ORIGINAL RESEARCH

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Nodal Response to Neoadjuvant Chemotherapy is a Better Predictive Factor of Survival Than Miller-Payne Scoring in Breast Cancer

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ABSTRACT Objective: Neoadjuvant chemotherapy (NAC) is a widely used treatment modality for breast cancer and may delay surgery for unresponsive patients. The objective of this study was to determine the predictive factors for complete pathological response and survival after NAC for the most appropriate patient selection before treatment. **Material and Methods:** Records of breast cancer patients with NAC between 2011 and 2015 were reviewed retrospectively. Statistical analysis was done using SPSS version 20.0 (SPSS Inc., Chicago, Illinois). **Results:** Twenty-six patients (22.6%) showed pathological Miller Payne Grade 5 response (T0), and three patients showed no measurable tumor, residue with separate tumor cells (T1 mi). The presence of HER2-neu expression (p=0.03), absence of estrogen receptor (ER) and progesterone receptor (PR) expression (p=0.001), and high histological grade (p=0.025) were found associated with complete pathological response. Tumor diameter and lymphoid infiltration showed no correlation with complete pathological response. Also, we found that patients who showed lower pathological nodal stage according to American Joint Committee on Cancer (AJCC), 8th edition had statistically significant longer survival period (p<0.05), but Miller-Payne Grade 5 response could not predict survival results [p=0.814 for overall survival (OS) and p=0.295 for progression-free survival (PFS)]. **Conclusion:** Neoadjuvant treatment would be more effective in tumors with ER-negative, HER-2 positive, and high-grade properties. Survival effect might be predicted earlier with pathologic nodal results according to AJCC cancer staging system, 8th edition.

Keywords: Breast neoplasms; neoadjuvant therapy; survival; drug therapy

Neoadjuvant chemotherapy (NAC) could eliminate existing potential micrometastases and prevent the growth of occult micrometastases that originated from released tumor cells during surgery, and also allowed breast-conserving at higher rates.[1] Though the main expected benefit of treatment modalities is to improve disease-free survival (DFS) and progression-free survival, investigators are trying to translate therapeutic results into better survival rates. It is critical to avoid under-treatment or overtreatment, despite a lack of clarity in determining the extent of the therapy and aiming for the best survival results.

Breast cancer has been staged using the American Joint Committee on Cancer (AJCC) Tumor, Node, and Metastasis (TNM) staging system since the first edition in 1977.[2] There are different neoadjuvant response evaluation systems, and "Miller-Payne Criteria" is accepted useful in various cancer centers; it is graded from 1 to 5; because the pathological examination has decision-making importance and has not been standardized yet.[3] Also, the clinical course of patients with pathologic complete response (pCR) remains unclear due to conflicting results.

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Could pCR be a surrogate marker for survival outcomes? This study attempted to evaluate the factors that predict response to neoadjuvant therapy and to assess the correlation between pathological responses and survival rates.

MATERIAL AND METHODS

PATIENTS

A total of 137 breast cancer patients admitted to the Medical Oncology Outpatient Clinic of our Faculty Hospital from January 1, 2011 to December 31, 2015, to receive NAC, were included in the current study. Sociodemographic characteristics of patients and the characteristics of the disease were determined retrospectively from respective patient files. Patients who could not be contacted, those whose pathological information could not be determined, and those who initially planned to receive NAC but were not operated upon for different reasons were excluded from the study (Figure 1). Therefore, 22 patients were excluded and the data of 115 patients were finally analyzed. Ethical approval for the study was obtained from Institutional Ethics Committee (Approval No: 83045809/604.01/02-44109, Approval date: 04.02.2016). All reported research was conducted in accordance with the guidelines outlined in the Declaration of Helsinki, 2008. Informed consent obtained from patients who are alive, and from legal heirs of patient who are died.

