 to 1.05	0.556	1	0.96 to 1.05	0.943
Residency						
Urban	Ref			Ref		
Rural	0.68	0.42 to 1.12	0.131	0.87	0.48 to 1.56	0.635
Menopause						
Pre-menopausal	Ref				Ref	
Peri-menopausal	1.6	0.93 to 2.77	0.092	1.25	0.55 to 2.83	0.598
Postmenopausal	0.86	0.49 to 1.54	0.62	0.69	0.18 to 2.67	0.588
Family history	0.84	0.49 to 1.45	0.53	0.94	0.5 to 1.77	0.848
Chronic illness	0.78	0.47 to 1.3	0.34	0.18	0.04 to 0.79	**0.023**
HTN	0.85	0.47 to 1.53	0.592	1.32	0.45 to 3.87	0.618
DM	1.17	0.67 to 2.04	0.58	4.14	1.14 to 15.11	**0.031**
CLD	0.86	0.21 to 3.5	0.83	0.44	0.07 to 2.98	0.404
HCV	0.63	0.15 to 2.58	0.522	5.35	0.79 to 36.31	0.086
ER	0.5	0.32 to 0.8	**0.004**	0.95	0.09 to 10.59	0.968
PR	0.66	0.41 to 1.04	0.074	17.84	1.57 to 202.51	**0.020**
HER2	1.87	1.17 to 3	**0.009**	0.85	0.43 to 1.64	0.62
Ki 67	1.01	1 to 1.02	0.093	1.02	1 to 1.05	0.088
T						
T1	Ref			Ref		
T2	1.8	0.84 to 3.83	0.128	2.21	0.94 to 5.22	0.070
T3	3.22	1.39 to 7.47	**0.007**	2.76	0.98 to 7.8	0.055
T4	3.7	1.11 to 12.31	**0.033**	1.16	0.24 to 5.71	0.855
N						
N0	Ref			Ref		
N1	0.18	0.07 to 0.51	**0.001**	0.34	0.1 to 1.1	0.072
N2	0.41	0.19 to 0.9	**0.026**	0.64	0.23 to 1.82	0.406
N3	0.55	0.25 to 1.19	0.129	0.7	0.15 to 3.31	0.654
N4	0.7	0.33 to 1.5	0.358	1.18	0.14 to 10.27	0.881
No. of positive lymph nodes	1.03	1 to 1.06	**0.041**	0.97	0.89 to 1.05	0.489
Extra nodal extension	0.78	0.48 to 1.27	0.32	0.63	0.32 to 1.25	0.187
Lymph vascular invasion	1.14	0.67 to 1.95	0.625	0.57	0.25 to 1.34	0.198
PNI	1.18	0.54 to 2.58	0.676	2.49	0.74 to 8.4	0.141
Differentiation						
well differentiated	Ref			Ref		
undifferentiated	1.02	0.64 to 1.62	0.949	1.15	0.65 to 2.01	0.636
Neo adjuvant	1.62	1.01 to 2.6	**0.047**	0.9	0.27 to 3	0.867
Palliative chemotherapy	7.16	4.45 to 11.52	**<0.001**	8.08	4.35 to 15.04	**<0.001**
Palliative hormonal	0.44	0.28 to 0.7	**0.001**	0.03	0.004 to 0.26	**0.001**

HR: Hazard ratio, CI: Confidence interval.

Wu Q et al. discovered that HER2 positive subtypes are more likely to cause lung metastasis than HER2 negative subtypes, while HR+/HER2 breast cancers rarely cause lung metastasis when compared to TN and HR/HER2+ subtypes in our study. Lung metastases are more common in the basal subtypes than predicted by gene expression analysis, while a different study indicated that the luminal-A subtypes had lower rates of lung recurrence than the other three categories (Wu. et al. 2017, Smid. et al. 2008).

It is worthwhile to talk about these intriguing findings from our study, which showed that patients with different tumor subtypes had unique metastatic patterns. 17.2% of luminal A patients had metastases, with visceral and bone metastases being the most common locations.



