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Original Article

Investigating Breast Cancer Metastatic Trends, Types, and Their Common Organs of Metastasis

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ABSTRACT

Background and Objectives: Breast cancer (BC) is the most prevalent cancer in women all over the world, and the leading cause of death is its metastasis. This study aimed to investigate the metastatic trends, molecular subtypes, and common organs of metastasis among women with BC in Sulaymaniyah, Iraq.

Patients and methods: A prospective, descriptive, cross-sectional study was conducted from January to May 2025 at two major oncology centers in Sulaimaniyah, Iraq. A total of 200 women with histopathological confirmed metastatic BC were enrolled. Data on sociodemographic, clinical, pathological, and molecular characteristics were collected through structured interviews and review of medical records.

Results: The majority of patients were aged 45–64 years (n=106, 53%) and presented with invasive ductal carcinoma (n=183, 91.5%). Luminal A was the most common molecular subtype (n=136, 68%), and most patients had high Ki-67 levels (>20%). Bone was the predominant site of metastasis (n=75, 37.5%), followed by the lung (n=40, 20%) and liver (n=18, 9.0%). Most metastatic events occurred within the first year after diagnosis. Advanced-stage disease and axillary lymph node involvement were common at presentation (n=197, 98.5%). The overall survival rate was 91.5%.

Conclusions: Bone is the most frequent site of metastasis in BC patients, with luminal A subtype predominating. The importance of high-quality screening and the timely formulation of intervention measures is evident given the early metastatic development and advanced stage of presentation.

Keywords: Breast neoplasms, molecular subtypes, prognosis, survival rate.

1 Introduction

Breast cancer (BC) is the most commonly diagnosed cancer in females worldwide, which claims 2.3 million new cases (11.7% of all cancers) and 685000 deaths in 2020 [1]. Modest declines in mortality have been documented in high-income countries, brought about by regular screening programs and therapeutic innovations, yet in low- and middle-income areas, rising incidences and a disproportionately high death rate are still some of the things that are being observed [2].

The etiology of BC has been described as being multifactorial and includes genetic predisposition, hormonal exposures, reproductive history, and lifestyle factors. BRCA1 and BRCA2 germline mutations are an important contributing factor, carrying a lifetime risk of 50-85%. Alternatively, the higher frequency single-nucleotide polymorphisms have a relatively smaller influence on BC predisposition [3]. Early menarche, late menopause, nulliparity, and delayed first childbirth can increase cumulative estrogen dose and risk [4]. Postmenopausal obesity and exogenous hormone use further elevate risk by augmenting peripheral estrogen synthesis and altering growth-factor signaling [5]. On the other hand, early pregnancy and extended breastfeeding have long-lasting protective effects by changing the mammary epithelium and changing the number of stem cells [6].

Despite the advances in early diagnosis and targeted treatment, metastasis has remained the greatest cause of BC deaths [7]. Dissemination also shows organ-specific tropism, the most eminent being bone, which targets about 70% of all patients with disseminated diseases. Additionally, metastasis occurs in 20-30% of cases in the lungs, 15-25% in the liver, and 10-30% in the brain [8,9]. Bone metastases often present with skeletal-related events, such as fracture and hypercalcemia, whereas visceral spread to

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the lung and liver portends poorer overall survival. Brain metastases, once established, are associated with a median survival of under one year, despite multimodal treatment [9].

Current literature offers extensive characterization of metastatic mechanisms; epithelial–mesenchymal transition, homing via chemokine gradients, and pre-metastatic niche formation, but gaps remain in comparative analyses of organ-specific trends across BC subtypes and populations [10,11]. Therefore, the present study is necessary to delineate contemporary metastatic trends of BC in Sulaimaniyah, Iraq. Also, to identify the cancer subtypes that most prone to metastasis and elucidate the organs preferentially colonized during the metastatic cascade.

