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Original Article

Clinicopathological features of breast cancer cases and their relationship with immunohistochemical findings

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Abstract

Aim: To determine the relationship between established prognostic markers and Ki67 proliferative index in breast cancer patients and investigate variations of prognostic parameters between material types (tru-cut biopsy or resection).

Material and Methods: Breast cancer cases reported in our laboratory between July 2015 and December 2019, as well as estrogen receptor (ER), progesterone receptor (PR), CerbB2, Ki-67 staining results, tumor type, histologic grade, tumor size, lymph node metastasis status parameters were obtained from the automation system. Tru-cut biopsy and resection materials were evaluated and the parameters were compared.

Results: 726 materials taken from 571 adult patients were included in this study. 297 (40.9%) of the cases were evaluated by tru-cut biopsy and 430 (59.1%) were resection material. The mean ER staining percentage was 86.5 (± 10.36) and it was 61.65 (± 22.84) for PR. Ki-67 proliferative index had an average value of 26.58 (± 17.67). There was no difference between the material types in terms of immunohistochemical markers, whereas there were differences between the two material types in histological grade results.

Conclusion: Besides established immunohistochemical prognostic markers, Ki67 proliferative index should be utilized in breast cancer cases and determination of histological grade in tru-cut biopsies is valuable for the clinical management of the tumor.

Keywords: Breast carcinoma; immunohistochemistry; Ki67; prognostic parameters

INTRODUCTION

Besides skin cancer, breast cancer is the most common type of cancer seen in women worldwide. According to data from the American Cancer Society, 13 million women are diagnosed with breast cancer annually and approximately 465,000 women die from breast cancer each year (1,2). While the lifetime probability of breast cancer in women is 4.8% in developed countries, this rate is 1.8% in developing countries (2-4). Incidence of breast cancer shows regional differences. The regions with the highest incidence are North America and Northern Europe, followed by Southern Europe and Latin America, respectively. The lowest rates of breast cancer are reported in Asia and Africa (5). In Turkey, breast cancer is the most common type of cancer in women with a prevalence of 23.8% (6,7). In the studies focused on people migrating from low-risk geographic regions to high-risk regions; it has been shown that after one or two generations, the frequency of the disease in this population reaches the frequency of high-risk areas. Therefore, geographical differences, lifestyle and environmental factors are thought to have an important role in the etiology of the disease (8). In high-risk regions; early menarche and obesity are thought to be the main contributors to the frequency of the disease. These factors are responsible for the prolonged estrogen exposition of the mammary gland. Late first pregnancy, low birth rate and short breastfeeding period which are characteristics of a modern lifestyle also contribute to an increased frequency of breast cancer. Risk factors that have been proved to be associated with breast cancer do not have the same impact on young and older patients. This can be explained by the hormonal condition which may be an important part in breast carcinogenesis and differentiation (9). On the other hand, there is also evidence of a reduction in mortality. This may be due to the possibility of early diagnosis by self-examination, screening by mammography or ultrasonography, and the introduction of more effective new treatment procedures (10). Recent advances in breast cancer treatment methods, particularly in chemotherapeutic treatments, have attracted attention (11). Treatment modalities are mainly determined by

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prognostic factors. Tumor size, lymph node metastasis status, ER, PR and CerB2 expression are important in determining treatment modality (10).

In our study, we evaluated our breast cancer cases and determined their histopathological types. We aimed to determine the relationship between established prognostic markers and the Ki67 proliferative index in these cases. We also examined the likelihood of these parameters to vary with the type of material (tru-cut biopsy or resection) and compared the data on these parameters between tru-cut biopsy and resection materials to contribute to treatment planning.

MATERIAL and METHODS

Breast cancer cases diagnosed in our hospital between July 1, 2015 and December 31, 2019 were determined retrospectively through the automation system and retrospective histopathological analyse wasn't performed .The demographic and clinical characteristics of the patients such as age, sex, lateralization, as well as immunohistochemical findings; ER, PR, CerbB2, Ki67 results, tumor type, histologic grade, tumor size, lymph node metastasis status were determined and their relationships were investigated. In addition, histological and immunohistochemical parameters were compared between material types when both types of materials could be obtained from the same patient. At the first diognosis, a microscope with the model of Olympus BX50F4, Japan was used and histopathological evaluation was performed as; ER and PR were considered positive for nuclear staining in ≥ 1% of tumor cells and, negative for nuclear staining in less than 1%. In addition, the severity of staining was classified as mild, moderate and strong. CerbB2 scoring was based on ASCO-CAP recommendations; negative (0 / +), equivocal (++), positive (+++). Tumor sizes were classified as; <2 cm (pT1), 2-5 cm (pT2) and >5 cm (pT3) while lymph node metastasis was classified as present or no observable metastasis (12,13). These data were compared between tru-cut biopsies and resection materials and the effect of the material type on the parameters was investigated.

