

Breast Cancer

Pathological Complete Response in Locally Advanced Breast Cancer after Neoadjuvant Chemotherapy: Survival Outcome and Its Relevance as a Surrogate End Point

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Abstract



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Keywords

- ▶ locally advanced breast cancer
- ▶ neoadjuvant chemotherapy
- ▶ pathological complete response
- ▶ surrogate end point

Background Pathological complete response (pCR) to neoadjuvant chemotherapy has emerged as a reliable surrogate marker for improved survival in breast cancer (BC), but its role as a surrogate end point is still controversial.

Aims and Objectives The aim of the study is to investigate the clinical course of BC patients with pCR and to evaluate the relevance of pCR as a surrogate end point for survival.

Materials and Methods This was a single-institution retrospective analysis done at Amrita Institute of Medical Sciences. Records of BC patients from 2004 to 2014 were analyzed. Disease-free survival (DFS) and overall survival (OS) were compared using the Kaplan–Meier method and log-rank test, respectively. pCR and survival association were evaluated using regression analysis (R^2).

Results Of 224 patients included in the study pCR rate was 15.2%. The median duration of follow-up was 61 months (range: 3–151 months). DFS (73.4 vs. 46.1%, $p = 0.032$) and OS (82.5 vs. 56.4%, $p = 0.022$) of pCR cohort was significantly higher than non-pCR cohort. Recurrence rate was significantly lower in the pCR cohort at: All distant sites ($p = 0.013$), visceral sites ($p = 0.007$), both bone and visceral sites ($p = 0.007$), and nodal sites ($p = 0.007$). There was no difference in the bone-only recurrence ($p = 0.315$). Death rate was significantly lower in pCR cohort ($p = 0.007$). The R^2 value for pCR as a surrogate for DFS and OS was 0.006 and 0.004, respectively.

Conclusion pCR is a favorable prognostic factor associated with improved survival. However, there is no association between pCR and survival.

Introduction

Neoadjuvant chemotherapy (NAC) is considered as the standard of care in the management of locally advanced breast cancer (LABC).¹ Pathological complete response (pCR) to NAC

has emerged as a reliable surrogate marker for improved overall and disease-free survival (DFS) following BC diagnosis.^{2–7} pCR is seen in ~15 to 40% of BC patients receiving NAC.⁸ We aimed to investigate the clinical course of BC patients at our institution whose index tumor has exhibited

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pCR after NAC. We also aimed to evaluate the relevance of pCR as a surrogate end point for survival.

Materials and Methods

This is a single-institution, retrospective review of patients with LABC who underwent NAC followed by definitive surgery during the years 2004 to 2014 in the department of breast and gynecology oncology. The study was conducted after obtaining approval from the institutional review board.

pCR was defined as: No evidence of residual invasive malignancy in the breast or axilla; patients with only residual ductal carcinoma in situ following NAC were included in the pCR cohort.

All patients with histology proven nonmetastatic BC and information on the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) status undergoing NAC were included in the study. All details of the initial staging, histology, type of surgery, and details of chemotherapy were collected.

The end points of the study were DFS and overall survival (OS).

Statistical Analysis

The descriptive statistics of treatment received, recurrence, morbidity, and mortality as of June 2017 are reported. The Kaplan–Meier method was used to calculate the survival rate and plot the survival curves. Differences in survival curves were examined using log-rank test. To evaluate the association between the pCR and the OS, regression analysis was performed. All analysis was performed using IBM SPSS for Windows (SPSS Inc, Chicago, Illinois, United States), version 20, and a p -value < 0.05 was considered to indicate statistical significance.

Results

Patient Characteristics

A total of 4219 new BC cases were seen in the hospital during this time period (2004–2014). Excluding patients of early and metastatic BC, those who came only for a second opinion or did not complete treatment at institution, those with incomplete treatment details available, and those who had concurrent chemoradiotherapy (RT) (as a part of another study), a total 224 patients met the inclusion criteria and hence were included in the analysis.

