



PATTERNS AND HISTOMORPHOLOGICAL PREDICTORS OF DISTANT METASTASIS IN INVASIVE BREAST CARCINOMA: A CLINICOPATHOLOGICAL STUDY

Pathology

Atul Beniwal*	Associate Professor, Department of Pathology, Kalpana Chawla Government Medical College, Karnal, Haryana, India*Corresponding Author
Indira	Associate Professor, Department of Anaesthesiology, Maulana Azad Medical College, New Delhi, India
Priyanka Dahiya	Professor, Department of Obstetrics and Gynaecology, Kalpana Chawla Government Medical College, Karnal, Haryana, India

ABSTRACT

Background: Distant metastasis is a major determinant of outcome in breast carcinoma. This study evaluated the distribution of distant metastasis and its association with demographic and histomorphological features in invasive breast carcinoma of no special type (IBC-NST). **Materials and methods:** This mixed retrospective-prospective study included mastectomy specimens with axillary lymph-node dissection diagnosed as IBC-NST over a 10-year period. Clinicopathological features were reviewed, and associations with distant metastasis were assessed using chi-square tests. **Results:** Of 141 patients, 26 (18.4%) developed distant metastasis. The liver was involved in 9 patients (6.4%), lungs in 7 (5.0%), and bone and brain in 4 each (2.8%); 2 patients (1.4%) had multiorgan metastases. Time to metastasis ranged from 3 to 57 months (mean, 16.7 months). Tumour grade ($p = 0.013$) and nipple-areola complex changes ($p = 0.038$) were significantly associated with metastasis. ER/PR status, skin changes, microscopic skin involvement, tumour size, and tumour fixation showed non-significant trends (p values 0.053–0.089). **Conclusion:** Distant metastasis occurred in 18.4% of this cohort. Higher tumour grade and nipple-areola complex changes were associated with metastasis on bivariate analysis. Larger studies with complete follow-up and multivariable analysis are needed to assess independent predictors.

KEYWORDS

Invasive Breast Carcinoma-no Special Type; Histomorphology; Prognostic Factors; Distant Metastasis.

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer among women and is the second most leading cause of mortality worldwide.¹ Inefficient early diagnosis and effective treatment remain crucial component for the increased breast cancer mortality in developing nations.² Distant metastasis is a major cause of morbidity and mortality in breast carcinoma. The risk is influenced by tumour stage and biology, including tumour size, lymph-node status, lymphovascular invasion, histological grade, hormone-receptor status, and HER2 status. Most of the metastases are seen within two or three years; however, they may also develop in the years following the initial diagnosis.³

Bone metastases represent the most common metastasis seen in patients with breast cancer. In a study performed by Niwinska et al⁴, The lungs are also a common site of metastasis in patients with metastatic breast cancer. Kawano et al. performed a study in patients with hormone positive stage IV breast cancer and reported the median survival in patients with lung metastasis to be 37 months.⁵

The levels of tumor markers such as CEA and Ca15.3 can be elevated in patients with metastatic breast cancer after development of metastasis. The level of increase in tumor markers varies between the patients. Pierga et al⁶ showed that CEA and Ca15.3 levels above the normal interval were poor prognostic factors for progression-free survival according to the univariate analysis.

Despite advances in systemic treatment, metastatic breast cancer has a heterogeneous clinical course. Identifying clinicopathological features associated with distant spread may support risk assessment and follow-up planning.

Materials and methods

This mixed retrospective-prospective study was conducted in the Department of Pathology at a tertiary-care hospital and included cases collected over 10 years. Available clinical records were reviewed for distant metastasis during follow-up.

Inclusion criteria: Mastectomy specimens with axillary lymph-node dissection diagnosed as IBC-NST were included.

Exclusion criteria: Male breast carcinoma, histological types other than IBC-NST, and cases lost to follow-up were excluded.

Institutional ethics approval and patient consent were obtained.

Gross findings were abstracted from pathology records. Available slides from primary tumours and axillary lymph nodes were reviewed to verify diagnoses and relevant features. Variables included tumour size and grade, nodal status, skin and nipple-areola complex changes, tumour fixation and consistency, ER/PR and HER2 status, necrosis, tumour emboli, and surgical margins.

Follow-up was based on institutional practice and available medical records. Visits were more frequent during the first three years, followed by six- to twelve-monthly visits in years four and five and annual visits thereafter. Clinical assessment and investigations were performed as indicated.

Variables assessed included age, laterality and tumour location, socioeconomic status, parity, symptom duration, tumour size and grade, skin and nipple-areola complex changes, tumour fixation and consistency, necrosis, tumour emboli, surgical margins, axillary lymph-node involvement, ER/PR and HER2 status, and distant metastasis.