Statistical analyses

Chi-square test was used where two groups were compared with distinct values and the Mann-Whitney U test was used in cases where two independent samples were selected from similarly distributed populations. Statistical analysis was performed with SPSS software (version 22.0, IBM, Armonk, NY, USA).

RESULTS

571 patients with a median age of 54.1 (ranging from 24 to 90) were included in this study (Table 1). Of these 571 patients, only 2 were male and 569 were female. There were 726 materials in total.

Table 1. The clinicopathologic features of the patients

Groups	Parameters	Frequency	Percentage
Material type	Tru-cut biopsy	297	40.9%
	Resections	430	59.1%
Biopsy location	Unknown	1	0.1%
	Right breast	321	44.2%
	Left breast	396	54.5%
	Both right and left breast	9	1.2%
Histologic grade	Unknown	113	15.5%
	Grade 1	46	6.3%
	Grade 2	369	50.8%
	Grade 3	199	27.4%
Lymph node status	Tru-cut biopsy	298	41.0%
	No information about lymph node status in a resection material	15	2.1%
	Lymph node metastasis present (Lymph node positive)	210	28.9%
	Lymph node metastasis not present (Lymph node negative)	204	28.1%
Histologic type	Unknown	46	6.3%
	Invasive Ductal Carcinoma / NST	528	72.6%
	Invasive Lobular Carcinoma	71	9.8%
	Medullary Carcinoma	6	0.8%
	Tubular Carcinoma	2	0.3%
	Papillary Carcinoma	3	0.4%
	Solid Papillary Carcinoma	2	0.3%
	Mixed Carcinoma	41	5.6%

	Malignant Philloides Tumor	3	0.4%
	Cribriform Carcinoma	4	0.6%
	Micropapillary Carcinoma	3	0.4%
	Invasive Ductal Carcinoma with Medullary Features	15	2.1%
	Inflammatory Breast Carcinoma	1	0.1%
	Adenoid Cystic Carcinoma	1	0.1%
	Lymphoma	1	0.1%
ER +/-	Estrogen Receptor Positive	594	85.5%
	Estrogen Receptor Negative	101	14.5%
ER intensity	None	1	0.2%
	Weak Staining	10	1.7%
	Moderate Staining	75	12.6%
	Strong Staining	507	85.5%
PR +/-	Progesteron Receptor Positive	533	77.1%
	Progesteron Receptor Negative	158	22.9%
PR intensity	Weak Staining	44	8.3%
	Moderate Staining	126	23.7%
	Strong Staining	362	68.0%
Cerbb2	Score 0, Negative	310	49.0%
	Score 1, Negative	126	19.9%
	Score 2, Positive	74	11.7%
	Score 3, Positive	123	19.4%
E-Cadherin	E-Cadherin Positive	561	89.8%
	E-Cadherin Negative	64	10.2%
Size	Unknown / No information given	300	41.3%
	Less than 2 cm	152	20.9%
	2-5 cm	221	30.4%
	More than 5 cm	54	7.4%

When the immunohistochemical prognostic markers of the cases were examined, the mean value of ER was 86.50 (± 10.36), and PR was 61.65 (± 22.84). Ki67 proliferative index had an average value of 26.58 (± 17.67). There was a weak positive linear relationship between ER and PR (r = 0.277 p <001). There was a negative correlation between ER and Ki67 proliferative index (r = -0.246 p <0.001). When resection materials were compared with lymph node metastasis and histologic grade and tumor size, a statistically significant relationship was found (p <0.001) (Table 2, 3).

