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Survival rate of Breast Cancer patients referring to the Radiotherapy center, 2005 to 2018

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ABSTRACT

Background: Breast cancer is one of the most common and worrying health problems in women around the world. Several factors, namely, age, breed, spread of disease, stage of diagnosis and lymph node involvement play a role in prediction of survival rate in breast cancer patients. This study was conducted aiming to determine the survival rate of women with breast cancer in Kerman, Iran. *Material and Methods:* This retrospective study was conducted on all female patients with breast cancer who were referred directly to the radiotherapy unit at Besat clinic and Shafa Hospital in Kerman, Iran from 2005 to 2018. The study sought to determine the survival probability of patients with breast cancer based on receptor status as well as other prognostic factors such as age, histopathology, stage/grade of tumor, metastatic status, and surgical procedures using the life table and Kaplan-Meier curves. Different subtypes were generated based on expression of ER, PR, Ki67 and HER2, positive (+) and/or negative (–). *Results:* The mean age at breast cancer diagnosis was shown to be 53.76 ±11.54. It was found that the survival rate of breast cancer patients with MRM surgery was higher than those with BCS (P=0.009). Overall survival has not been significantly different for type of stage. After four

years, survival of patients with HER2-positive was shown to decrease. Overall survival was statistically significant for Ki67 ≥ 15 and <15 (P= 0.002). Survival of patients with positive ER and PR was not different than those with negative ER and PR (P=0.64). Patients with metastasis to vertebra showed a better survival rate in primary stages compared to other parts of the body. *Conclusion:* Overall survival was different for two surgery methods, HER2 and Ki67 gene expression status and age at the time of diagnosis, which was statistically significant.

Keywords: Iran, Breast, Cancer, Survival Rate

1. INTRODUCTION

Breast cancer is the most common cancer among women in both developed and developing countries (World Health Organization, 2015). According to GLOBOCAN report, an approximate number of 1.38 and 1.67 million new breast cancer cases have been diagnosed in 2008 and 2012, respectively (Ferlay et al., 2014). Therefore, breast cancer accounts for 23% of all female cancers. The most prevalent cancers in females include breast or cervical cancer worldwide, with the exception of China (lungs), South Korea (thyroid), Mongolia and Vietnam (liver) (Nafissi et al., 2018). It is the second cause of death in developed countries as well as the third in less developed countries (Jemal et al., 2011). It is worth noting that approximately 41.000 women annually die from breast cancer (Winer et al., 2001). According to predictions by the World Health Organization, up to 2.3 million women will be diagnosed with breast cancer by 2015 (Yekta Kooshali et al., 2016). Female breast cancer incidence rates varied internationally by more than 13fold in 2008 between different countries, ranging from 8.0 cases per 100.000 in Mongolia and Bhutan to 109.4 per 100.000 in Belgium. North America and Northern Europe had the highest age standardized rates (ASR) while Asia and Africa had the lowest one (Global cancer facts & figures, 2007; Kelsey and Bernstein, 1996). On a global basis, the incidence of breast cancer increased by 3.1% annually between 1980 and 2010 (Forouzanfar et al., 2011).

Risk factors for breast cancer can include aging, genetic predisposition, personal history of breast cancer, exposure to types of radiation, cigarette (Amini et al., 2005), geographic influences, number of pregnancies, late menopause, early menstruation, obesity (Hajian et al., 2013) and first childbirth after age 30 (Hajizadeh et al., 2015). Depending on grading, staging, physical condition of the patient and her wishes, there are various methods to treat breast cancer (Yaghmaei et al., 2008). Overall, a five-year survival rate underlies the assessment of cancer services and the undertaken work representing the survival of patients with a type of cancer is in the fifth year of diagnosis (Vahdaninia et al., 2003).

