

**Research/Technical Note**

A Survival Analysis of Invasive Breast Cancer Patients with and Without in Situ Neoplasm

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Abstract: In situ neoplasm (or Carcinoma in situ (CIS)) is expression of malignant epithelial cells. This flat lesion is referred to as ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). Considering neoplasm leads one to an effectiveness survival analysis compared to the case that neoplasm is not attended. The objective of this research is to analyze statistically survival of invasive breast cancer patients considering 1) with in situ neoplasm, and 2) without in situ neoplasm, and providing a comparative analysis. This study attempts to reveal that the both medical history (such as diabetes, hypertension, and internal glands disorders such as hypo- and hyperthyroidism) and extra capsular extension play important roles in the hazard function of a patient's survival analysis. This statistical study indicates that 1) the survival rate of breast cancer patients with in situ neoplasm is more than one who is not initially supported by invasive carcinoma, and 2) in the case of existence of the both in situ neoplasm and invasive malignancy, after the 4th year, the life expectancy is increased compared to the one with only invasive malignant. The statistical analysis indicates that pathology type is recognized as a high hazard factor for a breast cancer patient.

Keywords: Survival Analysis, Invasive Breast Cancer, In Situ Neoplasm, Cox Regression

1. Introduction

Neoplasm can be categorized into two main branches: 1) invasive, and 2) non-invasive. In situ neoplasm is referred to as the abnormal growth of tissue. In this case the abnormal growth is limited to the ducts and lobules and it does not spread to the surrounding tissues. This condition is also known as ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS), respectively.

Literature addresses that different researchers have been contributed to the survival analysis of breast cancer patients. Movahedi et al. [1] proposed age, sex, pathology type, and geographic location as the main variables that are capable of effecting on the patients' survival analysis. Movahedi et al. [1] estimated rate of survival for breast cancer patients based on geographical region. Anwar et al. [2] focused on lobular carcinoma patients and analyzed the related information of

this patient type. Anwar et al. [2] considered surgery therapy method, and the rate of local recurrence to analyze the survival of these patients. Bane [3] also studied patients with DCIS type regarding the grade of malignancy. Bane [3] emphasized the importance of diagnosis of DCIS provided by a pathologist. Virnig et al. [4], and Hajilou et al. [5] reviewed treatment of DCIS patients' literature. Narod et al. [6] estimated mortality rate of breast cancer patients after diagnosing DCIS. They discussed that the most important factors corresponding to the high risk conditions are: 1) age at the time of diagnosis, and 2) skin color (white and black). Borgquist et al. [7] focused on the role of epidermal growth factor (Her2) on ductal carcinoma in situ. They concluded that Her2⁺ leads to decrease cancer recurrence as well as conversion of CIS to the invasive breast cancer type. Margolese et al. [8] evaluated hormone therapy drugs and its impact on menopausal women who has DCIS. Margolese et al. [8] studied only the women

who have been treated by lumpectomy surgery and radiotherapy. Atashgar *et al.* [9] analyzed survival model of the breast cancer patient with chronic diseases. The statistical analysis of the data indicated that chronic diseases can significantly affect the survival probability in breast cancer. As shown in table 1, although several survival models have been reported for breast cancer patients, literature indicates that the existence of in situ neoplasm effects for the case of invasive breast cancer have not been considered. A comprehensive comparative study of survival for invasive breast cancer with and without in situ neoplasm is capable of effecting the protocol of therapy.

Lobular carcinoma in situ (LCIS) is caused by unusual cells in lobules of a breast and not spread out of the basement membrane. This kind of cancer is rather rare and is more in women in the age range of 40-50 years old, but its manifestation is increasing in menopausal women [15]. Ductal

carcinoma in situ (DCIS) condition has potential of converting to the invasive form [16, 17]. Literature addresses that 20-50 percent of DCIS is affected by invasive breast cancer [18-20]. Decision about how to treat a breast cancer patient after surgery is contingent on the accuracy of estimating the behavior and outcome of the disease [21]. Patients who are affected by ductal carcinoma in situ have more possibility of affliction with malignancy compared to the normal population [22]. The conversion of ductal carcinoma in situ to invasive type is a key progression of a breast cancer [23, 24]. This research leads specialists to analyze effectively survival rate of patients' invasive breast cancer in the condition with in situ neoplasm and compare the survival of this patient type with the case of the patients without in situ neoplasm. In this comprehensive research, tissue and the pathology type of these patient types are also investigated.