When tumor size and histological grade were compared; Regardless of tumor size, histologic grade 2 tumors were the most common, whereas histologic grade 1 was more frequent (13.8%) in pT1 tumors and histologic grade 3 was more common in pT3 tumors (38.9%) (p <0.001). There was also a significant difference between tumor size

Table 2. The relationship of lymph node metastasis and histologic grade

		Histologic Grade				P value
		Grade 1 (n, %)	Grade 2 (n, %)	Grade 3 (n, %)	Unknown (n, %)	
Lymph Node Metastasis	Present	10	107	85	8	<0.001
		21.7%	29%	42.7%	7.1%	
	Absent	20	115	57	12	
		43.5%	31.2%	28.6%	10.6%	
	Unknown	0	6	5	4	
		0.0%	1.6%	2.5%	3.5%	

and Ki67 proliferative index (Figure 1). While ER and PR positivity were found to be significantly associated with histological grade (p <0.001), no significant relationship was found with lymph node metastasis status. (p = 0.347 and p = 0.501). CerbB2, one of the immunohistochemical prognostic markers, was also found to be significantly associated with histological grade (p <0.01) (Table 4).

Ki67 expression, which is known to be associated with poor clinical outcome, was compared with histological grade; as the grade increased, Ki67 expression increased (p <0.001) (Figure 2). However, there was no significant relationship between Ki67 expression and lymph node metastasis (p = 0.485). There was a negative linear correlation between Ki67 and ER and PR variables

Table 3. The relationship of lymph node metastasis and tumor size

		Size				P Value
		Unknown	<2 cm	2-5 cm	>5 cm	
Lymph Node Status	Tru-cut biopsies	296	2	0	0	<0.001
		98.7%	1.3%	0.0%	0.0%	
	No information about lymph node status in a resection material	2	8	5	0	
		0.7%	5.3%	2.3%	0.0%	
	Lymph node metastasis present (Lymph node positive)	2	48	117	43	
		0.7%	31.6%	52.9%	79.6%	
	Lymph node metastasis not present (Lymph node negative)	0	94	99	11	
		0.0%	61.8%	44.8%	20.4%	

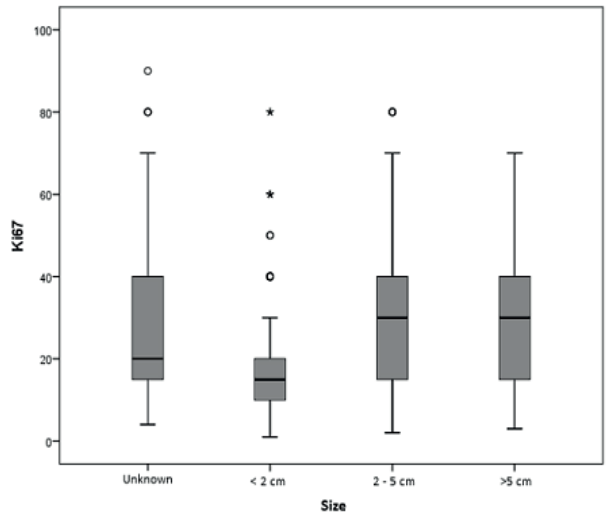

Figure 1. The relationship between tumor size and Ki67 proliferative index

(ER; r = -0.246 P <0.001 PR; r = -0.225 p <0.001). There was no significant relationship between age and histologic grade (p = 0.171), but the relationship between age and tumor size was significant (p<0.05). The mean age was 55 years in patients with tumor size <2 cm, and 48.5 years in patients with tumor size >5 cm (p = 0.028). It was noteworthy that patients with larger tumors were younger. There was no significant relationship between age and lymph node metastasis status (p = 0.499).

When tru-cut biopsies and resection materials were compared; the difference between histologic grades was significant (p = 0.016). However, frequency of grade 1 cases did not show a significant difference according to the material type (7.7% in tru-cut biopsies, 7.4% in resection materials), whereas grade 3 cases were frequently seen in resection materials (25% in tru-cut biopsies, 36.2% in resection materials). The most common grade in both groups was grade 2 (67.3% in tru-cut biopsies and 56.4% in resection materials).