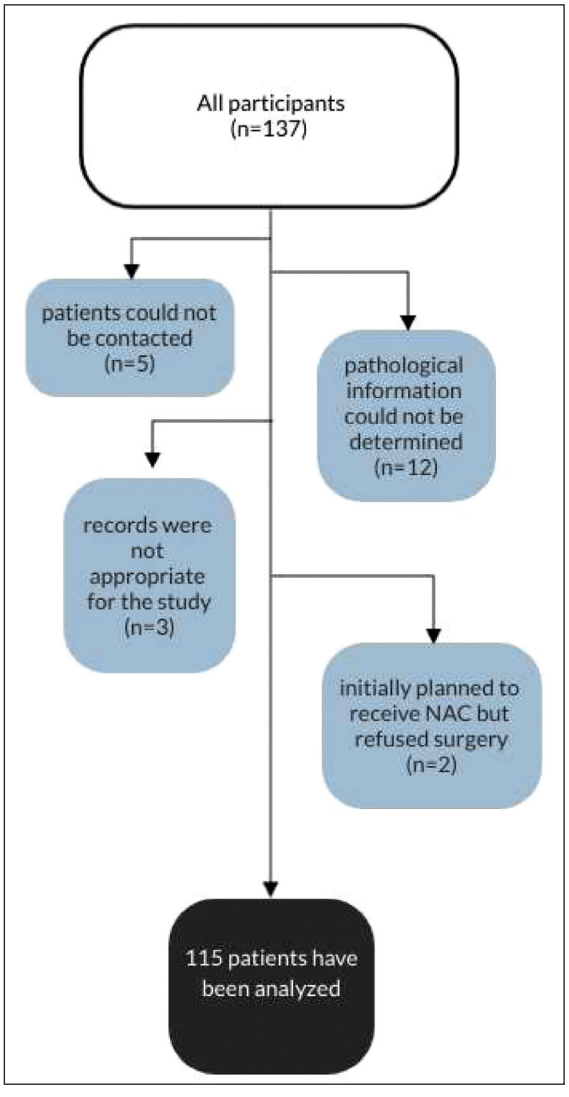

FIGURE 1: Flowchart of the study.

CLINICAL AND PATHOLOGICAL EVALUATION

In the evaluation of estrogen receptor (ER) and progesterone receptor (PR) expressions, cell nuclei staining of ≥1% was considered positive in immunohistochemistry (IHC). Human epidermal growth factor receptor 2 (HER-2/neu) expression was accepted as negative in patients with scores 0 and 1 but positive in patients with score 3 according to membrane positivity ratio in IHC staining. In situ hybridization (ISH) of HER-2neu gene expression was requested from all patients with a score of 2 to examine their positive or negative statuses.

Treatment regimens were based on clinician choice and they mostly included anthracycline and taxane-containing regimens. All patients with HER-2neu expression were given trastuzumab along with taxane therapy. Patients with inadequate response to clinical evaluation underwent chemotherapy or radiotherapy according to the clinician's choice. After the operation, adjuvant radiotherapy or chemotherapy was planned based on the current guidelines and considering the pathological and clinical features.

Evaluation of treatment responses was based on tumoral involvement in the pathological material of breast or lymph nodes. The patients were triaged according to Miller-Payne Score (MPS) in pathological response evaluations. Surgical and pathological staging were performed under AJCC 8th edition criteria.

STATISTICAL ANALYSIS

Microsoft Excel 2010 and software SPSS v.20.0 (SPSS Inc., Chicago, Illinois) were employed for data handling and statistical analysis, respectively. p value of <0.05 was accepted to be statistically significant. The length of time between the date of biopsy and the date of death or last known follow-up was defined as the overall survival (OS) time. DFS time was calculated as the duration between surgery date and the date of confirmed disease recurrence or death of the patient. Survival analyses excluded five patients with metastatic diseases from the beginning. Survival analysis was performed by using the Kaplan-Meier method. The factors that might affect the pCR were evaluated by Pearson's chi-square test.

RESULTS

PATIENT CHARACTERISTICS

The median age of the patients was 48 (range, 23-77) years. Three patients were found pregnant on the diagnosis. The most common indications for NAC were node-positive disease and inflammatory breast cancer. The median tumor size was 3.65 (range: 1-13.8) cm, and invasive ductal carcinoma showed the most common histology (80.8%, n=93). Each of the four patients with synchronous bilateral breast cancers was evaluated for two separate tumors for a pathologic response. One patient showed triple-negative histology, and the rest three patients had luminal A histology. Table 1 shows the sociodemographic data and histopathological features of the patients.