Table 1. Effective factors on breast cancer survival analysis.

Survival Factors								
Source	Gender	Race	Age	Familial History	Parity	Place of residence	Breast density	Tumor size
Virnig <i>et al.</i> (4)	*	*	*	*		*		
Anwar <i>et al.</i> (2)								
Anet <i>et al.</i> (10)		*						
Colzani <i>Et al.</i> (11)								*
Movahedi <i>et al.</i> (1)	*		*			*		
Faradmal <i>et al.</i> (12)								*
Bane <i>et al.</i> (3)		*					*	
Abadi <i>et al.</i> (13)								
Narod <i>et al.</i> (6)	*	*					*	
Borgquist <i>et al.</i> (7)								*
Elshof <i>et al.</i> (14)			*					

Survival Factors								
Source	No. Lymphnodes	Margins	BMI	Grade	Stage	Pathology	Estrogen status	Progesterone status
Virnig <i>et al.</i> (4)		*						*
Anwar <i>et al.</i> (2)	*							
Anet <i>et al.</i> (10)				*				
Colzani <i>Et al.</i> (11)	*					*		
Movahedi <i>et al.</i> (1)						*		
Faradmal <i>et al.</i> (12)	*			*				
Bane <i>et al.</i> (3)	*		*					
Abadi <i>et al.</i> (13)								
Narod <i>et al.</i> (6)			*			*		
Borgquist <i>et al.</i> (7)							*	*
Elshof <i>et al.</i> (14)								

Survival Factors							
Source	Mammography	Type of surgery	Hormonotherapy	Chemoprevention	Adj. Chemotherapy	Adj. Radiotherapy	
Virnig <i>et al.</i> (4)		*	*				
Anwar <i>et al.</i> (2)	*			*	*		
Anet <i>et al.</i> (10)							
Colzani <i>Et al.</i> (11)							
Movahedi <i>et al.</i> (1)							
Faradmal <i>et al.</i> (12)							
Bane <i>et al.</i> (3)							
Abadi <i>et al.</i> (13)	*	*	*		*		
Narod <i>et al.</i> (6)							
Borgquist <i>et al.</i> (7)							
Elshof <i>et al.</i> (14)		*					

2. Methods

In this research 1822 data files of the breast cancer patients who were referred to three breast cancer hospitals of Tehran in the period time of 2007 till mid 2016 are studied. The total number of the patients that referred to these hospitals originally is 2010 patients, but the incompleteness of data led the researchers to focus on 1822 individuals. In the first step, the uncompleted profile of all these patients including pathology, histopathology (IHC) and determination of metastases using image study were completed. In this extensive research the clinical data of the patients is an essential requirement. In the second step regarding ethical remarks all the required data were gathered and recorded structurally by interviewing with all the patients or their caregivers. In this research all data of all the patients, including 1) Age, 2) Job, 3) Ethnic, 4) Level of education, 5) Medical History, 6) Nipple-Skin Involvement, 7) Familial History, 8) Lymph nodes involvement, 9) Breast site, 10) Number of involved lymph nodes, 11) Her2 receptor, 12) Extra capsular extension, 13) Vascular-perineural invasion, 14) Estrogen receptor, 15) Type of surgery, 16) Progesterone receptor, 17) Stage, 18) Sentinel node status, 19) Tumor size, 20) Grade, 21) Metastasis, 22) Hormone therapy, 23) Number of metastasis, 24) Type of pathology, 25) Radiotherapy, 26) Chemotherapy, and 27) Status of the patients' survival, were

completely recorded. Table 2 shows the detail data of each of these prognosis factors. The prediction of outcomes based on a set of prognostic factors is a longstanding topic of interest in biostatistics [25].

In this research Kaplan- Meier diagram and Cox proportional hazards models are used to analyze the data of the 1822 patients. Literature indicates that Cox as a semi parametric model has been used by different researchers for survival analysis of patients. Although Cox considers no assumptions related to hazard initially, it provides the same results that parametric models are capable of providing. On the other hand, Cox is the most applicative model for the case that right censored data are exists. The basic assumption of this model is referred to as the constancy of hazard proportion of groups over the time [26]. The advantages of Cox regression lead researchers to prefer this approach compared to the parametric ones [27].

