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RESEARCH ARTICLE

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To study the survival analysis and recurrence pattern in women treated for breast cancer: Retrospective study, a tertiary cancer center experience from Sub-Himalayan Region of India

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Abstract

Background: Breast cancer is a leading health concern in India, comprising 25% of female cancers with significant mortality. This study was conducted at the Cancer Research Institute in the Northern Sub-Himalayan region of India from 2016 to 2021, evaluated 674 breast cancer cases to analyze factors that influence recurrence.

Methodology: Retrospective clinical audit assessing patients' survival outcomes using Kaplan–Meier curves and Cox proportional hazard regression. Factors including age, molecular subtype, TNM staging, and treatment modalities were evaluated.

Results: Notable findings include a high occurrence of breast cancer in young patients (24.48% ≤ 40 years) and varying recurrence rates among molecular subtypes with human epidermal growth factor receptor 2 neu-enriched (25.24%) and triple-negative breast cancer (22.58%) being the most common. Advanced T and N stages, neoadjuvant chemotherapy, and the number of nodes dissected showed significant associations with higher recurrence rates.

Conclusion: This study sheds light on survival and recurrence patterns in Northern Sub-Himalayan breast cancer patients, emphasizing the need for tailored treatment strategies, comprehensive follow-up care, with improved understanding of regional outcomes. These findings contribute valuable insights for optimizing patient care and improving survival rates in this region.

KEYWORDS

breast cancer, recurrence patterns, Sub-Himalayan region, survival analysis

1 | INTRODUCTION

Breast cancer is the most common malignancy among Indian women and a serious health concern for women of all ages. It is a significant public health issue, accounting for ~25% of all female cancers in India. In 2020, there were expected to be 162 468 new cases of breast cancer in India. It also accounts for about 14% of all female cancer deaths and is the primary cause of cancer-related mortality among Indian women. It is estimated that there were 87 090 deaths from breast cancer in India in 2020.[1] Indian women experience breast cancer at a younger age than Western women do; the 45–49 years age range has the highest incidence of breast cancer, whereas in Western nations, the 60–64 years age group has the highest incidence.

Understanding the survival outcomes and recurrence patterns in treated patients is essential for optimizing treatment regimens and enhancing patient care due to its heterogeneous and complicated nature. The prognosis of breast cancer is significantly influenced by age. Research has indicated that older patients typically experience higher survival outcomes than their younger counterparts. However, recurrence patterns can vary by age group.[2] Molecular subtype classification which includes triple-negative breast cancer (TNBC), human epidermal growth factor receptor 2 (HER2)-enriched, Luminal A, and Luminal B has emerged as a key component of breast cancer research. There are notable differences in recurrence patterns and survival rates between these subtypes. Specifically, TNBC is linked to a worse overall survival (OS) rate and an increased risk of recurrence.[3] A key factor in determining survival and recurrence is histological grade. An greater likelihood of recurrence and more aggressive behavior are frequently linked to high-grade malignancies.[4] Prognosis and treatment choices depend on the TNM staging system, which takes tumor size (T), lymph node involvement (N), and metastasis (M) into account. There is a correlation between lymph node involvement (N+) and advanced stages (T3 and T4) and lower survival rates.[5] Recent studies have shown increases in the OS rate of patients with breast cancer, which have been linked to advancements in treatment methods such as radiation therapy, targeted treatments, adjuvant chemotherapy, and immunotherapies.[6]

Neoadjuvant chemotherapy (NACT) is increasingly used to downsize tumors before surgery. It can influence recurrence patterns and increase the chance of breast-conserving surgery. A pathological complete response (pCR) to NACT has been linked to increased survival and decreased recurrence rates, according to studies.[7]

Recurrence occurs in about 30% of individuals with breast cancer after first therapies.[8] These relapses can be caused by distant metastases or locoregional metastases. Locoregional recurrence is linked to an elevated risk of distant recurrence and poorer survival.[9] Within the first 5 years following the diagnosis of the initial tumor, it can appear in different anatomical locations.[10] Tumor stage and treatment preference are two characteristics that affect incidence.[11]

Notably, compared with visceral metastasis, bone metastasis is more common as the first site of recurrence and has higher survival prospects. Additionally, single bone metastases have higher survival rates than many bone metastases.[12] Early detection and treatment of distant metastasis do not necessarily lead to better outcomes and are not a primary follow-up care objective. Understanding these recurrence patterns and predictive factors helps in making informed clinical decisions and personalized follow-up care.

