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ORIGINAL ARTICLE

Prognostic Utility of Cyclin D1 in Invasive Breast Carcinoma

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Abstract

Invasive breast carcinoma is the most common cancer among women worldwide. Increase in early detection of breast carcinoma by different diagnostic modalities led to decrease in cancer-related mortality and morbidity. Multiple factors and genes are implicated in breast cancer pathogenesis. Cyclin D1 is an important cell cycle regulatory protein involved in carcinogenesis of various human cancers including breast cancer. Aims of the present study were to evaluate the prognostic importance of cyclin D1 expression in invasive breast carcinoma and its correlation with other prognostic and predictive factors. Patients undergoing mastectomy for breast carcinoma were selected from January 2016 to June 2017 in a tertiary care hospital. Clinical history including demographic parameters was collected in the study pro forma. Immunohistochemical staining for ER, PgR, HER2 and cyclin D1 was performed on all cases. The clinicopathological parameters like age, tumour size, histologic grade, histological type, lymphovascular invasion, axillary lymph node metastasis, ER, PgR and HER2 status were compared and correlated with cyclin D1 expression. Cyclin D1 expression found in 60% cases of breast carcinoma. Expression of cyclin D1 showed a highly significant correlation with histological grade ($p = 0.000$). Cyclin D1 expression showed significant correlation ($p = 0.000$) with molecular subtypes. There was also significant correlation between cyclin D1 expression and ER ($p = 0.000$) and PgR ($p = 0.010$) status. This study revealed significant cyclin D1 expression in low grade, well-differentiated breast cancer. Therefore, we found cyclin D1 as a favourable prognostic marker in breast carcinoma.

Keywords Breast cancer · Cyclin D1 · Immunohistochemistry

Introduction

Breast cancer is the most frequent cancer among women representing 25% of all cancers, with an estimated 1.67 million new cancer cases diagnosed in 2012 [1]. In India, age-adjusted rate is high as 25.8 per 100,000 women and mortality 12.7 per 100,000 women [2].

Breast carcinoma is a heterogeneous disease clinically and pathologically [3]. Age, tumour size, histological grade, histological type, lymphovascular invasion, axillary lymph node (ALN) metastasis, hormone receptor, oestrogen, progesterone and human epidermal growth factor 2 (HER2) status are traditionally regarded as prognostic markers in patients with breast carcinoma. Cyclin D1 is emerging as a significant biomarker in invasive breast cancer, not still used as a routine prognostic tool in breast cancer, although it has shown its prognostic value in several studies [4, 5].

G1/S-specific cyclin D1 also called Bcl1 and PRAD1 oncogene is a protein in human, that is, encoded by the CCND1 gene, located on chromosome 11q13.3 [6]. Three to tenfold amplification of DNA on 11q13.14 is present in approximately 13% to 20% of the breast cancers [7] and cyclin D1 overexpression has been reported in up to 90% of human breast cancers [8]. Studies have shown that over-expressed cyclin D1 in breast cancer patients acts by binding directly to the oestrogen receptors (ERs) and propagate the downstream effects of oestrogen in a CDK independent and Rb independent fashion [9]. Studies have found associations between overexpression of cyclin D1 and breast cancer subtypes that are more indolent, are ER-positive, and have a better prognosis [10].

In the present study, we assessed the expression of cyclin D1 in invasive breast carcinoma, correlated the findings with the other known prognostic and predictive factors and thus evaluated the role of cyclin D1 as a prognostic marker in breast carcinoma.

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Materials and Methods

It was a cross-sectional observational study conducted in the Department of Pathology in collaboration with Department of Surgery after obtaining the approval from Institutional Ethical Committee. A total 50 patients were selected who were undergoing mastectomy over a study period of 18 months from January 2016 to June 2017. Patients who received neoadjuvant systemic therapy were excluded from this study. The specimens were sent to the Department of Pathology for further examination. Following haematoxylin and eosin (H&E) staining, immunohistochemical (IHC) staining done for ER, PgR, HER2 and cyclin D1 expression in all cases. The specimens were classified according to IHC staining into four molecular subtypes: luminal A, luminal B, HER2 and triple negative/basal like according to molecular classification [11]. Cyclin D1expression was also studied and correlated with molecular subtypes and clinicopathologic parameters.

