Int J Clin Exp Pathol 2015;8(9):9772-9781
www.ijcep.com /ISSN:1936-2625/IJCEP0012825

Original Article

Association between well-known histopathological criteria and overall survival in invasive ductal carcinoma

Aysenur Deger[1], Filiz Ozyigit[2], Ozlem Arik[3], Fatih Ekici[4], Ahmet Cinkaya[5], Mahir Tayfur[6], Hakki Deger[7]

[1]Department of Pathology, Faculty of Medicine, Dumlupinar University, Kutahya, Turkey; [2]Department of Pharmacology, Faculty of Medicine, Dumlupinar University, Kutahya, Turkey; [3]Department of Biostatistics, Faculty of Medicine, Dumlupinar University, Research Assistant Kutahya, Turkey; [4]Department of General Surgery, Kutahya Evliya Celebi Training and Research Hospital, Kutahya, Turkey; [5]Department of Radiation Oncology, Kutahya Evliya Celebi Training and Research Hospital, Turkey; [6]Department of Pathology, Faculty of Medicine, Erzincan University, Erzincan, Turkey; [7]Department of Neurosurgery, Kutahya Evliya Celebi Training and Research Hospital, Kutahya, Turkey

Received July 13, 2015; Accepted August 23, 2015; Epub September 1, 2015; Published September 15, 2015

Abstract: We investigated the effect of clinical features and well-known histomorphological parameters on survival of breast cancer. Material and methods: 44 patients with invasive ductal carcinoma were included in this study. We investigated the effect of age, breast cancer location (right/left), histological grade, largest diameter of the tumor, lymphovascular and perineural invasion on patient survival. IBM SPSS (Statistical Package for Social Sciences) 20 program was used for statistics. Cox proportional hazard regression model for survival analysis, log-log plot, life function graphs were used. Results were 95% confidence interval, significance ($P < 0.05$). Results: In univariate analysis, the left breast localization, high histological grade, large tumor size, lymphovascular invasion, perineural invasion has been shown that reduced the overall survival ($P < 0.05$). In multivariate analysis, only high histological grade, large tumor size and perineural invasion were identified as parameters negatively associated with patient survival ($P < 0.05$). On univariate and multivariate analysis, age was not associated with survival. Conclusion: The above results should be considered in the follow-up and treatment planning of invasive ductal carcinoma patients.

Keywords: Breast cancer, invasive ductal carcinoma, overall survival, histopathological criteria

Introduction

Breast cancer is the most common cancer in women, newly diagnosed with 1.38 million new cases each year worldwide, and covers 23% of all female cancers [1]. Breast cancer, represents the second cause of death from cancer in women [2].

Breast cancer is a major cause of mortality, treatment costs are also an economic burden for the country. The importance of breast cancer in public health cannot be ignored. Numerous studies on prognosis of breast cancer have an important place. Many studies show the effect of lymphovascular invasion (LVI), tumor histological grade, largest diameter of the tumor, the clinical features, histological criteria and patient age but less of them has information on perineural tumor invasion (PNI) and tumor location (right/left). We see different results regarding these prognostic criteria in these trials.

We wanted to investigate the importance of histomorphological criteria used meticulously on histopathological reports and the major clinical features certainly written on pathology reports related to prognosis of breast cancer. In this group we aimed to investigate the effect of patient age, tumor location, histological grade, tumor largest diameter, perineural invasion (PNI) and lymphovascular invasion (LVI) on overall surveillance.

Material and methods

A retrospective study was conducted on 44 female patients who were diagnosed with invasive ductal carcinoma between 2011-2013 in the Department of Pathology, DPU Medicine Faculty, Kütahya. The required information was

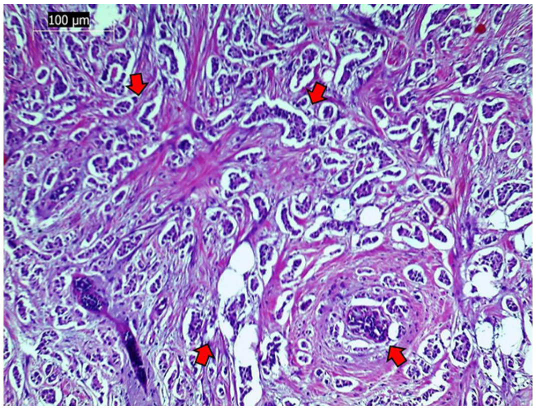

Figure 1. Grade I invasive ductal carcinoma atypical tumor ducts (arrow) H&E ×10.