The mean age of diagnosis was 48.6 years (range: 25–81 years). Out of 224 patients, pCR was seen in 34 (15.2% of NAC recipients) patients and non-pCR was seen in 190 (84.8% of NAC recipients).

–Table 1 summarizes the comparison of patient-, tumor-, and treatment-specific characteristics between the pCR and non-pCR cohorts. Mean tumor size in both the cohorts (pCR 5.9 cm and non-pCR 6.2 cm; $p = 0.601$) was comparable.

Triple-negative BC (TNBC) exhibited significantly higher pCR rate (pCR 64.7% and non-pCR 41.1%; $p = 0.014$). However, hormone receptor-positive (HR+) BC exhibited significantly

lower pCR rate (pCR 8.8% and non-pCR 31.1%; $p = 0.006$). There was no difference in the pCR rate of HER2-enriched BC (pCR 26.5% and non-pCR 27.8%; $p = 1.000$).

Outcome

The median duration of follow-up was 61 months (range: 3–151 months). Twenty-six patients (3 in pCR and 23 in non-pCR cohort) had follow-up of < 12 months and without any event (these patients could not be contacted even after multiple attempts), hence excluded from the survival analysis. The DFS (73.4 vs. 46.1%, log rank $p = 0.032$) and OS (82.5 vs. 56.4%, log rank $p = 0.022$) of patients with pCR was significantly higher than non-pCR patients (–Fig. 1A and B). The DFS of pCR patients at 5- and 10-year was 79.6 and 73.4%, whereas of non-pCR patient was 57 and 46.1%, respectively. The OS of pCR patients at 5- and 10-year was 89.4% and 82.5%, whereas OS of non-pCR patient was 70.3 and 56.4%, respectively.

A total of 80/198 (40.4%) patients recurred during the study period. Significantly lower number of patients recurred in the pCR cohort (21.9% in pCR and 44% in non-pCR cohort; $p = 0.013$). Recurrence at distant site was significantly lower in the pCR cohort (18.6% in pCR and 39.8% in non-pCR cohort; $p = 0.013$). Bone only as a site of distant recurrence was not different in the two cohorts ($p = 0.315$), but distant recurrence at visceral sites (12.5% in pCR and 36.8% in non-pCR cohort), both bone and visceral sites (nil in pCR and 10.2% in non-pCR cohort), and nodal site (nil in pCR and 3.6% in non-pCR cohort) was significantly lower in pCR cohort (–Table 2).

A total of 62/198 (31.3%) patients died during the study period. BC-specific deaths were significantly lower in pCR cohort (12.5% in pCR and 33.1% in non-pCR cohort; $p = 0.007$). Death due to Adriamycin-induced toxicity was seen in 4/198 (2%) of patients: 1 in pCR cohort and 3 in non-pCR cohort. Three (1.8%) patients died due to other causes in non-pCR cohort (–Table 2).

Linear Regression between Pathological Complete Response and Outcomes (Disease-Free Survival and Overall Survival)

To evaluate the surrogacy of pCR, the regression analysis was applied. The R^2 value for pCR as a surrogate for DFS was 0.006 ($p = 0.294$) and OS was 0.004 ($p = 0.407$) suggestive of minimal association between pCR and DFS and OS.

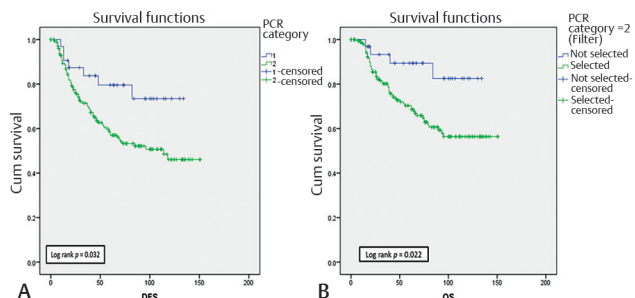


Fig. 1 Survival analysis in pathological complete response and nonpathological complete response cohort: (A) disease-free survival (DFS) (B) overall survival (OS).

