RESEARCH ARTICLE

Predictive Factors of Survival Time of Breast Cancer in Kurdistan Province of Iran between 2006-2014: A Cox Regression Approach

Asrin Karimi[1], Ali Delpisheh[1]*, Kourosh Sayehmiri[2], Hojjatollah Saboori[3], Ezzatollah Rahimi[3]

Abstract

Background: Breast cancer is the most common cancer and the second most common cause of cancer-induced mortalities in Iranian women, following gastric carcinoma. The survival of these patients depends on several factors, which are very important to identify in order to understand the natural history of the disease. Materials and Methods: In this retrospective study, 313 consecutive women with pathologically-proven diagnosis of breast cancer who had been treated during a seven-year period (January 2006 until March 2014) at Towhid hospital, Sanandaj city, Kurdistan province of Iran, were recruited. The Kaplan-Meier method was used for data analysis, and finally those factors that showed significant association on univariate analysis were entered in a Cox regression model. Results: the mean age of patients was 46.10±10.81 years. Based on Kaplan-Meier method median of survival time was 81 months and 5 year survival rate was 75%±0.43. Tumor metastasis (HR=9.06, p=0.0001), relapse (HR=3.20, p=0.001), clinical stage of cancer (HR=2.30, p=0.03) and place of metastasis (p=0.0001) had significant associations with the survival rate variation. Patients with tumor metastasis had the lowest five-year survival rate (37%)and among them patients who had brain metastasis were in the worst condition (5 year survival rate= 11%±0.10). Conclusions: Our findings support the observation that those women with higher stages of breast malignancies (especially with metastatic cancer) have less chance of surviving the disease. Furthermore, screening programs and early detection of breast cancer may help to increase the survival of those women who are at risk of breast cancer.

Keywords: Breast cancer - survival - prognostic factors - Iran

Asian Pac J Cancer Prev, **15 (19)**, 8483-8488

Introduction

Breast cancer is a major cause of morbidity and cancer related mortality among women. The prevalence of breast cancer was reported as increasing in most of the Asian countries (Aini abdullah et al., 2013; Najafi et al., 2013). Iran is also sharing the same experience. The etiology of breast cancer is largely unknown; therefore there is no established primary prevention strategy. So, the main strategy is the establishment of screening protocols and early detection programs, which at least theoretically can improve the survival rates. Despite the increasing incidence, the survival rates of breast cancer patients in many developed countries were substantially improved. According to national cancer registry project report, breast cancer is the most common cancer and also the most common cause of cancer-related deaths of female population in Iran (Mohagheghi et al., 2009).

According to international agency for research on cancer, 4 million new cases of breast cancer has been diagnosed in 2004, and in contrast to the United States, the incidence rates is increasing in developing countries (IARC, 2006). Survival rate is the proportion of patients who survive for a specified period of time after diagnosis or treatment; it is a simple concept, but there are different ways to estimate it. For analysis of the survival of cancer patients during a specific period using population-based cancer registries data, relative survival rate as an estimate of net survival rate is a better measure than the observed survival and cause-specific survival (Esteve et al., 1990).

For cancer patients, survival rates have been accepted as the main criteria to measure the impact of treatment on cancer control (Ederer et al., 1961). Calculating mean lifetime in different groups of populations and assessment of effective factors in order to achieve healthy life is one of the challenges of scientists in various branches of biology and medicine. The population life time is a random statistical variable, therefore predicting it is not

*[1]Department of Epidemiology, Faculty of Health, Ilam University of Medical Sciences, [2]Prevention of Psychosocial Injuries Foundation, Research Center, Ilam, [3]Department of Radiation-Oncology, Towhid Hospital, Sanandaj, IR Iran *For correspondence: alidelpisheh@yahoo.com*

possible except through the use of statistical methods (Klein and Moeschberger, 1997; Hosmer and Lemeshow, 1999). Prognostic factors of breast cancer have already identified by using non-parametric survival methods such as Kaplan-Meier and Cox proportional hazard (PH) in many studies (Moran et al., 2008Akhsan and Aryandono, 2010; Khodabakhshi et al., 2011), the latter is used when the effect of covariates on the hazard ratio is desired. Review of literature shows the extensive use of the Cox PH regression model for hazard rate or instantaneous risk of a given event (Orbe et al., 2002; Moran et al., 2008). However, the basis and the most important assumption underlying this model is the proportionality of hazard rates, which may not be held in some situations. Where PH assumption is not met, it is improper to use standard Cox PH model as it may entail serious bias and loss of power when estimating or making inference about the effect of a given prognostic factor on mortality (Moran et al., 2008). A review of survival analysis in cancer journals reveals that only 5% of all studies using Cox PH model considered the underlying assumption (Orbe et al., 2002).