Most of the patients were treated with anthracycline and taxane with a 3-weekly regimen. Dose modifications were done in four patients due to side effects; two patients received neoadjuvant hormone therapy due to their advanced age. Neoadjuvant radiotherapy was given to two patients due to insufficient response. Also, additional chemotherapy treatments with gemcitabine were planned for these two patients. Five patients with oligometastatic disease underwent surgery after response evaluation.

PATHOLOGICAL RESULTS

The median tumor size was 1.7 (range: 0.1-13) cm during postoperative evaluation. No measurable tumor was detected in 29 patients (24.4%); of them, three patients showed a few tumor cells on the background of fibrotic tissue (T1 mi). The number of patients with pCR in lymph nodes (ypN0) was 45 (39.1%). Two of the five metastatic patients had MPS Grade 5 response, which confirmed clinical regression before surgery.

Evaluation of patients with MPS Grade 5 responses showed that all patients were female. A total of ten patients (38.5%) had inflammatory breast carcinoma. During the follow up, four patients showed distant metastasis post-treatment. The tumor stages before treatment were T1 for two patients (7.7%), T2 for 12 patients (46.2%), T3 for two patients (7.7%), and T4 for ten patients (38.5%). All the patients, except one, were radiologically node-positive. ER expression was noted in eight patients; of them, only four were associated with PR. Seventeen patients were HER2-positive; two of them were of score two and confirmed by fluorescence in situ hybridization. Histological subtypes of patients and their response rates are presented in (Table 2). In the lymph node staging of the patients after surgery, one had a pathological node (pN1), and three had pathological node (pN2). Data were evaluated with the Pearson's chi-square test in terms of factors that might affect the pCR of the tumor. High tumor grade, negative hormone receptors, and HER-2 positivity were found statistically significant (Table 3).

Recurrence and Survival Results

Disease recurrence was detected in 38 patients (33%), four of whom had local recurrence, and the rest 34 had distant metastases. When a patient with primary unresponsiveness was excluded, the earliest relapse was detected within two months and at the latest after 80 months. Of the patients with recurrence, only four displayed previous MPS Grade 5 responses and distant metastases.

At the median follow-up time of 50.3 months, the 5-year DFS rate of all patients was 64.1%±4.8%. At the median follow-up with 54.5 months, the OS rate was 75.2%±4.5% for all cohorts. Age, menopausal status, tumoral ER-PR-HER-2 status, grade, and/or inflammatory character did not show a significant effect in survival analysis. Postopera-

TABLE 1: Distribution of patient characteristics.

Clinical characteristic				n (%)
Age	≤50			70 (60.9)
	>50			45 (39.1)
Gender	Male			2 (1.8)
	Female			113 (98.2)
Menopausal Status	Post			41 (42.7)
	Pre			55 (57.3)
	Unknown			17
Localization	Right breast			65 (56.5%)
	Left breast			46 (40%)
	Bilateral			4 (3.5%)
Tumoral clinic properties	Multifocal			18 (15.7%)
	Multicentric			22 (19.1%)
	Inflammatory tumor			56 (48.7%)
Pathological Characteristics*				
	Pre-Treatment Characteristics		Post-Treatment Characteristics	
T stage	cT1	10 (8.5%)	ypT0	26 (21.8%)
	cT2	44 (37.3%)	ypT1 mi	3 (2.5%)
	cT3	6 (5.1%)	ypT1	42 (35.4%)
	cT4	58 (49.1%)	ypT2	26 (21.8%)
			ypT3	13 (10.9%)
			ypT4	9 (7.6%)
N stage	Negative	2 (1.8%)	ypN0	45 (37.8%)
	Positive	109 (98.2%)	ypN1	25 (21%)
	Unknown	4	ypN2	32 (26.9%)
			ypN3	17 (14.3%)
ER status[a]	Positive	68 (61.8%)	Positive	62 (72.1%)
	Negative	42 (38.2%)	Negative	24 (27.9%)
	Unknown°	9		
PR status[a]	Positive	55 (50%)	Positive	47 (56%)
	Negative	55 (50%)	Negative	37 (44%)
	Unknown°	9		
HER2-neu status[a]	Positive	38 (34.5%)	Positive	33 (33.7%)
	Negative	72 (65.5%)	Negative	65 (66.3%)
	Unknown°	9		
Grade[a]	Grade 1	-	Grade 1	-
	Grade 2	56 (62.2%)	Grade 2	45 (77.6%)
	Grade 3	34 (37.8%)	Grade 3	13 (22.4%)
	Unknown	29		
Ki-67	45.8±26.5 (Mean±SD)		18.1±23.8 (Mean±SD)	
	2-95 (Range)		1-90 (Range)	