In conclusion, providing individualized and efficient care for patients with breast cancer requires an understanding of survival analysis, recurrence trends, and the factors that influence them. Recent studies have brought attention to the changing face of breast cancer treatment, highlighting the importance of histological grading, targeted medicines, and molecular subtyping. To improve breast cancer patients' quality of life and survival rates even more, more research is needed. Therefore, the purpose of this research is to investigate patterns of illness recurrence and evaluate the effects of clinicopathological and therapeutic factors on outcomes.

2 | MATERIAL AND METHODS

This was a retrospective study from prospectively maintained database of Breast cancer patients operated at Department of Surgical Oncology, Cancer Research Institute, Himalayan Institute of Medical Sciences, between January 2016 till December 2021. The study was approved by the Institutional Ethics Committee (Ref.No:SRHU/HIMS/RC/2023/203).

Patients were recruited from Out patient department and pre operative workup was done in the line of following: mammography, biopsy, ultrasonography (USG), or magnetic resonance imaging, contrast-enhanced computed tomography (CT), positron emission tomography CT scan. The molecular subtypes, luminal (or hormone receptor positive), HER2-enriched, and TNBC, were identified either by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). The 8th edition American Joint Committee on Cancer guidelines were implemented in the identification of stage. The presence of nodal metastasis was precisely detected using USG. Grade and tissue of origin were detected using either IHC or FISH. Further, cases with disease detection at ≤40 years were grouped as "younger" cohort, whereas those at >40 years were grouped as "older" cohort. Median follow-up time was 38 months. Outcomes included local recurrence (LR)-free survival and Distant recurrence-free survival. Locoregional recurrence was defined as a biopsy proven recurrence of the primary breast cancer within the ipsilateral breast, chest wall, axillary, internal mammary, or supraclavicular lymph nodes. Distant recurrence was defined as a biopsy proven recurrence in any other location of the body.

2.1 | Statistical analysis

The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences software, IBM, ver 25.0.

The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data with normal distribution were presented as the means ± SD and the data with non-normal distribution as median with 25th and 75th percentiles (interquartile range). The data normality was checked by using Kolmogorov–Smirnov test. The cases in which the data was not normal, nonparametric test were used. The following statistical tests were applied for the results: the analysis involved the use of specific statistical tests for different types of variables. Quantitative variables that were not normally distributed were assessed using the Mann–Whitney test, whereas qualitative variables were examined through the χ^2 test. In cases where an expected cell value was <5, the Fisher's exact test was applied. Kaplan–Meier survival analysis curve was used to assess actuarial OS

rate, recurrence-free survival rate, LR-free survival rate, regional recurrence-free survival rate, and distant mets-free survival rate. Univariate and multivariate cox proportional hazard regression was used to find out factors affecting recurrence. For statistical significance, $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics distribution

A total of 674 females were included in the study; median age was 50 (41–61) years with 509 patients (75.52%) elderly and 165 patients (24.48%) as young breast cancer patients. Histologically, the majority of patients (451 patients, 66.91%) had infiltrating ductal carcinoma (IDC) Grade II. IHC revealed that 291 patients (43.18%) had Luminal B, 159 cases (23.59%) had TNBC, 105 patients (15.58%) had HER2 neu-enriched, and 100 patients (14.84%) had Luminal A. Clinical assessments showed that 408 cases (60.53%) had T2 disease, 119 patients (17.66%) had T3 disease, and 94 patients (13.95%) had T4 disease. Additionally, 256 cases (37.98%) had N0 disease, whereas the remaining patients were clinically node-positive. Angiolymphatic invasion was observed in 416 cases (62.93%) and perineural invasion was present in 119 cases (18.00%).

3.2 | Treatment characteristics

Among the patients, 115 patients (17.06%) received NACT. Then, 501 (74.33%) underwent simple mastectomy (SM) and 173 patients (25.67%) opted for breast conservation surgery. Furthermore, 620 patients (91.99%) underwent axillary lymph node dissection (ALND) and 54 patients (8.01%) underwent sentinel lymph node biopsy (SLNB).

On histopathological analysis, post-NACT, 13/115 patients (1.93%) achieved a pCR. Then, 394 patients (58.46%) were pT2, 134 patients (19.88%) were pT3, 69 patients (10.23%) were pT4, and 66 patients (9.79%) were pT1. Next, 338 (50.15%) cases were pathologically negative lymph nodes and rest of the patients had positive nodal disease.