Response variable of this research is referred to as the patient survival time (in month). This time includes the interval time of finishing the treatment process until the investigation time of this study. The status of each breast cancer patient (dead or alive) is addressed in this interval time by the database of this research. In the case that the status of a patient is not clear, the data is assumed as a censored data.

Table 2. The frequency distribution of characteristics of patients with breast cancer.

Row	Parameter		No.	Percent	Row	Parameter		No.	Percent
1	Age	< 50	897	49.23	2	Job	House Worker	1141	62.6
		50≤	923	50.65			Employee	240	13.17
		Persian	1014	55.65			Diploma-	677	37.15
3	Ethnic	Turkish	218	11.96	4	Education	Diploma	438	24.03
		Other	128	7.02			Educated	242	13.28
5	Medical History	Yes	430	23.6	6	Nipple-Skin Involvement	Yes	123	6.75
		No	795	43.63			No	1526	83.75
7	Familial History	Yes	188	10.31	8	Lymph Node	Yes	932	51.15
		No	1606	88.14			No	806	44.23
9	Breast Site	Right	877	48.13	10	Number of Lymph Node Involvement	0	800	43.9
		Left	891	48.9			January 3rd	445	24.42
11	Her2 Receptor	Positive	494	27.11	12	Extra capsular Extension	Yes	82	4.5
		Negative	1140	62.56			No	1603	87.98
13	Vascular-perineural Invasion	Yes	654	35.89	14	Estrogen Receptor	Positive	1226	67.28
		No	986	54.11			Negative	425	23.32
15	Surgery	Radical Mastectomy	1022	56.09	16	Progesterone Receptor	Positive	1145	62.84
		BCS	750	41.16			Negative	506	27.77
		I	442	24.25			18	Sentinel Node Involvement	Yes
II	789	43.3	No	1495	82.05				
17	Stage	III	188	10.31	20	Grade	I	119	6.53
		IV	248	13.61			II	794	43.57
		2Cm<	354	19.42			III	815	44.73
19	Tumor Size	2-5Cm	1025	56.25	22	Hormone therapy	Yes	1260	69.15
		5 Cm <	181	9.93			No	390	21.4
		Yes	248	13.61			Carcinoma In situ	63	3.45
21	Metastasis	No	1560	85.62	24	Pathology	Carcinoma Invasive	1087	65.59
		I	211	11.58					
23	No. Metastasis	II	42	2.3					

Row	Parameter	No.	Percent	Row	Parameter	No.	Percent		
25	Radiotherapy	III	19	1.04	26	Chemotherapy	Carcinoma In situ	596	32.71
		Yes	1751	96.1			Yes	1747	95.88
		No	69	3.78			No	71	3.89
27	Survival	Alive	1154	63.33					
		Death	202	11.08					

3. Results

This comprehensive analysis of breast cancers’ data indicates that:

1. The lowest and the highest age for these patients are addressed by 23 and 93 years old, respectively.
2. Out of these patients, 923 individuals are more than 50 years old, so that 128 individuals of these patients (about 18 percent) unfortunately died before the completion of this research.
3. The classification indicates that 897 individuals are less than 50 years old, so that 75 patients (about 11 percent) unfortunately died before the completion of this research.
4. Pathology type of 91 percent of the studied patients is ductal carcinoma (in situ and invasive), 5.6 percent is lobular carcinoma (in situ and invasive), and 3.4 percent is categorized in other types (such as Paget).

5. The pathology type for 59.65% of the patients is invasive carcinoma, and 32.71% have experienced invasive carcinoma with in situ neoplasm.
6. 202 patients (11.08%) died, 1154 (63.33%) are alive, and a number of 466 patients are not addressed the status clearly.

Table 2 shows the information structurally in details. Table 3 shows 1, 2, 3... and 9 years survival rate considering pathology types. Regarding that the completion of therapy for some patients have not reported for 9 nine years completely, the 9th year survival analysis is calculated only for the group of patients with at least 9 years therapy. In another word, for this patient type, at least a minimum of 9 years of therapy is required. The consideration indicates that out of 1822 patients, carcinoma in situ has been recorded only for 63 cases. Additionally, since incomplete files of some patients with carcinoma in situ are addressed, calculation of 4 to 9 years survival of these patients with carcinoma in situ is not possible.

Table 3. The Survival probability of patients considering Pathology type.