Understanding the biological behaviors of breast cancer and identifying its prognostic or predictive factors may help to improve the outcome (Yang et al., 2011). Cancer survival is considered as an essential component of cancer surveillance systems that support cancer prevention and control. Survival from breast cancer is associated with the value of prognostic factors such as stage, age, histology and grade, along with treatment efficiency (Ugnat et al., 2004). Age is an important risk factor for breast cancer, however, it has been also suggested that patient age at the time of diagnosis is related to breast cancer survival. Moreover, in spite of controversial data, it has been implicated that young and old age may be adverse prognostic factors (Brandt et al., 2015). Clinicians still tend to rely on reliable and inexpensive traditional histopathological features and readily available tumor markers such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) (Parise and Caggiano, 2014). It is noteworthy that nearly 75% of all breast cancers are ER-positive and 65% are PR-positive. Moreover, breast cancers which contain either estrogen or progesterone receptors are called hormone receptor-positive, accounting for about two-thirds of all breast cancers (Poorolajal et al., 2016).

A number of other molecules such as proliferation antigen Ki67 have been also assessed (Yang et al., 2001). Ki67 is a nuclear protein associated with cellular proliferation which was originally identified by Gerdes et al. (Gerdes et al., 1983). To optimize breast cancer treatment and avoid unnecessary chemotherapy, several multi-gene tests of risk assessment in early breast cancer have been developed in the last years including different proliferation-related genes—among others Ki67 (Inwald et al., 2013).

Despite relatively large number of breast cancer incidences in the country (Fallahzadeh et al., 2014), the importance of evaluating the survival rate and the average age of the patients involved in breast cancer to assess therapeutic strategies and achieve a better control of risk factors for breast cancer, there is no rough estimate of the average survival age of breast cancer in Kerman, Iran. This study was conducted to examine breast cancer survival rate of the patients in Kerman, Iran from 2005 to 2018.

2. MATERIAL AND METHOD

This retrospective study was conducted on all the breast cancer patients who were referred directly to the radiotherapy unit at Besat clinic and Shafa Hospital in Kerman, Iran from 2005 to 2018. Factors retrieved from the computer database included date of first hospital attendance, date of diagnosis, date of first definitive treatment, age and menopausal status at diagnosis, date of last follow-up and date of death (where applicable). The database also provided us with the information on clinical tumor size, histological type and grade, the status of pathological axillary node, type of treatment (chemotherapy or radiotherapy), surgical procedure (Breast Conserving Surgery (BCS) or radical), mutation status, the status of estrogen (ER) and progesterone (PR) receptors expression, HER-2/neu and Ki-67 gene expression status, and ultimately stage and mortality rate. In case of a defect in the database, comprised of information received via phone call, the sample was excluded from the study.

Data Evaluation

Statistical analysis of the data was carried out by means of Statistical Package for Social Sciences (SPSS) 22 for windows software. Moreover, the use was made of the log-rank test so as to assess the influence on survival of delay in presentation and total delay in univariate analyses.

Ethical committee approval code

This study was confirmed by ethical committee of Kerman University of Medical Sciences, Kerman, Iran. The ethical committee approval code is IR.KMU.AH.REC.1397.090.

3. RESULTS

Results of multivariate statistical analysis of patients are listed in Table I. In this retrospective study, the outcome of 373 patients with breast cancer was analyzed, suggesting that the survival rate was different for two surgery methods, HER2 and Ki67 gene expression status and age at the time of diagnosis, which was a statistically significant difference. Additionally, it was found that the two surgery methods were different with regard to 10 years survival rate and that HER2-positive cases accounted for 93% of 10 years survival rate. Furthermore, the findings showed that women aged 40-50 years had five years survival rate higher than other ages, which was a statistically significant difference. Also, three years survival rate was different in patients with metastases compared to various areas of the body, such that this survival rate was lower in patients with metastasis to liver and lung. Also, it was shown that three, five and 10 years survival rate were not different for stages 1, 2 and 3. Also, the overall survival rate of these patients did not show a statistically significant difference. According to Fig.1, the overall survival rate of patients with breast cancer decreases over time.