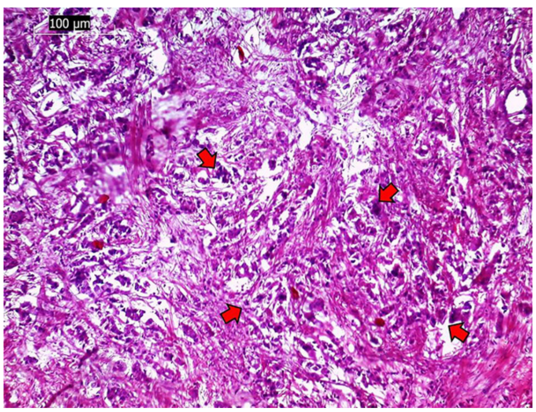

Figure 2. Grade II invasive ductal carcinoma attypical tumor cells and ducts (arrow) H&E ×10.

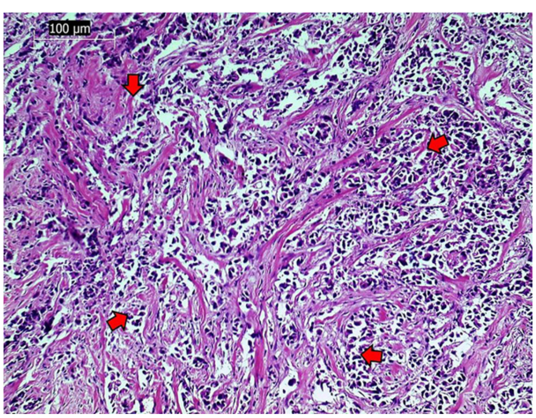

Figure 3. Grade III invasive ductal carcinoma atypical tumor nests (arrow) H&E ×10.

collected from the treatment records of the patients maintained at the Hospital Data. All data including age, lateralization (right-left) and pathological characteristics [grade (Bloom-

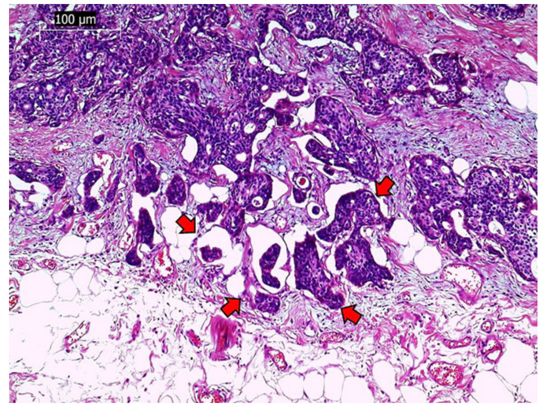

Figure 4. Invasive ductal carcinoma, lymphovascular invasion (arrow) H&E ×10.

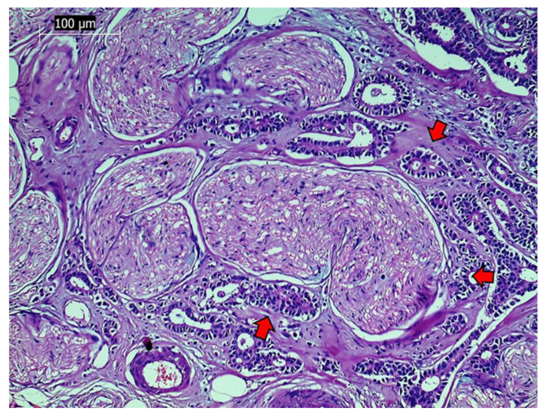

Figure 5. Invasive ductal carcinoma, perineural invasion (arrow) H&E ×10.

Richardson grade), perineural and lymphovascular invasion, tumor size] were recorded. There was no case of bilateral breast tumor between these 44 patients.

Patients were divided into 5 groups according to their age. Macroscopic measurements recorded in histopathology report were considered to determine the largest diameter of the tumor. Also to re-evaluate retrospectively invasive tumor diameter, hematoxylin eosin stained slides were measured, and the largest diameter of invasive tumor lesions were recorded for each subject (in situ carcinoma lesions component were excluded from the largest tumor diameter). AJCC TNM classification was used for grouping patients according to the largest tumor diameter [3].

On hematoxylin eosin stained slides from the pathology archives, histological grade, lympho-

Table 1. Used variables and levels

Variable	Variable levels	Total number of cases (n)	%	Number of failure cases	Number of censored cases
Age	1. ≤ 39	6	13.6	2	4
	2. 40-49	9	20.5	3	6
	3. 50-59	9	20.5	4	5
	4. 60-69	9	20.5	4	5
	5. ≥ 70	11	25.0	5	6
Breast localization	1. Right breast	23	52.3	11	12
	2. Left breast	21	47.7	7	14
Tumor diameter	1. T1 ≤ 2 cm	12	27.3	6	6
	2. T2: 2-5 cm	27	61.4	9	18
	3. T3 > 5 cm	5	11.4	3	2
Perineural invasion	0. Negative	26	59.1	8	18
	1. Positive	18	40.9	10	8
	1. Positive	23	52.3	12	11

