RESEARCH ARTICLE

Is complete pathological response truly a complete response in breast cancer?

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Abstract

Objective: To check if complete pathological response in breast cancer is a good prognostic factor.

Method: The retrospective study was conducted at the Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, and comprised data from January 2012 to December 2015 of all patients who received neo-adjuvant chemotherapy and had no distant metastasis at diagnosis. Mastectomy patients were excluded. Complete pathological response was defined as no detectable tumour cell in breast and axilla on pathological examination of the resected specimen. Tumour characteristics and 5-year disease free survival and overall survival were recorded. Data was analysed using SPSS 20.

Results: Of the 353 patients whose data was evaluated, 91(25.8%) had complete pathological response. Mean age at diagnosis was 43±10 years. Among them, 62(68%) patients had grade III tumour, 39(42.9%) were negative for oestrogen receptor, 58(63.7%) were negative for progesterone receptor, 25(27.5%) were positive for human epidermal growth factor receptor 2, and 26(28.6%) patients were triple negative. Overall, 28((30.7%) patients had recurrence; 20(71.4%) had distant metastasis, 6(21.4%) had local recurrence, and 2(7.14%) had contralateral cancer. The 5-year disease-free survival and overall survival rates (Kaplan-Meier Survial curve) were 70% (28 patients-recurrence) and 87% (15 patients-deaths), respectively.

Conclusion: Despite complete disappearance of tumour, a significant number of patients developed recurrences.

Keywords: Complete pathological response, Neo-adjuvant chemotherapy, Survival, Metastasis. (JPMA 73: 280; 2023)

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Introduction

Breast cancer is the second most common cancer worldwide and the first most common among women.[1] The incidence is estimated to be 1 in 9 women[2] in the local population. Mortality from breast cancer has declined in the West due to screening programmes.[3]

Breast cancer is increasingly treated with neo-adjuvant chemotherapy (NACT) to reduce the disease burden and to directly evaluate treatment response in vivo, which can provide additional prognostic information.[4]

With the advent of NACT, more patients are managed with breast conservation surgeries (BCS) due to better resectability, with similar survivals as in cases of mastectomy.[5] Due to variability in tumour behaviour, the response to chemotherapy is also variable. Patients with ypT0N0(complete pathological response), meaning no detectable tumour by pathological examination of the resected tumour, are the ones who achieved complete pathological response (CPR). As pathologically, chemotherapy response is 100%, it is agreed that these patients are expected to have the best outcomes.

Many studies have proved better long-term outcomes, including disease-free survival (DFS) and overall survival (OS).[6]

However, cases are seen in regular clinical practice that attain CPR, but then develop local or distant recurrence and die of it. The current study was planned to check if CPR in breast cancer is a good prognostic factor.

Materials and Methods

The retrospective study was conducted at the Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, and comprised data from January 2012 to December 2015 of patients who underwent BCS for invasive breast cancer after NACT. Patients with upfront surgery, mastectomy or distant metastases at presentation were excluded. BCS was defined as removal of only part of the breast tissue where the tumour was located. Usually 20% or less of tissue is removed, which is contrary to mastectomy in which the entire breast tissue, including nipple and areola, is removed.

Lymph node (LN) staging was done before starting chemotherapy by either fine needle aspiration (FNA) of axilla in radiologically enlarged nodes or by staging sentinel lymph node biopsy (SLNB) in radiologically normal-looking nodes under general anaesthesia (GA). All LNs were negative at final surgery post-chemotherapy

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(pN0).

After exemption from the institutional ethics review board, data was collected through the Human Information System (HIS) electronic database of the hospital. Variables recorded were age, tumour biology, clinical staging and survival outcomes.

Every patient had detailed history and examination in the walk-in clinic and was referred to One-Stop Breast Clinic (OSBC) for detailed assessment and investigation. Investigations included baseline blood tests, mammogram, ultrasound breast, true-cut biopsy of breast masses and FNA of axilla. Metastatic workup included ultrasound abdomen and pelvis, chest radiograph (CXR) or computed tomography (CT) scan, where indicated, and bone scan. Every case was discussed in multi-disciplinary team (MDT) meetings. As the data is collected in real time and stored, it allows for accurate retrospective review.

Data was analysed using SPSS 20. Data was presented as median with range for skewed quantitative variables. For categorical variables, frequencies and percentages were reported. Correlation of different biological and clinical characteristics with recurrence was observed. Survival was calculated using Kaplan Meier survival analysis. P<0.05 was considered statistically significant.

Results

Of the 353 patients whose data was evaluated, 91(25.8%) had CPR. Mean age at diagnosis was 43±10 years. Among them, 62(68%) patients had grade III tumour, 39(42.9%) were negative for oestrogen receptor (ER), 58(63.7%) were negative for progesterone receptor (PR), 25(27.5%) were positive for human epidermal growth factor receptor 2 (HER2-Neu), and 26(28.6%) patients were triple negative. All patients received doxorubicine-taxol-based chemotherapy except 17(18.7%) who received HER-2 Neu-

Table-1: Patient characteristics (n=91).