Age

The present study examined a total of 373 women diagnosed with breast cancer in Kerman, Iran between 2005 and 2018. The mean age at breast cancer diagnosis was 53.76 ±11.54. The minimum and the maximum ages were 23 and 92 years, respectively.

Survival by the Type of Surgery

Of all 373 patients, 264 cases (70.8%) were treated through modified radical mastectomy (MRM) which resulted in death of 16 patients. The remaining 109 cases (29.2%) were treated via Breast Conserving Surgery (BCS), out of which five patients died. Overall, it was shown that the survival rate was different for the two types of surgery procedures (P=0.009). Fig.2 shows that the survival rate of breast cancer patients treated through MRM surgery was higher than those undergoing BCS.

Table 1 Estimation of Survival Rates in Breast Cancer Patients

Survival Rates									
variables		3-year survival rate (.) (95% CI)	*P-value***	5-year survival rate (.) (95% CI)	*P-value***	10-year survival rate (.) (95% CI)	*P-value***	Total of survival rate (95% CI)	*P-value***
Type of surgery	MRM	0.96 (0.93 -0.98)	0.18	0.94 (0.90 - 0.96)	0.13	0.92 (0.87-0.95)	0.03*	0.92 (0.87-0.95)	0.009*
	BCS	0.95		0.95		0.92		0.90	

		(0.89 -0.98)		(0.89-0.98)		(0.80-0.97)		(0.69-0.97)	
HER2	Yes	0.94 (0.89-0.97)	0.44	0.93 (0.86-0.95)	0.73	0.93 (0.86-0.96)	0.005*	0.92 (0.83-0.96)	0.01*
	No	0.95 (0.91-0.96)		0.91 (0.84-0.95)		0.91 (0.84-0.95)		0.92 (0.85-0.96)	
KI67	>=15	0.94 (0.91-0.97)	0.33	0.92 (0.87-0.95)	0.74	0.92 (0.87-0.95)	0.16	0.92 (0.88-0.95)	0.002*
	<15	0.96 (0.79-0.99)		0.89 (0.60-0.97)		0.89 (0.60-0.97)		0.87 (0.54-0.97)	
ER &PR	Positive	0.94 (0.91-0.96)	0.88	0.89 (0.82-0.93)	0.71	0.89 (0.82-0.93)	0.70	0.89 (0.83-0.93)	0.64
	Negative	0.97 (0.91-0.99)		0.97 (0.91-0.99)		0.97 (0.91-0.99)		0.97 (0.91-0.99)	
Metastasis-local	No	0.97 (0.94-0.98)	0.01*	0.95 (0.92-0.97)	0.31	0.95 (0.92-0.97)	0.56	0.96 (0.92-0.98)	0.37
	Vertebra	1		1		1		1	
	Lung And Liver	0.33 (0.07-0.62)		0.22 (0.04-0.51)		0.22 (0.04-0.51)		0.22 (0.04-0.51)	
	Brain	0.81 (0.23-0.97)		0.81 (0.23-0.97)		0.81 (0.23-0.97)		0.83 (0.27-0.97)	
	Other	0.77 (0.36-0.93)		0.55 (0.12-0.84)		0.55 (0.12-0.84)		0.51 (0.08-0.84)	
Cancer stages	Stage1	1	0.42	1	0.45	1	0.29	1	0.96
	Stag2	0.93 (0.89-0.96)		0.92 (0.85-0.95)		0.92 (0.85-0.95)		0.92 (0.85-0.95)	
	Stage3	0.96 (0.89-0.98)		0.92 (0.82-0.96)		0.92 (0.82-0.96)		0.92 (0.82-0.96)	
Age group (year)	21-30	0.80 (0.20-0.96)	0.3	0.80 (0.20-0.96)	0.03*	-	0.4	0.80 (0.20-0.96)	0.02*
	31-40	1		1		1		1	
	40-50	0.95 (0.87-0.98)		0.92 (0.81-0.97)		0.92 (0.81-0.97)		0.91 (0.77-0.96)	
	>50	0.94 (0.89-0.96)		0.91 (0.85-0.94)		0.91 (0.85-0.94)		0.92 (0.86-0.95)	
* statistically significant. (p<0.05)									
** *P* value determined by the log-rank test									

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; CI, confidence interval; BCS: breast conserving surgery; MRM, modified radical mastectomy.

