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The prognostic value of histological grade in the outcome of patients with invasive breast cancer

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Aim: Prognostic factors are useful for the prediction of survival in breast cancer patients. According to many studies, tumor size and lymph node stage are the most powerful predictors of tumor behavior. The aim of the present study was to investigate the prognostic value of tumor histological grade.

Materials and methods: The study included 214 operable breast cancer patients treated at the same institution that were evaluated to determine the prognostic value of tumor histological grade. Clinico-histopathological features of the patients were also evaluated for overall survival (OS) and disease-free survival (DFS).

Results: Tumor histological grade was an independent factor in cancer-specific survival (CSS) and disease-free survival (DFS) ($P < 0.001$). The prognostic value of histological grade for CSS and DFS was superior to that of all T stages and to pN0, pN1, and pN2 stages ($P < 0.001$).

Conclusion: A classification system including histological grade, as a nodal status-like factor, could be more reliable in predicting breast cancer outcome.

Key words: Breast neoplasms, prognosis, histological grade; survival

İnvazif meme kanserli hastaların sağ kalımını değerlendirmede histolojik derecenin prognostik değeri

Amaç: Prognostik faktörler meme kanseri sağ kalımını değerlendirmemize yardımcı olur. Bir çok çalışmada tümör boyutu ve lenf bezi tutulumu en güçlü prognostik faktörler olarak karşımıza çıkmaktadır. Bu çalışmadaki amacımız histolojik derecenin prognostik değerini araştırmaktır.

Yöntem ve gereç: Tek bir merkezde opere edilmiş 214 meme kanseri hastası histolojik derecenin prognostik değerini araştırmak için incelendi. Hastaların klinikohistopatolojik özellikleri, genel ve hastalıksız sağ kalıma olan etkileri açısından değerlendirildi.

Bulgular: Histolojik derece kansere özgü sağ kalımı ve hastalıksız sağ kalımı etkileyen bağımsız bir değişken olarak bulundu. Histolojik derecenin prognostik değeri tüm tümör boyutlarında ve N3 dışındaki tüm nodal tutulum evrelerinde TNM' ye göre üstün bulunmuştur.

Sonuç: Histolojik derece, TNM evreleme sistemi içine alınırsa hastaların sağ kalımının daha güvenilir olarak tayin edebileceğini düşünmekteyiz.

Anahtar sözcükler: Meme kanseri, prognoz, histolojik derece, sağ kalım

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Introduction

Breast cancer is the most common cancer observed in women, with a lifetime risk of up to 12% and a risk of death up to 5% (1). There are numerous prognostic factors used to assess survival in breast cancer patients. Some of the prognostic factors have been combined into the TNM classification or the more current Nottingham Prognostic Index (NPI), both of which are highly predictive for estimating long-term survival (2,3). TNM staging is based on primary tumor size, involvement of the regional lymph node, and the presence of distant metastases, while tumor size, grade, and lymph node status constitutes NPI staging (4-6). The identification of prognostic factors associated with either the metastatic or growth potential of the primary tumor could assist physicians in determining which patients need adjuvant therapy and predicting survival. Adjuvant therapy in high-risk patients could improve overall results.

The purpose of the present study was to determine the most important prognostic factors affecting the long-term outcome in breast cancer patients and to identify high-risk patients that might require adjuvant therapy.

Materials and methods

This single-institute retrospective cohort study included 214 consecutive patients with invasive ductal breast carcinoma that underwent modified radical mastectomy between 1992 and 2006. Patients with stage IV tumors, and those that underwent breast-conserving surgery or neoadjuvant chemotherapy were excluded. All patients had laboratory and radiological examinations, including blood count, biochemical analysis, CA 15-3, carcinoembryogenic antigen levels, chest X-ray, mammography, and ultrasound, as a part of their preoperative evaluation. All surgical interventions were performed by senior surgeons with at least 10 years of surgical experience in breast cancer patients. The same surgical technique and principles were utilized for all patients.