2 Patients and methods

2. 1 Study design and setting

This prospective descriptive cross-sectional study recruited 200 women with a confirmed history of metastatic breast cancer (MBC), from January to May 2025 at the Breast Diseases Center and Hiwa Cancer Hospital, Sulaimaniyah, Iraq. The participants were found through hospital admission records and oncology registries. All records of patients with BC who were hospitalized between 2020 and 2025 were reviewed.

2. 2 Inclusion criteria

Female adults aged ≥18 years with histopathology-confirmed BC that exhibited a distant metastasis as per the American Joint Committee on Cancer [12]. Patients diagnosed with MBC within the last 5 years were also included to maintain clinical accuracy and relevance.

2. 3 Exclusion criteria

Patients with non-metastatic BC, those with incomplete, missing medical records, and those with a history of other primary malignancies or those who had received treatment outside the study centers.

2. 4 Study protocol

The sample size was determined using a single proportion formula, considering 7% prevalence of BC in young women, a 5% margin of error, and a 95% confidence interval (Zα=1.96). The recruitment strategy employed consecutive sampling, whereby all individuals who presented at the institution and were eligible to participate in the study were invited until the desired sample size was achieved. Then patients' data were collected using a structured, validated (by a panel of oncology experts) questionnaire developed for this study. The questionnaire was administered through face-to-face interviews and supplemented with telephone follow-ups as needed. The investigative questionnaire patients' sociodemographic variable (age, marital status, ethnicity, education, occupation, residency, and body mass index), clinical/reproductive characteristics (parity, comorbidities, symptoms, prior breast issues, age at menarche, breastfeeding, regular follow-up, use of contraceptives, and menopausal status), and histopathology/immunohistochemistry reports to retrieve pathological and molecular variables (tumor type, grade, stage, ER/PR/HER2 status, and Ki-67 proliferation index). The triple-negative tumors are defined as estrogen-receptor (ER)-, progesterone-receptor (PR)-, and human epidermal growth factor receptor-2 (HER-2) negative, while HER2-positive tumors are defined as ER-/PR-negative, and HER2-positive. Data on management strategies (surgery, chemotherapy, radiotherapy, hormonal therapy), surgical procedures (type of breast and axillary surgery), complications, recurrence, and survival outcomes were also recorded.

2. 5 Statistical analysis

The Statistical Package for the Social Sciences (IBM, Armonk, NY, USA, version 25) was used to perform data analysis. The descriptive techniques, specifically frequencies and percentages, were used for categorical data, while the mean and standard deviation were used for continuous data.

3 Results

Regarding the patients' sociodemographic data, majority aged 45–64 years (n=106, 53%), married (n=167, 83.5%), Kurdish (n=165, 82.5%), housewives (n=140, 70.0%), literate (n=108, 54.0%), resided in rural (n=127, 63.5%), and obese (n=95, 47.5%) (Table 1).

Table 1: Sociodemographic characteristics of the women (n=200) with metastatic breast cancer.

Variable		Frequency	Percentage
Age (Years)	30 - 44	48	24
	45 - 64	106	53
	≥65	46	23
Marital status	Unmarried	33	16.5
	Married	167	83.5
Ethnic group	Kurd	165	82.5
	Arab	35	17.5
Occupation	Employee	60	30
	Housewife	140	70
Education	Illiterate	92	46
	Literate	108	54
Residency	Urban	72	36
	Rural	127	63.5

	Sub-rural	1	0.5
Body mass index	Underweight	1	0.5
	Normal	58	29
	Overweight	46	23
	Obese	95	47.5

In respect to patients' clinical data, majority were multiparous (n=158, 79%), had hypertension (n=74, 37.0%), normal thyroid function (n=172, 86.0%), and had a breast mass (n=118, 59.0%), while 2 (1.0%) were asymptomatic and presented for breast screening (Table 2).

Table 2: Clinical characteristics of study participants (n=200).

