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Impact of Pathological Complete Response in Breast Cancer Following Neoadjuvant Therapy on Patient's Outcome

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ABSTRACT

Background: Patients who achieve a pathological complete response (pCR) after neoadjuvant therapy have better outcomes than patients with residual disease. Despite the excellent prognosis associated with achieving a pCR, recurrence still occurs. The study was conducted to evaluate factors associated with tumor recurrence and survival among patients achieving pCR after neoadjuvant therapy.

Methods: We evaluated the medical records of patients with breast cancer who received neoadjuvant therapy and achieved pCR in our academic institute. The survival curve was estimated with the Kaplan-Meier method in patients who developed recurrence.

Results: In our retrospective study 2,360 received neoadjuvant therapy out of which 315 (13.3%) who achieved pCR were included in this study. The mean age was 45.85 (range 21-92 years) and the mean duration of follow-up was 41.2 months. The clinical tumor stage T1-T2 represented 55%, T3-T4 was 44.1%, and node-positive was 54%. The primary endpoint was the correlation between pCR achieved after neoadjuvant therapy and disease-free survival or overall survival. Predictors of pCR were clinical T-stage which received appropriate chemotherapy.

We observed that patients who had an increased risk of recurrence after achieving pCR were those with clinical stage III-IV, patients with mastectomy, and those with triple-negative tumor subtype.

Conclusion: Achieving pCR after neoadjuvant therapy is distinctly related to the improvement of survival; however, patients who achieved a pCR, women younger than 50 years of age and those with stage III/IV disease have a higher risk of developing distant metastasis.

INTRODUCTION

Invasive breast cancers are one of the most common types of malignancies in women. It is prevalent in every region of the world in women of any age post-puberty. Of women who develop breast cancer, approximately half of them have no recognizable and evident risk factor other than gender and age.[1] According to the World Health Organization, about 2.3 million women were diagnosed with breast cancer and 685,000 deaths worldwide in 2020. [2]Pakistan has the highest incidence of breast cancer among Asian countries: one in nine women is at risk of being diagnosed with breast cancer during their lifetime. The International Agency for Research in Cancer reported 34,066 new cases of breast cancer in Pakistani women in 2018 as reported by Punjab Registry. [3] Escalation in survival emerged with awareness along with advanced approaches for rapid detection and the treatment to eliminate the invasive disease. While the historic paradigm for treatment has been surgical intervention followed by systemic therapy, nowadays chemotherapy is prescribed in the neoadjuvant setting

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before definitive surgery. In the former days, neoadjuvant chemotherapy was administered to patients with locally advanced breast cancer. In the present day, the implementation of this approach has been extended to earlier-stage breast cancers, in order to downstage the tumor and permit breast-conserving surgery for patients who may have otherwise required mastectomy.[4]

It has been observed that the response of tumors to neoadjuvant chemotherapy may be prognostic for outcomes. Patients who achieve a pathological complete response following neoadjuvant chemotherapy may have a preferable and better overall survival in comparison to patients having only a partial pathological response.[5] Pathological complete response is the non-existence of invasive disease at surgical resection, which is a crucial prognostic factor for improving the disease-free survival rate and overall survival rate.

Although most of the ongoing research has established that a pathological complete response is associated with improved overall survival, there is also a small fraction of patients who achieve a pathological complete response that will develop disease recurrence and distant disease in a short interval of time.[6] There are various factors possibly related to distant metastasis after pathological complete response including clinical stage IIIB or higher at the time of initial diagnosis and premenopausal status.[7]

In a meta-analysis published in 2020 in clinical cancer research, patients who had a pathological complete response achieved a 5-year event-free survival of 88% and a 5-year overall survival of 94% while those without a pathological complete response had a 5-year event-free survival of 67% and a 5-year overall survival of 75%. [8]

The study was conducted to evaluate factors associated with tumor recurrence and disease-free and overall survival among patients achieving pCR after neoadjuvant therapy.

METHODS

Patient selection

In this retrospective study, records of female patients aged ≥ 18 years with primary breast carcinoma who received neoadjuvant systemic therapy and achieved pathological complete response were reviewed at Liaquat National Hospital, Karachi.

Duration

In the last 10 years, data of diagnosed breast cancer patients from the year 2012 to 2022 was collected from our hospital. A total of 9,752 patients were diagnosed with breast cancer, 2,360 (24.2%) patients received neoadjuvant therapy, and out of these 315 (13.3%) patients who achieved pCR, defined as no invasive disease in the breast and no tumor in the regional nodes, were included in the analysis of this study.