Tumor size, number of metastatic lymph nodes, lymphatic/vascular and perineural invasion, fat infiltration in the axillae, tumor grade, estrogen and progesterone receptor status, and c-erb-B2 were determined with histopathological examination. All tumors were graded using the modified Nottingham criteria of Bloom and Richardson, which consists of 3 important evaluations, including 1) tubule formation, 2) nuclear size, and 3) mitotic count (7). Each variable is scored from 1 to 3, and the sum of the scores is used to describe the NHG. Thus, a tumor that scores 3-5 is classified as histological grade 1, a score of 6-7 is grade 2, and a score of 8 or 9 is grade 3 (8). All histological examinations were performed by the same pathology unit based on data contained in the patients' medical charts. Fixation of the specimens was performed in 10% formaldehyde immediately following surgical excision.

Adjuvant chemoradiotherapy was administered to patients with stage 2A and higher tumors. Hormonotherapy was given to ER-positive premenopausal and postmenopausal patients. Overall survival (OS) was considered as last follow-up time or time to death. All mortality in the present study was disease specific. Disease-free survival (DFS) was considered as the time of surgery to the appearance of the first recurrence (locoregional or distant). Clinical, laboratory, and pathological factors were evaluated for their significance in the prognosis of breast cancer patients (Table 1). All histological and biochemical examinations were performed on untreated tumor specimens.

Factors affecting OS and DFS were analyzed using Kaplan-Meier survival analysis and comparisons were made using the log-rank test. Multivariate analysis was performed using Cox regression. P values < 0.05 were accepted as significant. A receiver operator characteristic (ROC) curve was used for cut-off values of age and tumor size. The Cox proportional hazards model was used to study the influence of grade on survival outcome.

Results

Mean age of the patients was 49 years (range: 28-81 years). Characteristics of the patients are presented in Table 1. A mean of 20 lymph nodes were dissected and the mean number of metastatic lymph nodes was 5. Median duration of follow-up was 41 months (range: 12-192 months). Mean OS was 145 months (range: 133-157 months) and mean DFS was 127

Table 1. Characteristics of the patients.

		n (%)
Age	<40	44 (20.6)
	≤40	170 (79.4)
Tumor size	≤4 cm	134 (62.6)
	>4 cm	80 (37.4)
pN	N0	85 (39.7)
	N1	48 (22.4)
	N2	46 (21.5)
	N3	35 (16.4)
Grade	1	72 (33.6)
	2	103 (48.1)
	3	39 (18.2)
TNM staging	1	21 (9.8)
	2A	50 (23.4)
	2B	34 (15.9)
	3A	49 (22.9)
	3B	24 (11.2)
	3C	36 (16.8)
Menopausal status	Pre	102(47.7)
	Post	112(52.3)
ER status	Positive	74(34.6)
PR status	Positive	82(38.3)
c-Erb-B2 status	Amplified	54(25.2)
Chemotherapy	Received	187 (87.4)
Radiotherapy	Received	86 (35.5)
Skin involvement	Positive	31 (14.5)
Fat infiltration in axillae	Positive	33 (15.4)
Lymphatic invasion	Positive	46 (21.5)
Vascular invasion	Positive	49(23.9)
Perineural invasion	Positive	29(13.7)

months (range: 113-141 months). The locoregional recurrence rate was 8.8% (19 patients), the distant metastasis rate was 27.5% (59 patients), and the overall recurrence rate was 30.8% (66 patients).

The 5-year and 10-year OS rates were 77% and 69%, respectively. Age > 40 years, tumor size > 4 cm, absence of metastatic lymph nodes, lower nodal status according to TNM staging, absence of level 3 lymph node involvement, lower number of metastatic lymph nodes when present, lower grade and TNM stage, absence of skin involvement and lymphatic invasion, and absence of fat infiltration in axillae were favorable factors for OS and DFS, according to univariate analysis ($P < 0.05$) (Tables 2 and 3). All significant variables in univariate analysis were entered into Cox's multivariate model. Tumor grade was the strongest prognostic factor, which retained independent prognostic significance in multivariate analysis ($P < 0.001$) (Table 4). The 5-year and 10-year DFS rates were 70% and 57%, respectively. Tumor grade and the number of involved lymph nodes were independent factors that influenced DFS in multivariate analysis ($P < 0.001$).

