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SURVIVAL ANALYSIS OF PATIENTS WITH INVASIVE BREAST CARCINOMA: ROLE OF HISTOMORPHOLOGICAL AND IMMUNOHISTOCHEMICAL FACTORS

Pathology

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ABSTRACT

Background: Histomorphological and immunohistochemical features are central to prognostic assessment in invasive breast carcinoma. This study evaluated the association of these features with survival in a tertiary-care hospital.**Methods:** This mixed retrospective–prospective observational study included 141 patients with invasive breast carcinoma of no special type (IBC-NST) who underwent modified radical mastectomy with axillary lymph-node dissection. Eight years of retrospective records and two years of prospective cases were reviewed. Gross, histological and immunohistochemical variables were recorded. Associations with 1-, 3- and 5-year outcomes were assessed using chi-square tests followed by backward logistic regression.**Results:** At the end of follow-up, 40/141 patients (28.4%) had died. Among patients evaluated at each time point, 131/141 (92.9%) were alive at 1 year, 54/82 (65.9%) at 3 years and 28/50 (56.0%) at 5 years. One-year outcome was associated with tumour fixation, size, surgical margins, nodal involvement and ER/PR status. Three-year outcome was associated with tumour consistency, nipple–areola complex changes, tumour size, skin findings/involvement, nodal status, ER/PR and HER2 status. Five-year outcome was associated with tumour size, nipple–areola complex abnormalities, ER/PR and HER2 status.**Conclusion:** Tumour burden, local extension, nodal involvement and hormone-receptor status were associated with survival outcomes. The time-specific proportions should be interpreted as observed proportions among patients with available follow-up, not Kaplan–Meier estimates.

KEYWORDS

Invasive Breast Carcinoma-NST, Survival, Histomorphology, Prognostic Factors.

INTRODUCTION

In developing countries, high breast cancer incidence and mortality are primarily attributed to a lack of awareness, inadequate screening programs, delayed diagnosis, and limited access to quality medical care.[1] Patients usually presents with breast lumps. Additionally, skin ulceration, nipple discharge and nipple retraction are rare secondary symptoms.[2] Despite multiple treatment options, including surgery, radiotherapy, chemotherapy, endocrine therapy, and immunotherapy, breast cancer incidence and mortality continue to increase globally.[3] Breast carcinoma is a biologically heterogeneous disease hence requires multidisciplinary management. Prognosis is influenced by tumour size, histological grade, axillary lymph-node status, lymphovascular invasion, surgical margins and the immunohistochemical profile. Oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status are particularly relevant because they inform both prognosis and treatment selection.[4] Gross and clinical findings may also reflect the extent of disease. Fixation to underlying tissues, changes in the overlying skin and abnormalities of the nipple–areola complex can indicate local extension. These findings are important to document alongside microscopic features, including tumour grade, necrosis, tumour emboli, skin involvement and nodal metastases. In settings where patients may present with advanced disease, a clear description of these variables can contribute to a more complete assessment of risk.[5,6,7] The present study evaluated the association of demographic, gross, histomorphological and immunohistochemical variables with survival at 1, 3 and 5 years among patients with invasive breast carcinoma of no special type treated at a tertiary-care hospital.

Materials and Methods

Study design and population

This observational study was conducted in the Department of Pathology at a tertiary-care hospital over a 10-year period, comprising eight years of retrospective cases and two years of prospective cases. The study included modified radical mastectomy (MRM) specimens with axillary lymph-node dissection diagnosed as invasive breast carcinoma of no special type (IBC-NST). Male breast cancers, histological types other than IBC-NST and cases lost to follow-up were excluded. The institutional ethics clearance and patient consent were obtained.

Pathological assessment and follow-up

Gross findings were abstracted from specimen records, and histological sections of the primary tumour and axillary lymph nodes were reviewed to confirm reported diagnoses and identify additional prognostic features. Recorded variables included tumour size, grade, consistency and fixation; nipple–areola complex and overlying skin abnormalities; microscopic skin involvement; surgical-margin status; axillary lymph-node involvement; tumour necrosis and tumour emboli; ER/PR and HER2 status; recurrence; distant metastasis; and mortality.