	No. event	No. censored	Mean survival time (years)	HR	95% Confidence Interval		P-value
					Lower Bound	Upper Bound	
Group 1	2 (6.9%)	27 (93.1%)	9.788	Ref			**<0.001**
Group 2	14 (18.67%)	61 (81.33%)	9.607	2.652	1.286	5.468	
Group 3	32 (41.03%)	46 (58.97%)	8.826	7.428	3.524	15.655	
Group 4	25 (41.67%)	35 (58.33%)	8.319	8.803	3.939	19.678	

HR: Hazard ratio, Statistical significance at P value<0.05

Figure 2. Overall survival analysis of breast cancer patients according to receptors at primary diagnosis

In 36 percent of Luminal B patients, metastases occurred. Bone metastasis was the most prevalent type of metastasis observed in this tumor category. Patients with high HER2 levels (65.4%) developed the site of their first metastasis. Many individuals in this category developed lung metastases, with bone and visceral metastases being the most prevalent metastatic patterns.

Among those who tested triple negative, 48.3% developed metastases. Most patients had a visceral exclusively metastatic pattern, with the lung being the most common site of metastasis. Furthermore, the gap may be due to the genetic or metabolic bases of metastasis, which can differ between races. According to Tagliabue G. et al.'s research and other reports, patients with HER2/HR positive tumors had the best survival rates, while those with HER2/HR negative molecular profiles had the lowest survival rates (Tagliabue. et al. 2021).

Howlader N. et al. discovered the greatest prognosis for cases of breast cancer with HR+ subtypes, and earlier research has corroborated this finding. Women with HR subtypes had a lower result, particularly those with triple-negative diseases. This was probably because there was no receptor target (such as ER, PR, or HER2) available for treatment (Howlader N. et al. 2014). Moreover, stage is among the most important factors affecting the chances of survival. For instance, regardless of subtype, the survival rate for patients with stage I disease was greater than 95% after four years of follow-up (Chen et al. 2017).

The statistics support similar conclusions: patients with positive ER receptors were significantly less likely to die than those with negative ER receptors, but patients with positive HER2 receptors were significantly more likely to die than those with negative HER2. Compared to individuals with T1 tumors, those with T3 and T4 tumors had a considerably increased risk of death. Patients with N1 and N2 lymph nodes involved in lymph node involvement had a significantly lower death rate than those without any LN involvement. A higher chance of dying was associated with more positive lymph nodes.

CONCLUSION

In summary, the pattern of breast cancer metastasis across various tumor receptor subtypes was the primary focus of our research. The overall and progression-free survival rates

of various molecular subtypes vary. These findings add to the evidence supporting the specific medication. Further investigation is required to identify the variables influencing metastatic distribution patterns and survival outcomes.

STRENGTHS AND LIMITATIONS

One limitation of our research was the inadequacy of registry data for tumor stage or receptor status in a considerable number of patients, making it unusable. Notwithstanding this limitation, the data yielded an interesting study that made it possible for us to link genetic profiles to characteristics of sickness in people of different ages, from different regions to diverse clinical settings. Our study has the advantage of using data that registry operators commonly collect, demonstrating that molecular typing investigations can be completed effectively without the time and expense associated with high-resolution studies.

LIST OF ABBREVIATIONS

AC: Adriamycin cyclophosphamide, BMI: body mass index, DFS: disease free survival, ER: estrogen receptor, FOMSCU: Faculty of Medicine Suez Canal University, FEC: 5fu epirubcin cyclophosphamide, HER2: human epidermal growth factor receptor 2, OS: overall survival, PFS: progression free survival, PR: progesterone receptor, SD: standard deviation.

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AUTHORS' CONTRIBUTIONS

SHS and MMA helped to conceptualize and design the piece. SHS and MMA collected data from patient's files. SHS and MMA contributed to the acquisition, analysis, and interpretation of the data. SHS and MMA reviewed and supervised the work. SHS and MMA wrote the first draft of the manuscript. All authors approved the final version of the manuscript.

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DATA AVAILABILITY

The data supporting the findings of this investigation are accessible from the corresponding author upon reasonable request.

ETHICS APPROVAL

Because this was a retrospective review of medical records, informed consent was waived, and the study was approved by the Suez Canal University Department of Clinical Oncology & Nuclear Medicine Research Ethics Committee.

- The final procedure was approved by FOMSCU's research ethics committee.
- Clinical data will be collected with the agreement of the FOMSCU study ethics committee.
- The research data came from patient files. Information confidentiality and patient privacy were maintained, with no personal information exposed. Only that research will make use of the data; additionally, patient contact was required to mitigate the difficulties related to incorrect recording and follow-up.
- Data analysis was displayed in a covert manner, without identifying the patients.

CONSENT FOR PUBLICATION

Not applicable

COMPETING INTERESTS

The writers claim to have no conflicting agendas.

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