RESEARCH ARTICLE

Reconsideration of Clinical and Histopathological Prognostic Factors in Breast Cancer Patients: A Single Center Experience

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Abstract

Background: The clinical course of the neoplasm may vary due to both patient and tumor cell characteristics. Aim: The aim of this study was to research the influence of certain clinical and pathological features on the prognosis of early stage breast cancer. Materials and Methods: This study included 117 women that were treated and followed-up in between the years 2001-2011. The demographic, clinical and histopathological features of the cases were reviewed retrospectively. Statistical analysis: In categorical comparisons between groups, cross-tab statistics were provided and significance levels were estimated using chi-square test. Cox regression analysis, Pearson and Spearman correlation tests, and the Kaplan-Meier test were also used. Results: With an average of 35-months follow-up, the mean disease-free survival of patients was 91 months and the mean overall survival time was 132 months. In the whole study group, the disease-free survival rates were 88, 84, 83 and 52%, while the overall survival rates 95, 94, 83, and 83% within the first, third, fifth and tenth years, respectively. The disease-free and overall survival rates were decreased with increasing tumor grades, though this was not statistically significant. The presence of lymphovascular invasion, positive staining with Ki67 and postmenopausal status were associated with shorter disease-free and overall survival times. In multivariate analysis, only age and Her2/neu receptor status influenced the prognosis significantly. Conclusions: In parallel to clinical, histopathological, and immunohistochemical prognostic features in breast cancer, in this study positive Her2/neu receptor status, a previously accepted poor prognostic factor, was found to have positive influence after trastuzumab treatment.

Keywords: Breast cancer - prognosis - receptor - Her2/neu - biological markers

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Introduction

Breast cancer is the most common malignant disease in women and second most common cancer related cause of death. It remains as an important health problem because of high mortality and morbidity rates (Taneja et al., 2010; Weigel et al., 2010; Drukker et al., 2013; Siegel et al., 2013). Therefore, clinical, histopathological, and immunohistochemical characteristics that are thought to be related to survival rates of this disease are the main subjects of many current studies.

In parallel with new information on tumor biology, clinical studies focusing on determining predictive and prognostic factors in breast cancer increased in number. Today, it is accepted that tumor cells have different biological behaviors in each breast cancer case. So, because of the presence of different subgroups without homogeneity in receptor status, it is known that disease course and treatment benefits differ for each case (Taneja et al., 2010). In many clinical studies, apart from hormone receptor and Her2/neu status, some immuno- histochemical characteristics of the tumor are reported to be separate prognostic factors for both survival and relapse. While many molecules and genetic mutations in different stages of carcinogenesis such as tumor cell proliferation, cell adhesion, inhibition of apoptosis, angiogenesis are accepted as predictive and/or prognostic factors, some have not yet taken a place in guidelines (Weigel et al., 2010; Drukker et al., 2013).

In this study, we aimed to assess in the early-stage breast cancer cases which applied to our department following surgical treatment, in the light of current information, clinical and histopathological characteristics which have positive or negative effect on breast cancer progress and their relationship with each other.

Materials and Methods

Among the early stage breast cancer patients treated and followed-up in Adnan Menderes University Medical School by Medical Oncology Department from 2001 to 2011, 117 who had available information and who could be reached are enrolled in this study. Patients were referred to our department with pathology results after curative surgery.

Demographic characteristics of patients such as

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age, height, weight, menopause status and histological characteristics of tumor such as tumor type, lymph node status, tumor size, and lymphovascular invasion were recorded. Information from patients' files were recorded including date of diagnosis, operation date, which breast the tumor is located and its localization, type of surgery, adjuvant chemotherapy initiation date and administered regimens in this therapy, adjuvant radiotherapy initiation date, information about hormonotherapy and trastuzumab if they were administered, relapse localizations, and time till the relapse, and whether if the patient was alive or not.