Table 4. Relationship of ER, PR and CerbB2 status with histological grade

		ER		PR		CerbB2 Score				P Value
		+ (n, %)	- (n, %)	+ (n, %)	- (n, %)	0 (n, %)	1 (n, %)	2 (n, %)	3 (n, %)	
Histologic Grade	Grade 1	42	2	40	4	26	12	0	0	<0.001
		7.1%	2.0%	7.5%	2.5%	8.4%	9.5%	0.0%	0.0%	
	Grade 2	340	15	300	48	155	77	48	47	
		57.2%	14.9%	56.3%	30.4%	50.0%	61.1%	64.9%	38.2%	
	Grade 3	123	69	108	86	72	28	15	62	
		20.7%	68.3%	20.3%	54.4%	23.2%	22.2%	20.3%	50.4%	
	Unknown	89	15	85	20	57	11	11	14	
		15.0%	14.9%	15.9%	12.7%	18.4%	14.9%	14.9%	11.4%	

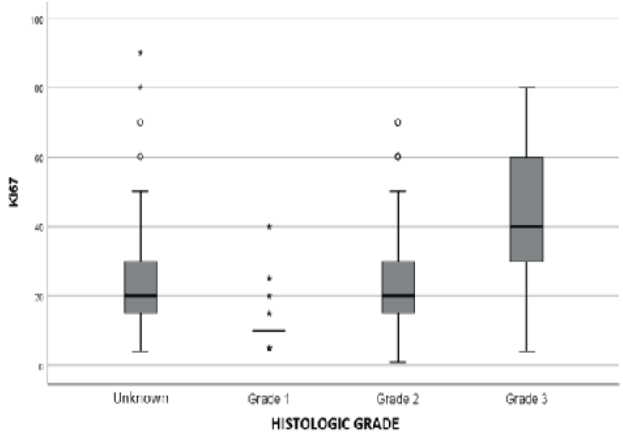

Figure 2. The relationship between histologic grade and Ki67 proliferative index

DISCUSSION

As in all over the world, breast cancer is a frequently seen type of cancer in Turkish women and it is possible to manage the treatment of this disease if the treatment is correctly chosen according to prognostic markers. In this study, we aimed to present additional data that may contribute to treatment by examining the histopathological and clinical features of 571 patients diagnosed with breast cancer. We planned to determine the possible relationship by comparing the Ki67 proliferative index with established parameters and to reveal the possible effect of material type on prognostic markers in breast cancer. Thus, we aimed to determine immunohistochemical and histomorphological parameters that should be evaluated in different material types in breast cancer cases. The median age of our cases was 54.1 (range; 24 to 90) and there were similar results in the literature such as 48.8 (± 13.5) and 58.6 (± 12.4) (14). The most common histological type was invasive carcinoma with no special type (NST) (n = 528, 72.6%), whereas the most common histologic grade was grade 2 (n = 369, 50.8%). Most of the available materials were resection materials (n = 430, 59.1%), while tru-cut biopsies were in the minority (n = 297, 40.9%). In cases where both tru-cut biopsies and resection materials were evaluated in our laboratory, we were able to investigate the effect of the type of material on prognostic markers. We have seen similar results among immunohistochemical markers. However, there were differences between the histological grade given in tru-cut biopsies and the resection materials of the same cases. Out of 155 patients whom we had both tru-cut biopsy and resection material, 20 patients have seen an increase in tumor grade from biopsy to resection, while the reverse was true for only 4 patients. Since the tumor structure seen in tru-cut biopsy does not necessarily reflect the whole tumor, there may be differences in the assessment of nuclear pleomorphism, tubule formation, and mitosis. Therefore, the histological grade may be scored differently in resection materials. However, it should be noted that in our study, these differences entirely consisted of one score up or down, as there were no patients who had histologic grade difference between biopsy and resection of more than one. It has been reported in the literature that histologic grade can be given in core biopsies, but the grade can be scored lower in these specimens due to inaccuracies especially in the evaluation of mitosis (15). Because of the negligible difference we observed in our cases, we think that histological grade should be disclosed in tru-cut biopsies as it may contribute to neoadjuvant chemotherapy planning. On the other hand we should keep in mind the importance of inter-observer variability on the evaluation of the histological grade. In a cohort including pathology reports of 33,043 patients from 39 laboratories , the authors observed substantial inter- and intra-laboratory variation in histologic grading. They reported that, after case-mix correction, 20 laboratories (51.3%) showed a significantly grading differences. These differences were also observed among pathologists within laboratories (16). Although our study wasn't specifically designed to assess intra- and inter-observer variability; in order to minimize the confounding effects, only those cases which were reported by the consensus of four pathologists were chosen.