Table 2. For each variable the Cox proportional hazard regression analysis

Variable	Coefficients	Std. error	*P*-value	Exp(β)	Confidence interval (95%) Exp(β)
Age					
1. ≤ 39			0.752	1	0.179-5.139
2. 40-49	-0.041	0.856	0.962	0.960	0.097-1.836
3. 50-59	-0.864	0.751	0.250	0.421	0.106-2.052
4. 60-69	-0.701	0.755	0.313	0.467	0.181-2.871
5. ≥ 70	-0.328	0.706	0.642	0.720	
Breast localization					
1. Right breast			0.000*	1	
2. Left breast	0.066	0.509	0.008*	1.069	0.394-2.899
Histopathological grade					
1. Grade I			0.000*	1	
2. Grade II	1.675	1.116	0.013*	5.338	0.599-47.574
3. Grade III	1.868	0.526	0.015*	6.477	0.170-50.337
Tumor diameter					
1. T1 ≤ 2 cm			0.036*	1	
2. T2: 2-5 cm	-1.950	0.781	0.029*	0.142	0.032-0.638
3. T3 > 5 cm	-1.287	0.766	0.011*	0.276	0.060-1.275
Perineural invasion					
0. Negative			0.000*	1	
1. Positive	1.535	0.565	0.007*	4.643	1.533-14.063
Lymphovascular invasion					
0. Negative			0.000*	1	
1. Positive	-0.548	0.512	0.028*	0.578	0.212-1.577

*P-value is small 0.05.

vascular and perineural tumor invasion were re-evaluated retrospectively.

Bloom-Richardson criteria were used for the histopathological evaluation of the tumor [3]. They were grouped as grade I, grade II, grade III (**Figures 1-3**). LVI was defined as the presence of the tumor cells in an endothelial-lined space a best judged in peritumoral breast tissue. Stromal retraction around tumor cell nests within the tumor itself was considered LVI negative [3, 4]. Assessment was made in hematoxylin eosin stained slides. We didn't use any specific immunohistochemical marker for evaluation of vascular wall. The patients were grouped as the LVI positive and negative (**Figure 4**).

Perineural invasion was assessed to be positive in the perineurium or neural fascicles within the breast parenchyma [3, 4]. The cases have been grouped into PNI positive and PNI negative (**Figure 5**).

Survival analysis of patients was performed using the age, localization of the tumor, histological grade, largest diameter of the tumor, PNI, LVI values. The effect of the data on overall survival was evaluated.

Statistical analysis

IBM SPSS (Statistical Package for Social Sciences) Statistics 20 program was used for the evaluation of the findings obtained in this study. Data were analyzed by descriptive statistical methods (frequency, percent), as well as sur-

Table 3. By stepwise method, the estimated coefficients of the variables in the model

Variabale	Coefficients	Std. error	*P*-value	Exp(β)	Confidence interval (95%) Exp(β)
Histopathological grade					
1. Grade I			0.021*	1	
2. Grade II	2.828	1.366	0.038*	16.917	1.162-246.234
3. Grade III	2.947	0.565	0.045*	19.052	0.193-301.582
Tumor diameter					
1. T1 < 2 cm			0.038*	1	
2. T2: 2-5 cm	-1.288	0.888	0.167	0.293	0.051-1.671
3. T3 > 5 cm	-2.088	0.844	0.013*	0.124	0.024-0.648
Perineural invasion					
0. Negative			0.000*	1	
1. Positive	-1.738	0.640	0.007*	0.176	0.050-0.617

*P-value is small 0.05.

vival analysis evaluations, Cox proportional hazard regression model, log-log plot, life (survival) function and hazard (risk) function graphics were used. Results at 95% confidence interval, significance $P < 0.05$ level were evaluated.

Survival analysis is defined as a set of methods for analyzing data like treatment, factors relating life expectancy, where the outcome variable is the time until the occurrence of death [5].

Events described in the study with survival analysis, which may not occur in specified frame time. Data from any source may be left out for various reasons [6].

Using semi-parametric regression model of Cox proportional hazard regression model survival analysis we will determine the dependent variable to have the most effect in life expectancy and how much influence it has on progress of the illness, it's reliability and see if it is available to be used in future survivals [7].

In this study, age, breast localization, pathological stage, tumor size, perineural invasion, the blood and lymph vessel invasion variables have been grouped and included in the analysis by using the SPSS program. These variables and the variable levels are given in **Table 1**. The death of the patient is expressed as failure. At the end of the study period, the patients that are not faced with failure were defined as censored.

Results

Among 44 followed-up patients 18 (41%) were failure, 26 (59%) were observed censorship (**Table 1**).

