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Survival Models in Breast Cancer Patients

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Abstract

Background: Breast cancer is the most prevalent malignancy among Iranian women. Five and ten year survival is one of the indicators used for evaluation of the quality of care after surgery. In this study, we used several survival models to determine risk factors, survival times and life expectancies of different types of surgery.

Methods: This study was performed on 310 patients who underwent surgery during a ten years period. Logistic regression and Cox regression models were used to analyze the factors leading to death. The Kaplan-Meier method (non-parametric) was used to estimate the survival rate. The log-rank test was used to compare survival in different groups. To compare life expectancy of different types of surgery, we used the actuarial life table method.

Results: Logistic regression showed that stage, grade, age and history of benign malignancy had significant relationship with death. Log-rank test showed that there was a significant difference between survival for patients with different stages, age and history of benign tumors. Cox regression model demonstrated that the variables of stage, grade, age and benign problems were the major risk factors. Actuarial life table model showed that the life expectancy for all patients was 10.03 years. This life expectancy in early stages of breast cancer for mastectomy and lumpectomy were 8.99 and 8.35 years, respectively, which was not significant.

Conclusion: It can be concluded that the higher stage, grade, age and history of benign tumor were, the most important risk factors were correlated to mortality in breast cancer patients. This study showed that there was no significant difference between life expectancies of mastectomy and lumpectomy surgery.

Keywords: Survival models; Breast cancer; Actuarial life table

Introduction

Cancer is the second leading cause of death in developed countries (12.6%) and it is a public health problem worldwide. In developed countries, prostate, breast and colon cancers are more common ones.[1] In Iran, it is the third cause of deaths after cardiovascular diseases and accidents.[2] If this trend continues, by the year 2020, the world will be encountered with 15 million new cases, two thirds of which will be in the newly industrialized and developing countries..[3]

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Breast cancer is the most prevalent malignancy among women and its prevalence was reported 21%. It is one of the slow growing types of cancers. Recent researches showed that its incidence rate is increasing and the age of the onset is decreased. Some known risk factors include stage, grade, family history, age at diagnosis, menopause status, monarch age and positive history of benign tumors.[3]

In Iran, this cancer is the most lethal one among women. The prevalence of breast cancer was reported 25.4% and deaths due to breast cancer were 12.3%.[2,4] In southern Iran, it was at the top of 10 prevalent cancers in the area with a crude rate of 11.58 and age specific incidence rate of 18.06.[5]

In southern Iran, it was demonstrated that the majority of patients were diagnosed with an advanced

tumor size. Five-year overall survival was 58%. There was a significant correlation between survival of breast cancer patients and family income, smoking, metastases to bone and lung, tumor size and grade, lymph node ratio, and number of involved nodes.[6]

In this study, we applied several survival models to determine risk factors, survival length and life expectancies of different types of surgery.

Materials and Methods

From 1994 to 2003, the information of breast cancer patients in Shiraz, southern Iran were collected from Hospital-based Cancer Registry of Nemazee Hospital affiliated to Shiraz University of Medical Sciences. After diagnosis, all patients had undergone either mastectomy or lumpectomy and followed during a ten-year period. Information on stage, grade, age at diagnosis, history of benign tumors and type of surgery were provided. These factors were categorized respectively as early, locally advanced and advanced for their stages; I, II and III for their grade; less than 48 and more than 48 years (menarch age)[7]; and presence or absence of a benign tumor history.[8]

Patients in the early stage underwent either lumpectomy or mastectomy but in other stages only mastectomy was done. Regardless of the tumor grade, they had undergone either mastectomy or lumpectomy. Survival was considered as the time period between diagnosis and death (or last visit) of patient. Standard statistical methods could not be used for longitudinal and censored data, because these data were usually skewed and survival lengths were censored due to immigration, treatment, etc. For analyzing of data, Kaplan-Meire and Log-rank tests were used to compare the survival lengths in different groups.[9,10] Logistic and Cox regression models were used to find odds ratio and proportional hazards of the affecting factors leading to death.[11,12]

Finally, actuarial life table method was applied to compare life expectancies for different types of surgeries.[13,14] For actuarial life table, the distribution of N patients based on their status in each follow up interval was shown in Table 1. According to the actuarial life table method[11], the probability of death in the interval [x, x+1) is:

$$q_x = \frac{D_x}{N_x - \frac{W_x}{2}}.$$

This method supposes that the withdrawal patients were observed for half of the period, so the term $N_x - \frac{W_x}{2}$, shows the number of patients at risk. The probability of survival in the corresponding interval is: $P_x = 1-q_x$