Mean age (years)	42.6±9.65)	
Mean size (mm)	33±7.94	
T- size on presentation	84 (92%) were T2	6% were T1,2% were T3
Tumour type	2 (2.2%) ILC	Rest were IDC
Grade	62(68%) Grade III	Grade II 29 (32%)
ER (Oestrogen Receptor)	ER Positive 52 (57.1%)	ER Negative 39 (42.9%)
PR (Progesterone Receptor)	PR Positive 33 (36.3%)	PR Negative 58 (63.7%)
HER-2 Neu	HER-2 Neu Positive 25 (27.5%)	HER-2 Neu Negative 63.7%) Equivocal 8 (8.8%)
Triple negative	26 (28.6%)	
LN positivity at presentation	64 (70.3%)	50 (55%) (FNA),14 (15%) (SLNB)
Recurrences	28 (30.7%)	20 (22%) were Distant
Deaths at 5 years	15 (16%)	

ILC: Invasive lobular carcinoma, IDC: Invasive ductal carcinoma, HER-2: Human epidermal growth factor receptor 2, LN: Lymph node, FNA: Fine needle aspiration. SLNB: Sentinel lymph node biopsy.

Table-2: Disease recurrence.

Metastasis type	n (%)
Contralateral	2 (2.2)
Local	6 (5.5)
Distant + Local	2 (2.2)
Distant	18 (19.8)
Total	28 (30.7)

Table-3: Recurrence correlation and intrinsic subtypes.

Recurrence (30.7%)	n (%)	*p*-value
Grade III (68%)	16 (17.6)	0.393
II (32%)	10 (11)	
ER (Oestrogen Receptor)		
Positive (57%)	16 (18)	0.592
Negative (43%)	10 (11)	
PR (Progesterone receptor)		
Positive (36%)	9 (10)	0.043
Negative (63.7%)	17 (18.7)	
HER-2 Neu		
Positive (27.5%)	14 (15.4)	0.331
Negative (63.7%)	10 (11)	
Triple Negative (28.6%)	5 (5.5)	0.212
Non-Triple Negative (71.4%)	21 (23)	
LN at presentation		
Positive (70.3%)	22 (24.2)	0.078
Negative (29.7%)	4 (4.4)	

HER-2: Human epidermal growth factor receptor 2, LN: Lymph node.

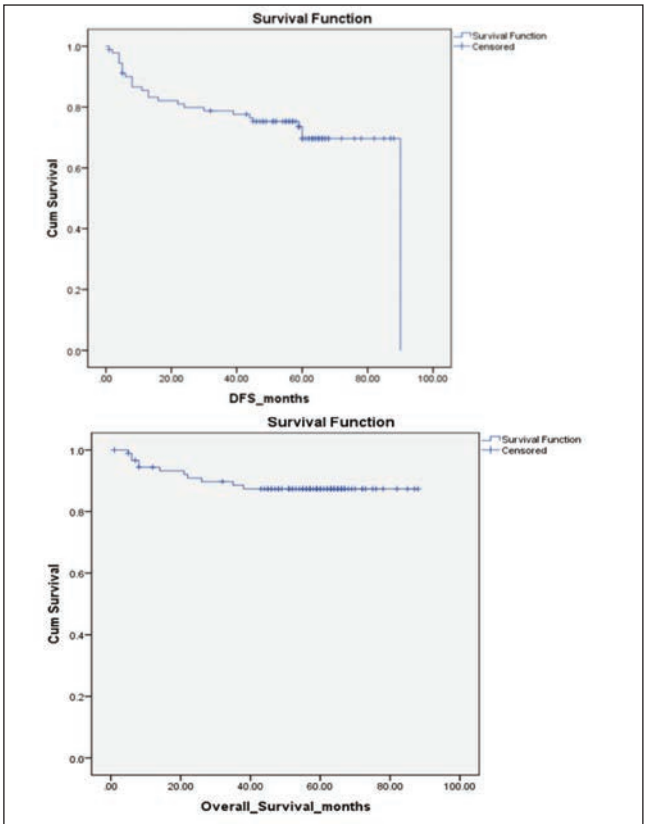

Figure: Disease-free survival (DFS) and Overall survival (OS) curves.

targeted therapy. Detailed patient data was noted and correlated (Table 1) Overall, 28((30.7%) patients had recurrence; 20(71.4%) had distant metastasis, 6(21.4%) had local recurrence, and 2(7.14%) had contralateral cancer (Table 2).

When different factors were compared with recurrence, PR-positive tumours showed lesser recurrence (p=0.043) (Table 3).