The ages of 44 patient files included in the present study were 6 (13.6%) < 39, 9 (20.5%) 40-49, 9 (20.5%) 50-59, 9 (20.5%) 60-69 and 11 (25%) > 70 years. Among these patients, 23 (52.3%) had tumor on their right breast, 21 (47.7%) on their left breast. According to the histopathological grade 1 (2.3%) Grade I, 25 (56.8%) Grade II, 18 (40.9%) were observed to be Grade III.

Tumor size was smaller than 2 cm in 12 patients (27.3%), 2-5 cm (61.4%) in 27 patients, and greater than 5 cm with 5 patients (11.4%).

According to the perineural invasion and lymphovascular invasion, 18 patients (40.9%) were perineural invasion positive and 26 patients (59.1%) were perineural invasion negative, 23 patients were (52.3%) lymphovascular invasion positive, 21 patients were (47.7%) lymphovascular invasion negative.

Cox proportional hazard regression analysis results made separately and obtained for each variable are shown in **Table 2**.

In **Table 2**, Breast localization, histological grade, tumor size, perineural invasion and lymphovascular invasion were the variables found to be factors affecting the mortality of breast cancer patients ($P < 0.05$). In Cox proportional hazards regression analysis, the first level of the variable is taken as the reference level. When the values for the other significant exp(β) variables were reviewed in terms of breast localization, the risk was 1.069 times greater (in terms of death) for a tumor in the left breast than the right breast, and the confidence interval for the risk was obtained as 0.394 to 2.899. For the histopathological grade variable, it can be said that Grade II carries 5.338 times more

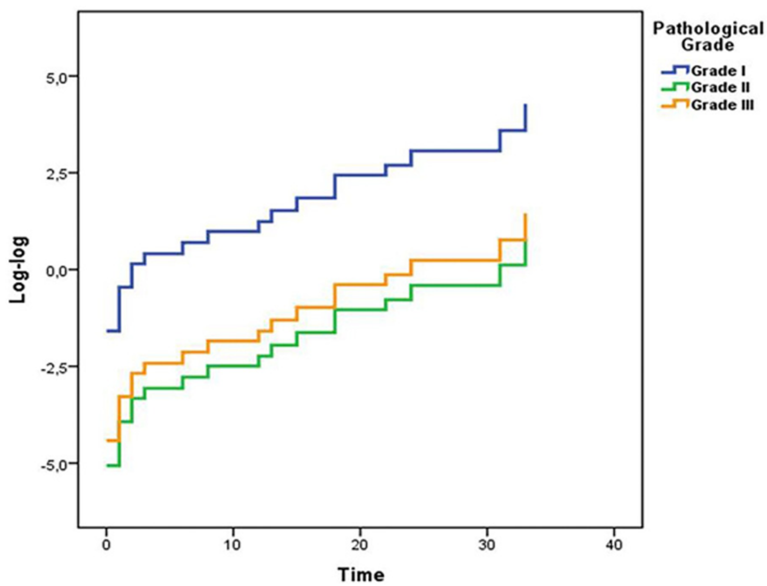

Figure 6. Histopathological grade variable for log-loggraph.

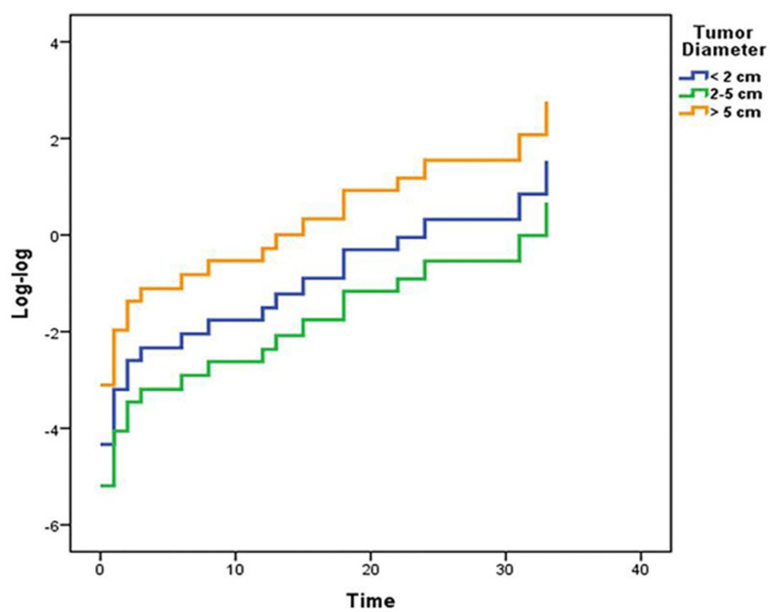

Figure 7. Tumor size variable for log-loggraph.

risk than Grade I, and Grade III carries 6.477 times more risk than Grade I. The confidence intervals for these risks were 0.599 to 47.574 and 0.170 to 50.337 respectively. In relation to the variable of the diameter of the tumor, a diameter of 2-5 cm (according to the reference level, which is less than 2 cm) can be considered 0.142 times higher in terms of risk. The confidence interval here was calculated as 0.032 to 0.638.