The survival of breast cancer patients depends on factors such as genetic, age at diagnosis, access to care, stage of cancer, weight, phisical activity status, alcohol consumption, social, economic, enviromental factors and ethnicity (Rafiqullah khan et al., 2014). Identifying prognostic factors in patients with breast cancer plays an important role in treatment and care of patients. Although several studies have been conducted to determine those factors affecting survival and disease-free survival rates in patients with breast cancer, patients of the country participated in the studies had different features from patients of other countries; an issue that has paid little attention. Determinants in each study differed from many other studies, and the effect of such factors is discussed (Khodabakhshi et al., 2011).

Breast cancer patients' survival rate and affecting factors have not been evaluated in Kurdistan province; hazard function distribution is also not clear in Iran. The aim of this study was determination of effective factors on breast cancer survival rate in Kurdistan province, Iran during 2006-2014.

Materials and Methods

Through a retrospective study, data were sourced mainly from pathology report of the patients and hospital database record. Three hundred and thirteen patients with breast cancer who had been hospitalized at the Towhid Hospital, Sanandaj city, Kurdistan province, Iran were recruited. Inclusion criterion was definite diagnosis of breast cancer during a seven-year period from 2006 onward. Clinical data such as the stage of disease were obtained through a structured questionnaire and the patients' clinical record. Vital status and date of death were determined through phone call and also by official death certificates, with maximum follow-up of 96 months. Survival time (in month) was calculated from the date of diagnosis through the date of death or last follow-up (the end of March 2014). Patients who were alive at the end of the follow-up period were censored. Overall, 84patients were excluded from analyses according to exclusion criteria (5 cases were outlier, 79 patients due to indeterminate date of death or current status, most of them were Iraq subsidiary). Overall 229 patients were enrolled. If the date of death for survival analysis was unknown, the patient excluded from survival analysis, but remained for other assessments (descriptive variables). Clinical and pathologic variables were age of patient, clinical stage of disease(determined according to AJCC TNM staging system for breast cancer) (AJCC, 2002), date of diagnosis, type of surgery (MRM or lumpectomy), tumor laterality (right or left), Estrogen receptor status, Progesterone receptor status, P53 amplification, HER-2 positivity, metastasis of tumor, and the site of metastasis. Relapses were entered into parametric regression models for multivariate analysis in order to assess the relationship between the characteristics and prognostic factors for survival.

Statistical analysis:

Statistical analyses were performed using SPSS software for windows, version 16(SPSS Inc. Chicago, IL, USA). Kaplan-Meier curves were constructed for survival analysis and the Log rank test was used to determine the differences in survival. The survival of a patient is referred to as the number of months from the date of diagnosis to the date of death, or to the date of the end of the study for patients who were still alive or date of loss of follow-up. Cox multivariate analysis was also performed to analyze prognostic factors.

To evaluate the proportional hazard assumption three methods were used including: The Graphical (diagram Log (S) t *vs* time), and analytical (Time-Varying covariate method) (Sayehmiri et al., 2010). $p<0.05$ was considered to indicate a statistically significant difference.

Results

In this retrospective study, a total of 313 patients were enrolled; according to exclusion criteria for survival analysis, data of 229 patients were evaluated. Among all (n=229) patients 181 (79%) were alive and the rest were dead. Median follow-up time was 39 months, ranging from 6-96 months.

The mean age of patients at the time of diagnosis was 46.10±10.81 years (ranging from 22-76). About 207 (67.6%) were under 50 years. Based on Kaplan-Meier method, median survival was 81 months, and 5 year survival rate was 75%±0.43.The difference between these two age groups was not statistically significant (p=0.1).