Four-micron sections were prepared from each formalin-fixed and paraffin-embedded tissue sample and stained with antibody against ER (monoclonal mouse anti-human; Clone: 1D5; Dako), PgR (monoclonal mouse anti-human; Clone PgR 636, Dako), HER2 (polyclonal rabbit antihuman antibody against c-erbB-2 oncoprotein, Dako) and against cyclin D1 (monoclonal Rabbit Anti-Human, Clone EP12, Dako). Normal tonsil tissue was used as positive control and negative control was achieved by omission of the primary antibody in cyclin D1.

Table 1 Quantification of ER/PgR immunostaining

Proportion score	Positive cells, %	Intensity	Intensity score
0	0	None	0
1	< 1	Weak	1
2	1–10	Intermediate	2
3	11–33	Strong	3
4	34–66		
5	> = 67		

Interpretation of Immunostaining

ER/PgR All cases with at least 1% of positive cells were considered positive [12] and quantification was done using Allred scoring system [13].

The Allred score combines the percentage of positive cells and the intensity of the reaction product in most of the carcinoma. The 2 scores were added together for a final score with 8 possible values. Scores of 0 and 2 were considered negative. Scores of 3 to 8 were considered positive. For ER/ PgR staining, tissue of endocervix known to be ER/ PgR positive was used as a positive control and negative control was achieved by omitting the primary antibody (Table 1).

HER2 Interpretation of HER2 immunostaining was done according to ASCO/CAP guidelines [14] (Table 2).

Cyclin D1 immunohistochemical intensity and distribution were semi-quantitatively scored using the Allred score method [12]. Only nuclear staining was considered specific. With this method, the intensity of the immunohistochemical reaction as viewed under the light microscope was recorded as 0, negative (no staining of any nuclei even at high magnification); 1, weak (only visible at high magnification); 2, moderate (readily visible at low magnification) or 3, strong (strikingly positive even at low power magnification). The proportion of positive cells and intensity scores was then added to obtain a total score, which ranged from 0 to 8 [12]. Tumours were then categorised into groups: negative expression (total scores 0–2), intermediate expression (total scores 3–5) and strong expression (total scores 6–8). [15] (Figs. 1, 2, 3, and 4).

Statistical Analysis

All data were thoroughly maintained on Microsoft Excel worksheet. Mean values with standard deviation were calculated for quantitative variables, whereas proportions represented qualitative variables. The chi-square test was conducted to assess the correlation between clinicopathological parameters. Statistical analyses were performed using SPSS software version 20.0 (IBM, Armonk, New York, USA). Two-tailed $p < 0.05$ was considered statistically significant.

Table 2 Interpretation of HER2 immunostaining

Result	Criteria
Negative (score 0)	No staining observed or incomplete, faint/barely perceptible membrane staining in < = 10% of invasive tumour cells
Negative (score 1+)	Incomplete, faint/barely perceptible membrane staining in < = 10% of invasive tumour cells
Equivocal (score 2+)	Incomplete and/or weak to moderate circumferential membrane staining in > 10% of invasive tumour cells or, complete, intense, circumferential membrane staining in < = 10% of invasive tumour cells
Positive (score 3+)	Complete, intense, circumferential membrane staining in > 10% of invasive tumour cells

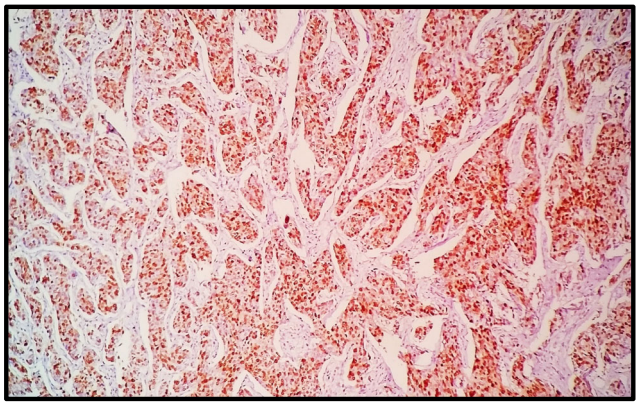

Fig. 1 Cyclin D1 strong positive expression in invasive ductal carcinoma of no special type (× 100)