OS and DFS were significantly related to tumor grade ($P < 0.001$). A significant difference was observed between the groups with the greatest separation between grades 1-2 and grade 3 (Figure 1). When the relationship between grade and survival time was stratified by TNM staging, survival time significantly decreased as grade increased (Table 5). Tumor grade was an independent prognostic factor in node-positive patients as well as in node-negative patients, both for OS and DFS (Figures 2 and 3). OS was 36.13 months (95% CI 14.55-47.71) and 40.71 months (95% CI 29.84-51.58) for grade-3 patients that were node-negative ($P < 0.001$) and node-positive ($P < 0.001$), respectively. DFS was 47.80 months (95% CI 21.75-73.85) and 31.68 months (95% CI 21.75-73.85) for grade-3 patients that were node-negative ($P = 0.018$) and node-positive ($P < 0.001$), respectively (Table 6).

Discussion

Prognostic factors help physicians to identify patients in whom OS and DFS may be improved by adjuvant therapy. Currently, the TNM system is the most widely used measure to assess the prognosis in invasive breast cancer patients. Although each of the measures in the TNM system were proved to be independent prognostic factors in the present study, as well as in many previous studies (3,9-19), according to our findings the TNM system failed to differentiate between favorable and unfavorable patient groups in our group of breast cancer patients. In the present study we observed that patients with grade 1 and grade 2 tumors had very favorable OS rates, as

Table 2. Univariate analysis of the parameters for OS.

		Overall survival %	Overall survival 95% CI	Log rank	P
Age	<40	93.0	72-113		
	≤40	132.9	121-144	9.23	0.0026
Tumor size	≤4 cm	140.6	129-152		
	>4 cm	77.6	63-92	18.73	<0.0001
Metastatic lymph node	No	139.6	126-152		
	Yes	107.8	63-92	13.93	<0.0001
pN	N0	139.5	126-152		
	N1	137.2	120-154		
	N2	104.4	79-128		
	N3	54.7	38-71	43.06	<0.0001
Level 3 involvement	No	140.6	129-151		
	Yes	60.3	46-74	38.41	<0.0001
Metastatic lymph node number	0	140.8	128-153		
	1-5	141.7	125-158		
	>5	59.0	45-72	54.46	<0.0001
Grade	1	159.8	150-168		
	2	125.3	110-139		
	3	40.8	30-50	81.13	<0.0001
TNM	1	137.0	123-150		
	2A	145.0	131-158		
	2B	131.8	105-158		
	3A	112.0	87-136		
	3B	110.2	77-143		
	3C	54.7	38-71	44.34	<0.0001
Neoadjuvant chemotherapy	No	126.6	115-137		
	Yes	40.17	30-50	8.00	0.005
Skin involvement	No	126.3	114-138		
	Yes	100.4	73-127	4.05	0.044
Fat infiltration in axillae	No	135.8	124-147		
	Yes	54.9	36-73	39.50	<0.0001
Lymphatic invasion	No	130.5	118-142		
	Yes	94.0	72-115	6.37	0.012

Table 3. Univariate analysis of the parameters for DFS.

		Disease free survival %	Disease free survival 95% CI	Log rank	P
Age	<40	70.7	50-91		
	≤40	111.3	98-124	12.47	<0.0001
Tumor size	≤4 cm	114.4	101-127		
	>4 cm	65.8	52-79	13.94	<0.0001
Metastatic lymph node	No	127.9	112-142		
	Yes	80.9	66-95	14.41	<0.0001
pN	N0	125.1	109-140		
	N1	127.5	106-148		
	N2	55.5	39-71		
	N3	49.1	30-67	41.02	<0.0001
Level 3 involvement	No	113.1	100-125		
	Yes	56.4	40-72	19.53	<0.0001
Metastatic lymph node number	0	125.4	110-140		
	1-5	104.1	84-123		
	>5	50.9	35-65	34.05	<0.0001
Grade	1	125.5	103-141		
	2	102.4	86-118		
	3	33.7	23-43	40.76	<0.0001
TNM	1	127.4	106-148		
	2A	125.7	107-144		
	2B	126.3	103-149		
	3A	65.9	48-82		
	3B	84.2	49-119		
	3C	49.1	30-67	36.6	<0.0001
Neoadjuvant chemotherapy	No	103.4	91-115		
	Yes	35.1	20-49	3.72	0.054
Skin involvement	No	107.7	95-119		
	Yes	69.1	41-96	9.34	0.002
Fat infiltration in axillae	No	112.4	100-124		
	Yes	42.8	24-60	29.41	<0.0001
Lymphatic invasion	No	108.6	95-121		
	Yes	76.6	54-98	4.97	0.026