Clinical Data

The data was collected after approval from the hospital authorities in keeping with ethical considerations. Patients' demographic data, clinical stage, tumor characteristics, treatment, and outcomes were retrospectively obtained from medical records and summarized using frequencies. Survival data were assembled from the combined use of the medical record, telephonic communication, and documentation on follow-up data.

Molecular subtype

The patients were classified based on immunohistochemistry (IHC). Hormone receptor-positive cases were Estrogen receptor and/or Progesterone receptor positive. Tumors with Her 2neu score of 0 or 1+ were regarded as HER2-negative, and those with a score of 3+ were regarded as HER2-positive. Tumors with a 2+ staining score on Immunohistochemistry (IHC) were tested for Fluorescence In-Situ Hybridization (FISH) test. The patients with Her 2-positive histology were given Anti-Her 2 therapy.

The patients were classified into 5 subtypes based on immunohistochemistry (IHC) according to St. Galen's Guidelines as follows: [9] Luminal A-like (ER and/or PR Positive, HER2negative, and Ki67 < 14%), Luminal B-like (ER and/or PR Positive, HER2-negative, and Ki67 > 14%), B Her (ER and/or PR Positive and Her2- Positive), Her2 Positive ((ER-negative, PR-negative, and HER2- positive) and Triple-negative (ER-negative, PR-negative, and HER2-negative).

Pathological assessment:

All patients undergoing neoadjuvant therapy were sent to the radiologist and marker clips were placed in the tumor before the start of the systemic therapy. Ultrasound of the axilla was done in all the patients and biopsy was done and marker clip was placed in patients with suspicious nodes. After Neoadjuvant therapy with the help of imaging, the surgeon localized the clips and removed the tumor area and clipped nodes. The targeted tissue removal was confirmed by imaging. The specimen was then sent to the lab, coded as post-neoadjuvant therapy. The slides were reviewed by a pathologist for reporting a pathological complete response; however, in case of uncertainty, consultation with other pathologists or discussion at intradepartmental meetings was carried out. The histopathology department of our academic

institute deals with a significant volume of breast pathologies of all nature; therefore, our pathologist has good experience in evaluating breast tissue.

Before concluding a complete pathological response, thorough sampling from the tumor bed was done. In cases where the tumor bed was not apparent then clinical and radiological information especially regarding the tumor site was taken. The radiologist helped to localize the tumor bed with the needle when needed.

Definition of Pathological complete response

A Pathological complete response (pCR) is defined as no residual invasive tumor within the breast and lymph nodes (stage ypT0 ypN0 or ypT0/Tis ypN0) after neoadjuvant chemotherapy with an improved long-term benefit concerning disease-free survival and overall survival.[10]

Disease-free survival was determined from the date of surgery to the first documented distant or local recurrence on last follow-up. Overall survival was measured from the date of surgery to the date of death or last follow-up. The loco-regional or distant recurrences were evaluated through physical examination and radiological imaging.

Neoadjuvant Regimen

Most of the patients (N=303, 96.1%) had received Anthracycline and Taxane-based chemotherapy. The remaining 12 patients received Carboplatin (N=6, 1.9%) and Cisplatin (N=6, 1.9%).

The HER2-positive group included 130 patients and of those, 106 (81.5%) patients received anti-Her2 therapy. Also, 81.1% of patients received chemotherapy in combination with Transtuzumab alone while 18.9% of the patients received chemotherapy in combination with Transtuzumab and Pertuzumab.

Statistical Analysis

For data analysis, IBM SPSS Statistics for Windows, Version 25, and Medcalc v 20 were used. Mean and standard deviation were evaluated for quantitative variables. Frequency and percentage were evaluated for qualitative variables. The chi-square test and Fisher's exact test were applied to determine the association as appropriate. Survival analysis was done using Kaplan-Meier's log-rank test. P-value ≤ 0.05 was considered significant.

RESULTS

The demographic and clinical data of the 315 patients included in the analysis are shown in Table 1. The mean age was 45.85 (range 21-92 years). The mean duration of follow-up was 41.2 months. Most of the patients were premenopausal 219 (69.5%). Clinically T1-T2 represented 55%, T3-T4 44.1%, and node-positive was 54% at clinical assessment that included physical examination and radiology. Pathologically confirmed positive nodes were seen in 175 (60%) patients. Also, 285 (90.4%) of the patients had invasive ductal carcinoma (IDC) histology. Out of 315 patients, 130 (41.2%) were triple negative and 130 (41.2%) of the patients were Her2 positive. Other baseline clinicopathological criteria are outlined in Table 1.