Four hundred and sixteen patients (62.93%) had angiolymphatic invasion and 119 patients (18.00%) had perineural invasion. Median Ki67% was 40%, median number of nodes dissected were 14,[10–19] and median number of positive nodes were 4.[2–7,20]

3.3 | Outcomes

The median follow-up period for patients was 38 months, ranging from 1 month to 95 months. Of the 674 patients, 118 (18.61%) developed recurrence overall and 84 patients (13.25%) were dead. Among those with recurrence, 81 patients (68.64%) had distant metastasis only, 18 patients (15.25%) had LR only, and four cases (3.39%) had regional recurrence only. Additionally, six patients (5.08%) experienced both LR and distant metastasis, whereas another six patients had both regional recurrence and distant metastasis. Finally, two patients (1.69%) had both local and regional recurrence, and one patient (0.85%) had LR, regional recurrence, and distant metastasis.

The distribution of recurrence was analyzed in relation to various factors, including age, IHC, clinical T and N stages, NACT, histological IDC grades, and the number of dissected and positive nodes. The analysis revealed that there was no statistically significant difference in recurrence rates among different IHC subtypes, including Luminal A (12.09%), Luminal B (16.48%), HER2 neu-enriched (25.24%), and TNBC (22.58%), with a $p = 0.071$.

However, a significant difference in recurrence rates was observed in relation to clinical T stage, where patients in advanced stages (3, 4A, 4B, 4C, and 4D) had notably higher recurrence rates (29.46%, 20%, 34.12%, 42.86%, and 40%, respectively) compared with those in earlier stages (1 and 2 with 15.15%, and 11.63%, respectively), with a $p < 0.0001$. Similarly, significant differences in recurrence rates were found based on clinical N stage, with higher rates in advanced stages (2A, 2B, and 3C) (26%, 33.33%, and 33.33%, respectively) compared with earlier stages (0 and 1 with 11.25% and 22.98%, respectively), with a $p = 0.003$. Patients who received NACT exhibited a significantly higher recurrence rate (31.19%) compared with those who did not receive NACT (16%), with a $p = 0.0002$. Additionally, there were no statistically significant differences in recurrence rates among different Histological IDC grades, including IDC 1 (15.56%), IDC 2 (18.59%), and IDC 3 (20.59%), with a $p = 0.566$.

Furthermore, a significant association was observed between the total number of nodes dissected and positive nodes concerning recurrence ($p < 0.05$). Patients with recurrence had a higher number of nodes dissected (16, with a range of 12.25–21) and positive nodes (4, with a range of 0–9) compared with those without recurrence (median of 14 nodes dissected with a range of 11–19 and one positive node with a range of 0–3), with respective $p = 0.015$ and <0.0001.

3.4 | Survival analysis

At a median follow-up of 38 months (range: 1–95 months), Kaplan–Meier analysis revealed the actuarial survival rates at the end of 3 years (88.56%), 5 years (81.60%), and the end of the study (38.90%). Similarly, Kaplan–Meier analysis showed actuarial recurrence-free survival rates at the end of 3 years (83.26%), 5 years (77.21%), and the end of the study (62.98%)(Figures 1 and 2).

3.5 | Discussion

This research encompasses a significant group of non metastatic breast cancer patients hailing from the hilly region in Northern Sub-Himalayas, India. It offers valuable information regarding their survival rates. To better understand the significance of these findings, let's delve deeper into the study's implications (Tables 1–3).