Table 1 Patient-, tumor-, and treatment-specific characteristics in pathological complete response and nonpathological complete response cohorts

Variables	pCR (n = 34), n (%)	Non-pCR (n = 190), n (%)	p-Value
Age (y)			
Median (range)	46 (26–81)	48.5 (25–81)	0.602
Menopausal status			
Premenopausal	19/34 (55.9)	104/190 (54.7)	1.000
Postmenopausal	15/34 (44.1)	86/190 (45.3)	
T size (cm)			
Mean (range)	5.9 (3–15)	6.2 (2–15)	0.601
Intrinsic subtype			0.012
Luminal	3/34 (8.8)	59/190 (31.1)	0.006
HER2 enriched	9/34 (26.5)	53/190 (27.8)	1.000
Triple negative	22/34 (64.7)	78/190 (41.1)	0.014
Histopathological subtype			
Ductal	32/34 (94.2)	176/190 (92.6)	0.939
Lobular	1/34 (2.9)	8/190 (4.2)	
Others	1/34 (2.9)	6/190 (3.2)	
Type of NAC			
Only anthracycline	9/34 (26.5)	54/190 (28.4)	0.877
Anthracycline + taxane	23/34 (67.6)	121/190 (63.7)	
Others (CMF, only taxane)	2/34 (5.9)	15/190 (7.9)	
Number of NAC cycles before surgery			
<50% cycles	4/34 (11.8)	21/190 (11.1)	0.893
>50% cycles	29/34 (85.3)	160/190 (84.2)	
Complete (6/8)	1/34 (2.9)	9/190 (4.7)	
Type of surgery			
Mastectomy	31/34 (91.1)	170/190 (89.5)	0.526
Breast conservation surgery	3/34 (8.8)	20/190 (10.5)	
DCIS			
Absent	29/34 (85.3)	62/190 (32.6)	0.011
Present	4/34 (11.8)	127/190 (66.8)	
Missing	1/34 (2.9)	1/190 (0.52)	

Abbreviations: CMF, cyclophosphamide, methotrexate, 5-fluorouracil regimen; DCIS, ductal carcinoma in situ; NAC, neoadjuvant chemotherapy; pCR, pathological complete response.

Discussion

It has been clearly established that a pCR at the time of surgery defined as ypT0 ypN0 or ypT0/is ypN0 is associated with a favorable outcome in all patients who achieve it.^{9,10} pCR is seen in ~15 to 40% of BC patients receiving NAC.⁸ Using the recommended definition of pCR (ypT0/is ypN0), the pCR rate in the current study was 15.2% and achievement of pCR at the time of surgery was associated with the survival benefit.

The recurrence rate of 29% in pCR patients is almost identical to the rate of 13 to 25% reported in the literature.^{5,11–14} The highest recurrence rate was observed in patients presented with advanced stage, 71.4% of recurred patients had cT3 and cT4, and all of them had lymph node metastasis. Dawood

et al demonstrated that higher clinical stage was associated with worse outcomes even after achievement of pCR.¹⁵

The highest pCR rate in TNBC and lowest in HR+ tumors in the current study is in agreement with that reported in the literature.^{16,17} Our study did not show an equivalent pCR rate in HER2 enriched tumors owing to our inability to use anti-HER2 therapy due to cost concerns. von Minckwitz et al demonstrated that pCR appeared to be a reasonable surrogate end point for patients with luminal B/HER2-, ER/ PR/HER2+, and for TNBC, but not for those with luminal B/ HER2+ or luminal A tumors.¹⁶ However, in the current study, we found that out of 7 recurred patients: 4 had TNBC, 2 had ER/PR negative/HER2+ tumor, and 1 had ER/PR/HER2+. Thus, even for the subset of patients for whom pCR is a good prognosticator, its accuracy is not 100%.