A tumor diameter of 5 cm carries 0.276 times more risk than a diameter of 2 cm. The confidence interval for this risk was found to be 0.060 to 1.275. The presence of perineural invasion led to a 4.643 times higher risk of death than for patients without perineural invasion. The confidence interval was 1.533 to 14.063. Finally, for lymphovascular invasion, the associated risk of death was 0.578 times higher than for patients without lymphovascular invasion, with a confidence interval of 0.212 to 1.577 having been obtained.

Next, the six independent variables were examined together using Stepwise 2 Log L. The figures showing very little increase and the largest *P* values with variable patterns were removed from the method. Thus, a model was obtained in which the important factors affecting survival were taken into account. A 5% error level and a 95% confidence level were chosen. This model is given in **Table 3**.

An examination of **Table 3** indicates that, of the six variables, the only factors found to affect the mortality of patients with breast cancer were histological grade, tumor size, and perineural invasion ($P < 0.05$). Analysis into these variables was therefore conducted.

Cox proportional hazards regression was found to be significant in relation to the model. For the histopathological grade variable, the risk of dying from breast cancer was 16.917 times higher for Grade 2 patients, compared with Grade 1 patients (at a 95% confidence level). The confidence interval obtained was 1.162 to 246.234. The risk was 19.052 times higher for Grade 3 patients than Grade 1 patients (95% confidence level) and the confidence interval

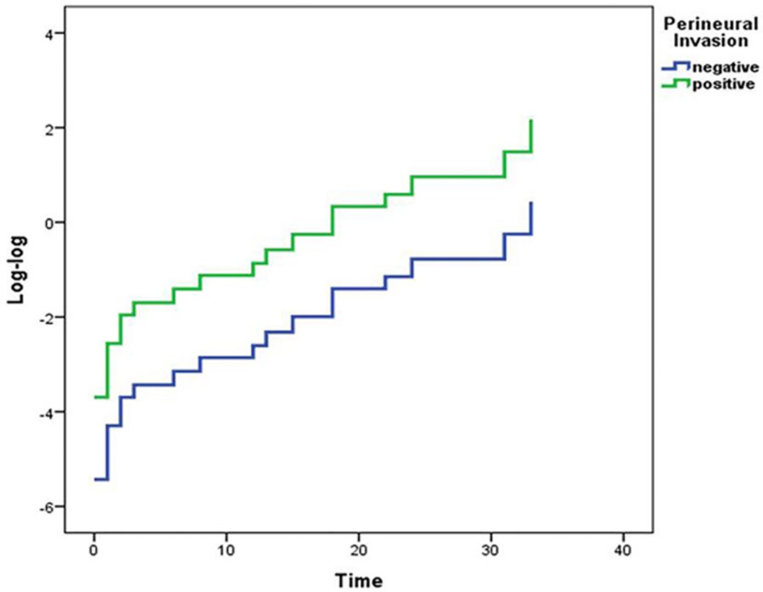

Figure 8. Perineural invasion variable log-loggraph.

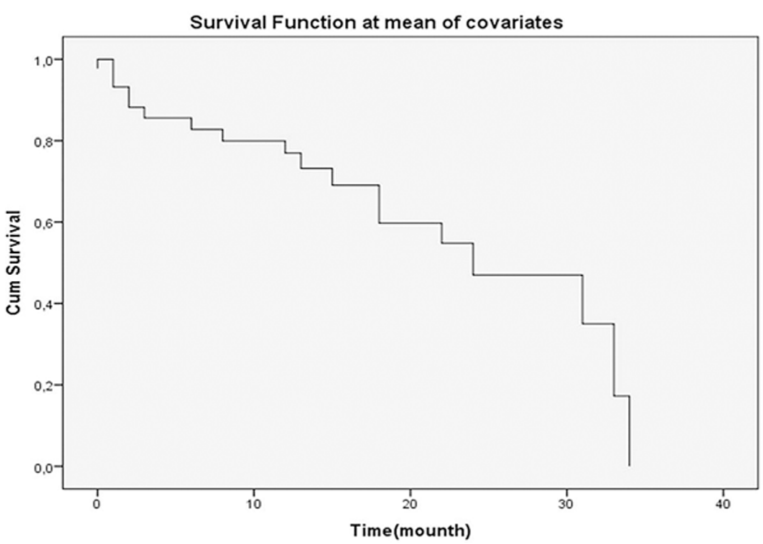

Figure 9. Overall survival function graph.

was found to be 0.193-301,582. Therefore, for patients with breast cancer, a more advanced histopathological stage brings an increased risk of dying from the disease.