Data from 282 patients were gathered as we were unable to trace 33 patients' status. In the study, 38 (13.5%) of the patients developed recurrence, out of those 219 (77.6%) < 50 years. Patients with stage III-IV (84.2%) had the most recurrence. Recurrence was higher in patients with ER-negative (47.4%), PR-negative (68.4%), or Her-2 negative (31.6%) tumor subtype Table 1.

Out of 38 patients who experienced recurrence, 5 (13.1%) had local recurrence while 32 (84.21%) patients had distant recurrence (8 patients had liver metastasis, 5 patients had bone metastasis, 4 patients had metastasis in the lung, 7 patients had brain metastasis and 8 patients had distant metastasis involving multiple organs).

Among the patients with triple-negative histology (N= 130, 41.2%), 12 (9.23%) patients developed distant recurrence while 3 (2.3%) patients had local recurrence, and 19 (14.6%) of the patients expired.

Of those who had Her2 positive histology (N= 130, 41.2%), 8 (11.7%) patients had distant recurrence while 6 (8.82%) patients expired.

Out of 130 patients who were HER-2 positive, 24 patients did not receive anti-Her2 therapy. Among them, 8 (33.3%) had distant recurrence and expired while 5 (20.8%) patients had local recurrence and expired.

The percentages of recurrence were compared among the breast cancer subtype that included Luminal A, Luminal B, Luminal B Her, Her 2 positive and triple negatives. It was noted that recurrences occurred more in triple-negative (N=15, 39.4%), luminal B Her (N=8, 21.0%), and Her 2 positive (N=7, 18.4%) subtype and least in luminal A (N= 3, 7.89%) subtype.

Regarding the survival rate, the best survival pattern was for women with the luminal A subtype followed by the luminal B subtype. Her 2 and triple-negative subtypes had the worst survival rate showing a difference in survival between molecular subtypes (P= 0.018) (Table 1)

It was noted that patients with T1 disease had more triple negative (N=22, 37.9%) and her 2 positive (N= 15, 25.8%) molecular subtype.

Also, 44 patients had stage IV disease on presentation; they received neoadjuvant

Table 1. Patients' demographic and clinical data at presentation, Disease Recurrence after pCR, Survival and factors effecting it(to be continued)

Characteristics	Total patients N=315	Recurrence			Survival Status		
		Yes	No	P-value	Alive	Expired	p-value
Age Group				0.579			0.875
≤35 years	59(18.7)	8(21.1)	41(16.8)		42(17.7)	7(15.6)	
36-50 years	160(50.8)	21(55.3)	126(51.6)		122(51.5)	25(55.6)	
>50 years	96(30.5)	9(23.7)	77(31.6)		73(30.8)	13(28.9)	
Histopathological Diagnosis				0.165			0.011
Invasive Carcinoma	16(5.1)				13(5.5)	1(2.2)	
Invasive Ductal	285(90.4)	34(89.4)	221(9.5)		217(91.5)	38(84.4)	
Invasive Lobular	8(2.5)	3(7.9)	5(2)		3(1.3)	5(11.1)	
Invasive Papillary	3(1)	0(0)	2(0.8)		2(0.8)	0(0)	
Metaplastic	3(1)	0(0)	3(1.2)		2(0.8)	1(2.2)	
T Stage				0.001			0.000
T1	58(18.7)	12(31.6)	38(15.5)		36(15.1)	14(31.1)	
T2	117(37.1)	5(13.2)	101(41.4)		99(41.8)	7(15.6)	
T3	57(18.1)	7(18.4)	51(20.9)		52(21.9)	6(13.3)	
T4	82(26)	14(36.8)	54(22.1)		50(21.1)	18(40)	
Clinical N Status				0.396			0.109
N0	143(45.4)	15(39.5)	113(46.3)		109(46	19(42.2)	
N1	142(45)	17(44.7)	112(46.9)		109(45.9))	18(40)	
N2	30(9.5)	6(15.8)	19(7.8)		19(8.0)	8(17.8)	
Systemic Metastatic Status				0.000			0.000
Positive	44(14)	18(47.4)	18(7.4)		14(5.9)	22(48.9)	
Negative	271(86)	20(52.6)	226(93)		223(94)	23(51.1)	
Stage				0.000			0.000
Stage I	27(8.57)	1(2.6)	24(9.8)		22(10.1)	1(2.2)	
Stage II-A	67(21.2)	1(2.6)	61(25)		66(25.3)	2(4.4)	
Stage II-B	66(21)	4(10.5)	56(23)		56(23.6)	4(8.9)	
Stage III-A	37(11.7)	5(13.2)	34(13.9)		35(14.7)	4(8.9)	
Stage III-B	72(22.9)	9(23.7)	49(29.1)		47(19.8)	11(24.4)	
Stage III-C	2(0.6)	0(0)	2(0.8)		1(0.4)	1(2.2)	
Stage IV	44(14)	18(47.4)	18(7.4)		14(5.9)	22(18.9)	