Table 2 Outcome in pathological complete response and nonpathological complete response cohorts

Variables	pCR (n = 32), n (%)	Non-pCR (n = 166), n (%)	p-Value
Overall recurrence	7 (21.9)	73 (44)	0.013
Local recurrence	1 (3.1)	7 (4.2)	
Distant recurrence	6 (18.6)	66 (39.8)	
Site of distant recurrence			
Bone only	2 (6.3)	5(3)	0.315
Visceral	4 (12.5)	61 (36.8)	0.007
1 site	3 (9.4)	28 (16.9)	
>1 site	1 (3.1)	10(6)	
Bone + visceral	–	17 (10.2)	
Nodal metastasis	–	6 (3.6)	
Death	4 (12.5)	58 (34.9)	0.007
Breast cancer specific death	4 (12.5)	55 (33.1)	
Death due to other cause	–	3 (1.8)	

Abbreviation: pCR, pathological complete response.

We found that six out of seven patients recurred within 48 months (<5 years) of diagnosis, out of which four recurred within 18 months. There was equivalent median survival of relapsed patients in pCR cohort (40 months) and non-pCR cohort (37 months). Similar observation was revealed by Fayanju et al in their study; they suggested that such a short interval between diagnosis and recurrence reflects failure of NAC in these patients despite achieving pCR.¹⁸

Cortazar et al⁹ and Berruti et al¹⁹ demonstrated minimal association between the effect of the treatment on pCR and the effect on event-free survival (EFS) and OS. They found that the R^2 values for pCR as a surrogate for EFS and OS were extremely low. NeoALTTO trial demonstrated the largest absolute improvement in pCR rate, but it failed to demonstrate the impact on survival.²⁰ Consistent with the previously reported results, we found that the R^2 values for pCR as a surrogate for EFS and OS were extremely low at 0.006 and 0.004, respectively.

Rose et al proposed three limitations of pCR to be used as a surrogate end point for improved survival.²¹ First, cancer is a micrometastatic systemic therapy, whereas pCR is a measure of effectiveness of the treatment only on the primary tumor. Short interval of recurrence and similar median survival of recurred patients in pCR and non-pCR cohort in the current study reflect the possibility of micrometastatic disease that continued to progress regardless of pCR. Second, effective treatment may not necessarily lead to increased pCR rate. In the current study, the treatment-specific characteristics were similar between the pCR and non-pCR cohort. Majority of the patients in both the cohorts received the standard anthracycline- and taxane-based regimen, with no difference in the timing of NAC and surgery. Third, additional pCRs achieved from an investigational therapy may simply occur in patients who would have been cured by standard treatment alone. In the current study, we did not find any difference in pCR rate of HER-2-enriched tumors because of the nonavailability of the standard anti-HER-2 treatment.

Our study has the limitations of being a single-institution retrospective analysis with small sample size, and the nonavailability of the grade of tumor, which is one of the most important prognosticators in BC. Despite these limitations, to the best of our knowledge, this is the first Indian series where detailed analysis of the outcome of patients with pCR is done. Furthermore, our study is one of the few individual series where the issue of considering the pCR as a surrogate end point in clinical trials has been addressed. Our study might be helpful in adding evidence to the ongoing debate of use of pCR as an end point in clinical trials.

Conclusion

Thus, pCR is a favorable prognostic factor for individual patients undergoing treatment. pCR could be used as a marker that helps clinician in tailoring and reducing the intensity of subsequent treatment in patients with pCR as compared with non-pCR. However, its use as a surrogate end point in clinical trials is still a debatable issue. The current evidence, including the results of our study, does not demonstrate the strong association between the pCR and survival. Usage of pCR rate as an end point in clinical trials requires the establishment of strong association ($R^2 > 0.75$) in prospective trial.

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Nil.

Conflicts of Interest

There are no conflicts of interest.

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