Tumor laterality in 133 (42.5%) was in right breast, 152 (48/5%) in left breast and 28 (8.9%) were indeterminate. Tumor laterality wasn't a prognostic factor for survival (p=0.119) (Table 1).

One hundred and twenty four patients had stage III (48.2%) and 7 patients (2.7%) had stage IV disease. Clinical Stage of disease was not determined to be prognostic factor for survival (p=0.119), but after recoding, the patients that were at clinical stage III or IV of the disease had lower survival rates than those at stage I or II; this difference was statistically significant (p=0.03).

The median±(SD) survival rate for patients under 50 years at the time of diagnosis was 81±5.54 months and annual survival rate in this group was higher than patients over 50 years. Cox regression model was estimated as: h (t)=h0 (t) e 0.021 age shows that one year increasing in age rises 0/02 hazard of death. Patients who had brain metastasis had the lowest median survival rate (33±7.11) (Table 3). The lowest 5-year survival rate was for patients who had stage IV of breast cancer (0%). This results emphasizes that early diagnosis of breast cancer (e.g. at lower stages) may be accompanied with better prognosis. The highest 5-year survival rate was for patients with non-metastatic disease (89%).

Univariate analysis showed that age of patient at diagnosis, type of surgery, Estrogen and Progesterone receptor status, HER-2 positivity, P53 status and the laterality of the tumor had no significant effect on survival rate of the patients. In contrast, having metastasis (p=0.0001), cancer relapse (p=0.0001), site of metastasis (p=0.0001), and clinical stage of disease (p=0.03) were significantly correlated to the survival rate (Table 2).

Prognostic factors for breast cancer survival were analyzed by Cox multivariate analysis. The analyzed factors were metastasis, relapse of cancer, clinical stage, and site of tumor metastasis. The results are shown in Table 3. Proportional assumption was met for all factors which entered to Cox regression. Based on our results the risk of death for patients with metastasis is 9.06 times higher than for other patients (HR=9.06; 95%CI=4.43-18.50). Also the risk of death for patients who had recurrent disease was 3.20 times higher than patients without that (HR=3.20; 95%CI=1.55-6.61). Patients with brain metastasis had the least probability of surviving and the highest risk of death (HR=16.56; 95%CI=7.01-39.09). Clinical stage of cancer is one of the most important prognostic factors for survival. Our data analysis showed a similar result: the risk of death for patients with stages III and IV disease is 2.30times higher than that for patients with stages 0 through II. Based on Kaplan-Meier curve the 5-year survival rates for patients with and without metastasis were 37% and 89%, respectively (Figure 1).

Table 2. The Number of Alive and Dead Breast Cancer Patients in All of Sub-Groups

Factor		Alive (%)	Dead (%)	P*
Age	<50	130 (83.9)	25 (16.9)	0.1
	50≥	51 (69.9)	22 (30.1)	
Clinical stage	stage 0	3 (100)	0 (0)	0.09
	stage I	11 (73.3)	4 (26.7)	
	stage II	69 (89.6)	8 (10.4)	
	stage III	67 (66.9)	19 (22.1)	
	stage IV	2 (33.3)	4 (66.7)	
Metastasis	Yes	13 (28.3)	33 (77.1)	0.0001
	No	166 (91.7)	15 (8.3)	
Relapse	Yes	4 (22.2)	14 (77.8)	0.0001
	No	173 (83.6)	34 (16.4)	
site of Metastasis	Bone	10 (41.7)	14 (58.3)	0.0001
	Brain	1 (9.1)	10 (90.9)	
	Other	1 (10)	9 (90)	
Surgery	MRM	116 (77.9)	33 (22.1)	0.49
	Lumpecomy	49 (94.23)	3 (5.77)	
ER	Negative	34 (77.2)	87 (86.1)	0.3
	Positive	10 (22.7)	14 (13.9)	
PR	Negative	38 (72)	12 (24)	0.1
	Positive	84 (87.5)	12 (12.5)	
HER-2	Negative	63 (88.7)	8 (11.3)	0.2
	Positive	52 (78.8)	14 (21.2)	
P53	Negative	26 (76.5)	8 (23.5)	0.3
	Positive	48 (85.7)	8 (14.3)	
Tumor laterality	Right	87 (83.7)	17 (16.3)	0.2
	Left	87 (78.4)	24 (21.6)	

