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Original Article

The relationship between Ki-67 index and axillary lymph node metastasis in breast carcinoma

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Abstract

Aim: Breast cancer is the most common type of cancer in women. The presence and number of metastatic lymph nodes in the axilla are the most significant prognostic factors in breast cancer. In addition, tumor size, lymphovascular invasion, perineural invasion, histopathological type and grade of the tumor are among the best-known prognostic factors. Ki-67 is expressed in G1, S, G2 and M phases of the cell cycle but not in the G0 phase, which allows it to be used as a marker for proliferating cells. The purpose of this study is to determine the relationship between Ki-67 Index and classical prognostic factors in breast cancer patients and to investigate its effect on axillary lymph node metastasis.

Material and Methods: 46 patients, who were diagnosed as breast carcinoma in Sivas Cumhuriyet University Medical Faculty Surgical Oncology Department and who underwent a modified radical mastectomy and axillary lymph node dissection between 2017 and 2019 were included in this study. Histological tumor type, stage, status of axillary lymph nodes and Ki-67 Index were evaluated retrospectively from the pathology reports of the patients. The patients were grouped under three categories according to Ki-67 Index.

Results: Regarding the grouping of the patients according to Ki-67 Index, the ones below 15% formed the first group, between 15-29% the second group, and above 30% the third group. The distribution of the patients according to negativity-positivity of axillary lymph node metastasis in the groups was as fallow: First group, 7 (41.2%) negative - 10 (58.8%) positive; Second group 4 (33.3%) negative - 8 (66.7%) positive; Third Group 3 (17.6%) negative - 14 (82.4%) positive. Of the 46 patients included in the study, 14 (30.4%) were negative for axillary lymph node metastasis and 32 (69.9%) were positive. In our study, the relationship between the increase of Ki-67 Index and axillary lymph node positivity was found to be statistically significant.

Conclusion: In this study, we investigated the relationship between Ki-67 Index and classical prognostic markers, especially lymph node metastasis. Proliferation is an important indicator used to predict prognosis and treatment response in breast cancer. In our study, Ki-67 Index, one of the cell proliferation markers, was found to be positively correlated with axillary lymph node metastasis and other prognostic factors. Therefore, Ki-67 Index was shown to be a significant prognostic indicator in breast cancer.

Keywords: Axillary lymph node; breast cancer; Ki-67

INTRODUCTION

Breast cancer is the most common type of cancer in women, it is also the second most common cause of death after lung cancer (1,2). Its prevalence is 22-26% according to epidemiological studies and the mortality risk due to breast cancer is around 18% (3,4). Surgery is the first and most effective option in the treatment of breast cancer, and it includes all interventions applied to the breast and axilla. Prognostic and predictive factors are used to determine prognosis and appropriate treatment methods in breast cancer (5). The presence and number of metastatic lymph nodes in the axilla is one of the most important prognostic factors. In addition, tumor size, lymphovascular invasion, perineural invasion, histopathological type and grade of the tumor are among the best-known prognostic factors (6,7). The state of axilla is closely related to survival and disease-free survival. Knowing the state of axilla is very important in the planning and execution of adjuvant therapy. Five-year survival rate was reported to be 94% for the patients without axillary metastasis, 85% for the patients with 1-3 lymph node involvement, and 58% for the ones with 4 and more lymph node involvement, while disease-free survival rates in the same series were 83%, 73% and 38%, respectively (8).

Ki-67 is a nonhistone nuclear cortex protein encoded by the MKI67 gene. It is expressed in the G1, S, G2, and M phases of the cell cycle, but not in the G0 phase, which allows it to be used as a marker for proliferating cells.

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Although its function is not known, it is thought to play a role in cell division and RNA synthesis (9-10). Ki-67 Index, which indicates the percentage of the number of immunostained nuclei among the total number of nuclei of tumor cells, is frequently associated with the clinical course of cancers. It was shown that Ki-67 Index was associated with poor clinical outcomes in patients with breast cancer (11,12). It was also shown to predict chemotherapy response in patients with breast cancer diagnosed with axillary lymph node involvement and in the ones treated with neoadjuvant chemotherapy (13,14). As stated in St Gallen 2011 consensus report; the criterion used to differentiate between luminal A and B tumors is that Ki-67 Index of most of the negative HER-2 patients were 14% or lower. The consensus report published in 2015 suggested that local laboratory median Ki-67 values should also be considered. The cut-off of Ki-67 Index was accepted to be between 20-29% by the majority of the participants (15,16).

The purpose of this study is to determine the relationship between Ki-67 Index and classical prognostic factors in breast cancer patients and to investigate its effect on axillary lymph node metastasis.

MATERIAL and METHODS

Experimental Design

Forty-six patients, who were diagnosed as breast carcinoma in Sivas Cumhuriyet University Medical Faculty Surgical Oncology Department and who underwent a modified radical mastectomy and axillary lymph node dissection between 2017 and 2019 were included in this study. Histological tumor type, stage, and status of axillary lymph nodes and Ki-67 Index were evaluated retrospectively from the pathology reports of the patients. TNM staging system revised by AJCC in 2017 was used for staging. The percentage of Ki-67 was recorded. The patients were grouped under three categories according to Ki-67 levels, as below 15%, between 15-29%, and 30% and above.