For the tumor diameter variable (at a 95% confidence level), a diameter greater than 5 cm was found to be significant. For patients with tumors of a diameter greater than 5 cm, the risk of dying from breast cancer was 0.124 times higher than for patients with tumors of less than 2 cm. The confidence interval was calculated as 0.024-0.648.

Finally, for the perineural invasion variable, those patients who were perineural invasion positive had a 0.176 times higher risk of death than those without perineural invasion. The confidence interval was 0.050-0.617.

To test the assumption of the proportionality of the variables used in a model, log-log or In-In can be analyzed with the help of log-log or In-In graphics. Use of log-log survival curves for examining assumptions of proportionality is thus considered a graphical approach. For this data set, given that the Cox proportional hazards regression model was considered appropriate, it was expected that the results would parallel the log-log curve.

The explanatory variables were inserted into the model log-log graphs, as shown in (**Figures 6-8**):

When the histopathological grade variable for the log-log graph is analyzed in relation to the risk statuses of Grade I, Grade II and Grade III breast cancer, it can be said that there is proportionality between the histological grades because they are parallel; they do not intersect.

When the tumor size variable is analyzed using the log-log graph for tumor diameters of less than 2 cm, 2-5 cm and greater than 5 cm, it is clear that the information does not intersect; it is parallel. It can therefore be stated that there is proportionality between the different tumor diameter levels.

For the perineural invasion variable, when the log-log plot is examined in terms of perineural invasion and non-invasion, the data is parallel and does not intersect. Thus, it can be said that there is proportionality within the perineural invasion variable.

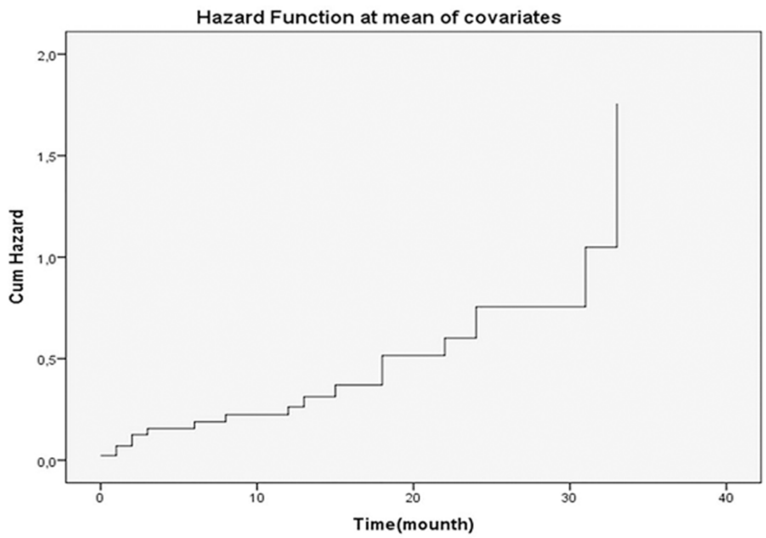

Figure 10. General hazard (risk) function graph.

For follow-up period (time), the examination of the life and hazard graphics, breast cancer patients decreased probability of living due to illness, probability of death (risk) is increasing during the time (**Figures 9**, **10**).

In all the studied data, the patient's age, the analysis in both univariate and multivariate analysis has been shown to no affect the overall surveillance.

Discussion

Breast cancer is the most common cancer in women, and its incidence is increasing worldwide. After pulmonary cancer, breast cancer represents the second leading cause of female death [1, 2]. The condition is an important cause of morbidity and mortality worldwide; many survival studies have been conducted in relation with breast cancer. Varying results for these survey studies are available in the literature.

Several studies with different age limits have found that breast cancer that occurs at a young age has high mortality and high recurrence rates, which were determined to be independent poor prognostic factors for these patients [8-10]. In contrast, other researchers were not in agreement that early onset breast cancer is associated with a poor prognosis [11]. Gnerlich et al. reported that early stage disease and tumor biology contributed to the poorer outcomes and increased mortality of younger women diagnosed with early stage breast cancer [9]. Biphosal Thapa et al. reported from Nepal that breast cancer in young women tends to have more aggressive biological features [1]. In the same report, it was acknowledged that little medical research has been conducted in young patients; therefore, most of the attention has been drawn to young patients who have been diagnosed with the more advanced stages of breast cancer, which could influence the results [1]. Several studies have supported the conclusion that age itself had no influence on the prognosis; instead, the association of a poor prognosis with a young age at diagnosis is explained by the higher proportion of aggressive tumors found in younger women in terms of higher T stage, positive lymph nodes, endocrine non-responsiveness, high grades and high proliferating fractions [12].

In one of the studies, the patients were divided into groups based upon their ages: either under 35 years or over 35 years. In five of the survey studies, patients were divided into groups of those younger than 40 years and those 40 years of age and older. In our study, we separated the participants into five groups according to age of the patients, which kept the age limit narrower.