T: Tumor; ER: Estrogen receptor; PR: Progesterone receptor; SD: Standard deviation.

*Four bilateral tumors were considered as two separate tumors in the classification of tumoral features; [a]Some patients were evaluated only preoperatively, some only postoperatively, some in both; °Evaluated postoperatively.

tive pathologic nodal staging was found significantly associated with 5-year DFS and OS. Although numerically improved survival was observed, patients with MPS Grade 5 response had no different survival results as compared with others (Table 4, Figure 2).

TABLE 2: Pathological response rates of patients according to histological subtypes.

		Miller Payne grading				
		Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
		n (%)	n (%)	n (%)	n (%)	n (%)
Histological subtypes	Triple negative	3 (16.7)	5 (15.2)	1 (5.3)	2 (18.2)	8 (30.8)
	Her-2neu positive	2 (11.1)	1 (3)	2 (10.5)	3 (27.3)	10 (38.5)
	Luminal B	3 (16.7)	12 (36.4)	6 (31.6)	6 (54.5)	7 (26.9)
	Luminal A	10 (55.6)	15 (45.5)	10 (52.6)	0 (0)	1 (3.8)

DISCUSSION

NAC offers a possibility for a successful surgical operation by reducing tumor size in locally advanced breast carcinoma and allows breast-conserving surgery. Neoadjuvant therapy is aimed to prevent the progression of these micrometastases after surgery. Though, complete response rates after neoadjuvant therapy range between 20 and 30%, nearly 20% of patients may not respond to chemotherapy.[4,5] These patients are exposed to unnecessary chemotherapeutic toxicity with ineffective treatment and miss the chance of early surgery.

TABLE 3: Factors predicting complete response.

	p value
Menopausal Status	0.527
Tumor Site	0.494
Inflammatory Disease	0.315
Multifocality	0.963
Multicentricity	0.757
Histological Subtype	0.964
High Grade	**0.025***
ER negativity	**0.001***
PR negativity	**0.001***
HER2-neu positivity	**0.03***

ER: Estrogen receptor; PR: Progesterone receptor.

The definition of pCR varies in the extant literature. Some studies have defined the absence of tumor cells in breast tissue as a complete response, while others highlighted the absence of tumors in both breast and axillary lymph nodes as a complete response.[6-8] AJCC TNM 8th edition defines pCR as an absence of any tumor cell on breast and nodal specimens; pN0 refers to no tumor cell on lymph node.[2] In the MPS system, Grades 1-4 are categorized as a partial pathological response (pPR) and grade 5 as pCR.[3] We evaluated the response either according to the AJCC 8th edition and MPS as a comparable factor in our pathology unit. In this

TABLE 4: Postoperative pathological response characteristics and survival results.

		5-years DFS		p value	5-years OS		p value
Miller-Payne Grade							
Grade 1	n=18	53.3%±12.9	(n=15)		68.2%±11.8	(n=16)	
Grade 2	n=33	72.7%±8.3	(n=30)		76.9%±8.7	(n=31)	
Grade 3	n=19	58.2%±12.1	(n=17)	**0.295**	81.4%±9.7	(n=17)	**0.814**
Grade 4	n=11	60%±15.5	(n=10)		80%±12.6	(n=10)	
Grade 5	n=26	79.2%±9.6	(n=22)		85%±8	(n=23)	
Pathologic Nodal Status							
pN0	n=45	71.6%±7.3	(n=40)		82.9%±6.6	(n=41)	
pN1	n=25	69.6%±9.6	(n=23)	**0.020**	81.3%±8.7	(n=24)	**0.010**
pN2	n=31	61.9%±9.6	(n=27)		75.9%±8.8	n=28)	
pN3	n=17	35.7%±12.8	(n=14)		40.2%±13.6	(n=14)	

DFS: Disease-free survival; OS: Overall survival.