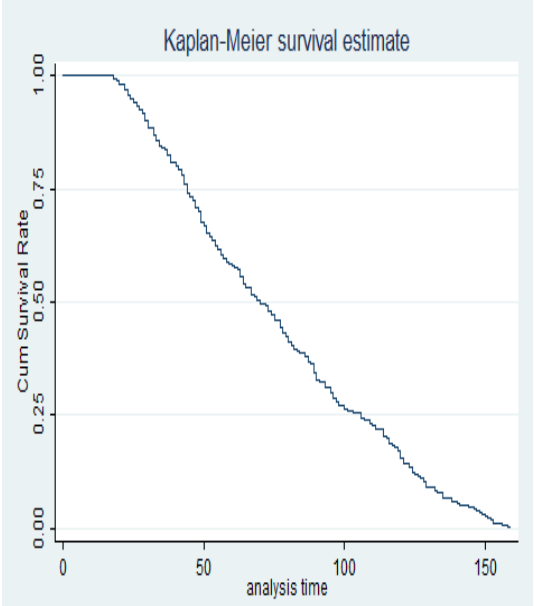

Fig.1 Overall Survival Rate for Breast Cancer Patients

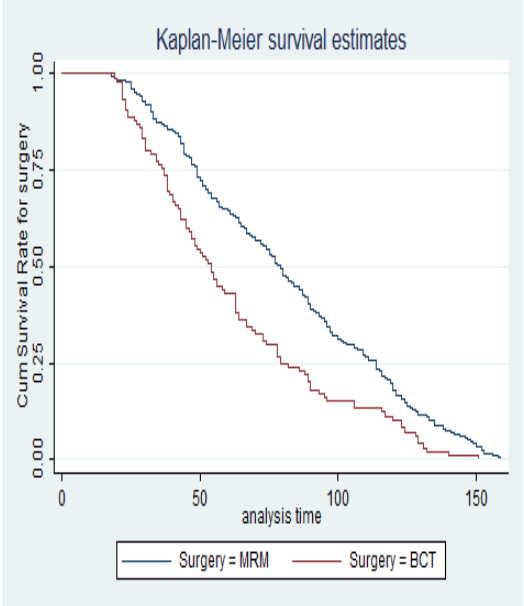

Fig.2 Survival Rate of Breast Cancer Patients For Two Types Of Surgery

Survival by Stage of Tumor

Out of 373 patients, 13 cases (3.5%), three cases (0.8%), 114 cases (30.6%), 119 cases (31.9%), 77 cases (20.6%), 18 cases (4.8%), and 29 cases (7.7%) were diagnosed with stages 1A, 1B, 2A, 2B, 3A, 3B and 3C, respectively. All of the patients with stages 1A, 1B and 3C survived while eight patients with stage 2A, seven patients with stage 2B, four patients with stage 3A and two patients with stage 3B died. Fig.3 demonstrates that the overall survival rate has not been significantly different for stage type.