For Statistical analysis, Associations between clinico-pathological variables and distant metastasis were assessed using chi-square tests. A p value < 0.05 was considered statistically significant. The analysis was bivariate; independent effects cannot be inferred from these results.

RESULTS

Table 1. Distribution of distant metastatic sites

Metastatic site	Patients (n)	Percentage (%)
Liver	9	6.4
Lung	7	5.0
Bone	4	2.8
Brain	4	2.8
Liver, lung, bone	2	1.4
No metastasis	115	81.6
Total	141	100

Among 141 patients, 26 (18.4%) developed distant metastasis and 115 (81.6%) had no documented distant metastasis during the reported follow-up. The liver was the most frequently recorded site, followed by lung; bone and brain involvement were each reported in four patients. Two patients had metastases involving the liver, lung, and bone. Mean time to metastasis was 16.7 months (range, 3–57 months).

Table 2: Association between clinicopathological variables and distant metastasis with no statistical significant P value

No.	Variable	Category	Patients with metastasis (%)	p value
1.	Socio-economic status	High	15.7%	0.135
		Low	27.3%	
2.	Site of lump	Right	12.7%	0.162
		Left	22.1%	
3.	Surgical margin	Free	16.8%	0.317
		Involved	25%	
4.	Tumor emboli	Absent	12.7%	0.162
		Present	22.1%	
5.	Axillary lymph nodes involved (number)	Not involved	10.9%	0.117
		1-3	13.1%	
		4-7	19%	
		>10	35.7%	
6.	HER2	Negative	15.7%	0.173
		Positive	25.6%	

No statistically significant associations were observed for socioeconomic status ($p = 0.135$), tumour laterality ($p = 0.162$), surgical-margin status ($p = 0.317$), tumour emboli ($p = 0.162$), axillary lymph-node category ($p = 0.117$), or HER2 status ($p = 0.173$). Metastasis frequency was numerically higher in some subgroups, but these differences did not reach statistical significance.

Table 3: Association of prognostic variables and distant metastasis with borderline statistical significant P value (showing positive numerical trends)

No.	Variable	Category	Patients with metastasis (%)	p value
1.	ER/PR	P/P	9.8%	0.053
		P/N & N/P	14.3%	
		N/N	26%	
2.	Overlying Skin	Normal	14.1%	0.071
		Abnormal	26.5%	
3.	Skin Involvement by tumor cells	Not involved	17.2%	0.087
		Involved	42.9%	
4.	Tumor size	Up to 2 cm	15.4%	0.089
		>5cm	28.9%	
5.	Tumor fixity to underlying tissue	Mobile	14.3%	0.086
		Fixed	26%	

ER/PR status showed a trend toward association with metastasis ($p = 0.053$): metastasis was reported in 9.8% of ER/PR-positive cases and 26.0% of cases negative for both receptors.

Overlying skin changes ($p = 0.071$), microscopic skin involvement ($p = 0.087$), tumour size ($p = 0.089$), and tumour fixation ($p = 0.086$) also showed numerical trends but were not statistically significant.

Table 4: Association of statistically significant factors with metastasis

No.	Variable	Category	Patients with metastasis (%)	p value
1.	Tumor grade	Grade-I	0%	0.013
		Grade-II	11.3%	
		Grade-III	27.9%	
2.	Nipple areola complex	Normal	12.9%	0.038
		Abnormal	26.8%	

Metastasis frequency increased across tumour grades: 0% in grade I, 11.3% in grade II, and 27.9% in grade III ($p = 0.013$). Nipple-areola complex changes were also associated with metastasis (26.8% with changes vs 12.9% without; $p = 0.038$).

DISCUSSION

Distant metastasis and comparison with published studies: Distant metastasis was documented in 26 of 141 patients (18.4%) in the present cohort. This proportion is comparable to the 17.3% reported by Fritz et al.⁷ in invasive carcinoma of no special type and the 18% reported by Yucel et al.⁸ after a mean follow-up of 54 months. Differences between studies may reflect variation in case selection, disease stage, treatment, follow-up duration, and criteria used to document metastasis. These comparisons suggest that the frequency observed in our cohort is within the range reported in similar clinical settings.