Follow-up information was obtained from hospital records and documented follow-up visits. The source protocol described visits every 3–6 months during the first three years, every 6–12 months during years four and five, and annually thereafter, with history and physical examination and additional investigations when clinically indicated.

Statistical analysis

Associations between clinicopathological variables and outcomes were assessed using chi-square tests. Variables identified as statistically associated with survival at each time point were entered into backward logistic regression models. Receiver-operating-characteristic curve analysis was used in the original analysis to select classification cut-offs. The numbers available for the 1-, 3- and 5-year analyses differed (141, 82 and 50, respectively); accordingly, the percentages reported below are observed proportions in the evaluable groups and should not be interpreted as Kaplan–Meier survival estimates.

RESULTS

Study cohort and overall outcomes

A total of 141 patients with IBC-NST who underwent MRM with axillary lymph-node dissection were included. At the end of the study, 101 patients (71.6%) were alive and 40 (28.4%) had died. Among the patients who died, recorded survival ranged from 2 to 46 months, with a mean of 19.1 months. More than half of the deaths (21/40; 52.5%) occurred within 16 months of treatment.

Observed survival at 1, 3 and 5 years

For the 1-year analysis, all 141 patients were included: 131 (92.9%) were alive and 10 (7.1%) had died by the end of the first year. The 3-year analysis included 82 patients, of whom 54 (65.9%) were alive and 28 (34.1%) had died. For the 5-year analysis, 50 patients were evaluable; 28 (56.0%) were alive and 22 (44.0%) had died. Because the denominator decreased at later time points, these values represent

observed proportions in the respective analysis groups rather than cumulative survival estimates accounting for censoring.

Table 1. Observed survival proportions at the three follow-up time points.

Follow-up	Patients analyzed	Alive, n (%)	Died, n (%)
1 year	141	131 (92.9)	10 (7.1)
3 years	82	54 (65.9)	28 (34.1)
5 years	50	28 (56.0)	22 (44.0)

Factors associated with 1-year survival

Chi-square analysis identified tumour fixation to underlying tissues, tumour size, surgical-margin status, axillary lymph-node involvement and ER/PR status as variables significantly associated with 1-year survival. These variables were entered into a backward logistic regression model. The source analysis reported tumour fixation, surgical-margin status and ER/PR status as the principal contributors to prediction. The model classified 78.6% of patients who survived and 90.0% of those who died correctly, with an overall classification accuracy of 79.4% at the selected probability cut-off of 0.070. These figures describe classification in the study sample and should not be interpreted as external validation.

Table 2. Variables reported as associated with 1-year survival.

Analysis stage	Variables/findings reported
Bivariate analysis	Tumour fixation; tumour size; surgical-margin status; axillary lymph-node involvement; ER/PR status
Backward logistic regression	Tumour fixation, surgical-margin status and ER/PR status were reported as the main contributors
Classification performance	78.6% of survivors and 90.0% of deaths classified correctly; overall accuracy 79.4%; cut-off 0.070

Factors associated with 3-year survival

For the 3-year outcome, bivariate analysis showed associations with tumour consistency, nipple–areola complex abnormalities, tumour size, skin involvement by tumour, axillary lymph-node involvement, overlying skin abnormalities, ER/PR status and HER2 status. The backward logistic regression analysis identified tumour consistency, nipple–areola complex abnormalities, overlying skin abnormalities and ER/PR status as the main contributors described in the source manuscript. The model correctly classified 72.2% of patients who survived and 82.1% of those who died, with an overall classification accuracy of 75.6% at a cut-off of 0.360.

Table 3. Variables reported as associated with 3-year survival.