Immuno- histochemical staining of tumor cells with estrogen and/or progesterone receptor with a rate of >1% was considered as positive for hormone receptor status. Similarly, immuno- histochemical detection of human epidermal growth factor receptor-2/neu (Her2/neu) expression with a value of +3 or positive results with fluorescent in situ hybridization out of whose immuno-histochemical staining are +2, were considered as Her2/neu over-expression.

While staining of tumor cells with a rate of 20% or more was considered as ki67 positive, for p53 expression staining of cells with a rate of 11% or more is considered as positive criterion.

Ethics

The protocol for this retrospective study was compatible with the local ethical guidelines. The study was approved by the Academic Committees in our center and written informed consents were obtained from all participants.

Statistical analyses

The data are expressed as the mean±standard deviation or the median and interquartile range (25-75%). The distribution of variables was analyzed with the Kolmogorov-Smirnov test. Quantitative variables with normal distribution were analyzed with a two-tailed, independent Student's t test. Nonparametric variables were analyzed with the Mann-Whitney U test. However, qualitative parameters were analyzed with the Chi-square test and Fisher's test. The Kruskal-Wallis test was used for comparisons between clinical and demographic variables.

In categorical comparisons between groups, cross-tab statistics were provided and significance levels were estimated using chi-square test. Prognostic values of demographic and tumor characteristics were assessed with Cox regression analysis according to forward model. For relationships of same characteristics with survival and with each other, Pearson and Spearman correlation tests were used. Disease-free survival is estimated as time between diagnosis and first relapse and overall survival is estimated as time between diagnosis and death. Their impacts on life were evaluated with Kaplan-Meier test.

A value of $p<0.05$ was accepted as statistically significant. All analyses were performed using Statistical Program for Social Sciences version 15,0 for Windows.

Results

Mean age of 117 female patients in this study was

Table 1. Demographic, Clinical and Histopathological Features of all Patients in this Study

Features			n, % mean±std.dev.
Age (years): n, (mean±std.dev)			117, (55±12)
Age at diagnosis (years): n, (mean±std.dev)			117, (52±12)
Family history for breast cancer			
	Absence		104 (89)
	Presence		13 (11)
Menopausal status	Postmenopausal		66 (56)
	Premenopausal		51 (44)
Time of the menopause: n, (mean±std.dev)			66, (48±4)
Body mass index	Obesity (>30 kg/m^2)		27 (26)
(kg/m^2)	Over-weight (25-30 kg/m^2)		37 (37)
	Normally (<25 kg/m^2)		37 (37)
Histological type	Invazive ductal carcinoma		94 (80)
	Invazive lobular carcinoma		9 (8)
	Inflammatuary carcinoma		7 (6)
	Atipical medullary, tubular and other		7 (6)
Localization of tumour in the breas		Upper outer quadrant	52 (50)
		Lower outer quadrant	5 (5)
		Upper inner quadrant	3 (3)
		Lower inner quadrant	12 (11)
		Unknown	16 (15)
Multifocality or multicentricity			
	Absence		16 (14)
	Presence		101 (86)
Operation type	Radically mastectomy		76 (65)
	Breast-conservation surgery		41 (35)
Axillary approaches	Axillary dissection		97 (83)
	Sentinel lymph node sampling		27 (17)
Tumour grade		1	7 (6)
		2	73 (62)
		3	21 (18)
		Unknown	16 (14)
Tumour size [mean±std.dev: 2.2±0.9 (cm)]			
		<2 cm	19 (16)
		2-5cm	58 (50)
		>5 cm	39 (33)
Nodal status		N0	55 (47)
		N1	26 (23)
		N2	18 (15)
		N3	18 (15)
Lymphovascular invaison		Absence	29 (25)
		Presence	70 (60)
		Unknown	18 (15)
Stage (TNM)		I	21 (18)
		II	84 (72)
		III	12 (10)
Estrogen receptor status		Positive	69 (59)
		Negative	48 (41)
Progesterone receptor status		Positive	68 (58)
		Negative	49 (42)
Her2/neu status		Positive*	41 (35)
		Negative	76 (65)
Main molecular subtype of tumor		Luminal A	50 (43)
		Luminal B	29 (25)
		Her2- positive	18 (15)
		Triple negative	19 (16)
Ki67 staining	Absence		67 (58)
	Presence		39 (33)
	Unknown		11 (9)
p53 status	Absence		73 (62)
	Presence		37 (32)
	Unknown		7 (6)
Ki67 scoring	<20%		67 (58)
	20-50%		20 (17)
	>50%		19 (16)
	Unknown		11 (9)
p53 scoring	Negative		73 (62)
	Score 1		9 (8)
	Score 2		16 (14)
	Score 3		12 (10)
	Unknown		7 (6)