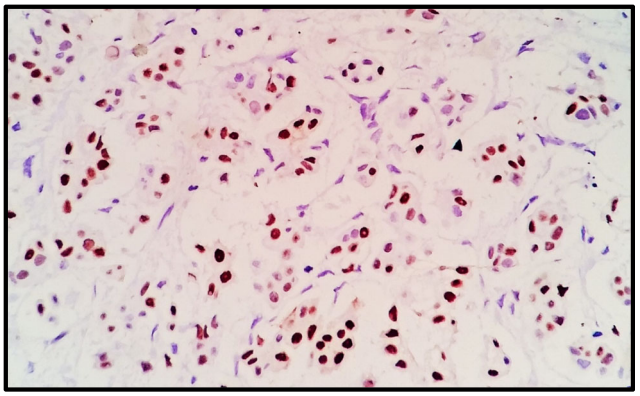

Fig. 3 Cyclin D1 strong positive expression in mucinous carcinoma (× 400)

Results

There were total 50 cases; all were female. Age ranged from 30 to 65 years, mean age (± standard deviation) of the patients was 46.5 ± 8.94 years. There were 31 cases of breast carcinoma in the age group of 41–60 years (62%) followed by 16 cases (32%) in the age group of 21–40 years, and 3 cases (6%) in age group of 61–80 years. Twenty-eight cases (56%) occurred in the right breast. Eighteen cases (36%) were located on upper outer quadranty. Size of the tumour ranged from 2 to 9 cm; mean tumour size was 5.18 ± 1.77 cm. Twenty-seven cases (54%) of tumours were in the T2 group.

There were 42 cases (84%) of infiltrating ductal carcinoma of no special type (IDCNST) followed by 4 cases (8%) of mucinous carcinoma, 2 cases (4%) of invasive lobular carcinoma and there were 2 cases (4%) of metaplastic carcinoma. Mucinous and metaplastic carcinoma are not graded according to modified Bloom-Richardson grading system. A total of 44 cases were graded. Grade II tumour were most prevalent, 25 cases (56.8%) followed by 16(36.4%) cases of grade III and 3 cases (6.8%) were grade I. Lymphovascular invasion was present in 46 cases (92%). Axillary lymph nodes were involved by tumour cells in 24 cases (48%).

Regarding the hormone receptor status, ER, PgR and HER2 expression were positive in 29 cases (58%), 12 cases (24%) and 24 cases (48%) of tumours, respectively. Triple negative subtypes were present in 16 cases (32%), followed by luminal B subtypes in 15 cases (30%), HER2 subtypes in 13 cases (26%) and luminal A subtypes in 6 cases (12%).

A total of 30 cases (60%) showed positive cyclin D1 expression. Cyclin D1 expression was strong positive in 14 cases (28%), intermediate in 16 cases (32%) and negative/weak in 20 cases (40%). The correlations between cyclin D1 expression and clinicopathological factors are summarised in Table 3.

No significant correlation found between cyclin D1 expression and age, tumour size and histological types. Lymphovascular invasion and axillary lymph node were also not significantly correlated with cyclin D1 expression. There was statistically significant ($p = 0.000$) correlation between cyclin D1 expression and histological grade (Table 4).

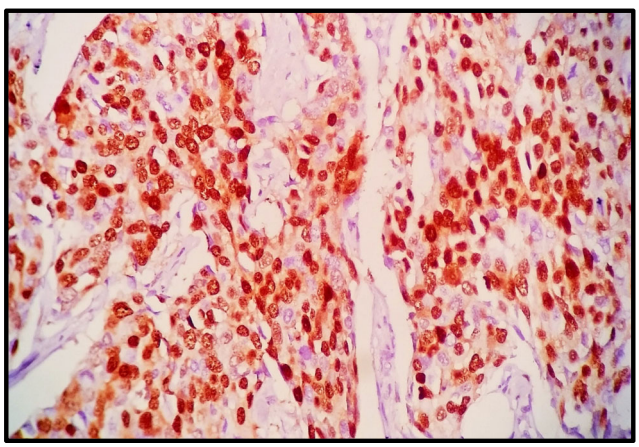

Fig. 2 Cyclin D1 strong positive expression in invasive ductal carcinoma of no special type (× 400)

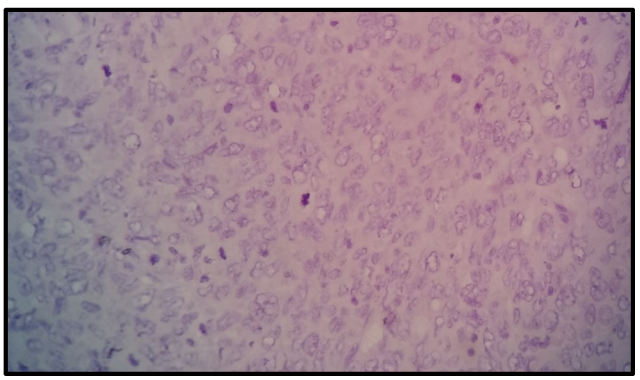

Fig. 4 Cyclin D1 negative expression in invasive ductal carcinoma of no special type (× 400)