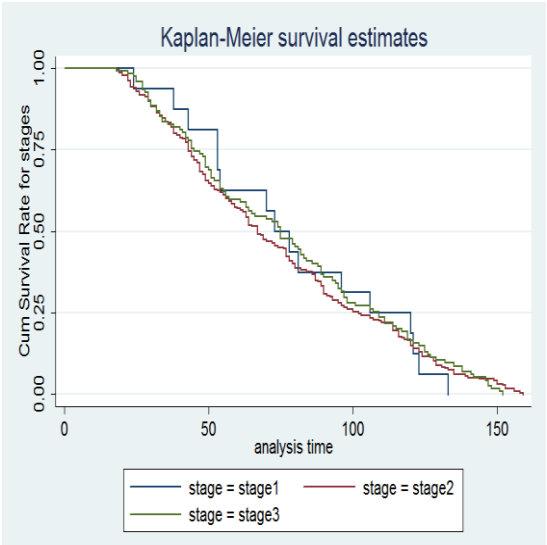

Fig.3 Survival Rate of Breast Cancer Patients for Various Stages

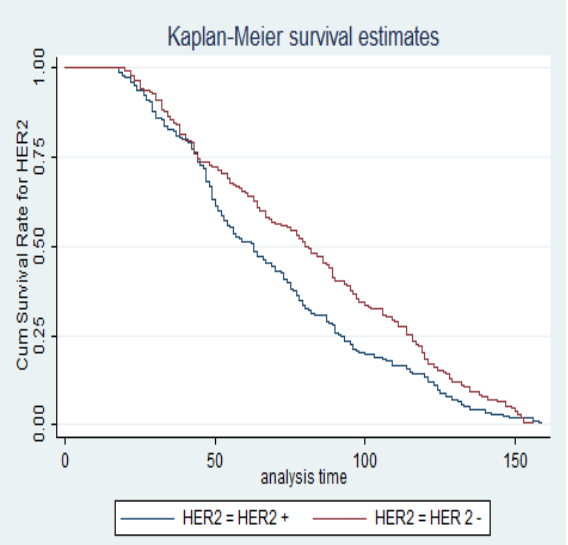

Fig.4 Survival Rate Of Breast Cancer Patients For HER2

Survival by HER2 Expression

Although early detection with no lymph node involvement and small tumor size are important in patients with breast cancer, the type of bio-marker involved should be also considered when survival is investigated. According to the findings, out of 373 patients, 189 cases (50.7%) were HER2-positive, out of whom nine patients died. The remaining 184 patients (49.3%) were HER2-negative, from whom 12 patients died. Fig.4 shows that the survival rate of patients with HER2+ was higher than HER2- in the first four years of illness. However, after four years, overall survival rate of patients with HER2- was higher than HER2+.

Survival by Ki67

Out of the 373 patients, 319 cases (85.5%) were ≥ 15 for Ki67 from whom, 19 patients died and the remaining 54 cases (14.5%) were <15 for Ki67 from whom, two patients died. Fig.5 indicates that the survival rate of patients with Ki67 ≥ 15 was higher than other patients (for cut-off of 15%). The overall survival rate was shown to be statistically significant for Ki67 ≥ 15 and <15 (P= 0.002).