*immunohistochemical or FISH

53±12 years (age range 30-80) and their mean age at diagnosis was 52±12 years (age range 26-82). While only one of these patients were observed without treatment, systemic adjuvant therapies and/or radiotherapy were given to remaining 116 patients.

Demographic and clinical characteristics of patients and histological and immuno-histological characteristics of tumor are shown in Table 1.

Patients' hormone receptor and Her2/neu status and stratification by receptors is pre-sented in Table 1.

In follow-up period average of 35 months (range: 3-153 months), patients' mean estimated disease-free survival was 91 months (range: 75-108 months), mean overall survival was 132 months (range: 119-145 months).

83 patients (71%) were disease-free and still in follow-up, 25 patients (21%) were being treated for metastatic disease. With one of them being co-morbid, a total of 9 (8%) patientshad lost their lives.

Disease-free survivals in overall study group were 88% in first year, 84% in third year, 83% in fifth year, and 52% in 10th year. Same values were 95%, 84%, 83%, and 83% for overall survival, respectively.

Results of disease-free survival and overall survival are indicated in Table 2, 3, and 4.

Tumor size was in a linear relationship with pathological node status and number of nodes involved (r=0.22, O=0.017, r=0.245, p=0.008, respectively). Relapse risk in patients with lymphovascular invasion was increased 3.3 times (95% confidence interval; CI 1.4-7.5; p=0.006), and death risk was increased 2.2 times (95%CI 1.5-3.4; p=0.014). Also lympho-vascular invasion in our patients was in a moderate linear relationship with T stage (r=0.210, p=0.023), pathologic nodal stage (r=0.250, p=0.007), and number of nodes involved (r=0.260, p=0.005).

In postmenopausal patients, disease-free and overall survival times were worse compared to premenopausal patients. In both groups there was no significant difference

Table 2. Rate of Disease-free Survival (DFS) for all Patients and for pT (Pathological tumor stage) and pN (Pathological nodal stage)

Study variables		1-year DFS rate (%)	3-year DFS rate (%)	5-year DFS rate (%)	10-year DFS rate (%)
All patients		88	84	83	52
pN	N0	89	64	42	
	N1	67	67	67	
	N2	72	72	72	
	N3	69	40	40	
pT	T1	89	80	57	
	T2	79	61	45	
	T3	74	61	61	
	T4	52	41	35	

Table 3. Rate of Overall Survival (OS) for all Patients and for pT (Pathological tumor stage) and pN (Pathological nodal stage)

Study variables		1-year OS rate (%)	3-year OS rate (%)	5-(%) OS rate (%)	10-year OSrate(%)
All patients		95	94	83	83
pN	N0	100	91	81	
	N1	90	80	80	
	N2	89	89	89	
	N3	87	87	87	
pT	T1	100	92	92	
	T2	96	86	76	
	T3	88	88	88	
	T4	61	52	47	

Table 4. Disease-free Survival and Over-all Survival of Patients as Study Variables