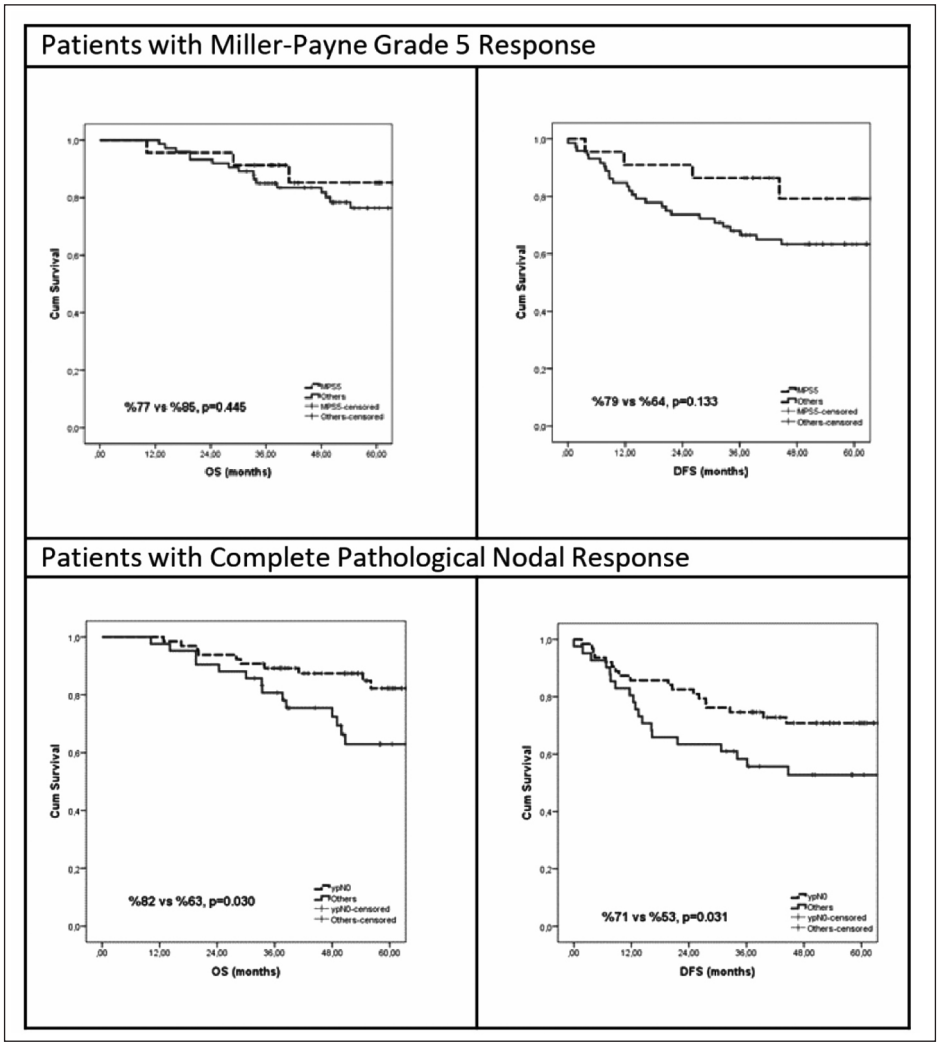

FIGURE 2: Survival curves of patients according to pathological response.

study, MPS Grade 5 responses were documented in 26 cases (22.6%). Importantly, patients with pN0 showed statistically significant survival results, but such a relation with MPS could not be established.