Table 1. Median & 1-5 Years Survival Rates of Breast Cancer Patients According to Possible Prognostic Factors

Factor		Survival rate (%)					Median of Survival, Month 95% CI
		1 year	2 year	3 year	4 year	5 year	
Age	<50	98	94	89	85	78	81±5.54 (70.1- 91.85)
	50 ≥	95	88	76	68		
Clinical stage	stage 0						
	stage I			83			
	stage II	98	97	95	80	73	
	stage III	95	88	80		74	
	stage IV			66	33	0	
Metastasis	Yes	94	76	59	44	37	46±2.7 (40.7-51.2)
	No	98	97	93		89	
Relapse	Yes		92	85	57	35	56±7.4 (41.33-70.66)
	No	98	93	87	84	81	
site of Metastasis	Bone	88	83	70	56	49	56±19.8 (17.02-94.97)
	Brain	90	63	34	22	11	33±7.1 (19.05-46.94)
	Other	77	66		44	33	44±2.9 (38.15-49.84)
Surgery	MRM	98	92	86	81	74	
	Lumpectomy		97	93			
ER	Negative	95	90	83		73	73±6.8 (59.65-86.34)
	Positive	99	96	93	82	65	76± 9.68(57.01-94.98)
PR	Negative	85	89	83		66	73±5.7 (61.63-84/36)
	Positive		97	94	84	76	76±12.9 (50.7-101.2)
HER-2	Negative		96	91		82	
	Positive	96	93		75		73±5.3 (62.43-83.56)
P53	Negative		97		63	47	58±4.6 (48.89-67.10)
	Positive	96	92	88			
Tumor laterality	Right	96	94	90	87	79	
	Left	98	93	84	81	71	81± 8.7(63.84-98.15)

Table 3. Multivariate Cox Regression Analyses for Patient with Breast Cancer in Kurdistan Province in Iran between 2006-2014

Factor	β	SE	HR (95% CI)	p value
Metastases (Yes *vs* No)	2.204	0.36	9.06 (4.43- 18.50)	0.0001
Relapse (Yes *vs* No)	1.164	0.37	3.20 (1.55-6.61)	0.002
site of Metastases				
NO	reference	reference	1	reference
Bone	1.735	0.45	5.66 (2.30-13.9)	0.0001
Brain	2.807	0.43	16.56 (7.01-39.09)	0.0001
Other	2.252	0.48	9.50 (3.68-24.5)	0.0001
Clinical stage(III, IV *vs* I, II	0.83	0.4	2.30 (1.04-5.11)	0.03

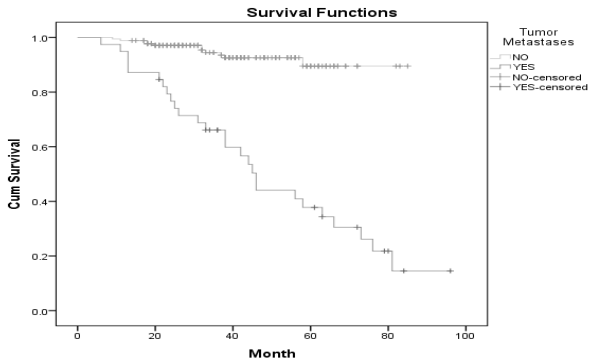

Figure 1. Kaplan-Meier Survival Curve of Breast Cancer Patients for the Factor Metastasis

Cox regression model using time-varying covariate approach was estimated as: (h (t) =h0 (t0)*e $^{1.44\pm0.23h\ (t)}$) the time-varying covariate model shows that the hazard of death in patients with tumor metastasis has had an increasing trend during follow-up time (HR=4.24; 95%CI=0.08-224.4).

Discussion

In present study, our objective was to determine prognostic factors for breast cancer patients' survival. Unfortunately, known prognostic factors are unable to accurately define the prognosis of a given patient, although it has been studied frequently. This study has investigated many factors of breast cancer patients. The strength of the study was using Cox regression after evaluating proportionality of hazard by three techniques graphical, analytical and time-varying approach on variables and calculation of five survival rate seperately for sub-groups analysis and as the hospital radiotherapy machine is equipped type, this study included patients with a variety of different features because breast cancer patients were reffered to the hospital from different west parts of Iran.