Table 1. Patients' demographic and clinical data at presentation, Disease Recurrence after pCR, Survival and factors effecting it(continue)

Characteristics	Total patients	Recurrence			Survival Status		
	N=315	Yes	No	P-value	Alive	Expired	p-value
Initial Distant Mets Location							
(n=36)							
Bone		7(38.8)	5(27.7)	0.775	4(28.6)	8(36.3)	0.339
Liver		5(27.7)	7(38.9)		4(28.6)	7(31.8)	
Lung		6(33.3)	7(38.9)		6(42.9)	7(31.8)	
Surgery Procedure				0.020			0.000
Conservation	135(42.8)	12(31.5)	106(43.4)		106(43.9)	12(26.6)	
Mastectomy	180(57.1)	26(68.4)	138(56.5)		131(56.1)	33(73.3)	
Her2				0.378			0.138
Positive	130(41.3)	13(34.2)	105(43)		104(43.9)	14(31.1)	
Negative	185(58.7)	25(68.8)	139(57)		133(56.1)	31(68.9)	
ER				0.354			
Positive	116(36.8)	17(44.7)	90(36.9)		87(36.7)	9(20)	0.327
Negative	199(63.2)	21(55.3)	154(63.1)		150(63.3)	36(80)	
PR				0.753			
Positive	70(22.2)	8(21.1)	57(23.4)		56(23.6)	9(20)	0.596
Negative	245(77.8)	30(78.9)	187(76.6)		181(76.4)	36(80)	
Luminal				0.281			
Luminal A	10(3.17)	3(7.89)	6(2.45)		7(3)	5(11.1)	0.018
Luminal B	45(14.2)	5(13.1)	38(15.5)		44(18.6)	5(11.1)	
Her 2 positive	61(19.4)	7(18.4)	43(17.6)		51(21.5)	6(13.3)	
Luminal B Her	69(21.9)	8(21.0)	50(20.4)		57(24.1)	9(20)	
Triple negative	130(41.2)	15(39.4)	107(43.8)		78(32.9)	20(44.4)	

The Chi-square/fisher exact test was applied.
P<0.05 was considered as significant.

chemotherapy, and there was a complete disappearance of the metastatic involvement that was confirmed through radiological investigation before the surgery. Out of 44 patients, 15 (34.8%) patients developed distant recurrence, 3 (6.81%) patients had local recurrence, and 21(48.8%) patients expired.

Kaplan-Meier curve was used to analyze the survival status in patients who developed recurrence after achieving a Pathological complete response (P-value= 0.000) (Figure 1).

Table 2. N and T Cross tabulati

		T1	T2	T3	T4	Total
N	N0	36	65	21	21	143
	N1	21	49	33	39	142
	N2	2	3	3	22	30
Total		59	117	57	82	315

Table 3. T1 and Molecular subtypes

	Her 2 positives	Luminal B	Luminal A	Luminal B Her2	Triple-negative	Total
T 1	15	9	2	10	22	58