Distribution and timing of metastasis: The liver was the most frequently recorded site in this cohort (9 patients; 6.4%), followed by the lungs (7; 5.0%); bone and brain involvement were recorded in four patients each (2.8%). Two patients had multiorgan metastases involving the liver, lungs, and bone. Yucel et al.⁸ reported liver and lung metastases in 9.2% and 8.4% of cases, respectively. Other published work identifies bone, lung, liver, and brain among the common sites of breast-cancer spread.⁹ The mean time to metastasis in our study was 16.7 months, with a range of 3–57 months. Although many metastases occur during the first two to three years, later presentation is also recognised; follow-up therefore remains important beyond the immediate postoperative period.^{8,10}

Tumour grade and metastasis: Tumour grade was significantly associated with distant metastasis ($p = 0.013$). No metastasis was recorded among grade I tumours, compared with 11.3% of grade II and 27.9% of grade III tumours. This stepwise increase supports the relationship between higher histological grade and more aggressive tumour behaviour. One study showed that increase in tumor grade has increase risk of metastasis.¹¹ Previous studies have also identified grade as an important prognostic factor in metastatic breast cancer; Porter et al. described its prognostic relevance, while Jimeno et al. and Liu et al. reported that high-grade disease continued to be associated with poorer outcomes after metastasis.^{12,13,14} The present study, however, assessed the occurrence of metastasis rather than survival after metastasis, and its bivariate results should not be interpreted as evidence of an independent effect.

Nipple-areola complex and skin changes: Nipple-areola complex changes were also significantly associated with metastasis (26.8% in patients with changes versus 12.9% in those without; $p = 0.038$). Such changes—including retraction, erosion, or ulceration—may indicate more extensive local disease. The association should be interpreted as a clinicopathological relationship rather than a causal effect. Overlying skin changes and microscopic skin involvement showed non-significant trends: metastasis was recorded in 26.5% of patients with clinical skin changes versus 14.1% without, and in 42.9% of patients with microscopic skin involvement versus 17.2% without. The latter difference is notable in magnitude but did not reach statistical significance in this cohort ($p = 0.087$). These findings warrant validation in a larger series.

Hormone receptors, HER2, and tumour size: Metastasis was recorded in 9.8% of ER/PR-positive cases and 26.0% of cases negative for both receptors; the association approached, but did not reach, statistical significance ($p = 0.053$). HER2-positive cases also had a numerically higher metastasis frequency than HER2-negative cases (25.6% versus 15.7%), although this association was not statistically significant ($p = 0.173$). Yucel et al. reported prognostic differences according to hormone-receptor status in metastatic disease, and Ryberg et al. identified ER status as a prognostic factor. Previous literature has also described more aggressive behaviour in triple-negative breast cancer, including visceral spread.^{8,15,16} In our study, these observations are descriptive and do not establish independent predictive value. Tumour size showed a similar non-significant trend, with metastasis in 15.4% of tumours up to 2 cm and 28.9% of tumours larger than 5 cm ($p = 0.089$). Tumour size has been reported as relevant to prognosis after metastatic disease develops.¹⁷

Lymph-node involvement, tumour emboli, and other variables: Metastasis frequency was numerically higher in some categories of axillary lymph-node involvement, including 35.7% among patients with more than 10 involved nodes, compared with 10.9% among node-negative patients. However, the overall association was not statistically significant in the present analysis ($p = 0.117$), and the reported categories should be interpreted in light of the distribution of cases. Tumour emboli were associated with metastasis in 22.1% of cases compared with 12.7% when emboli were absent, but the difference was also non-significant ($p = 0.162$). Porter et al. reported a higher frequency of metastasis in cases with tumour emboli than in those without.¹² Tumour fixation, surgical-margin status, laterality, and socioeconomic status likewise showed numerical differences that did not reach statistical significance. These findings may reflect limited statistical power and should not be treated as proof that the variables lack prognostic relevance. Few studies show that increase in tumor burden with increase in lymph node involvement were the most important predictors of metastasis.^{18,19}

Clinical and pathological implications: The findings reinforce the value of complete documentation of mastectomy specimens and axillary lymph nodes. Recording tumour size and grade, nodal burden, skin and nipple–areola complex involvement, tumour emboli, receptor status, and surgical margins provides clinicians with information relevant to postoperative risk assessment and treatment planning. In this cohort, grade and nipple–areola complex changes were the only variables with statistically significant bivariate associations with distant metastasis. The other observed trends may be clinically relevant, but they require confirmation and should be considered alongside established staging and biomarker information rather than used in isolation.

Limitations:

This study has limitations. It was conducted at a single tertiary-care centre and included 141 patients, of whom 26 developed distant metastasis. The analysis was bivariate and did not adjust for potential confounding between tumour size, grade, nodal status, receptor profile, and other variables. The retrospective component also had limitations on the completeness of clinical records and follow-up documentation which were taken care by painstaking efforts.