Statistical Analysis

SPSS 15.0 for Windows was used for statistical analysis. Regarding descriptive statistics, frequency, percentages, mean, standard deviation, minimum and maximum of categorical variables were given. The differences between categorical variables in independent groups were tested by Chi-square method. Monte-Carlo simulation was applied when the necessary conditions are not met. The relationship between ordinal and numerical variables was examined by Spearman Correlation analysis. The significance level was taken as $p<0.05$.

RESULTS

Regarding the grouping of the patients according to Ki-67 level, the ones below 15% formed the first group, between 15-29% the second group, and 30% and above the third group. The distribution of the patients according to negativity-positivity of axillary lymph node metastasis in the groups was as fallow: First group, 7 (41.2%) negative -10 (58.8%) positive; second group 4 (33.3%) negative -8 (66.7%) positive; Third Group 3 (17.6%) negative -14 (82.4%) positive. Of the 46 patients included in the study, 14 (30.4%) were negative for axillary lymph node metastasis and 32 (69.9%) were positive. In our study, the relationship between the increase of Ki-67 Index and axillary lymph node positivity was found to be statistically significant ($p = 0.039$). The figures are shown in Table 1.

Regarding the age of the patients, the youngest patient was 30-year-old and the oldest one was 75-year-old at the time of diagnosis; the mean age was 51.70 ± 9.56 years. 19 (41.3%) cases were under 50, while 27 (58.6%) were over 50. Tumor sizes varied between 1 and 9 cm with a mean diameter of 4.65 ± 1.89. The macroscopic tumor diameter of 8 cases (17.3%) was between 1-2 cm, 22 (47.8%) of them was between 2-5 cm, and 16 (34.7%) of them was over 5 cm. No spread to the chest wall or skin was detected. 32 patients (66.1%) had invasive ductal carcinoma, 6 patients (13.0%) had invasive lobular carcinoma, 3 patients (6.5%) had mucinous carcinoma, 2 patients (4.3%) had medullary carcinoma and 3 patients (6.5%) had mixed breast carcinoma.

Minimum number of lymph node dissections in the axilla was 6, whereas the maximum number was 26. Lymph node metastasis was observed in 32 (69.6%) of the cases.

Table 1. The relationship between axillary lymph node metastasis and Ki-67 Index

			Axillary Lymph Node			
			Negative	Positive	Total	P
Ki-67 Index	<%15	n	**7**	**10**	**17**	0.039
		%	41.2	58.8	100.0	
	%15-%29	n	4	8	17	
		%	33.3	66.7	100.0	
	>%30	n	3	14	12	
		%	17.6	82.4	100.0	
Total		n	14	32	46	
		%	30.4	69.6	100.0	

Regarding all of the patients with lymph node involvement, 15 (32.6%) of them had 1-3 lymph node metastases, whereas 17 (36.9%) of them had 4-9 metastases. The distribution of the patients according to TNM staging was: 2 patients (4.3%) in IA, 8 patients (17.3%) in IIA, 11 patients (23.9%) in IIB and 25 patients (54.3%) in IIIA. The details of the clinicopathological features of the cases are shown in Table 2.

Table 2. Clinicopathological features of the cases

		n	%
Age	Under 50	19	41.3
	Over 50	27	58.6
Tumor Diameter	0-2 cm	8	17.3
	2-5 cm	22	47.8
	Over 5 cm	16	34.7
Histological Type	Invasive Ductal Carcinoma	32	69.5
	Invasive Lobular Carcinoma	6	13.0
	Medullary Carcinoma	2	4.3
	Mixed Breast Carcinoma	3	6.5
	Mucinous Carcinoma	3	6.5
Lymph Node Metastasis	None	14	30.4
	1-3	15	32.6
	4-9	17	36.9
TNM	IA	2	4.3
	IIA	8	17.3
	IIB	11	23.9
	IIIA	25	54.3