Table 4. Multivariate analysis of the factors influencing OS and DFS.

	Relative risk	95% CI	P
Overall survival			
Grade			<0.001
Grade 1			
Grade 2	4.25	1.24-14.58	
Grade 3	17.97	5.21-61.95	
Fat infiltration in axillae	2.77	1.49-5.14	0.002
Disease-free survival			
Nodal status			<0.001
N0			
N1	0.65	0.25-1.69	
N2	2.54	1.25-5.18	
N3	3.06	1.48-6.33	
Grade			<0.001
Grade 1			
Grade 2	1.83	0.86-3.88	
Grade 3	4.72	2.05-10.83	

Table 5. Survival rates (5-10 years) of the patients according to the relationship between tumor grade and TNM stage.

	Stage 1	Stage 2A	Stage 2B	Stage 3A	Stage 3B	Stage 3C
Grade 1	100%	94%	100%	100%	100%	66% (5 years)
Grade 2	100%	73% (10 years) 92% (5 years)	90% (5-10 years)	83% (5-10 years)	67% (5-10 years)	53% (5-10 years)
Grade 3	0%	50% (5 years)	50% (5 years)	36% (5 years)	0%	22% (5 years)
P	<0.001	0.029	0.052	<0.001	0.022	0.329

Table 6. OS and DFS of the patients according to nodal status and tumor grade.

		OS (95% CI)	P	DFS (95% CI)	P
N(-)	G 1	151.29 (142.26-160.33)	<0.001	138.15 (121.79-154.50)	0.018
	G 2	132.35 (109.15-155.54)		118.34 (93-96-142.71)	
	G 3	36.13 (14.55-47.71)		47.80 (21.75-73.85)	
N(+)	G 1	155.96 (139.94-171.99)	<0.001	97.00 (75.56-118.46)	<0.001
	G 2	116.60 (99.08-134.13)		91.04 (70.60-11.48)	
	G 3	40.71 (29.84-51.58)		31.68 (21.26-42.10)	