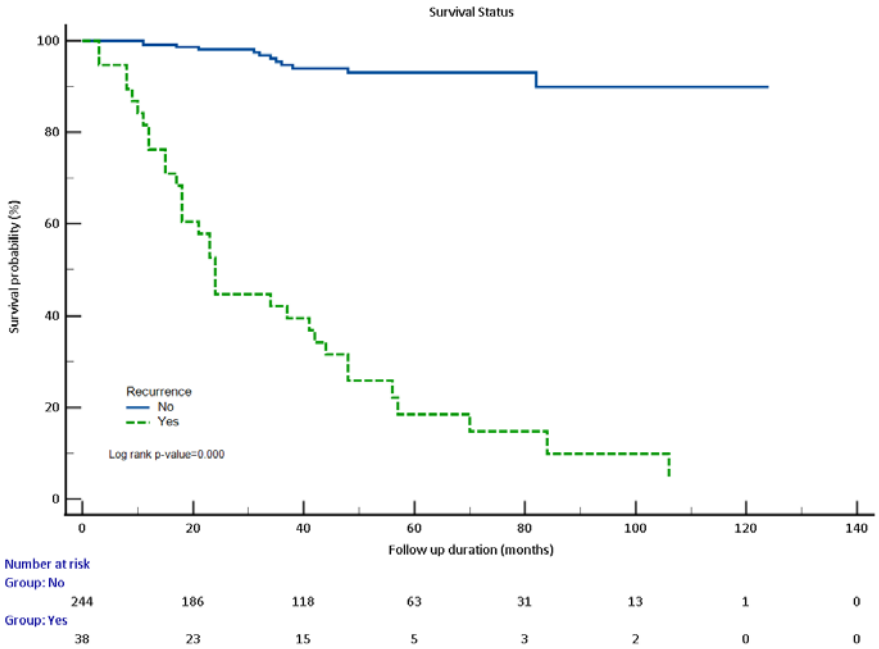

Figure 1. Survival analysis

DISCUSSION

Breast cancer is a globally occurring malignancy and constitutes a major burden on public health. The disease occurs worldwide and accounts for one-fourth of all cancer cases in women. [11] This disease has a varying degree of biological subtypes with distinct prognostic significance. Formerly, neoadjuvant chemotherapy was reserved for locally advanced disease, but it is now frequently given for various purposes including the conversion of locally advanced or unresectable disease or a surgically resectable disease, downstaging the disease that allows breast conservation, and delivering prognostic details that make changes in therapy possible in case of unresponsive tumor.[12]

Following neoadjuvant therapy, pathological evaluation of the residual tumor provides preliminary prognostic details. Patients who achieve a Pathological complete response have a desirable disease-free and overall survival. Despite the favorable outcomes with pathological complete response, some patients will develop recurrence. Pathological complete response is achieved in only 20% to 30% of patients, and its predictive value depends on tumor biology.[13] Patients with human epidermal growth factor receptor HER2-positive and triple-negative tumors are good candidates for neoadjuvant chemotherapy as they have a higher probability of achieving pCR. Research has also put forward a solution for early detection of patient subpopulations that benefit from an intervention.[14]

For example, Pertuzumab received FDA approval in 2013 for HER2-positive patients based on pCR criteria, in the absence of long-term data in the neoadjuvant setting.[15]

In our study, it has been shown that among patients who achieved a pCR, patients with stage III or more or those who have undergone mastectomy as opposed to breast conservation are at an increased risk of developing metastasis after a pathological complete response. Also, patients with T1 tumors had more recurrence than T2 and T3, the reason being that in our data, 81% of patients with T1 tumors had aggressive biology, Her2 positive and triple negative (Table 2 and Table 3). Although only a small percentage of breast cancer patients who achieve a pathological complete response have a systemic recurrence, we were able to identify factors that independently predict distant metastasis. The results of our study indicated that patients with stage III/IV and those who underwent mastectomy as opposed to breast preservation were more likely to have a poor outcome despite achieving a pathological complete response.

Systemic therapy aims to eliminate occult residual distant metastasis to eventually improve disease-free and overall survival. Recognition of patients who will have a pathological complete response in such circumstances has been an important objective in many studies.[16] In addition to the potential clinical benefits that are achieved by downstaging, neoadjuvant therapy allows direct and early observation of the response to treatment, which could lead to modifications of the treatment plan in the event of poor response.[17] The challenge remains to identify a treatment prototype for the patients who do not achieve pCR after neoadjuvant therapy to improve the survival outcomes.[18]

Besides recurrence in some patients, achieving a Pathological complete response plays a crucial part in the outcome of breast cancer.[19] The strongest association between a pathological complete response and long-term outcome is in patients with aggressive breast cancer subtypes (triple negative; hormone-receptor-positive, high-grade, and HER2-negative; HER2-positive and hormone-receptor-negative).[20] Given the considerable progress in survival for individual patients who attain pathological complete response, we believe that neoadjuvant systemic therapy will guide the treatment modification[21] to produce a considerable increase in the frequency of pathological complete response and result in long-term improvements in disease-free survival or overall survival.[22]

Limitations

This study shows that even after pCR there are factors which increase the risk of recurrence. Our limitation is that we used retrospectively reviewed data and a multicentric prospective study will be needed to identify the patients at risk of recurrence, withclose follow-up and management changes to avoid recurrence.

CONCLUSION

This retrospective study identifies the clinical and pathological response of breast cancer to neoadjuvant therapy. Pathological complete response is considered as an important prognostic factor for survival outcome, but we observed that among patients who achieved a pCR, patients with stage III/IV disease and who underwent a mastectomy and those with triple-negative subtype had a higher risk of developing distant metastasis. Even if Her2 neu positive patients achieved pCR without anti her2 therapy, they had increased chance of disease relapse.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

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DATA AVAILABILITY

Not Applicable.

ETHICAL CONSIDERATIONS

Not Applicable.

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