The importance of ER, PR and CerbB2 status in determining the clinical management of breast cancer is known. In addition, tumor size, lymph node metastasis, and distant metastasis are important parameters according to the TNM system used in staging (12). Patients who are determined to be positive for ER and PR, have high sensitivity to hormone therapy (17). Amplification or overexpression of CerbB2 in breast carcinoma is associated with poor prognosis, short disease-free interval and short survival time in both node negative and positive patients (18). Ki67 is a nuclear non-histone protein, and a proliferation marker. It is expressed in the G1, S, G2 and M phases of the cell cycle but not the G0 phase (17). According to the immunohistochemical data obtained in our study, ER and PR were positive in most of our cases (n=598, 82.3% and n=523, 72%). CerbB2 overexpression was in the minority (n = 123, 16.9%). When compared with the literature, there were very different data. In a study of 2492 patients, the authors reported that while ER and PR positivity was 77.8% and 68% in German women, these rates were 45% and 38% in Sudanese women (14). While our results were consistent with the results of German women, we found a much higher ER and PR positivity than Sudanese women. In another study, it was emphasized that while these rates were 54.4% and 55.7% in women under 40 years of age, they increased to 66.3% and 59% over 40 years of age (19). In another study of 150 cases, much lower rates were reported as 32.7% and 25.3% (20). In another study reported as 50-80% of ER positivity, the importance of endocrine therapy was emphasized and it was reported that these treatments were modeled on antagonizing the effect of estrogen (21). Another study reported that PR positivity varies in the range of 60-70% and that these rates increase in elderly patients (22). In our study, we found a weak positive correlation between

ER positivity and age (r = 0.182, p <0.01). The CerbB2 positivity we obtained was 16.9% and there were different data in the literature such as 41.4%, 31%, 24.7%, 22.3%, 17.5% and 17.3% (17,23,20,19,14,24). Some of these studies found that CerbB2 status was associated with histological grade (24,19,20), while others associated it with Ki67 proliferative index (23). In our study, we found a significant relationship between CerbB2 and histological grade (p <0.001). All of the negative cases of CerbB2 were histologic grade 1. 64.9% (n = 48) of cases with equivocal CerbB2 (score 2, ++) were evaluated as histologic grade 2, and 20.3% (n = 15) of these tumors were evaluated as histologic grade 3. In the remaining cases, histological grade information was not available in the reports. Cases with a score of CerbB2 positive (score 3, +++) were frequently evaluated as histologic grade 3 (50.4%, n = 62). In our study, we found that as histologic grade increased, Ki67 proliferative index was also increased (p <0.001]. There was also a significant linear relationship between tumor size and Ki67 index (p <0.001). As we expected, in similar fashion to known literature we found a negative linear correlation between Ki67 proliferative index and ER, PR expression. In the literature, the Ki67 level was associated with histological grade, tumor size, ER, PR and CerbB2 status of the tumor (25). In another study of 125 cases, the authors argued that the Ki67 proliferative index was related to histologic type, histologic grade, ER and PR status, and molecular type of tumor, and they defended that there was no relationship between CerbB2 status and age (26). On the other hand we should not ignore many previous studies with concordance of HER2 analysis which reported different agreement results. A multicenter concordance study with a total of 30 breast cancer samples reported an average of 69.3% concordance rate was found between study centers and the reference center in determining immunohistochemical staining of HER2. This rate was found to be 60.0% for 1+ samples, and 81.0% for 3+ samples. When analyzed ac¬cording to negative (0-1+), equivocal (2+), positive (3+) classification, the average concordance rates naturally increased up to 89.6% (1). On the other hand, Thomson's study showed that the inter-observer agreement for staining intensity for each antibody was good for 0+ and 3+ groups but poor for 1+ and 2+ groups (27). Two studies analyzing the con¬cordance between different centers have shown that samples showing 100% concordance are positive or negative samples, and that equivocal (2+) samples were not fully concordant (28,29). As with evaluation of histological grading, only those cases reported by the consensus of four pathologists were chosen.

CONCLUSION

In addition to the established prognostic markers of the tumor, the correlation of Ki67 proliferative index with tumor size, histologic grade, ER, PR and CerbB2 status was demonstrated in our study. Although we didn't observe a significant relationship with lymph node involvement, we think that the utilization of Ki67 proliferative index in every case of breast cancer is valuable for the clinical management of the tumor. It is also clear that immunohistochemical results should be disclosed in tru-cut biopsies. In addition, with regard to the histological grade of the tumor, the possibility of different results in resection materials should be kept in mind. However, since this difference is negligible, we believe that histological grade information should be noted in tru-cut biopsy reports for the clinical management of the patient.

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