Table 3 Correlation between cyclin D1 expression and clinicopathologic factors

Prognostic parameters		Cyclin D1 expression				*p* value
		n	Strong positive (*n* = 14)	Intermediate positive (*n* = 16)	Negative (*n* = 20)	
Age Group	21–40	16	2	7	7	0.246
	41–60	31	10	8	13	
	61–80	3	2	1	0	
Tumour Size	T1	1	1	0	0	0.077
	T2	27	8	5	14	
	T3	22	5	11	6	
Histologic type	IDCNST	42	10	15	17	0.157
	Lobular	2	1	0	0	
	Mucinous	4	3	1	0	
	Metaplastic	2	0	0	2	
LVI	Present	46	13	13	20	0.119
	Absent	4	1	3	0	
Axillary lymph node	N1	26	8	4	14	0.144
	N2	14	4	8	2	
	N3	8	2	3	3	
	N4	2	0	1	1	

All grade I tumours showed strong positive cyclin D1 expression and 48% of grade II and 37.5% of grade III tumours showed negative cyclin D1 expression.

Cyclin D1 showed statistically significant ($p = 0.000$) correlation with molecular subtypes. 83.3% of luminal A tumours showed strong positive cyclin D1 expression and 75% of triple-negative type tumours were cyclin D1 negative (Table 5).

There was statistically significant correlation between cyclin D1 expression and ER ($p = 0.000$) and PgR ($p = 0.000$) status. 52.4% of ER positive and 58.4% of PgR positive tumours showed positive cyclin D1 expression. 62.1% of ER-negative tumours shower negative cyclin D1 expression. No significant correlation ($p = 0.127$) found between cyclin D1 expression and HER2 status (Table 6).

Discussion

In our study, 62% (31 cases) patients were in 41–60 years. Study by A. Khemka et al. expressed that the peak incidence of breast carcinoma was between 40 and 44 years [16]. Our study was also nearly supportive to it. We found 54% cases (27 cases) in the T2 group. Zubair Ahmed et al. also showed 44.16% patients in the T2 group which was almost similar to our study [17].

In the present study, there was 84% (42 cases) of tumours were invasive ductal carcinoma of no special type. Previous study also found invasive ductal carcinoma as the most common form of invasive breast carcinoma [18]. In our study, 56.8% of tumours (25 cases) were of grade II (Bloom Richardson Grading). Another recent Indian study by Ravikumar et al. found 67.5% of grade II breast carcinoma in their study [19].

In the present study, 92% (46 cases) breast carcinoma showed lymphovascular invasion. We found statistically significant ($p = 0.000$) correlation between histologic grading and lymphovascular invasion which supports previous study of Rakha et al. [20].

There was 32% (16 cases) of tumours in triple-negative type in our study. Kim et al. in their study on 776 consecutive cases of breast carcinoma have found an incidence of triple

Table 4 Correlation of cyclin D1 expression to histologic grading (*n* = 44)

Histologic grading	Cyclin D1 expression			*p* value
	Strong positive (*n* = 11)	Intermediate positive (*n* = 15)	Negative (*n* = 18)	
Grade I	3 (100%)	0	0	0.000
Grade II	6 (24%)	7 (28%)	12 (48%)	
Grade III	2 (12.5%)	8 (50%)	6 (37.5%)	

Table 5 Correlation of cyclin D1 expression to molecular subtypes

Molecular subtypes	Cyclin D1 expression			*p* value
	Strong positive ($n = 14$)	Intermediate positive ($n = 16$)	Negative ($n = 20$)	
Luminal A	5 (83.3%)	1 (16.7%)	0	0.000
Luminal B	6 (40%)	7 (46.7%)	2 (13.3%)	
HER2	1 (7.7%)	6 (46.15%)	6 (46.15%)	
Triple negative	2 (12.5%)	2 (12.5%)	12 (75%)	

negative phenotype to be 30% [21] which is in near concordance with the present study.