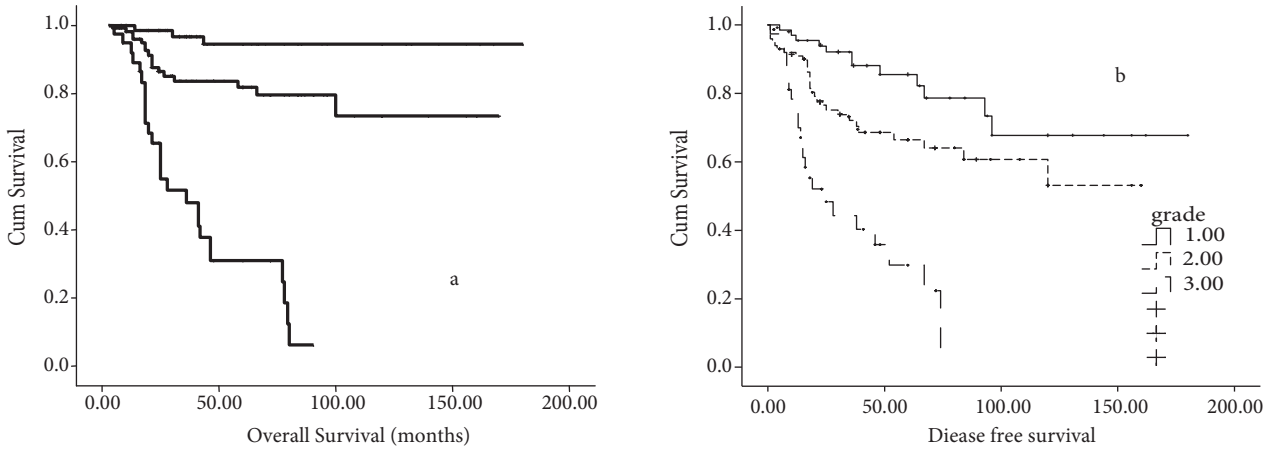

Figure 1. OS for all patients according to histological grade 1-3 (P < 0.001) (a). DFS for all patients according to histological grade 1-3 (P < 0.001) (b).

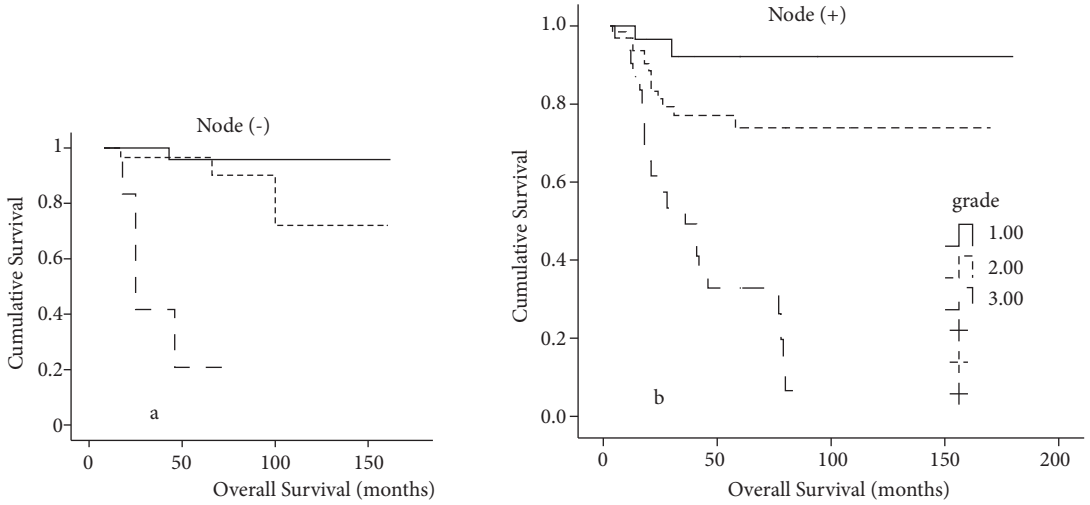

Figure 2. OS for node-negative patients according to histological grade 1-3 (P < 0.001) (a). OS for node-positive patients according to histological grade 1-3 (P < 0.001) (b).

compared to those with grade 3 tumors, independent of their TNM stage, except for TNM stage-3C patients. We also observed that when the relationship between OS and tumor grade was stratified by TNM staging, survival of grade-3 stage-1 patients was lower than the survival of grade-1 or 2 stage-3C patients (Table 6). This highlights that the TNM staging system alone might be misleading in the prediction of prognosis. To the best of our knowledge similar findings have not been previously published in the English language literature. Due to this intrinsic weakness of TNM staging, that is, the inability to differentiate prognostic subgroups of patients with similar histological grades, some patients might not obtain the expected benefits of adjuvant therapy and others might receive unnecessary adjuvant therapy. We think if tumor grade were integrated into the staging of invasive breast cancer, patients would be stratified more precisely and those that might require adjuvant therapy would be identified more accurately; hence, OS and DFS would improve.