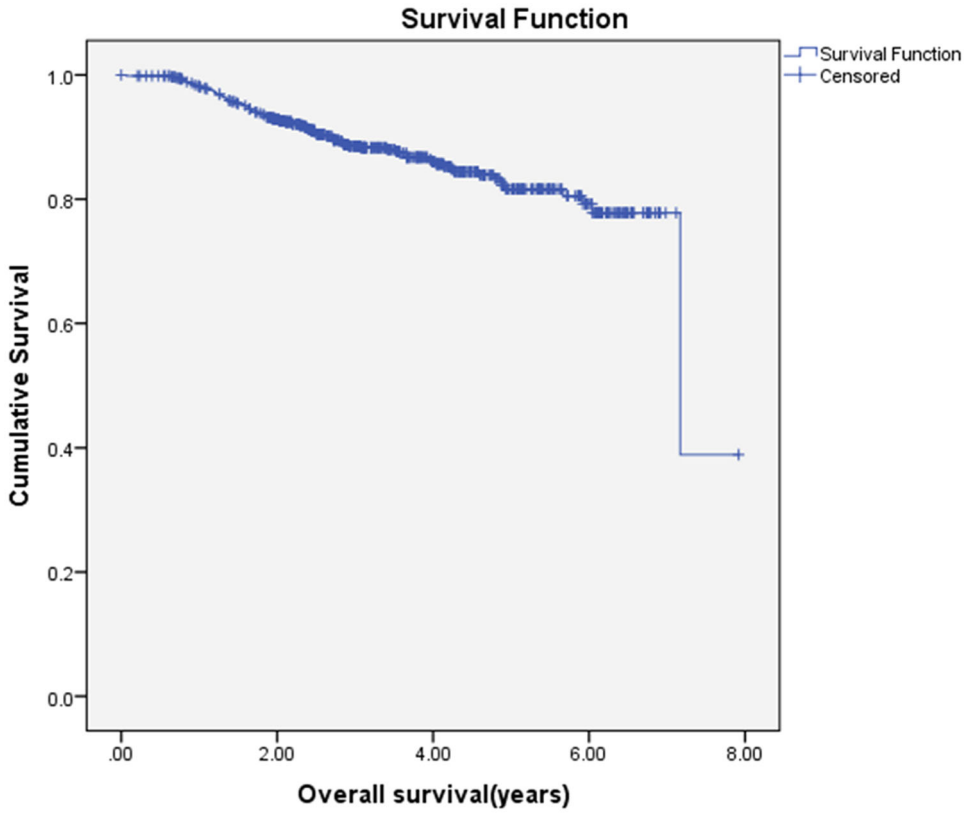

FIGURE 1 Kaplan–Meier survival analysis curve of overall survival.

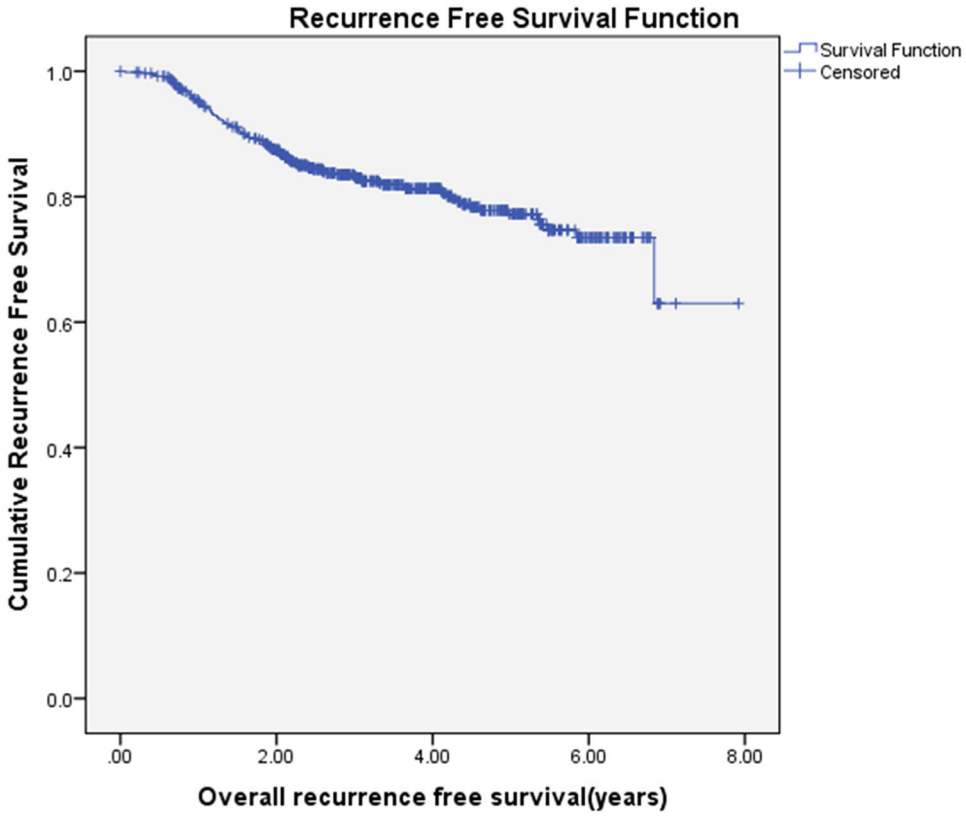

FIGURE 2 Kaplan–Meier survival analysis curve of recurrence-free survival.