Breast cancer is uncommon in very young women (<35 years old), only accounting for fewer than 4% in Western countries (Wei et al., 2013). Like as previous studies in Iran, median age of breast cancer patients at the time of diagnosis was lower than in developed countries (Korizumi et al., 2010; Khodabakhshi et al., 2011; Thakur et al., 2014).

In this study, Kaplan-Meier method showed that for some variables such as: ER, PR, HER-2, P53, surgery (MRM, lumpectomy), age of patient, and tumor laterality were not prognostic factors for survival. But we found statistically significant relationship between metastasis (p=0.0001), site of metastasis (0.0001), relapse of cancer (0.001) and clinical stage (p=0.03) with survival. The risk of death for patients with tumor metastasis was very higher than for patients without it. Prognosis of patients with earlier stages was favorable compared to patients with advanced stages. Lower survival of high stages of breast cancer patients highlights the importance of screening programs for general population. The effect of clinical stage on survival confirmed by significant correlation on survival analysis; a result that is similar to some other studies (Tsan garis et al., 1992; Moradi Marjaneh et al., 2008; Akhsan and Aryandono, 2010; Khodabakhshi et al., 2011)

There are a few studies that compared the survival rates of breast cancer patients with metastasis in different sites. The risk of death in patients with brain metastasis was 16.56 times higher than non-metastatic patients; for the rest of metastatic patients (except bone secondaries) the risk was 9.50 times higher than non-metastatics. The majority (n=24) of metastases was in bones. Brain metastasis accompanies with poor prognosis; without treatment, the patients will survive only about one month (Saha et al., 2013). Brain metastases were increased in recent years due to increased survival of cancer patients and widespread use of imaging modalities (Nicholas et al., 1766). In adults, lung cancer, breast cancer and melanoma are the most common causes of brain metastases respectively. In a study conducted in Yazd, central Iran, breast was the primary site for the majority of brain metastases (Akhavan et al., 2014).

We observed that the most important cause of shorter survival for breast cancer patients is the presence of distant metastasis. In a study conducted by (Kaviani et al., 2013) lymph node metastasis was not responsible for poorer survival in obese breast cancer patients. For metastasis to occur cancer cells have to attain a specific genotype and epigenotype, which allows them to disseminate from the primary tumor mass, survive, and then proliferate at secondary sites. Breast cancer cells have a distinct epigenomic DNA methylation profile which affects their metastatic potential (Thakur et al., 2014). Recent reports have shown that C-X-C chemokine receptor 4, TNF-α and IL-6 play an important role in metastasis (Tripsianis et al., 2013; Jiyang et al., 2014).

Comparing to western countries, the overall survival rates are still low in developing societies. Five- year survival rates of more than 80% have been reported in European countries (Berrino et al., 2007).

Our study is consistent with some previous studies

which showed that expression of ER (p=0.3) was not a predictor of survival (Tsan garis et al., 1992; Wolberg et al., 1999; Horita et al., 2001), although there are some contradicting researches (Akbari et al., 2007; Korizumi et al., 2010). Our study were in accordance with many studies (Dawood et al., 2008; Moradi Marjaneh et al., 2008) that revealed PR and HER-2 do not have effect on survival, but in some studies HER-2 was a prognostic factors (Khodabakhshi et al., 2011). Protein P53 was not prognostic factor for survival. This outcome agreed with a study in Mashhad (Moradi Marjaneh et al., 2008). Effects of breast cancer biomarkers on survival in different studies have had different results, probably because of ethnic factors and different features of breast cancer patients. ER, PR, HER-2 and P53are routinely checked in breast cancer specimens, are reliable, inexpensive and useful for treatment decision making; the results of these tests are recorded in cancer registries, allows population-based researches and makes them reasonable substitute for the more expensive molecular subtyping. It is suggested to conduct other studies with larger sample sizes to determine definite effects of biomarkers on survival.