Study variables	Disease-free survival ; months (range)	p value*	Overall survival months (range)	p value**
Menopausal status				
Pre-	26 (8-96)	0.037*	33 (12-96)	0.024**
Post-	20 (2-144)		27 (3-153)	
Body-mass index				
Normal	21 (3-144)	0.650	27 (12-153)	0.960
Over-weight	23 (3-134)		27 (3-134)	
Obesity	19 (2-96)		26 (13-96)	
Histological type				
Invasive ductal carcinoma	25 (2-144)	0.004*	29 (2-153)	0.018**
Invasive lobular carcinoma	30 (5-110)		30 (9-110)	
Inflammatuvary carcinoma	10 (3-21)		21 (14-37)	
Other	31 (13-67)		31 (13-67)	
Stage				
I	29 (12-80)	0.502	30 (17-80)	0.390
II	21 (2-144)		26 (3-153)	
III	37 (7-90)		42 (14-90)	
pT				
T1	27 (8-90)	0.059	29 (13-90)	0.720
T2	26 (2-110)		30 (3-110)	
T3	21 (4-144)		25 (12-153)	
T4	11 (11-11)		33 (33-33)	
pN				
N0	26 (3-144)	0.071	28 (3-153)	0.260
N1	19 (2-86)		26 (12-86)	
N2	29 (3-110)		37 (17-110)	
N3	18 (5-96)		21 (9-96)	
Ratio of metastatic node/dissected node				
≤25%	26 (2-144)	0.021*	30 (3-153)	0.160
25-50%	21 (3-110)		33 (17-110)	
50-75%	37 (4-96)		45 (15-96)	
≥75%	14 (5-21)		16 (9-32)	
Lymphovascular invasion				
Presence	19 (3-134)	0.001*	24 (9-134)	0.006**
Absence	28 (2-144)		30 (3-153)	
Tumor grade				
Grade 1	36 (16-144)	0.205	36 (16-153)	0.890
Grade 2	25 (2-110)		29 (3-110)	
Grade 3	19 (12-90)		19 (12-90)	
Estrogen receptor				
Positive	26 (2-134)	0.630	28 (3-134)	0.220
Negative	21 (5-144)		28 (12-153)	
Progesteron receptor				
Positive	25 (2-134)	0.368	28 (3-134)	0.970
Negative	23 (3-144)		28 (3-153)	
Hormone receptor status				
Positive	26 (2-134)	0.480	29 (3-134)	0.950
Negative	21 (5-144)		25 (12-153)	
Biological sub-type				
Luminal A	26 (2-134)	0.009*	28 (3-134)	0.400
Luminal B	26 (4-110)		31 (13-110)	
Her-2 over-expressed	23 (13-90)		23 (13-90)	
Triple negative	18 (5-144)		25 (12-153)	
Her2 expression status				
Positive	25 (4-110)	<0.001*	30 (13-110)	0.170
Negative	23 (2-144)		27 (3-153)	
Staining with ki67				
Positive	26 (3-110)	0.240	30 (9-110)	0.310

between hormone receptor status, tumor degree, Her2/neu status, disease stage, node involvement, ki67 and p53 staining characteristics (p>0.05). However, in postmenopausal women, there was a higher rate of lymphovascular invasion (46% *vs* 29%; p=0.47) and mostly T3 tumor (38% *vs* 28%; p=0.51) was present. There was no significant relationship between Her2/neu status and other study variables.

In 29% of patients (n=29) distant metastasis was observed, in 3% (n=4) local relapse in similar histological characteristics was observed and in 1% (n=1) a second cancer in similar histological type in opposite breast was observed. In 10% of patients (n=11) bone metastasis, in 5% (n=6) lung metastasis, in 3% (n=4) liver metastasis, in 1% (n=1) both bone and brain metastasis, and in 1% (n=1) isolated brain metastasis were observed.

Mean age of patients with metastasis was 64 years (age range 30-88) and it was statistically more than patients without metastasis (mean age 52, range 34-84) (p=0.001). In post-menopausal women, metastasis rate was 36% (n=24) and this rate was significantly higher compared to premenopausal women (18%, n=89) (p=0.038).

In multivariate analysis, age and Her2/neu status for disease-free survival were found as prognostically significant (OR 1.08 95%CI 1.05-1.14; p=0.001 and OR 0.135 94%CI 0.31-0.59; p=0.008, respectively). On overall survival, only age was significantly effective (OR 1.08, 95%CI 1.05-1.14; p=0.001).