The importance of histological grade was also proposed in previous studies (6,7,20). The basic problem remains that in many of these studies the prognostic value of histological grade was studied in series of patients that were heterogeneous in terms of

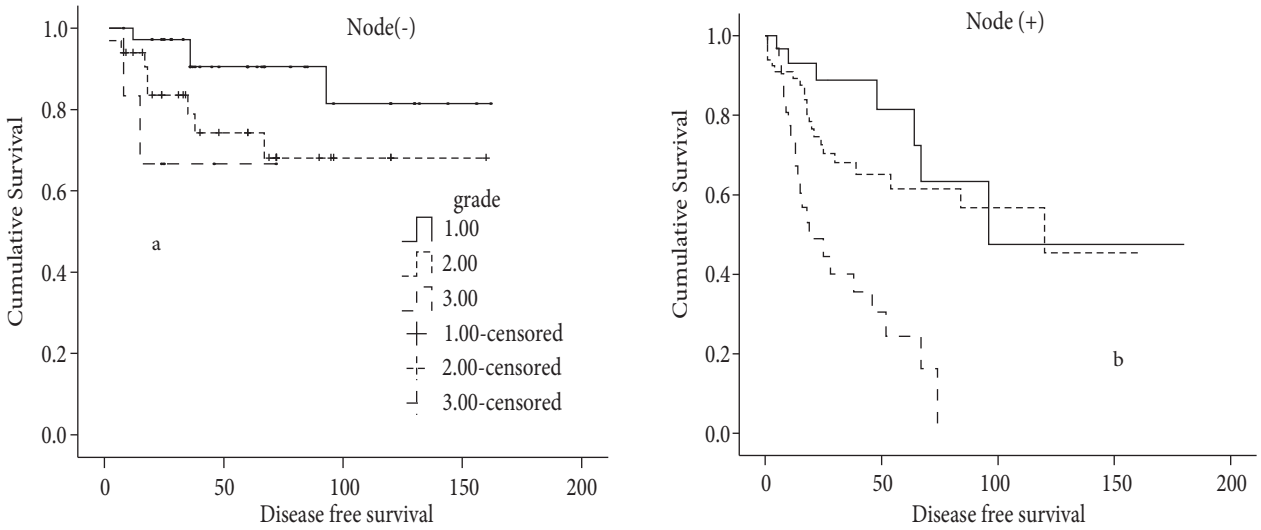

Figure 3. DFS for node-negative patients according to histological grade 1-3 (P = 0.018) (a). DFS for node-positive patients according to histological grade 1-3 (P < 0.001) (b).

stage and treatment, and therefore were unsuitable for correctly determining the pure prognostic value of any marker (8,16,20). In the present study homogeneity was obtained by assessing the prognostic factors for node-negative and node-positive breast cancer patients separately. A homogeneous group was obtained by selecting the patients that underwent mastectomy and axillary dissection for breast cancer.

In the present study tumor grade was superior to TNM staging for predicting OS and DFS in each stage, except stage 3C. Another important finding of our study that should be mentioned separately is the importance of tumor grade as a significant prognostic factor in node-positive patients. We observed that tumor grade was a more precise prognostic factor than TNM classification, both in node-negative and node-positive patients; these results differ from those of most other studies that report tumor grade as a significant factor only in node-negative patients (9,17,20,22,23).

The search for a single independent prognostic factor in breast cancer has often produced conflicting results. The Nottingham Prognostic Index (NPI) was developed for this purpose. We think that when making predictions about survival in breast cancer patients it would be more appropriate to use tumor grade and nodal status together. Poor survival in patients with high-grade tumors might be underestimated when only TNM staging is used to determine the necessity of adjuvant therapy.

In addition to important findings, the present study has some limitations that should be mentioned. Due to the moderate number of patients included we think that series including larger number of patients are needed to reach a more definitive conclusion. The retrospective nature of this study may also be considered a limitation. There is increasing evidence that molecular profiling of primary tumors can provide important prognostic information. The lack of molecular profiling of primary tumors is another limitation of the present study. Molecular profiling provides information complementary to tumor stage and grade.

According to the results of the present study, there was a highly significant relationship between histological grade and prognosis: survival decreased as tumor grade increased . Histological grading has been shown to have good reproducibility and to be an important independent prognostic factor in breast cancer patients. When combined with pathological tumor size, lymph node involvement, and the NPI, excellent stratification for patient management can be achieved. Adjuvant therapy could be planned more precisely by using both tumor grade and lymph node involvement, and should be considered in patients with high-grade tumors, regardless of their TNM stage.

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