Analysis stage	Variables/findings reported
Bivariate analysis	Tumour consistency; nipple–areola complex abnormality; tumour size; tumour involvement of skin; axillary lymph-node involvement; overlying skin abnormality; ER/PR status; HER2 status
Backward logistic regression	Tumour consistency, nipple–areola complex abnormality, overlying skin abnormality and ER/PR status were reported as the main contributors
Classification performance	72.2% of survivors and 82.1% of deaths classified correctly; overall accuracy 75.6%; cut-off 0.360

Factors associated with 5-year survival

In the 5-year analysis, tumour size, nipple–areola complex abnormalities, ER/PR status and HER2 status were significantly associated with outcome in bivariate analysis. In the backward logistic regression model, nipple–areola complex abnormalities and ER/PR status were reported as the principal contributors. The model correctly classified 82.1% of patients who survived and 68.2% of those who died, with an overall classification accuracy of 76.0% at a cut-off of 0.460.

Table 4. Variables reported as associated with 5-year survival.

Analysis stage	Variables/findings reported
Bivariate analysis	Tumour size; nipple–areola complex abnormality; ER/PR status; HER2 status
Backward logistic regression	Nipple–areola complex abnormality and ER/PR status were reported as the main contributors
Classification performance	82.1% of survivors and 68.2% of deaths classified correctly; overall accuracy 76.0%; cut-off 0.460

Additional clinicopathological observations

The current study reported a relationship between tumour size and mortality: mortality was 15.4% for tumours measuring up to 2 cm and increased to 44.4% for tumours larger than 5 cm. Mortality was reported as 18.2% among grade I tumours and 38.2% among grade III tumours. Nodal burden also showed a gradient: mortality was 15.6% when no lymph nodes were involved, 23.8% when 4–7 nodes were involved and 71.4% when more than 10 nodes were involved.

Mortality was reported as 24.6% among patients without recurrence compared with 72.7% among those with recurrence. Similarly, mortality was 14.8% in the absence of metastasis and 88.5% when metastasis was present. By ER/PR grouping, mortality was reported as 14.8% when both receptors were positive, 57.1% when either ER or PR was negative, and 37.0% when both were negative.

DISCUSSION

In the present study, 28.4% of patients died, while 71.6% were alive at the end of follow-up. Among patients who died, survival ranged from 2 to 46 months, with a mean of 19.1 months.

Tumor size, tumor grade, skin involvement, axillary lymph node involvement, ER/PR status, recurrence, and distant organ metastasis were significantly associated with survival ($P < 0.05$). Surgical margin status, skin abnormalities, nipple–areolar complex abnormalities, fixation to underlying tissue, tumor emboli, and HER2 status showed associations with survival that were not statistically significant.

Previous studies have identified tumor size, tumor grade, lymph node status, and metastasis as important predictors of long-term breast cancer survival, including survival up to 20 years after diagnosis.[8] Other studies have also found tumor size, nodal status, and grade to be associated with survival after mutual adjustment.[9] Tumor size and lymph node status have repeatedly been linked to breast cancer mortality.[10]

Tumor size and survival

In the present study, mortality was 15.4% among patients with tumors measuring ≤2 cm and increased to 44.4% among those with tumors >5 cm. Tumor size is a strong prognostic indicator, even after 20 years of follow-up.[8] Narod et al.[11] reported that tumor size predicts 15-year survival irrespective of axillary lymph node status. They also observed that reducing mean tumor size was associated with a greater decline in mortality among node-positive than node-negative patients. One study observed that increase in tumor size was associated with high mortality.[12] Another study reported 5-year survival of 99% for tumors <1 cm, decreasing to 86% for tumors measuring 3–5 cm.[11]

Tumor grade and survival

Mortality in the present study was 18.2% for grade I tumors and 38.2% for grade III tumors. Previous studies have consistently shown that higher tumor grade is associated with poorer long-term survival.[8]

Axillary lymph nodes and survival

In the present study, mortality was 15.6% among patients without nodal involvement, 23.8% among those with 4–7 involved nodes, and 71.4% among those with >10 involved nodes. Fisher et al.[13] reported 5-year overall survival rates of 83%, 73%, 46%, and 28% for patients with negative nodes, 1–3 positive nodes, 4–12 positive nodes, and >13 positive nodes, respectively.