Upon univariate and multivariate analyses, we could not find any effect on the overall survival of the patient's age at diagnosis. A higher number of patients across the different age groups will be needed in further studies amongst this patient population.

When the investigations related to the localization of the tumor in the breast were reviewed, central/medial tumors were found to be less likely to involve the regional lymph nodes than lateral tumors. Lateral tumors were therefore less often node negative (65%) than central/medial tumors (74%). The tumor location was significant on univariate analysis of this association but not in regards to the multivariate analysis's magnitude of effect or predictors [4]. Differences in drainage patterns (with more frequent drainage to the internal mammary nodes observed in central/medial tumors) may explain this result [4].

Alieldin et al. have categorized tumor localization as either right or left. In both their univariate and multivariate analyses, they could not identify a relationship between tumor laterality and disease-free survival (DFS) [12]. We could not find many studies that were related to the laterality of breast tumors in the literature. In our study upon univariate analysis, patients with tumors located in the left breast were found to have a shorter overall survival. In multivariate analysis, the results were evenly distributed between left and right breast tumors, so we could not isolate a difference in overall survival based upon tumor side alone.

When viewed from an anatomical and physiological standpoint, the location of a tumor on either the left or the right breast cannot be expected to have an effect on patient survival. However, in our study, patients with left-side breast cancer were found to have a shorter overall survival than those with cancer on the right side.

Usually the left breast is lightly bigger than the rigt breast in the general population but there is not enough evidence that is breast size is associated with breast cancer [13].

Histological grades are also well-known prognostic factors for breast tumors. When we examined the effect of the tumor's histological grade on the survey, this factor appeared to be associated with a high histological grade and a poor DFS [12]. Young et al. reported that the nuclear grade affects the local recurrence and DFS as well [14]. The tumor's histological grade is a well-known prognostic factor, and high histological grades were reported to have a negative impact on patient survival [12, 14, 15]. In our study, the literature as well as the univariate and multivariate analyses indicated that a high histological grade was associated with decreased survival time. In the literature, a large tumor diameter was evaluated according to T stage and was seen as one of the most important factors affecting patient survival [14, 16].

Tumors with a largest diameter also impact lymph node metastasis. A positive lymph node above 4 and at least 4 in T1 and T2 tumors, respectively, are quite low [4]. In our study, univariate and multivariate analyses of the tumor diameter was seen as an important prognostic factor affecting the patient's overall survival. As the tumor diameter increases, patient survival is reduced.

In the majority of studies, the high rate of positive lymphovascular invasion (LVI) shows a close relationship with known markers of a poor prognosis. The presence of LVI can predict a worse outcome for patients with invasive breast cancer. LVI may also be used as an indicator of aggressive behavior and the metastatic ability (nodal and systemic) of the primary malignancy [4, 17, 18] and also LVI is an adverse prognostic factor of both relapse and survival in node-negative patients treated with mastectomy and systemic therapy [18].

Freedman et al. reported that LVIs that are accompanied by other poor prognostic factors have been previously mentioned, but LVI alone is not an independent determinant in terms of local regional recurrence or survival in multivariate analysis [19]. LVI is well-documented in breast tumors; although it is a marker of a poor prognosis, there is no consensus in the literature on this subject. Upon univariate analysis, we found that LVI shortens the overall survival; however, LVI was not found to affect the overall survival in multivariate analysis.

Compared to other prognostic factors, perineural invasion has received much less attention in the literature. Some studies have reported perineural invasion in the form of the direct infiltration of nerves, veins, and lymphatic vessels around the nerve tumor. In other studies, perineural infiltration is indicated as a completely separate entity with infiltration of lymphatic vessels and veins [15]. It is emphasized that this is not a true invasion but instead one that results from various other mechanisms that promote active epithelial proliferation into the perineural spaces, mechanical implantation due to biopsy trauma, and aberrant regeneration of neural or epithelial tissue [15].

Duraker et al. could not identify a correlation of DFS and PNI. Additionally, in earlier studies, no association was found between breast cancer recurrence and PNI [15]. In contrast, the study of Koca et al. revealed a significant relationship between PNI and DFS, and PNI was associated with the worst prognosis [20].

We have seen that in both univariate and multivariate analyses, PNI adversely affects the overall survival. Therefore, PNI should be considered as a separate prognostic factor that can indicate a poor prognosis.

In conclusion, left breast localization, high histological grade, largest tumor diameter, LVI, and PNI were found to negatively affect a patient's overall survival, upon univariate analysis. Multivariate analysis indicated that a high histological grade, large tumor size and PNI were poor prognostic factors that had a negative effect on patients' overall survival.