ER, PgR and HER2 expressions were positive in 58%, 24% and 48% of the cases, respectively. Mohammadizadeh et al. also found 54% of ER-positive tumours in their study [22].

Our study demonstrated cyclin D1 expression in 60% cases. Previous studies reported cyclin D1 expression in up to 80% of breast carcinoma with an average of 50% [23, 24].

There was statistically significant ($p = 0.000$) correlation between cyclin D1 expression and histologic grade. Study by Jaesik Chung, et al. also reported cyclin D1 overexpression in tumours of lower histological grade [25]. These relationships indicate that cyclin D1 expression is associated with less aggressive tumour characteristics. Nehad MR et al. also showed significant correlation between grade and cyclin D1 in their study [26].

Cyclin D1 showed statistically significant ($p = 0.000$) correlation with molecular subtypes. Which was consistent with the previous study of Guo Liying et al. [27]. Study by Jaesik Chung et al. also found significant overexpression of cyclin D1 in non-triple negative subtype [25]. So, according to these study, cyclin D1 expression is associated with non-aggressive breast carcinoma. Cyclin D1 showed statistically significant ($p = 0.000$) correlation with molecular subtypes and majority of luminal A subtype showed cyclin D1 strong positive expression. Our study is also consistent with recent study of Huang et al. who found that positive expression of cyclin D1 was correlated with lower TNM stage and fewer metastatic lymph nodes, and it was more common in ER-positive breast cancer than in the basal-like subtype [28].

We found a statistically significant relationship between cyclin D1 expression and ER ($p = 0.000$) as well as between cyclin D1 expression and PgR ($p = 0.010$). Lee et al. found positive relationship between hormone receptor status and cyclin D1 overexpression in breast carcinoma [29]. A study by JS Reis-Filho et al. found a strong correlation between cyclin D1 expression with expression of oestrogen receptor and progesterone receptor and an inverse correlation with the expression of basal markers including EGFR, cytokeratin 14, cytokeratin 5/6 and cytokeratin 17. They also reported tumours with high levels of cyclin D1 expression less frequently showed p53 immunohistochemical expression and lower proliferation rates in comparison to cyclin D1 low and moderate tumours [15]. There was no significant correlation ($p = 0.127$) between cyclin D1 expression and HER2 status.

Umekita et al. reported cyclin D1 overexpression as a poor indicator in breast cancer patient [30]. In contrast, we found cyclin D1 expression in low grade, well-differentiated breast tumours. Stendahl et al. reported that high levels of cyclin D1 were associated with an overall better prognosis than moderate or low cyclin D1 levels in untreated patients [31].

Thus, our study revealed cyclin D1 as a favourable prognostic marker in breast carcinoma and expression of cyclin D1 may be used in routine diagnostic evaluation of breast cancer.

Table 6 Correlation of cyclin D1 expression to ER, PgR and HER2 status

IHC staining	Cyclin D1 expression			*p* value
	Strong positive ($n = 14$)	Intermediate positive ($n = 16$)	Negative ($n = 20$)	
ER+	11 (52.4%)	8 (38.1%)	2 (9.5%)	0.000
ER−	3 (10.3%)	8 (27.6%)	18 (62.1%)	
PR+	7 (58.4%)	4 (33.3%)	1 (8.3%)	0.010
PR−	7 (18.4%)	12 (31.6%)	19 (50%)	
HER2+	5 (20.8%)	11 (45.8%)	8 (33.4%)	0.127
HER2−	9 (34.6%)	5 (19.2%)	12 (46.2%)	

Conclusion

Our study deals with the spectrum of cyclin D1 expression in breast carcinoma. We analysed cyclin D1 expression in different molecular subtypes and also in relation to other clinicopathological parameters. Our study revealed cyclin D1 expression was associated with better tumour characteristics and significant cyclin D1 expression occurred in low grade, well-differentiated breast cancer. These observations emphasised the importance of routine evaluation of cyclin D1 expression in breast carcinoma along with other traditional prognostic parameters.

Study Limitations and Future Scope

Survival analysis and follow-up study could not be done in the short study period. Therefore, larger population-based study with long follow-up period is required to delineate the impact of cyclin D1 status in long-term survival and outcome in breast carcinoma. Application of gene amplification techniques such as fluorescence in situ hybridization (FISH) and reverse transcription polymerase chain reaction (RT-PCR) is recommended to evaluate the prevalence and role of cyclin D1 amplification in breast carcinoma in Indian population.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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