Variable		**Frequency**	**Percentage**
Parity	Nullipara	42	21
	Multipara	158	79
Diabetes mellitus	Yes	64	32
	No	136	68
Hypertension	Yes	74	37
	No	126	63
Cardiac disease	Yes	30	15
	No	170	85
Thyroid function	Normal	172	86
	Hypothyroidism	26	13
	Hyperthyroidism	2	1
Symptoms	Breast mass	118	59
	Breast pain	34	17
	Cough & difficult breathing	11	5.5
	Bone pain or fracture	11	5.5
	Dizziness and headache	6	3
	Nipple bloody discharge	8	4
	None (Screening)	2	1
	Arm edema	1	0.5
	Breast edema with ulcer	3	1.5
	Axillary LN enlargement	5	2.5
	Breast itching and bruising	1	0.5

The majority of women experienced menarche between 11–12 years (n=104, 52%), did not have regular follow-up (n=116, 58%), postmenopausal (n=172, 86%), not practised breastfeeding (n=121, 60.5%), had no previous breast issues (n=149, 74.5%), and not used contraceptive pills (n=135, 67.5%) (Table 3).

Table 3: Reproductive and lifestyle characteristics of study participants (n=200).

Variable		**Frequency**	**Percentage**
Age of menarche (Years)	11 - 12	104	52
	13 - 14	86	43
	15 - 16	8	4
Regular follow-up	Yes	84	42
	No	116	58
Menopause	Yes	172	86
	No	28	14
Breastfeeding	Yes	79	39.5
	No	121	60.5
Previous breast problem	Yes	51	25.5
	No	149	74.5
Use of contraceptive pills	Yes	65	32.5
	No	135	67.5

The most common BC type was invasive ductal carcinoma (n=183, 91.5%), and most patients were in stage 4 (n=77, 38.5%), while the predominant molecular subtype was luminal A (n=136, 68%). Regarding pathological grade, the majority had grade 3 tumors (n=99, 49.5%), and the most frequent histological subtype was of no special type (n=181, 90.5%). Axillary lymph node metastasis was present in 197 (98.5%) patients, indicating a high rate of nodal involvement (Table 4).

Table 4: Clinicopathological features of metastatic breast cancer cases (n=200).

Variable		Frequency	Percentage
Type of breast cancer	Invasive ductal carcinoma	183	91.5
	Invasive lobular carcinoma	12	6
	Mixed lobular and ductal	5	2.5
Stage of cancer at diagnosis	Stage 1	8	4
	Stage 2	74	37
	Stage 3	41	20.5
	Stage 4	77	38.5
Molecular subtype	Luminal A	136	68
	Luminal B	33	16.5
	Her2 +VE	21	10.5
	Triple negative	10	5
Pathological grade	Grade 1	12	6
	Grade2	89	44.5
	Grade3	99	49.5
Histological subtype	No special type	181	90.5
	Medullary	4	2
	Classical type	5	2.5
	Micropapillary	7	3.5
	Mucinous	3	1.5
Axillary lymph node metastasis	Yes	197	98.5
	No	3	1.5

The most common site of metastasis was the bone (n=75, 37.5%), followed by the lung/pulmonary (n=40, 20%), and cervical lymph nodes (n=19, 9.5%). The least frequent sites of metastasis were skin and pancreas (n=1, 0.5% each) (Figure 1).