CONCLUSION

Distant metastasis was documented in 18.4% of patients with IBC-NST in this cohort. Tumour grade and nipple–areola complex changes were significantly associated with metastasis, while several other clinicopathological features showed non-significant trends. Careful recording of these features may support clinical assessment and further treatment.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71:209–249.
2. Male breast cancer: Epidemiology and risk factors. Abdelwahab Yousef AJ. *Semin Oncol.* 2017;44:267–272.
3. Dawood S, Broglio K, Ensor J, Hortobagyi GN, Giordano SH. Survival differences among women with de novo stage IV and relapsed breast cancer. *Ann Oncol.* 2010; 21(11): 2169–2174.
4. Niwińska A, Murawska M & Pogoda K. Breast cancer brain metastases: differences in survival depending on biological subtype, RPA RTOG prognostic class and systemic treatment after whole-brain radiotherapy (WBRT). *Ann Oncol.* 2010; 21(5): 942–948.
5. Kawano A, Shimizu C, Hashimoto K, Kinoshita T, Tsuda H, Fujii H et al. Prognostic factors for stage IV hormone receptor-positive primary metastatic breast cancer. *Breast Cancer.* 2013; 20(2):145–451.
6. Pierga JY, Hajage D, Bachelot T, Delaloge S, Brain E, Campore M et al. High independent prognostic and predictive value of circulating tumor cells compared with serum tumor markers in a large prospective trial in first-line chemotherapy for metastatic breast cancer patients. *Ann Oncol.* 2012; 23(3): 618–624.
7. Fritz P, Klenk S, Goletz S, Gerties A, Simon W, Brinkmann F et al. Clinical impacts of histological subtyping primary breast cancer. *Anti Cancer Research.* 2010; 30(12):5137–5144.
8. Yücel B, Bahar S, Kaçan T, Seber MM, Celaseen MG, Bahuci A et al. Importance of Metastasis Site in Survival of Patients with Breast Cancer. *Auatın J of Med Oncol.* 2014; 1(2):1–7.
9. Koo JS, Jung W, Jeong J. Metastatic breast cancer shows different immunohistochemical phenotype according to metastatic site. *Tumori.* 2010; 96(3):424–32.
10. Dewis R, Gribbin J. Breast Cancer: Diagnosis and treatment. An assessment of need. Cardiff: National Collaborating Centre for Cancer (UK);2009. National Institute for Health and Clinical Excellence: Guidance.
11. Gao, C. · Wang, J. · He, P. · et al. Metastatic pattern of breast cancer by histologic grade: a SEER population-based study. *Discov Med.* 2022; 34(173):189–197
12. Porter GJR, Evans AJ, Pinder SE, James JJ, Cornford EC, Burrell HC. Patterns of metastatic breast carcinoma: influence of tumor histological grade. *Clinical Radiology.* 2004; 59(12):1094–1098.
13. Jimeno A, Amador ML, González-Cortijo L, Tornamira MV, Ropero S, Hornedo J et al. Initially metastatic breast carcinoma has a distinct disease pattern but an equivalent outcome compared with recurrent metastatic breast carcinoma. *Cancer.* 2004; 100(9): 1833–1842.
14. Liu MT, Huang WT, Wang AY, Huang CC, Huang CY, Chang TH et al. Prediction of outcome of patients with metastatic breast cancer: evaluation with prognostic factors and Nottingham prognostic index. *Support Care Cancer.* 2010; 18(12): 1553–1564.
15. Santos GT, Prolla JC, Camillo ND, Zavalhia LS, Ranzi AD, Bica CG. Clinical and pathological factors influencing the survival of breast cancer patients with malignant pleural effusion. *J Bras Pneumol.* 2012; 38(4):487–493.
16. Ryberg M, Nielsen D, Osterlind K, Skovsgaard T, Dørmannowsky P. Prognostic factors and long-term survival in 585 patients with metastatic breast cancer treated with epirubicin-based chemotherapy. *Ann Oncol.* 2001; 12(1): 81–87.
17. Yavas O, Hayran M, Ozisik Y. Factors affecting survival in breast cancer patients following bone metastasis. *Tumori.* 2007; 93(6): 580–586.
18. Chen, W. · Wang, C. · Fu, F. · et al. A model to predict the risk of lymph node metastasis in breast cancer based on clinicopathological characteristics *Cancer Manag Res.* 2020; 12:10439–10447
19. Ye, L.J. · Suo, H.D. · Liang, C.Y. · et al. Nomogram for predicting the risk of bone metastasis in breast cancer: a SEER population-based study. *Transl Cancer Res.* 2020; 9:6710–6719