Clinical follow-up of patients that includes advanced treatment planning and consultation of the above results should be considered. The literature contains extensively varied survey results regarding patients with breast cancer; these results were likely affected by regional and environmental differences and genetic variations. Many more studies will be needed on this subject.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Aysenur Deger, Department of Pathology, Faculty of Medicine, Dumlupinar University, Kutahya, Turkey. E-mail: ayhade@yahoo.com

References

[1] Thapa B, Singh Y, Sayami P, Shrestha UK, Sapkota R, Sayami G. Breast cancer in young women from a low risk population in Nepal. Asian Pac J Cancer Prev 2013; 14: 5095-5099.
[2] Zob D, Vasilescu M, Gruia M, Anghel R. Breast cancer. Screening criteria. Chirurgia (Bucur) 2013; 108: 557-562.
[3] Tavassoli FA. Pathology of The Breast. Mc Graw-Hill; 1999. pp. 38-46.
[4] Wong JS, O'Neill A, Recht A, Schnitt SJ, Connolly JL, Silver B, Harris JR. The relationship between lymphatic vessell invasion, tumor size, and pathologic nodal status: can we predict who can avoid a third field in the absence of axillary dissection? Int J Radiat Oncol Biol Phys 2000; 48: 133-137.
[5] Özdamar K. Spss ile Biyoistatistik. Kaan Kitapev, 2003.
[6] Kleinbaum DG. Survival Analysis: a Self-Learning Text. New York: Springer; 2012. pp. 1-253.
[7] Fleming TR, Lin DY. Survival analysis in clinical trials: past developments and future directions. Biometrics 2000; 56: 971-983.
[8] Dirier A, Burhanedtin-Zincircioglu S, Karadayi B, Isikdogan A, Aksu R. Characteristics and prognosis of breast cancer in younger women. J BUON 2009; 14: 619-623.
[9] Gnerlich JL, Deshpande AD, Jeffe DB, Sweet A, White N, Margenthaler JA. Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. J Am Coll Surg 2009; 208: 341-347.
[10] Wei JT, Huang WH, Du CW, Qiu SQ, Wei XL, Liu J, Zhang GJ. Clinicopathological features and prognostic factors of young breast cancers in Eastern Guangdong of China. Sci Rep 2014; 4: 5360.
[11] Purushotham A, Shamil E, Cariati M, Agbaje O, Muhidin A, Gillett C, Mera A, Sivanadiyan K, Harries M, Sullivan R, Pinder SE, Garmo H, Holmberg L. Age at diagnosis and distant metastasis in breast cancer--a surprising inverse relationship. Eur J Cancer 2014; 50: 1697-1705.
[12] Alieldin NH, Abo-Elazm OM, Bilal D, Salem SE, Gouda E, Elmongy M, Ibrahim AS. Age at diagnosis in women with non-metastatic breast cancer: Is it related to prognosis? J Egypt Natl Canc Inst 2014; 26: 23-30.
[13] Weiss HA, Devesa SS, Brinton LA. Laterality of breast cancer in the United States. Cancer Causes Control 1996; 7: 539-543.
[14] Kim KJ, Huh SJ, Yang JH, Park W, Nam SJ, Kim JH, Lee JH, Kang SS, Lee JE, Kang MK, Park YJ, Nam HR. Treatment results and prognostic factors of early breast cancer treated with a breast conserving operation and radiotherapy. Jpn J Clin Oncol 2005; 35: 126-133.
[15] Duraker N, Caynak ZC, Türköz K. Perineural invasion has no prognostic value in patients with invasive breast carcinoma. Breast 2006; 15: 629-634.
[16] Fisher B, Dignam J, Tan-Chiu E, Anderson S, Fisher ER, Wittliff JL, Wolmark N. Prognosis and treatment of patients with breast tumors of one centimeter or less and negative axillary lymph nodes. J Natl Cancer Inst 2001; 93: 112-120.
[17] Gurleyik G, Gurleyik E, Aker F, Aktekin A, Emir S, Gungor O, Saglam A. Lymphovascular invasion, as a prognostic marker in patients with

invasive breast cancer. Acta Chir Belg 2007; 107: 284-287.

[18] Truong PT, Yong CM, Abnousi F, Lee J, Kader HA, Hayashi A, Olivotto IA. Lymphovascular invasion is associated with reduced locoregional control and survival in women with node-negative breast cancer treated with mastectomy and systemic therapy. J Am Coll Surg 2005; 200: 912-921.

[19] Freedman GM, Li T, Polli LV, Anderson PR, Bleicher RJ, Sigurdson E, Swaby R, Dushkin H, Patchefsky A, Goldstein L. Lymphatic space invasion is not an independent predictor of outcomes in early stage breast cancer treated by breast-conserving surgery and radiation. Breast J 2012; 18: 415-419.

[20] Koca E, Kuzan TY, Dizdar O, Babacan T, Sahin I, Ararat E, Altundag K. Outcomes of locally advanced breast cancer patients with ≥ 10 positive axillary lymph nodes. Med Oncol 2013; 30: 615-617.