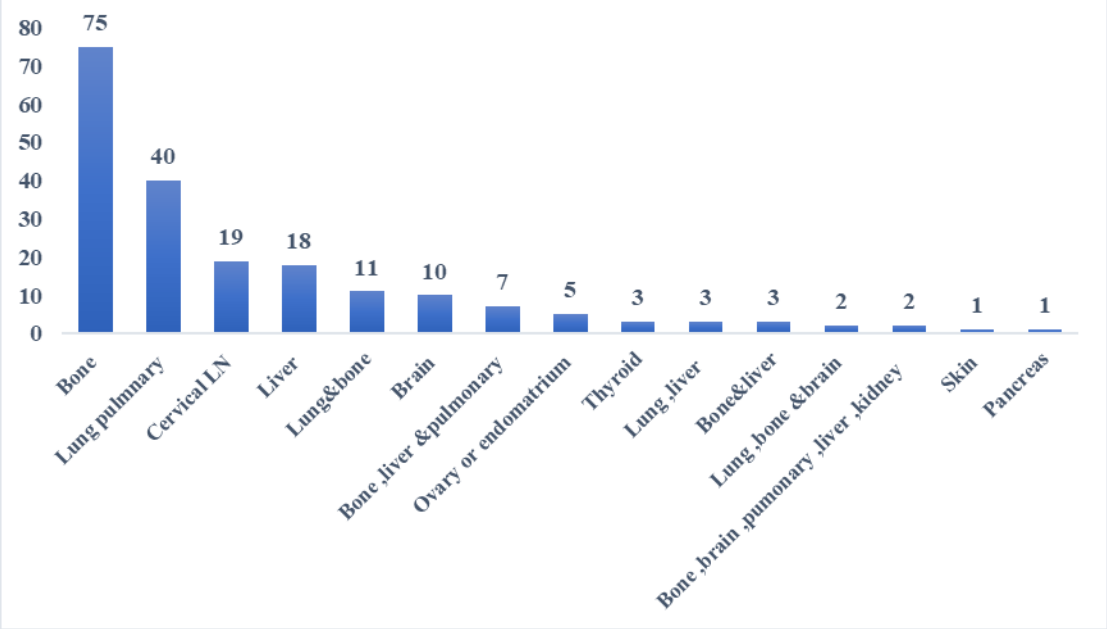

Figure 1: Distribution of metastatic sites among breast cancer patients (n=200).

Furthermore, the patients' data indicate that most metastatic occurrences occur within the first year post-initial diagnosis (n=70), after which the incidence is markedly decreased, with a slight surge noted at year 3 and another around year 7. Beginning in year 4, metastasis progressively diminishes, with infrequent and sporadic instances persisting for up to 18 years following diagnosis (Figure 2).

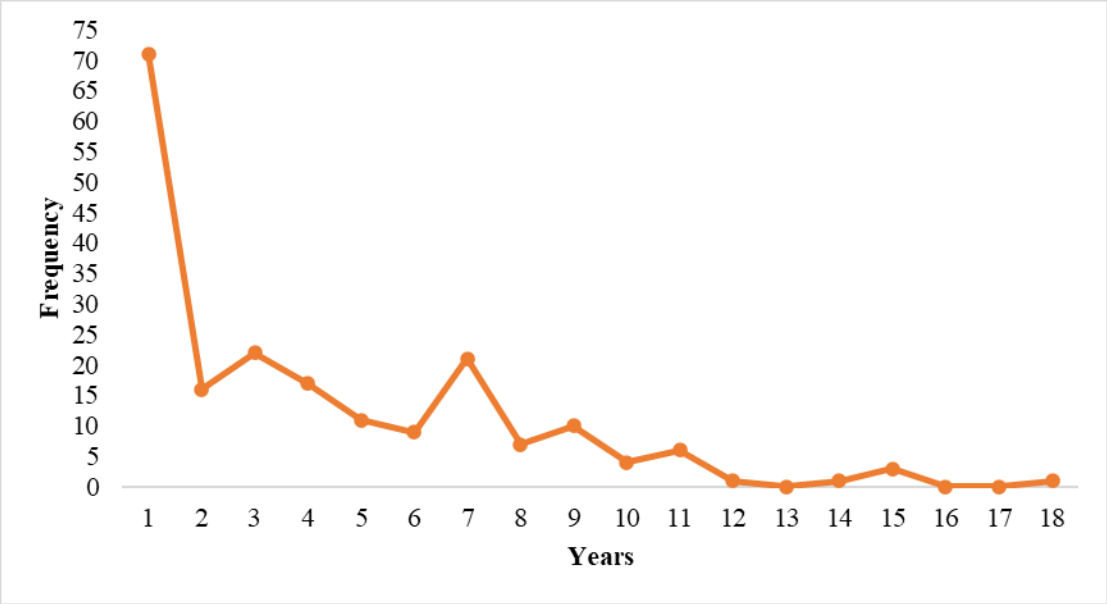

Figure 2: Patients' breast cancer metastasis at the time of diagnosis.