Hormone receptor positivity is a strong predictor of response to endocrine therapy. In particular, the benefits of adjuvant therapy are indisputable. Hormone receptor positivity and NAC response showed an inverse relationship.[9] Many studies examining neoadjuvant treatment responses highlighted ER status as a determinant marker of chemosensitivity.[10] Similarly, ER negativity and PR negativity are statistically significant factors that affect the development of pCR. These studies have highlighted that despite complete response to ER-negative tumors, DFS rates were remarkably lower than in ER-positive tumors because that ER negativity leads to more aggressive tumor growth. In contrast, several studies could not detect any association between negative ER expression and anthracycline-based chemotherapy response.[11,12] The HER2-neu gene expression was reported to be positive in approximately 30% of breast cancers.[9] Increased expression of HER-2neu is associated with resistance to docetaxel treatment in vitro, also trastuzumab treatment is thought to sensitize breast cancer cells to docetaxel.[13] Conversely, HER2-positivity has shown an increase in the anthracycline susceptibility of the tumor due to the increase of topoisomerase 2 alpha (TOP2A) expression on chromosome 17 (at band 17q12-q21).[14] Moreover, in a study evaluating triple-negative patients, patients

with a HER2-neu gene score of 2 showed greater chemosensitivity than the negative group.[15] Tumors with high histological grades tend to be more aggressive. Believably, cells are more likely to respond to chemotherapy during the division phase due to the high cell division rates. Supporting this hypothesis, findings have suggested that tumors with high histologic grade may predict the pCR in anthracycline-containing neoadjuvant therapy.[10-12] In the current study, hormone receptor negativity, HER-2neu positivity, and higher grade scores are statistically significant factors that affect pathological complete response development, corroborating previous findings.

Evaluating chemotherapy response is essential to predict survival rate and guide future chemotherapy. Despite several studies with contradicting results, the survival rate was significantly prolonged in patients with pathological complete response after NAC than those without response.[11,16,17] In the National Surgical Adjuvant Breast and Bowel Project 18 study on approximately 1,500 patients, both DFS and OS rates were found significantly longer in patients who received a clinical and pathological complete response after nine years of follow-up.[7] Until now, the evaluation of pathological response primarily involves quantitative assessment and is often inconsistent with clinical response. There are different systems to evaluate the pathological responses other than MPS, such as Chevallier, NSABP B-18, Pinder, Sataloff, and Smith systems.[7,18,19] However, the efficacy of these methods is poor in predicting outcomes. The different classification systems were compared in some studies, and the results showed that the systems, those include lymph node response, are better in predicting survival.[20] We, therefore, evaluated the correlation of survival and pathological nodal status and showed a statistically significant relation. Based on these results, TNM results is seems to better predict survival after neoadjuvant treatment.

CONCLUSION

Overall, it can be concluded that negative ER and PR receptors, high tumor grade, and HER-2 positivity are key determinants of the pathological complete response obtained by chemotherapy regimens. Also, survival is better predicted with pathologic nodal staging rather than MPS grade. Currently, there is no standard method to assess the pathological response to primary chemotherapy in patients with breast cancer. Hence, the standardization and improvement of methods to assess the response to induction chemotherapy are urgently needed and clinicians and researchers are suggested to conduct studies considering the above also.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Zeynep Hande Turna, Fuat Hulusi Demirelli, Naziye Ak;* ***Design:*** *Zeynep Hande Turna, Fuat Hulusi Demirelli, Naziye Ak;* ***Control/Supervision:*** *Zeynep Hande Turna, Fuat Hulusi Demirelli, Naziye Ak, Nail Paksoy, Mehmet Velidedeoğlu;* ***Data Collection and/or Processing:*** *Naziye Ak, Nail Paksoy, Mehmet Velidedeoğlu;* ***Analysis and/or Interpretation:*** *Naziye Ak, Nail Paksoy, Mehmet Velidedeoğlu;* ***Literature Review:*** *Naziye Ak, Nail Paksoy, Zeynep Hande Turna;* ***Writing the Article:*** *Naziye Ak, Nail Paksoy, Zeynep Hande Turna;* ***Critical Review:*** *Zeynep Hande Turna****,*** *Fuat Hulusi Demirelli, Naziye Ak, Nail Paksoy, Mehmet Velidedeoğlu;* ***References and Fundings:*** *Naziye Ak, Nail Paksoy, Mehmet Velidedeoğlu.*

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