The probability of being alive till x=j for patients who were alive at x=i was: $\hat{P}_{ij} = \frac{l_j}{l_i}$. They were used to compute 1, 3, 5 and 10-year survival rates. Other life table columns can be computed using q_x values. For the last group, the value of life expectancy was computed by.[13]

$\hat{e}_t = \frac{1}{2} + \frac{1-q_t}{q_t}$, when $\hat{q}_t$ is the last nonzero q_x.

Results

Tables 2-5 show the distribution of patients' status based on their stage, grade, age at diagnosis and the history of benign tumors. These results showed that the survival status of patients was correlated to stage, grade, age and history of benign tumors. Also, Tables 6 and 7 showed the odds ratio and proportional hazard of death for this disease based on logistic regression model and cox regression model. These models showed that the chance of death increased in locally advanced and advanced stages, grade III, age more than 48 years and positive history of benign tumors. The results were almost the same for both logistics and Cox models.

Table 1: The Distribution of patients according to their status in the follow up interval [x , x+1)

Status	Total	Observed in all period	Withdrawal
Total	N_x	m_x	n_x
Survived	$S_x + W_x$	S_x	W_x
Death	D_x	d_x	d_x'

Table 2: Distribution of Patients' Status by to their Stage

Stage Status	Early No. (%)	Locally Advanced No. (%)	Advanced No. (%)	Total No. (%)
Alive	151 (79)	37 (19)	3 (2)	191 (100)
Death	22 (39)	25 (45)	9 (16)	56 (100)
Total	173 (70)	62 (25)	12 (5)	247 (100)

$c^2 = 39.5$

$p < .001$

Table 3: Distribution of Patients' Status by to their Grade

Grade Status	I No. (%)	II No. (%)	III No. (%)	Total No. (%)
Alive	66 (35)	92 (48)	32 (17)	190 (100)
Death	11 (20)	31 (55)	14 (25)	56 (100)
Total	77 (31)	123 (50)	46 (19)	246 (100)

$c^2 = 5.14$,

$p = .08$

Table 4: Distribution of Patients' Status by to their Age at diagnosis

Age Status	< 48 No. (%)	>48 No. (%)	Total No. (%)
Alive	162 (64)	92 (36)	254 (100)
Death	16 (28)	40 (72)	56 (100)
Total	132 (42)	178(58)	310 (100)

$c^2 = 23.3$

$p =< .001$

Table 5: Distribution of Patients' Status by their Benign Tumor History

Benign Tumor History Status	Positive No. (%)	Negative No, (%)	Total No, (%)
Alive	68 (32)	141 (68)	209 (100)
Death	36 (66)	18 (34)	54 (100)
Total	104 (39)	159 (61)	263 (100)

$c^2 = 20.9$

$p =< .001$

Table 6: Odds Ratio of Death for Breast Cancer Patients According to their Risk Factors (Logistic Regression)

Variable	Levels	OR	95% C.I.	*P*
Stage	Early	1		
	Locally Advanced	4.64	(2.35, 9.12)	<0.001
	Advanced	20.59	(5.17, 81.9)	<0.001
Grade	I	1		
	II	2.02	(0.94, 4.3)	0.07
	III	2.62	(1.07, 6.43)	0.03
Age at Diagnosis	<48	1		
	>48	4.4	(2.3, 8.3)	<0.001
History of Benign	No	1		
Tumors	Yes	4.15	(2.2, 7.8)	<0.001

Table 7: Proportional risk of death for breast cancer according to their risk factors (Cox Regression)

Variable	Levels	PH	95% C.I.	*P*
Stage	Early	1	-	
	Locally Advanced	4.17	(2.35, 7.41)	<0.001
	Advanced	4.83	(2.21, 8.55)	<0.001
Grade	I	1	-	-
	II	2.005	(1.01, 3.99)	0.048
	III	2.055	(0.93, 4.5)	0.074
Age at Diagnosis	<48	1		
	>48	3.39	(1.89, 6.56)	<0.001
History of Benign Tumors	No	1		
	Yes	2.94	(1.67, 5.19)	<0.001

The Kaplan-Meier curves showed that there were significant differences between the patients' survival curves. Patients in early stage, grade I, age less than 48 and without a history of benign tumors experienced higher survival curves (Figure 1). Table 8 shows the results of the Log-Rank test for these variables. These results were confirmed by Kaplan-Meier Curves in Figure 1.