Lymph node involvement is an important indicator of long-term survival.[8] Node-positive patients have been reported to have approximately 4–8 times the mortality risk of node-negative patients.[8] Prognosis also worsens as the number of involved nodes increases. Few studies observed that there is better outcome of patients with smaller tumor size and minimal node involvement.[14,15] Michaelson et al[10] found that, among patients with tumors of the same size, each additional positive lymph node was associated with an approximately 6% increase in the risk of death.

Recurrence, metastasis, and survival

In the present study, mortality was 24.6% in patients without recurrence, compared with 72.7% in those with recurrence. Similarly, mortality was 14.8% in patients without metastasis and 88.5% in those with metastasis.

Previous studies have reported poorer long-term survival in patients with recurrence or metastasis.[16] One study found that, after 10 years following surgery, the probability of surviving an additional 10 years for patients with grade I tumors <1 cm was 0.89; this decreased to 0.72 with recurrence and 0.18 with metastasis.[17]

ER/PR status and survival

In the present study, mortality was 14.8% among patients whose tumors were ER/PR-positive, 57.1% when either ER or PR was negative, and 37% when both ER and PR were negative.

Prognostic factors for 1-, 3-, and 5-year survival

The 1-, 3-, and 5-year survival rates in the present study were 92.9%, 65.9%, and 56%, respectively.

Gajalakshmi et al.[18] reported 1-, 3-, and 5-year overall survival rates of 79.9%, 58.4%, and 47.5%, respectively. Bradley et al.[19] reported a 5-year survival rate of 46% among patients with breast cancer in Mumbai. Rezaianzadeh et al.[9] reported 3- and 5-year survival rates of 76% and 58%, respectively. Fritz et al.[20] reported 1-, 3-, and 5-year survival rates of 97.2%, 83.7%, and 75.4%, respectively, among patients with ductal carcinoma in Germany. A 2007 study reported cumulative median 5-year overall survival rates of 65% in developed countries, 56% in developing countries, and 61% worldwide.[21]

Histomorphological prognostic factors for 1-year survival

Bivariate analysis identified the following histomorphological factors as significantly associated with 1-year survival:

- Tumor fixation to underlying tissue, Tumor size, Surgical margin status, Axillary lymph node involvement and ER/PR status

Backward logistic regression identified tumor fixation to underlying tissue, surgical margin status, and ER/PR status as the strongest contributors to predicting 1-year survival among the five associated factors.

The model correctly classified 78.6% of survivors and 90% of deaths during the 1-year follow-up after surgery.

Histomorphological prognostic factors for 3-year survival

Bivariate analysis identified the following factors as significantly associated with 3-year survival:

- Tumor consistency, Nipple–areolar complex abnormality, Tumor size, Skin involvement by tumor, Axillary lymph node involvement, ER/PR status, HER2 status and Abnormal overlying skin

Backward logistic regression identified tumor consistency, nipple–areolar complex abnormality, and ER/PR status as the strongest contributors to predicting 3-year survival among the eight associated factors.

The model correctly classified 72.2% of survivors and 82.1% of deaths during the 3-year follow-up after surgery.

Histomorphological prognostic factors for 5-year survival

Bivariate analysis identified the following factors as significantly associated with 5-year survival:

- Nipple–areolar complex abnormality, Tumor size, ER/PR status and HER2 status

Backward logistic regression identified nipple–areolar complex abnormality and ER/PR status as the strongest contributors to predicting 5-year survival among the four associated factors.
The model correctly classified 82.1% of survivors and 68.2% of deaths during the 5-year follow-up after surgery.

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