Kind Of Pathology	Survival probability (in year)								
	1	2	3	4	5	6	7	8	9
Carcinoma In situ	100%	100%	91.66%	-	-	-	-	-	-
Carcinoma Invasive	95.61%	91.16%	84.55%	75.32%	73.02%	71.57%	56.92%	50%	19.35%
Carcinoma In situ-Invasive	96.83%	93.45%	90.03%	78.20%	74.92%	72.86%	61.96%	57.22%	22.22%
All	96.25%	90.10%	86.22%	78%	74.15%	72.33%	68%	66.56%	18.51%

Atashgar et al. [21] analyzed survival model of the breast cancer patient without considering neoplasm. Table 4 addresses a survival Cox model of this research based on the approach of Atashgar et al. [21], while Table 5 indicates a survival Cox model of this research considering neoplasm. In another word, Table 4 shows the results of this research in the case that this research follows the survival approach proposed by Atashgar et al. [21]. Considering neoplasm of Table 5 leads to some new factors that affect the survival model significantly. Although the model based on neoplasm consideration removes tumor size factor, the consideration conveys some important factors including pathology, extra capsular, medical history, and education. The model of Movahedi et al. [1] also considered pathology without existing of tumor size. The analysis leads that the Akaike information criteria (AIC) corresponding to Tables 4 and 5 are 1102.62 and 773.85, respectively. AIC addresses the relative quality of models for a given data set statistically. This analysis indicates that consideration of neoplasm in this research allows performing a better survival model compared to the survival model approached by Atashgar et al. [21].

Table 4. The Results of the Cox Proportional Hazard Model approaching atashgar et al [21].

Parameter	β	SE	Sig	HR (95 % CI)
Age	0.071	0.01	0	1.074
Tumor Size	0.115	0.032	0	1.122
Metastasis	1.882	0.211	0	6.565
Hormone therapy	-0.708	0.152	0.001	0.493

Table 5. The Results of the Cox Proportional Hazard Model considering neoplasm factor.

Parameter	β	SE	Sig	HR (95 % CI)
Age	0.858	0.268	0.001	2.36
Medical History	-1.219	0.353	0.001	0.29
Pathology	-0.186	0.306	0.545	0.83
Number of lymph Node	0.115	0.045	0.011	1.12
Extra capsular extension	0.839	0.432	0.037	2.31
Metastasis	1.299	1.272	0.046	3.66

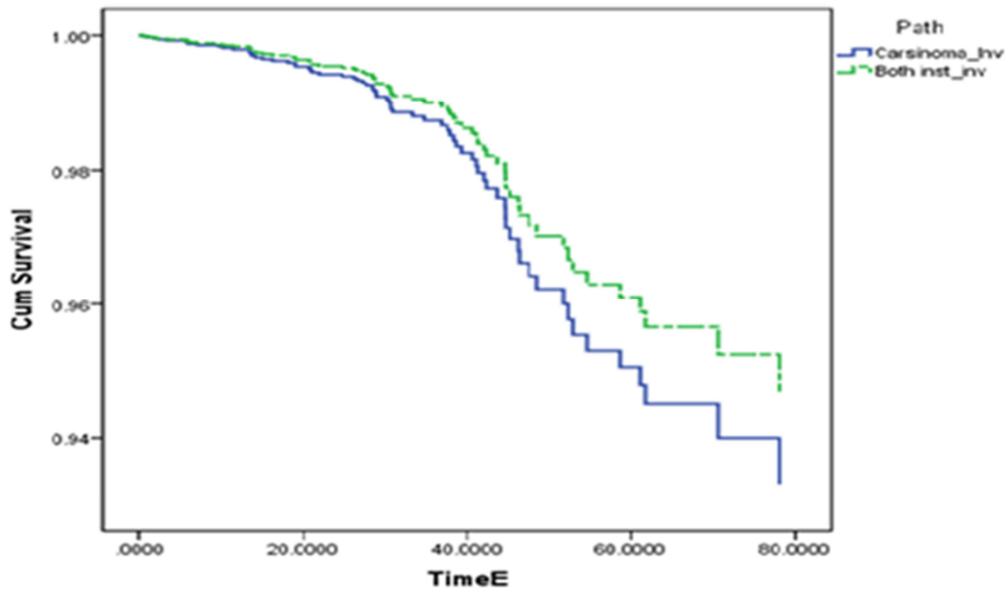


Figure 1. Kaplan-Meier graph of survival curve considering pathology.