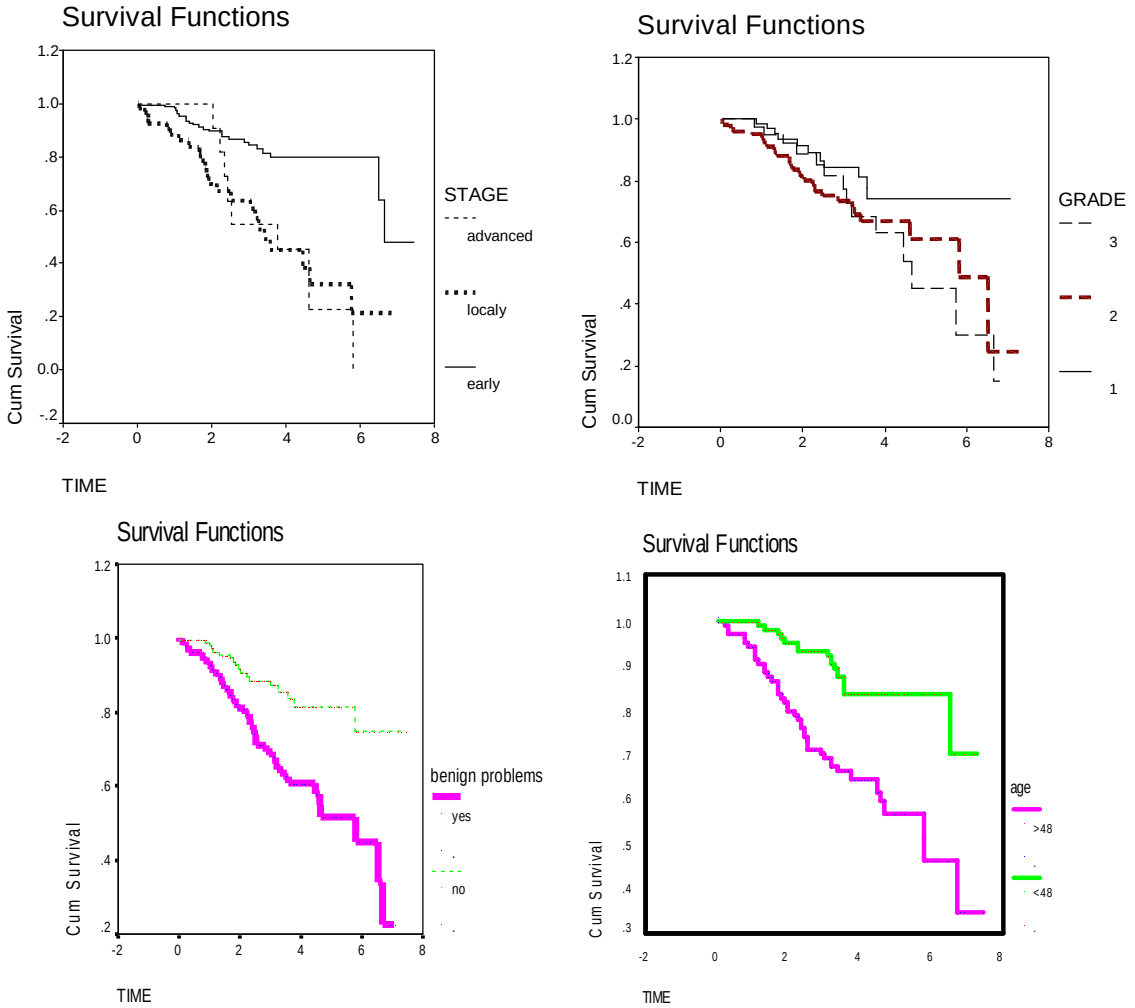

Figure 1: Kaplan- Meier survival curves for some important variables.