Discussion

Although it might seem like a repetition of previous studies, we aimed to compile data of our early stage breast cancer patients in own institute and determine aspects of it that is consistent with literature, approach our patients and their tumor cells from our own perspective and understand them better.

While in beginnings of late century, breast cancer patients had an average survival of 3 years, today these rates are for one year 98%, for three years 85%, and for five years 82% (Goldhirsch et al., 2007). In our study, our patients' survival was in one year 95%, in three years 84%, and in five years 83%. These rates were generally consistent with literature data.

Many studies are conducted to understand the natural progression of breast cancer and to find better prognostic and predictive indicators of this disease. Until today, more than 150 prognostic factors are identified. However, in clinical practice very few of these factors are being used. Today, nodal metastasis, tumor size, histological type, tumor degree, presence of lymphovascular invasion, hormone receptor and Her2/neu status, and patient's age at diagnosis are main prognosis related characteristics that are being used. Independent from all patient and tumor related characteristics; most important prognostic factor of breast cancer is axillary involvement (Kröger et al., 2006; Taneja et al., 2010; Weigel et al., 2010; Jung et al., 2013).

In previous studies, it was reported that in patients with 1 to 3 node involvement five year survival rate was 73%, with 4 to 12 it was 46%, and with more node involvement it was 28%. However, in node-negative breast cancer patients five year survival rate was reported as 83%. Overall, in patients with node involvement mortality rate was 20% (Carter et al., 1989; Rosen et al., 1992; Truong et al., 2008). We can explain the inconsistency of our study with the literature with our relatively short follow-up periods.

In patients without nodal involvement, most important prognostic factor is tumor size. While in tumors smaller than 1 cm, five year survival rate was reported by Carter et al. (1989) as 99%, this rate is 89% in tumors with a size of 1 to 3 cm, and 86% in tumors with a size of 3 to 5 cm. When it comes to disease-free survival rates, according to rates reported by Rosen et al. (1992); 20 year disease-free survival rate was 88% in tumors smaller than 1 cm, in tumors with a size of 1.1 to 3 cm it was 72 cm, and in tumors with a size of 3.1 to 5 cm it was 59%. In current studies, it is stated that in tumors smaller than 1 cm, other prognostic factors should be considered for adjuvant therapy decision (Lai et al., 2011). In our study, we could not find any significant relationship between tumor size and disease-free/overall survival. Similarly, also in univariate and multivariate analyses, tumor size was not found as a prognostic factor. This situation may be related to relatively small number of patients.

In our study, we could not reach a distinct conclusion about tumor degree as an important prognostic factor. Inconsistent results may be related to relatively small number of patients.

In our study most important prognostic factor that is prominent is lymphovascular invasion. A significant relationship between lymphovascular invasion and risk of recurrence was shown by Rosen et al. (1989). In this study, while recurrence rate in stage 1 breast cancer patients with lymphovascular invasion was 38%, in patients without lymphovascular invasion this rate was 22% (Rosen et al., 1989). In current guidelines, presence of lymphovascular invasion is reported as an important prognosis indicator in node-negative breast cancer patients with borderline tumor size (Rakha et al., 2012).

In contrary to the literature, we have found that postmenopausal breast cancer patients had worse survival rates. This inconsistent result may be related to our use of only adjuvant endocrine therapy option on 12% of patients, beyond high lymphovascular invasion rate and large tumor size in postmenopausal women.

In breast cancer, endocrine approach is an important part of the treatment. Grann et al. (2005) showed in their study that estrogen and progesterone receptor status was an independent prognostic factor in breast cancer. In a study (EBCTCG) (1998), high rates of estrogen positivity reduced death risk related to cancer by 31%. However, another study (Dunnwold et al., 2007) reported that postmenopausal breast cancer patients with high estrogen receptor expression had that same bad prognosis of hormone receptor negative breast cancer patients.

But in ATAC (Dowsett et al., 2008) and BIG 1-98 (Viale et al., 2007) studies, it is found that breast cancer patients with different levels of estrogen receptor expression benefited from tamoxifen and aromatase inhibitors with a similar rate. In current guidelines based on current literature data, it is stated that hormone receptor

status has mainly a predictive value.