In this study, to analyze the impact of explanatory variables on breast cancer patients' survival, semi parametric Cox regression is used. Stepwise approach is also used to design an adequate regression model assuming $\alpha=0.05$. Table 5 indicates that variables including 1) patient age, 2) Medical history, 3) number of involved lymph nodes, 4) extra capsular extension, and 5) metastasis significantly impact on the analysis of a breast cancer patient's survival. Although Table 5 shows that pathology type is not a significant variable under consideration of $\alpha=0.1$, analysis of Kaplan-Meier graph (Figure 1) leads one to a remarkable influence of neoplasms as well as survival calculations on patients (Table 3). In other words, neglecting pathology type is capable of leading analysis of the patients with in situ neoplasm to a significant error. Hence pathology type is allowed to evaluate as a significant variable. The conclusion allows us to place the pathology factor in the proposed survival model of this study.

4. Discussion

Usual ductal hyperplasia (UDH) and atypical ductal hyperplasia (ADH)/low-grade ductal carcinoma in situ (LG-DCIS) are biologically distinct, intraductal, epithelial proliferations with different clinical implications. Usual ductal hyperplasia can even contain apocrine metaplastic cells [28]. Ductal carcinoma in situ (DCIS) is a risk factor for incomplete resection of breast cancer. Detecting DCIS around breast cancer before treatment may therefore alter surgery [29] Wu et al. [30] also considered the Prognostic value of ductal carcinoma in situ component in invasive ductal carcinoma of the breast. Literature indicates that about 30 percent of ductal carcinoma in situ lesions during a certain time become invasive breast cancer [19]. Ductal carcinoma in situ treatment with a combination of surgery, radiotherapy, and hormone therapy prevents local recurrence for 10-15 percent of the patients; however 50 percent of cases become

invasive breast cancer [31-33]. Due to abnormal behavior of carcinoma in situ, it is recommended that CIS should be detected at earlier stage. Conversion of CIS to invasive case is a key occurrence. This comprehensive research using statistical analysis proposed a survival model considering pathology type. The analysis of this research indicates that breast cancer patients with in situ neoplasms (without regarding the stage of disease) are placed in a higher survival rate compared to the patient type who refers to a therapeutic center initially with invasive carcinoma. The higher rate is due to tendency of recurrence for an invasive case without in situ neoplasm. Where the rate of this case is more compared to a breast cancer patient with a diagnosed in situ neoplasm. The analysis of Kaplan-Meier diagram (Figure 1) also indicates that diagnosis of in situ neoplasm before invasive malignancy increases longevity after the 4th year than a case with only the invasive malignancy. The statistical analysis indicated that pathology type (with a relative hazard of 0.831) is recognized as a high hazard factor for breast cancer patients. This means that a patient who refers initially with invasive carcinoma have 0.831 fold more hazard of death compared to an invasive breast cancer with neoplasm that diagnosed with in situ. Hence timely diagnosis of carcinoma in situ not only thereby increasing the chance of patient lifetime, but also the timely diagnosis remarkably improves the mental status of a breast cancer patient.

5. Conclusion

This research focused on analyzing statistically survival of invasive breast cancer patients considering with in situ neoplasm, and without in situ neoplasm conditions. The results of this research revealed that the both medical history and extra capsular extension play important roles in the hazard function of a patient's survival analysis. The statistical analysis of this study indicated that 1) the survival rate of

breast cancer patients with in situ neoplasm is more than one who is not initially supported by invasive carcinoma, and 2) in the case of existence of the both in situ neoplasm and invasive malignancy, after the 4th year, the life expectancy is increased compared to the one with only invasive malignant. The statistical analysis indicated that pathology type is recognized as a high hazard factor for a breast cancer patient. The proposed model of this research also addressed that age is evaluated as one of the most important hazard factor. It indicates that death hazard for patients with the age of more than 50 years old are increased by about 2.35 times. This research also addressed that the survival rate of breast cancer patients for the first year is 96.25%. This result is close to the estimated survival addressed by literature. The results of this research indicate that the estimated survivals of the 3th and 5th years for breast cancer patients are 86.22% and 74.15%, respectively. The survival analysis addresses that the estimation for the 3th year is more than other studies, but the survival of the 5th year is as the same as other researches. The Statistical analysis of this study shows that in addition the age at the time of diagnosis, some factors including education, lymph nodes involvement, type of surgery, metastasis and hormone therapy have a significant role in the proposed model clearly.

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