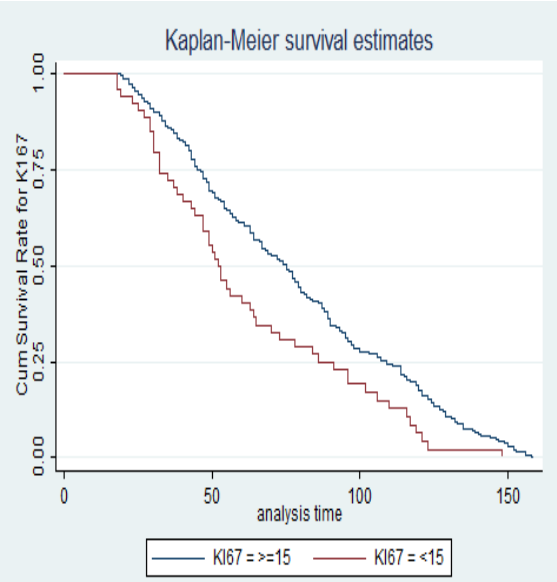

Fig. 5 Survival Rate of Breast Cancer Patients For Ki67

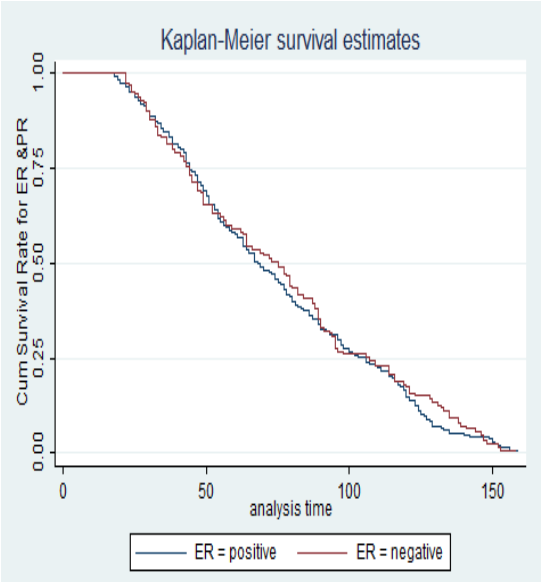

Fig.6 Survival Rate of Breast Cancer Patients For ER & PR

Survival by ER and PR

Of 373 patients, 243 cases (65.1%) were positive and 130 cases (34.9%) were negative in terms of ER and PR expression, respectively. Out of 243 cases positive for ER, 19 cases and of 130 cases negative for PR, two patients died. Fig. 6 shows that the survival rate of patients with positive ER and PR was not different from those with negative ER and PR (P=0.64).

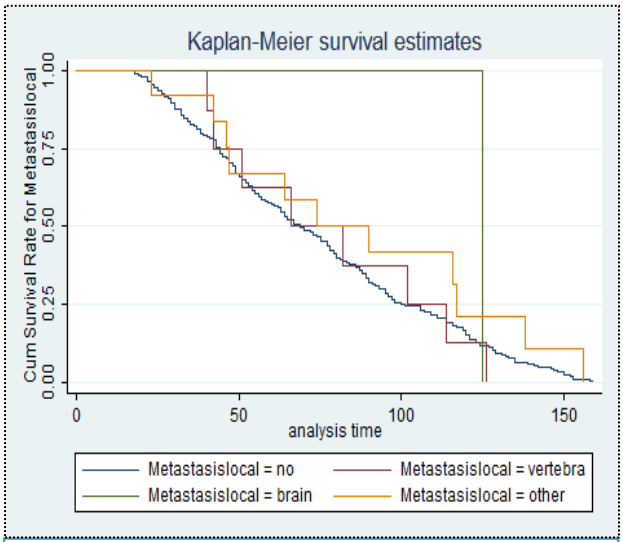

Fig.7 Survival Rate of Breast Cancer Patients for Metastasis-Local

Survival by Metastasis Local

Out of 373 patients, 341 patients (91.4%) did not experience metastasis. The metastasis was as follows: eight cases (2.1%) metastasis to vertebra, one case (0.3%) to other breast, five cases (1.3%) to lung, six cases (1.6%) to brain, four cases (1.1%) to liver and eight cases (2.1%) to other parts. Fig.7 depicts that the survival rate of patients without metastasis reached <50% after a five-year period. Also, the survival rate of patients with metastasis to different parts of the body decreased two to three years after onset or diagnosis a disease, while patients with metastasis to vertebra had better survival in primary stages.