The 5-year DFS and OS rates were 70% (28pattients had recurrence) and 87% (15 patients died), respectively (Figure).

Discussion

Chemotherapy has brought a ground-breaking change in the management of breast cancer. It has not only reduced mortality but has also helped in evolving surgical approach from radical to less invasive techinues.[7,8] Thus, indirectly it has improved quality of life. The chemotherapy decision of being in adjuvant or neo-adjuvant setting depends on tumour stage and histological type. One obvious advantage of neo-adjuvant chemotherapy is its measurable impact in vivo, which obviously cannot be determined once the tumour is out of the body as is the case in adjuvant setting. Because of the heterogeneity of breast cancer, the tumour response is variable and is difficult to be predicted beforehand. Although many studies have shown some known tumour characteristics that can be helpful in predicting response, the problem with breast cancer is that most of its genome is not characterised or known that renders every breast cancer to behave differently despite having same characteristics in term of histology.

The current study highlighted the fact that complete response, contrary to what the name indicates, is not always a complete response because a significant proportion in the sample was not cured (30.7%).

Many researchers have worked on the factors that may have an association with the chemo response. Patients with ER-negative and PR-negative and HER-2-Neu-amplified breast cancer phenotypes are more likely to achieve CPR through neo-adjuvant therapy.[7]

However, among those with residual disease, the survival was the worst for triple negative and HER-2-Neu-enriched type compared to survival in hormone receptor-positive tumours.[8,9] In the current study, only grade III tumours (68%) and ER-negative tumours (64%) were common. However, the study did not compare tumour biology markers with the group that did not achieve CPR, which is a limitation.

Although many studies are done to see if chemo response can be predicted beforehand by studying tumour biology, there are no defined tumour characteristics that would respond more to NACT. In future, rather than tumour biology, the focus should be on molecular level or genetics in connection with chemo response.

The prediction of chemo response cannot be correctly made, but many researchers believe better chemo response leads to better survival, especially in those who achieved a complete response and there in no residue in surgical specimen from both breast and axilla.[10,11]

Published studies have reported better survival in CPR group compared to those who did not achieve CPR.[12-14]

In the current study, the DFS was 70% while OS was 87%. It was lesser than earlier studies (DFS 90%, OS 84%)[13] but one reason was that T1 disease at presentation was only 5%, while the rest were T2 (>2cm) at presentation; also 71% were LN-positive at presentation.

However, one study found that locally advanced breast cancer (LABC) (tumour [T]2, T3, node [N]0 or N1, metastasis [M]0, which was majority of the current population) showed no difference in DFS (p=0.67) or OS (p=0.41) between patients achieving a CPR and those with residual disease.[15] One meta-analysis concluded not to use CPR as a surrogate endpoint for DFS and OS in patients with breast cancer.[16]

Many studies have worked on finding the factors that may predict recurrence. In one study, achieving CPR in triple negative breast cancer was associated with better DFS (p<0.001) compared to receptor-positive types (p=0.39).[10] Others found HER-2 Neu status and axillary metastases as independent predictors of recurrence in patients with CPR.[17,18] A meta-analysis studied 27,895 patients. Those with a CPR after NACT had significantly better DFS, particularly for triple negative and HER-2 Neu disease.[19] In the current study, only PR-positive tumours that achieved CPR showed lesser recurrences (p=0.043), while the rest of tumour characteristics did not do well in recurrence terms. In one study, no factors were linked with recurrence, but it found Afro-American race as the only independent predictor of recurrence post-CPR.[20]

The pattern of recurrence in the current study was somewhat interesting, as most of recurrences were distant (20% distant vs 6% local), while all were metastasis-free at presentation. Distant metastasis was found at one or multiple sites in bone, liver, lungs, brain and mediastinal nodes. The reason might be that tumour biology of distant metastasis gets changed, so same chemotherapy was not as effective as it was on local/primary site. Because local disease recurrence was less common, the future might be total omission of surgery in patients with complete

response.

One limitation of the current study was that it did not compare tumour biology markers with those who did not achieve CPR. Another possible limitation is that out of 25 HER-2-Neu-positive patients, only 17 received Herceptin. Equivocal (2+) status was found in 8 patients in whom further fluorescence in situ hybridization (FISH) testing was missed. It means not all HER-2-Neu-positive patients received Herceptin, which could have led to recurrence, but the recurrence score for positive and negative patients was not statistically significant.

One thing that could not be explained is the reason why almost one-third of the patients in the study had recurrence even after successful eradication of all tumour cells. A lot of work on molecular and genetic levels needs to be done to see this kind of tumour behaviour and to find the undetected tumour cells that caused the recurrence after successful treatment completion.

Conclusion

Despite complete disappearance of tumour, a significant number of patients developed recurrences. The focus should be on such patients who were assured of having the best outcomes. So far, all known tumour biological factors have not shown to be either a definitive predictor of the response or of the recurrence.

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