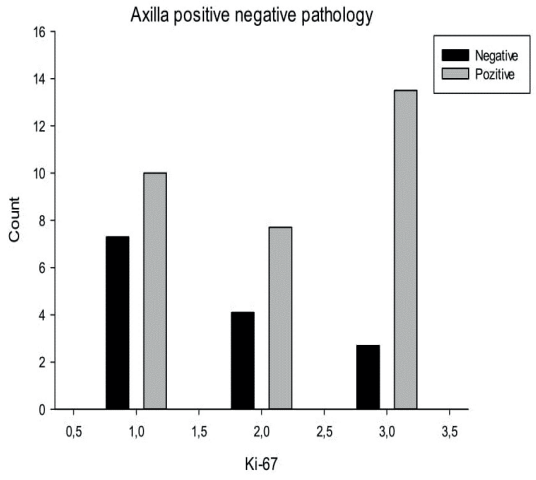

Figure 1. The distribution of axillary lymph node metastasis in Ki-67 groups

The review of Ki-67 Index according to age revealed that there was no difference among patients under and over 50 years. The analysis of Ki-67 Index according to tumor diameter showed that Ki-67 Index of the patients having a tumor of 0-2 cm and 2-5 cm diameter were between 15-29%, whereas Ki-67 Index of the patients whose tumor size is over 5 cm was above 30%. The examination of Ki-67 Index according to histological type of the tumor showed that the mean Ki-67 Index of the patients with invasive ductal carcinoma was between 15-29%, whereas the mean Ki-67 Index was over 30% in patients with invasive lobular carcinoma, medullary carcinoma, and mixed breast carcinoma. On the other hand, the mean Ki-67 Index of mucinous carcinoma cases was below 15%. The review of Ki-67 Index according to TNM staging showed that Ki-67 Index increased as the stage increased (Figure 1).

DISCUSSION

Breast cancer is the most common malignant tumor among women across the world (17,18). Ki-67 is a nuclear cortex protein expressed in G1, S, G2 and M phases of the cell cycle and is therefore used as an indicator in proliferating cells. In breast cancer, the classical prognostic factors used to predict the course of the disease and to decide the best treatment option are age, tumor size, lymph node status, histologic grade, lymphovascular invasion, and tumor stage (19). Among them, the strongest prognostic markers are lymph node involvement, tumor size and histologic grade (19,20). Especially the presence of lymph node metastasis and the tumor size forms the basis of TNM staging, which is one of the most significant prognostic determinants of the disease (19,21). Survival rate, recurrent disease, recurrence interval, and treatment success are directly correlated with the number of positive axillary lymph nodes. The higher the number of positive lymph nodes, the worse the prognosis. The presence of lymph node metastases and the number of lymph nodes contribute significantly to the determination of adjuvant systemic treatment (19). In addition to these classic and important parameters, more up-to-date parameters are needed for new target treatments. For this purpose, we investigated the relationship between Ki-67 Index and classical prognostic markers, especially lymph node metastasis.

E. de Azambuja et al. found Ki-67 Index to be associated with prognosis in both axillary lymph node-negative and axillary lymph node-positive patient groups (12). Petrelli et al. included 64,196 patients with early-stage breast cancer in the meta-analysis, and Ki-67 Index being over 10% was found to be associated with poor prognosis. The patients were then divided into two groups, as Ki-67 Index below 25% and above 25%, and the difference between these two groups was found to be highly significant. In the study performed by Tashima et al., Ki-67 Index was found to be associated with prognosis (22).

Trihia et al. showed that there was a correlation between Ki-67 Index and lymph node metastasis in lymph node metastasis positive patients (23). Our study discovered that the axillary lymph node positivity was increased with the increase of Ki-67 Index.

In our study, the evaluation of the breast cancer according to histopathological subtype showed that invasive ductal carcinoma (69.5%) was commonly observed and Ki-67 Index was homogeneously dispersed among these patients. Regarding the subtypes, Ki-67 Index of the patients with mucinous cancer, which is known to have a better prognosis than other types, was below 15%. Ki-67 Index of most of the patients with invasive lobular carcinoma, medullary carcinoma, and mixed breast carcinoma was over 30%. According to the literature, invasive ductal carcinoma is the most common histopathologic type and Ki-67 Index of this group was consistent with our study (24).

As a result of the analysis performed by Viale et al., Ki-67 Index was found to be associated with high tumor histological grade and pathological tumor size (25). Inwald et al. examined 3,658 patients with operated breast cancer and Ki-67 Index was found to correlate with the most prominent tumor size (26). Ki-67 antigen has been shown to be an important prognostic indicator in breast cancer patients with a tumor diameter of below 1 cm (27). Tumor size is the most significant independent prognostic factor after ALN involvement (28). In our study, Ki-67 Index was found to be positively correlated with pathological tumor size.

Sahin et al. worked on the patients with axillary lymph node-negative stage I / II breast cancer and Ki-67 Index was found to be associated with the stage of the tumor (29), which is consistent with the tumor diameter and stage findings of our study, where most of the patients were in stage IIB (23.9%) and IIIA (54.3%) and the tumor stage increased as Ki-67 Index increased.

In our study, Ki-67 Index of the patients under 50 and over 50 were very close to each other, thus it was concluded that the differentiation of Ki-67 Index according to age was not significant.

CONCLUSION

Proliferation is an important indicator used to predict prognosis and treatment response in breast cancer. In our study, Ki-67 Index, one of the cell proliferation markers, showed a positive correlation with axillary lymph node metastasis and other prognostic factors and Ki-67 Index was found to be an important prognostic indicator in breast cancer.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: In our study, a research involving direct intervention on humans or animals, no treatment methods or tools were used. Data scanning was performed retrospectively and ethics committee approval is not required.

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