4. DISCUSSION

The present study showed the relative three-, five- and ten-year survival rate of breast cancer patients. Breast cancer is a malignant tumor observed mainly in women. Significant variables involved in assessment of survival rate in this study included patients' age, type of surgery and HER2 and Ki67 expression. According to the findings, the mean age at diagnosis was 48.29±11.7, similar to other Iranian studies such as Afsharfard et al., (2013) (49.35±13.1) (Afsharfard et al., 2013), Najafi et al., (2013) (47.9±9.6) (Najafi et al., 2013) and Fouladi et al., (2011) (45.5±12.3) (Fouladi et al., 2011). However, it should be noted that the mean age is different in developed countries (Parkin and Fernandez, 2006 and Smigal, 2006). The findings revealed that the age when breast cancer occurs is a significant prognostic factor. Moreover, it was found that women aged 40-50 years old had a better five-year survival rate compared to those aged more than 50 years which is in line with other studies (Fisch et al., 2005 and Abdullah et al., 2013). Additionally, it was found that women aged 40 to 50 years old had a better survival rate than those aged less than 50, which is contrary to results obtained by Fallahzadeh et al., (2014) (Fallahzadeh et al., 2014). The study by AM Ugnat et al., (2004) demonstrated that patients aged 50–69 years old had the best outcome, which can probably be explained by the relatively good local control (through mammography screening) for this age group in Canada, even though there is no significant difference in survival rate among the age groups, namely, 40–49, 50–59 and 60–69 years old (Ugnat et al., 2004).

In the study by Akbari et al., (2011), the overall 10-year survival rate after surgery through BCS was reportedly 81% while the previous studies by Akbari et al (2008) showed that the overall 10-year survival rate in patients treated through BCS equaled 78% (Akbari et al., 2011).

In the present study, three- and five-year survival rate was not shown to be statistically significant for the type of surgery. Yet, the ten-year survival rate and overall survival rate were found to be better in MRM than in BCS.

The breast cancer stage proved to be the most significant independent prognostic factor for determining survival rate. In this study, nearly 66% of all patients were diagnosed with stages I and II. Regular mammography combined with regular clinical breast examination may offer the best opportunity to increase the detection percentage of early stage cases. The findings showed that the frequency distribution of stages was similar and the relative survival rates by stage were contrary to the data reported by the American Cancer Society and AM Ugnat et al., (Ugnat et al., 2004).

According to studies conducted in the past 12 years, estrogen receptor (ER), progesterone receptor (PR), and P53 were available, and HER2 oncogene was available only for seven years. Only was ER found to be related to age, suggesting that older patients enjoyed increased ER positivity, which possibly explains the better prognosis with increased age (Moradi-Marjaneh et al., 2008 and Hashemi et al., 2006 and Sirati and Ghahari, 2007).

It should be noted that a tremendous difference was seen in the reported HER2 (14%-71%), apparently coming from the differences in measurement of HER2 and the test quality (Nafissi et al., 2018). Findings of the study by Sartor CI suggest that as expression of HER-2 increases, so does cellular resistance to radiation, resulting in high recurrence rate after surgery (Sartor, 2000). Haffty et al., conducted a case-control study and showed that increased HER-2 expression was a predictive factor for breast cancer recurrence in the group experiencing recurrence compared with the control group (Haffty et al., 1996). In another study by Lopez-Guerrero and his colleagues, HER-2 status was not shown to have an impact on survival rate of the patients with recurrence (contrary to the patients without recurrence) (López-Guerrero et al., 2006). Moreover, the study by Poorolajal J et al., (2016) demonstrated that ER-positive/PR-positive/HER2-negative was associated with the lowest mortality rate. Regardless of ER and/or PR being positive or negative, it was shown that HER2-positive subtype was associated with a higher risk of cancer mortality. In other words, HER2-positive is an independent poor prognostic factor, whether or not ER/PR is positive or negative (Poorolajal J et al., 2016). In the present study, overall survival rate of HER2-positive patients was higher than HER2-negative ones in the first four years of illness. Nonetheless, after four years, overall survival rate of patients with HER2- was higher than HER2+.