According to the American Cancer Society, breast cancer survival rates in the United States are relatively high, with a 91% survival rate at 5 years postdiagnosis and 84% at 10 years.[13] In contrast, a study by Viral et al.[14] in India reported a 5-year OS of 79% and a 10-year breast cancer-specific survival of 70%. Another Indian study by Doval et al.,[15] which included only early operable breast cancer patients, found a 5-year OS of 94.1% and a disease-free survival (DFS) of 88.1%. These differences may be attributed to variations in demographics, health care access, and tumor characteristics. What stands out in our study is that it includes both early and advanced breast cancer cases. The results show that the 3- and 5-year OS rates were relatively high at 88.56% and 81.60%, respectively, with corresponding DFS rates at 3 and 5 years being 83.26% and 77.21%. This suggests that despite challenges, Indian patients with breast cancer can achieve favorable survival outcomes, possibly due to advances in diagnosis and treatment however the rates are lower compared to western population.

Worldwide, ~20% of breast cancer patients experience disease recurrence.[16] Another study revealed 8%–10% of breast cancer cases present with locoregional recurrences after surgery and ~11%–30% of patients develop distant metastases.[17] Our study revealed similar rates that 18.61% of breast cancer cases experienced recurrence, with 15.14% of these cases developing distant metastases and a 13.25% mortality rate. These results underscore the persistent risk that breast cancer patients encounter after completing their treatment. They also emphasize the importance of maintaining a watchful eye through surveillance and implementing effective treatment strategies to tackle the possibility of recurrence, especially in a less accessible Sub-Himalayan terrain.

Breast cancer is a complex and heterogeneous disease, and understanding the factors associated with recurrence is crucial for optimizing patient care and outcomes. The study has identified several factors associated with recurrence:

There's a disparity in age and tumor stage at diagnosis between the Indian and Western populations. Younger Indian women often present with symptomatic, advanced-stage tumors, which are more likely to have poor differentiation and lympho vascular invasion, leading to higher recurrence rates.[18] In our study, a significant proportion of patients who developed recurrence were over 40 years old.

Research has shown varying LR rates based on breast cancer subtypes. HER2 neu-enriched and TNBC patients tend to exhibit higher recurrence rates, whereas Luminal A and B tumors have lower LR rates. According to a study by Wu et al.,[19] LR rates were highest among TNBC patients (12%), followed by Her2 neu-enriched patients, 8%. Although our research noted a recurrence distribution that seemed to lean towards HER2 neu-enriched and TNBC cases, this distinction did not reach statistical significance. This lack of statistical significance may be due to the relatively brief follow-up period, and it suggests that a more extended follow-up period is necessary to obtain definitive and conclusive results.

Advanced clinical tumor stages (cT3 and cT4) were associated with significantly higher recurrence rates compared with earlier stages (cT2 and cT1)[21,22] Similarly, higher nodal stage correlated with higher

TABLE 1 Patient characteristics distribution.

Patient characteristics	*n* (%)
Age (years)	
≤40 years	165 (24.48%)
>40 years	509 (75.52%)
HPE	
IDC 1	98 (14.54%)
IDC 2	451 (66.91%)
IDC 3	107 (15.88%)
Others	18 (2.67%)
IHC	
Luminal A	100 (14.84%)
Luminal B	291 (43.18%)
HER2 neu-enriched	105 (15.58%)
TNBC	159 (23.59%)
cT	
1	35 (5.19%)
2	408 (60.53%)
3	119 (17.66%)
4A	5 (0.74%)
4B	94 (13.95%)
4C	8 (1.19%)
4D	5 (0.74%)
cN	
0	256 (37.98%)
1	342 (50.74%)
2A	51 (7.57%)
2B	4 (0.59%)
3A	2 (0.30%)
3B	13 (1.93%)
3C	6 (0.89%)
Surgery performed	
BCS	173 (25.67%)
SM	501 (74.33%)
Axillary lymph nodes	
ALND	620 (91.99%)
SLNB	54 (8.01%)
pT	
0	11 (1.63%)
1A	10 (1.48%)
1B	3 (0.45%)

(Continues)

TABLE 1 (Continued)

Patient characteristics	*n* (%)
1C	53 (7.86%)
2	394 (58.46%)
3	134 (19.88%)
4A	4 (0.59%)
4B	60 (8.90%)
4C	1 (0.15%)
4D	4 (0.59%)
pN	
0	338 (50.15%)
1A	148 (21.96%)
2A	111 (16.47%)
3A	75 (11.13%)
3B	2 (0.30%)
NACT	115 (17.06%)
PCR	13 (1.93%)
Angiolymphatic invasion	416 (62.93%)
Perineural invasion	119 (18.00%)
Median Ki67%	40 (30–60)
Median Nodes dissected	14 (11–20)
Median positive nodes	4 (2–8)

Abbreviations: ALND, axillary lymph node dissection; BCS, breast cancer-specific; cT, clinical tumor stage; HER2, human epidermal growth factor receptor 2; IDC, infiltrating ductal carcinoma; IHC, immunohistochemistry; NACT, eoadjuvant chemotherapy; PCR, polymerase chain reaction; SLNB, sentinel lymph node biopsy; SM, simple mastectomy; TNBC, triple-negative breast cancer.