Usually a sentinel lymph node biopsy is performed before surgery and if cancer cells are foundthen surgery is conducted. Surgery including radiotherapy is usally the standard choice of treatment (Rafiqhullah Khan et al., 2014). Like some other studies (Tewsend et al., 2004; Branicadi et al., 2005), regarding the operation technique, our study showed that there is no statistically significant difference between patients with MRM and breast-conserving surgeries. So, it is reasonable to offer lumpectomy rather than mastectomy for some patients for whom the less aggressive operation is technically suitable.

Non-metastatic breast cancer patients have significantly higher survival rates than those with systemic metastases, so, mass screening and early detection programs may help in improving treatment outcome by diagnosing the disease in less advanced stages.

In conclusion, cancer-related mortality of breast cancer patients is almost always because of metastatic spread, thus in order to achieve higher survival rates and better quality of life, it is very important to understand mechanisms of gaining metastatic potential, in addition to prevention and treatment of metastasis. Based on data of health care cancer data base of Iran, the age of appearing of the disease and median age of breast cancer patients are almost one decade earlier than other countries. This can make earlier starting of screening programs in this population reasonable. Early diagnosis of breast cancer and early treatment can increase survival and likely prevent metastasis and relapse.

References

American joint committee on cancer AJCC Cancer staging mannual (2002). 3 Ed, New York-Berlin: Springer-Verlag.

Akbari M, Mirzaei H, Souri H (2007). 5-year survival of breast cancer in shoada-e-tajrish and jorjani hospitals. *Hakim Res J*, **9**, 39-44.

Akhsan A, Aryandono T (2010). Prognostic factors of locally advanced breast cancer patients receiving neoadjuvant and adjuvant chemotherapy. *Asian Pac J Cancer*, **11**, 759-61.

Akhavan A, Binesh F, Heidari S (2014). Survival of brain metastatic patients in Yazd. *Asian Pac J Cancer Prev*, **15**, 3571-4.

Branicadi F, Chales A, Dana K, Biliary R, Schwartz S (2005). Principle of surgery. 8th ed. New York: McGraw- Hill, Medical Publishing Division.

Berrino F, Angelis RD, Sant M, et al (2007). Survival for eight major cancers combined for European adults diagnosed in 1995-99: results of th FUROCARE -4 study. *Lancet Oncol*, **8**, 773-83.

Dawood S, Broglio K, Esteva FJ, et al (2008). Deffinig prognosis for women with Breast cancer and CNS metastasis by HER-2 status. *Ann Ancol*, **19**, 1272-48.

Ederer F, Axtell LM, Cutler SJ (1961). The relative survival rate: A statistical methodology. *Natl cancer Inst Monogr*, **6**, 101-21.

Esteve J, Benhamou E, Croasdale M, Raymond L (1990). Relative survival and the estimation of net survival: Element for further discussion. *Stat Med*, **9**, 529-38.

Hosmer DW, Lemeshow S (1999). Applied Survival Analysis: Regression Modeling of Time to Event Data, New York John Wiley & Sons.

Horita K, Yamagoush A, Hirose K, et al (2001). Pronostic Factor affecting disease free Survival rate following surgical resection of primary Breast cancer. *Eur J Histochem*, **45**, 73-84.

International Agency for Research on Cancer (2006). Cancer Mondial [on line database]. Available from: URL: http // WWW-dep.iarc.fr/ Accessed Dec 7.

Klein JP, Moeschberger ML (1997). Survival analysis techniques for censored and truncated data, New York: Springer-Verlag.

Korizumi M, Yoshimoto M, Kasumi F, Iwase T (2010). An open cohort study of bone metastasis incidence following surgery in breast cancer patients. *BMC Cancer*, **10**, 381-85.

Khodabakhshi R, Gohari M, Moghadami Fard Z, Foadzi H, Vahabi N (2011a). Disease- Free survival breast cancer patients and identitification of related factors. *Razi J Med Sci*, **18**, 27-32.

Khodabakhshi R, Gohari MR, Moghadami Fard Z, Foadzi H, Vahabi N (2011b). Disease-free survival of breast cancer patients and identification of related factors. *Razi journal of Medical Sciences*, **18**, 27-32.