Ki67 is a biomarker capable of reflecting cell proliferation state. Tumor cell proliferation state is an established predictor of prognosis. Cumulative data on breast cancer demonstrates that Ki67 is a prognostic factor. However, its role as a prognostic marker in breast cancer is not yet conclusive as acceptance of Ki67 as a standard marker requires further research to be confirmed. In this

study, we investigated the prognostic value of Ki67 expression for five-year relapse-free survival (RFS) of 373 patients with breast cancer. The results showed that survival of patients with Ki67 ≥ 15 was higher than that other patients (Yang et al., 2011). De Azambuja et al., (2007) indicated that higher Ki-67 expression was associated with higher probability of relapse and lower survival rate in breast cancer patients (De Azambuja et al., 2007). Moreover, in their multivariate study of 3658 patients, Inwald et al., (2013) confirmed the prognostic relationship between high Ki67 and positivity of HER, negativity of hormone receptors, age, and tumor size (Inwald et al., 2013). In the multivariate analysis of luminal breast carcinoma, Gallardo et al. (2018) maintained that Ki67, with a cut-off value of 14% and as a continuous variable, was associated with shorter survival rate and poor prognosis (Gallardo et al., 2018). As regards the present study, survival rate of patients with Ki67 ≥ 15 was higher than that of other patients (for cut-off of 15%).

Receptor status of breast cancer cell is critical for hormone therapy. Poorolajal J et al., (2016) indicated that seldom do single hormone receptor positive tumors occur and that they have a shorter survival rate than double positive or double negative cancer cells (Poorolajal et al., 2016). Moreover, Ng et al., showed that 11.6% of breast cancer cells were ER+/PR– and 4.6% were ER–/PR+ (Ng et al., 2012). Rakha et al., indicated that ER+/PR– and ER–/PR+ tumors are biologically and clinically distinct subtypes of breast cancer that are associated with more aggressive characteristics (Rakha et al., 2001). In this study, survival of patients with ER+/PR+ was not different from that of patients with ER-/PR- (P=0.64).

Regarding the distant metastases, the study conducted by Emiroğlu et al., (2015) showed that there was no statistically significant difference between young and postmenopausal patients. High percentage of young patients receiving chemotherapy, limitations of patient size and short follow-up period in this study are among the reasons for such a finding (Emiroğlu et al., 2015). In a recent study performed by Bollen et al., it was shown a median survival time of 22.5 months (95 % CI 18.0–26.9) for the receptor positive category and 6.7 months (95 % CI 2.4–10.9) for the triple negative category ($p < 0.001$) (Bollen et al., 2015), suggesting that patients with bone metastases from triple negative breast cancer have a significantly worse prognosis than those with a receptor positive phenotype (Foerster et al., 2015). According to the literature, existence of additional extra-skeletal metastases is another important prognostic factor for survival (J. Wolf et al., 2016). Patients with bone only metastases were associated with longer breast cancer specific survival (BCSS) and overall survival, whereas lung, liver, and brain metastases at diagnosis of metastatic disease were associated with a poorer BCSS and overall survival. This finding is in line with that of the study by Wu et al., (Wu et al., 2017). In the study by Khanfir et al., the overall five-year survival and the median survival with single bone metastasis were respectively 36% and 23.3 months (Khanfir et al., 2013). In other previous studies by Coleman et al., (1997) and Pez et al., (2007), the median survival ranged from 24 to 48 months and the overall five-year survival reached 20% (Coleman et al., 1999 and Pez et al., 2007). In another study conducted by Coleman and Rubens (1987) on patients whose cancers were diagnosed in the 1970s and 1980s, the median survival was 24 months in patients with first recurrence in the skeleton, whereas it was three months after first relapse in the liver ($p < 0.01$) (Coleman and Rubens, 1987). It is noteworthy that hepatic metastases are generally associated with a poor prognosis. Conducting a retrospective study on a total of 500 breast cancer cases with liver metastasis, Pentheroudakis et al., (2006) reported a median survival rate of 16.4 months and an overall five-year survival of 8.5% (Pentheroudakis et al., 2006).

5. CONCLUSION

In sum, we compared the benefit of the ER/PR/HER2 subtyping of breast cancer. The ER/PR/HER2 subtype is inexpensive, simple, reliable, easy to interpret, reproducible, and readily available to clinicians without the need for further tests. Moreover, the prognostic significance of ER and PR expression and the heterogeneity of the HER2+ subtypes are more easily evident when applying only ER, PR, and HER2.

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