TABLE 2 Outcome distribution.

Outcome	Frequency	Percentage
Mortality	84	13.25%
Recurrence	118	18.61%
Local recurrence	27	4.26%
Regional recurrence	13	2.05%
Distant metastasis	96	15.14%

TABLE 3 Association of patient characteristics with recurrence.

Patient characteristics	Recurrence	*p*
Age (years)		
≤40 years	26 (16.67%)	0.472[a]
>40 years	92 (19.25%)	
IHC		
Luminal A	11 (12.09%)	0.071[a]
Luminal B	45 (16.48%)	
HER2 neu-enriched	26 (25.24%)	
TNBC	35 (22.58%)	
cT		
1	5 (15.15%)	<0.0001[a]
2	45 (11.63%)	
3	33 (29.46%)	
4A	1 (20%)	
4B	29 (34.12%)	
4C	3 (42.86%)	
4D	2 (40%)	
cN		
0	27 (11.25%)	0.003[a]
1	74 (22.98%)	
2A	13 (26%)	
2B	1 (33.33%)	
3A	0 (0%)	
3B	1 (8.33%)	
3C	2 (33.33%)	
NACT		
No	84 (16%)	0.0002[b]
Yes	34 (31.19%)	
HPE		
IDC 1	14 (15.56%)	0.566[a]
IDC 2	79 (18.59%)	
IDC 3	21 (20.59%)	
Nodes dissected	16 (12.25–21)	0.015[c]
Positive nodes		<0.0001[c]

Abbreviations: cT, clinical tumor stage; HER2, human epidermal growth factor receptor 2; IDC, infiltrating ductal carcinoma; IHC, immunohistochemistry; NACT, eoadjuvant chemotherapy; TNBC, triple-negative breast cancer.

[a]χ^2 test.

[b]Fisher's exact test.

[c]Mann–Whitney test.

recurrence rates. These findings highlight the importance of early detection and the role of tumor and nodal stage in recurrence risk.

Patients who received NACT had a significantly higher recurrence rate.[7] The relationship between NACT and recurrence is multifaceted, potentially reflecting the presence of more aggressive tumors with locally advanced and molecular subtypes requiring neoadjuvant treatment.

An increased number of nodes dissected and the presence of positive nodes were identified as significant predictors of recurrence. This underscores the importance of thorough lymph node evaluation and emphasizes lymph node status as a key prognostic factor. Although not statistically significant, trends suggested higher recurrence rates in patients with angiolymphatic and perineural invasion.[23,24] These factors may still hold clinical relevance as they influence cancer aggressiveness.

This study boasts of several notable strengths. To begin with, it benefits from a sizable sample of 674 breast cancer patients without metastasis, which enhances the credibility and relevance of the results for the broader population in Northern India, particularly in the Sub-Himalayan region. The inclusion of a larger sample size is pivotal in fortifying the robustness of the results. Moreover, the study adopts a multifaceted approach by examining various facets of patient outcomes, encompassing parameters such as OS, recurrence rates, and the categorization of recurrence into local, regional, or distant, thus offering a comprehensive perspective on disease progression and management.

However, certain limitations should be acknowledged. The study is constrained by its single-center design, which may introduce potential selection bias and limit the generalizability of its conclusions. Furthermore, it employs a retrospective methodology, which, while valuable for assessing existing data, might lack the systematic rigor associated with prospective studies. Additionally, the relatively short follow-up period should be considered when interpreting the findings, as it may not capture long-term outcomes.

In conclusion, this research significantly enhances our comprehension of breast cancer outcomes in India, particularly in the challenging, hard-to-reach Himalayan hilly terrain. It emphasizes the need for comprehensive approaches to tackle cancer recurrence and highlights the critical influence of patient age, tumor characteristics, and treatment methods on breast cancer outcomes. These results strongly support further investigations and personalized interventions to enhance the care and survival rates of breast cancer patients, not only in India but also in comparable environments.

DATA AVAILABILITY STATEMENT

Not applicable.

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