Hormone receptor positivity increases with age. In previous studies, hormone receptor positivity rate is reported as 55-65%. In our study, we found this rate as 68%. We found that this rate was 79% in patients above sixty years of age. Another result of our study that is in-consistent with literature is overall and disease-free survival rates in hormone-sensitive and non-hormone-sensitive patients. We explain this situation with our relatively small number of patients.

In 15 to 30% of breast cancer patients, Her2/neu over-expression and amplification is seen. In previous studies, it is reported that patients with nodal metastasis and Her2/neu over-expression had bad prognosis (Curigliano et al., 2009; Gonzales-Angulo et al., 2009). However, in node-negative patients it is shown that their prognoses will be worse in case of presence of Her2/neu over-expression. In our study we saw that Her2/neu receptor status had a significant effect on survival, but this relationship did not reflect on overall survival.

In HERA (Smith et al., 2007) study involving 5102 node-positive and high risk node-negative breast cancer patients, in women with breast cancer with adjuvant trastuzumab therapy administration for one year, survival rates were positively affected compared to patients without trastuzumab administration over two years of follow-ups. However, in results of Fin-Her (Joensuu et al., 2009) study showing that trastuzumab therapy for nine weeks also provides an advantage on disease-free survival; it is shown that trastuzumab therapy concomitant with docetaxel for nine weeks is effective, economic, and safe in side-effect aspect. Today in international guidelines, extension of anti-Her2/neu therapy in adjuvant setting to 52 weeks suggestion is in the foreground. Also, in a study of Rodrigues et al. (2010), it is stated that adjuvant therapy with trastuzumab, and long term suppression of Her2/neu receptor have positive effects on disease-free survival.

Biological group identified as triple-negative, without estrogen receptor, progesterone receptor, and Her2/neu expression consists of 10 to 15% of all breast cancer patients. Most of breast cancers related to mutant BRCA1 are reported as triple-negative patients (Nishimura and Arima, 2008). Patients in this group are generally younger, with higher axillary nodal involvement rate and with tumors with larger sizes and higher degrees. Because of these char-acteristics, they are considered to have aggressive progression. In our study, insufficient detection of events due to relatively small number of patients and short follow-up period did not allow characteristics of triple-negative breast cancer patients to be identified.

Despite many studies, prognostic characteristics of ki67 and p53 expression in breast cancer have not been clarified, yet. Today, especially in node-negative patients with small sized tumors, it is thought that these should be considered during treatment decision (Nishimura and Arima, 2008). However, ki67 staining over 20% is shown by Nishumara and Arima (2008) to be in a linear and significant relationship with young age, nodal involvement, large tumor size, hormone receptor negativity, p53 expression and Her2/neu over-expression. In our study, we did not find ki67 staining characteristics to be in any statistically significant relationship with metastasis rate and disease-free survival. However, it is found that in patients with highly stained tumors overall survival was affected negatively.

In a similar way, studies on p53 expression are also controversial. However, it is reported in a frequency of 20 to 50% in hereditary breast cancer patients. After the study of Ferrero et al. (2000), p53 expressions and mutations are considered to affect disease-free and overall survival negatively. In our study, probably due to our relatively small number of petients, no significant effect of p53 expression on survival could be shown.

In conclusion, this study of ours in 2011 which has relatively short follow-up times and small in numbers of patients, although till then studies on some new treatment options and prognostic molecules have been published, when inconsistent results according to infor-mation of its time are considered, it lets us think that we deal with one of most heterogenic patient groups of clinical oncology and what we know as right for breast cancer patients can always change. Today, clinical progression of each case with breast cancer and which treatment will be administered to these patients are determined by dealing with specific characteristics of patient and tumor separately. Therefore, it is obvious that a lot of histological, molecular, and genetic factors apart from prognostic and predictive factors accepted in international guidelines will continue to be studied. Thus, we are in an opinion that each breast cancer treatment center should examine its own data, and achieved results and also literature-based information should guide them on their clinical experience.

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