Most patients had high Ki-67 levels (>20%) (n=149, 74.5%), with only 4 (2.0%) showing low levels. A family history of BC was reported in 26 (13%) participants, mostly among first-degree relatives (n=22, 11%). The most common management approach was surgery combined with chemotherapy (n=68, 34.0%), followed by chemotherapy alone (n=58, 29%). Mastectomy was performed in 68 (34.0%) cases, while 50 (25%) underwent wide local excision. Axillary dissection was the most frequent axillary surgery (n=81, 40.5%), with sentinel lymph node biopsy performed in 35 (17.5%) cases. Surgery complications were reported in 17 (8.5%) patients, while adjuvant chemotherapy was administered to 116 (58%), and 74 (37%) received neoadjuvant chemotherapy. Recurrence occurred in 20 (10%) cases, and the overall survival rate was 91.5% (n=183) (Table 5).

Table 5: Treatment, biological markers, and outcomes among breast cancer patients (n=200).

Variable		Frequency	Percentage
Ki 67 levels (%)	Low (<10)	4	2
	Intermediate (10 - 20)	47	23.5
	High (>20)	149	74.5
Family history of BC	First degree	22	11
	Second degree	4	2
	None	174	87
Management	NACT and surgery	11	5.5
	Chemotherapy	58	29
	Hormonal and chemotherapy	27	13.5
	Surgery, chemotherapy, and radiotherapy	21	10.5
	Hormonal and radiotherapy	5	2.5
	Surgery and chemotherapy	68	34
	Biology and chemotherapy	8	4
	NACT then radiotherapy	1	0.5
	Biology tab	1	0.5
Type of breast surgery	Wide local excision	50	25
	Mastectomy	68	34
	Excisional biopsy	1	0.5
	Not done	81	0.4

Axillary Surgery Type	Sentinel lymph node biopsy	35	17.5
	axillary dissection	81	40.5
	Not done	84	42
Surgery Complication	Yes	17	8.5
	No	183	91.5
Chemotherapy	Neoadjuvant	74	37
	Adjuvant	116	58
	No	10	5
Recurrence	Yes	20	10
	No	180	90
Survival	Yes	183	91.5
	No	17	8.5

4 Discussion

The present study aimed to characterize the clinicopathological and sociodemographic profile of women with MBC in Sulaimaniyah, Iraq, and to define the distribution of metastatic sites and molecular subtypes. The study group consisted of middle-aged, married females of Kurdish ethnicity. Most tumors were high grade and presented at an advanced stage, with luminal A as the most common molecular subtype. The major distant metastatic site was bone, followed by lung and liver, while cerebral dissemination was relatively uncommon.

This study shows predominance of the patients in middle age (45-64 years) and a high rate of hormone-receptor (HR) positive types, especially the luminal A. This finding is in line with the epidemiological outcomes worldwide, which find BC in this metastatic stage to be highest in women in the range of their 5th and 6th decades of life and predominantly ER-positive [13]. However, the luminal A proportion observed here exceeds that reported by Ivory et al., which found luminal A in only 27% of newly diagnosed MBC cases, with luminal B (35%), HER2-Enriched (12%), and Basal-like (25%) being more common [13]. This discrepancy may reflect regional differences in screening practices or health-care access.