Kaviani A, Neishaboury MR, Mohammadzadeh N, et al (2013). Effects of obesity on presentation of breast cancer, lymph node metastasis and patients survival: A retrospective review. *Asian Pac J Cancer Prev*, **14**, 2225-9.

Moran JL, Bersten AD, Solomon PJ, Edibam C, Hunt T (2008a). Modelling survival in acute severe illness: Cox versus accelerated failure time model. *J Eval Clin Pract*, **14**, 83-93.

Moradi Marjaneh M, Homaei F, Shamsiyan A, et al (2008b). Relationship between HER-2, P53, Estrogen receptor, progestron receptor and survival rate in Iranian women with breast cancer, **1**, 7-17.

Mohagheghi MA, Mosavi-Jarrahi A, Malekzade R, et al (2009). Cancer incidence in tehran metropolis: the first report from the tehran population-based cancer rigestery 1998-2001. *Arch Iran Med*, **12**, 15-23.

Nicholas EM, Patchell RA, Regine WF, Kwok Y (1766). Palliation of brain and spinal cord metastases. in perez and bradys principles and practice of radiation oncology, USA, 6th. Edition page.

Nor Aini A, Wan R, Nor Asia M, et al (2013a). Survival rate of breast cancer patients in Malasiya: a population-based Study. *Asian Pac J Cancer Prev*, **14**, 4591-4.

Najafi B, Anvari S, Atrkar Roshan Z (2013). Disease free survival among molecular subtypes of early stage breast

cancer between 2001 and 2010 in Iran. *Asian Pac J Cancer Prev*, **14**, 5811-6.

Orbe J, Ferriera E, Nunez-Anton V (2002). Comparing proportional hazards and accelerated failure time models for survival analysis. *Stat Med*, **21**, 3493-510.

Rayter Z, Gazet JC, Ford HT, Easton DF, Commbes RC (1990). The Comparison of conservative surgery and radiotherapy with mastectomy in the treatment of early breast cancer. *Eur J Surg Oncal*, **16**, 486-92.

Rafiquhhah Khan HM, Saxena A, Gabbidon K, et al (2014a). Survival analysis for white non-hispanic female breast cancer patients. *Asian Pac J Cancer Prev*, **15**, 4049-54.

Rafiqhullah Khan HM, Saxena A, Gabbidon K, Rana S, Uddin Ahmed N (2014). Model-based survival estimates of female breast cancer data. *Asian Pac J Cancer Prev*, **15**, 2893-900.

Sayehmiri K, Alimoghaddam K, Ghavamzadeh A (2010). Comparision of prognostic factors and death hazard function of acute myeloid leukemia and acute lymphoblastic leukemia patients after bone marrow transplanation. *Int J Hematol Oncol Stem Cell Res*, **4**, 19-28.

Saha A, Ghosh SK, Roy C, et al (2013). Demographic and Clinical profile of patients with brain metastases: A retrospective study. *Asian J Neurosurg*, **8**, 151-61.

Tsan garis TN, Knox SM, Cheek JH (1992). Tumor Hormon receptor statue and recurrences in premenopausal patients with node-negative Breast carcinoma. *Cancer*, **69**, 984-7.

Tewsend M, Neauchamp R, Daniel SB, Matto X, Kenneth L (2004). Sabiton text book of surgery. 17th ed. Amesterdam; Elsevier.

Tripsianis G, Papadopoulou E, Romanidis K, et al (2013). Overall survival and clinicopathological characteristics of patients with breast cancer in relation to the expression pattern of HER-2, IL-6, TNF-α and TGF-β1. *Asian Pac J Cancer Prev*, **14**, 6813-20.

Thakur S, Singla A, Chen J, et al (2014). Reduced ING1 levels in breast cancer promotes metastasis. *Oncotarget*, 1-13.

Wolberg WH, Street WN, Mngasarian OL (1999). Importance of nuclear morphology in breast cancer prognosis. *Clin Cancer Res,* **5**, 3542-48

Wei XQ, Li X, Xin XJ, Tong ZS, Zhang Sh (2013). Clinical features and survival analysis of very young (age<35) breast cancer patients. *Asian Pac J Cancer Prev*, **14**, 5949, 52.