Table 8: Median Survival Time and Log-Rank test for Breast Cancer Patients According to their Risk Factors

Variable	Levels	Median Survival Time	$c^2_{Log-Rank}$	P
Stage	Early	64		
	Locally Advanced	60	9.15	0.01
	Advanced	60		
Grade	I	68		
	II	60	0.11	0.70
	III	61		
Age at Diagnosis	<48	45		
	>48	64	21.19	<0.001
History of Benign Tumors	No	65		
	Yes	60	4.84	0.04

By applying the actuarial life table technique, 1, 3, 5 and 10-year survival rates for these patients were 97%, 82%, 70% and 53%, respectively. The life expectancies resulted from actuarial life table for early stage in different types of surgeries are shown in Table 9. The difference between these two life expectancies (8.99 and 8.35) was not statistically significant (p=0.0602).

Table 10 shows survival rates in different stages. This table contains 5 year survival for Carolina state (1997) for comparison purpose.[15] It is obvious that 10-year survival rate for early stage patients were higher than other groups.

Discussion

Breast cancer is a non-contiguous disease whose risk factors were investigated in recent decades. Some risk factors are controllable, and some such as sex and family history are not. In this study, mean and median age for breast cancer patients in Shiraz was 47.06 and 46, respectively. The results showed that stage was a very important risk factor. Early stage patients had a higher survival curve and experienced higher survival rates. The chance of death for locally advanced and advanced stage patients was 4.64 and 20.59 times more

Table 9: Actuarial life table for early stage of breast cancer by the two types of surgery.

Interl (x , x +1)	Mastectomy			Lumpectomy		
	q_x	l_x	e	q_x	l_x	e
0-1	0.009	100000	8.99	0.0	100000	8.35
1-2	0.059	99100	8.07	0.092	100000	7.35
2-3	0.036	90181	7.82	0.033	90800	7.05
3-4	0.059	86935	7.15	0.093	87804	6.28
5-6	0.0	81806	6.51	0.0	79638	5.87
6-7	0.0	81806	5.51	0.0	79638	4.87
6-7	0.28	81806	4.51	0.330	79638	3.87
7-8	0.0	58900	5.07	0.0	53358	4.53
8-9	0.0	58900	4.07	0.0	53358	4.53
9^t	-	58900	3.07	-	53358	2.53
	$\hat{e}_t = \frac{1}{2} + \frac{1-0.25}{0.28} = 3.07$			$\hat{e}_t = \frac{1}{2} + \frac{1-0.33}{0.33} = 2.53$		

Table 10: 10-Year Survival Rates (%) for Breast Cancer Patients According to their Stage

Year Survival Rates	Early	Locally Advanced	Advanced
1-Year	99	98	88
3-Year	85	80	55
* 5-Year	79	62	30
10-Year	54	53	19
* 5- Year (Carolina 1997)	94	79	53

than that in the early stage. Adnan Ezzat and Madras Raja[16] in a survey in Saudi Arabia in 1997 found that there was a significant difference among patients' survival curves according to their stages and early stage patients experience a higher survival curve than the other stage patients. This result has been confirmed in another research in Taiwan by Wei Shuwang et al.[17] Furthermore, Simsek[8] (2000) in Carolina showed that this factor had a significant effect on death.

Grade is another important risk factor; the risk of death for patients with grade II and III were 2.02 and 2.62 times more than the risk for patients with grade I. These results showed that patients with grade I experienced a higher survival curve.

Age at diagnosis is an important risk factor. This factor plays a crucial role in patients' career. We categorized patients based on monarch age to less and more than 48 years as described by Ayatollahi et al. (2003)[7] for monarch age in Shiraz to be 48 years). Patients older than 48 years had a lower survival curve and the chance of death was 4.4 times more than patients younger than 48 years old. Ezzat et al.[16] in a survey in Saudi Arabia in 1997 categorized ages of patients to less than 40, 41-60 and more than 60 years, and found that there was a significant difference among patients' survival curve according to their age groups. Simsek[8] (2000) in Carolina showed that the probability of death for patients aged more than 65 years was 1.26 times as much as that for other patients.

Kaplan-Meier curve and Log-Rank test showed that patients with positive history of benign tumors had a lower survival curve than the patients without the history, and the chance of death for these patients was 4.15 times as much as that for the patients without benign tumor history.

Our results showed that stage, grade, age at diagnosis and positive history of benign tumors were crucial risk factors and could increase the chance of death. It is concluded that if the disease is diagnosed in the primary stage and grade, it will be controllable and increase the patients' survival time.

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