Histological subtypes were examined in the present report, and it was found that 91.5% of cases were composed of invasive ductal carcinoma, which coincides with the findings of the global analysis, where ductal histology of MBC is the cause of approximately 70-80% of cases [14,15]. The significant percentage of axillary lymph node involvement is consistent with the known predilection of ductal cancers to spread through lymphatics [16]. Pathological grading favored higher grades in this cohort, which is consistent with the idea that MBCs may require more aggressive histological features than those of early-stage disease [17].

An examination of the metastatic pattern also reveals that the most common area encountered is the bones, followed by the bronchopulmonary and cervical node locations. These data are in agreement with the most typical metastatic tropism pattern of BC, whereby the most frequent metastases were in the bones, particularly in the HR-positive tumors [18,19]. However, in a very recent study by Zhang et al., relating distant metastasis cases to the 15 most common metastatic patterns, bone was the most metastatic location (21.3%), followed by the lung (16.1%), and then the liver (9.2%) [19]. A subsequent investigation by Tambe et al. indicated that the prevalent locations for distant metastatic disease were the pleura (20%), bone (18.71%), lung (16.13%), and liver (11.26%) [20]. The temporal distribution, showing a peak in metastasis occurrence within the first 5 years post-diagnosis, aligns with natural history studies that demonstrate most recurrences occur within the first 5 years [21]. Obesity was extraordinarily high, and about a 3rd of the people were using contraceptive pills [22]. Obesity has been associated with elevated risk of HR-positive BC and may affect metastatic potential via adipokine signalling [23]. Additionally, exogenous hormonal exposure can alter tumor biology, but its effect on metastasis is more controversial [24]. The high Ki-67 proliferation index (74.5% with >20%) correlates with the aggressive tumour behaviour and advanced presentation observed in this cohort. This finding is consistent with another study from similar populations, which showed higher proliferative indices [25]. The overall survival rate of 91.5% appears favorable; however, this may reflect the relatively short follow-up period and requires longer-term assessment for accurate prognostic evaluation. These findings underscore the need for enhanced screening programs and earlier detection strategies in the population of Iraq to improve outcomes and reduce the burden of advanced-stage BC.

This study has some limitations, including its cross-sectional nature, which precludes the establishment of causal associations and long-term predictions of outcomes beyond the study's time frame. The selection strategy for recruiting the patient cohort was limited to tertiary oncology centers, which may have introduced a bias because patients at these centers are not representative of those treated at primary or secondary care institutions. The possibility of extracting data from medical records is based on their completeness and accuracy, which are, in turn, compromised by errors in documentation or the inability to find specific data related to molecular subtyping and treatment peculiarities. Lack of a control group that generalises by having patients with non-metastatic BC makes it impossible to draw a direct comparison of risk factors and metastatic nature between early and advanced cases of BC.

5 Conclusions

The invasive ductal carcinoma and the luminal A molecular subtype are the most common types of BC, while bone is the most

common place for cancer to spread, followed by the lungs and liver. Most metastatic events occur within the first year after diagnosis, highlighting the importance of closely monitoring patients and treating them promptly. The fact that many people have advanced-stage cancer and nodal involvement at diagnosis shows that early detection and public health education are still problems. Thus, it's important for women to have personalised screening, quick diagnosis, and care from a team of professionals to help those with BC in this area get better. More multicenter, long-term studies are needed to confirm these results and look into how changing treatment methods affects metastatic patterns and survival from BC.

Declarations

Ethical considerations

The Ethical Committee of the College of Medicine, University of Sulaimani reviewed and approved the study protocol (No.337-October, 2024). The permission was taken by Sulaimani Directorate of Health, Sulaimaniyah, Iraq All the participants received detailed information regarding the purpose of the study, methodology, potential risks and voluntary nature of participation before data were collected and signed an informed consent form.

Conflict of interest: Both authors assert the absence of any conflict of interest.

Data availability: Upon reasonable request, the data from the research can be obtained from the corresponding author.

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