Recurrence in breast cancer

Analysis with frailty model

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ABSTRACT

Objective: To determine the value of known prognostic factors for metastasis in breast cancer by accounting for patient-specific effect of patients who received surgical treatment followed by adjuvant treatment using the frailty model.

Methods: One hundred seventeen women with breast cancer who underwent surgery followed by adjuvant therapy at 3 hospitals in Tehran, Iran between 1995 and 2003 were enrolled in this study. Women with defined breast cancer with no distant metastases at time of diagnosis that have undergone modified radical mastectomy or breast-conserving surgery were enrolled. Tumors were classified according to the Tumor, Node, Metastasis (TNM) system of the American Joint Committee on cancer. Grading was performed according to Scarff-Bloom-Richardson method. Estrogen receptor (ER) was measured by immunohistochemistry method. The patients have been followed regularly by routine clinical laboratory profile, serologic markers (CEA, CA15-3) and para-clinical examinations; furthermore, we have followed missing materials by other access ways such as calling.

Results: Median follow up time for patients was 26 months after surgery. During the follow up time 44 (38%) patients developed metastasis and 20 (45%) of these 44 patients experienced the second metastasis. The median disease-free survival for patients in the study was 49.6 month. The median time to experience second metastasis after the first one was 22.5 months. Risk of occurrence of a metastasis in the first year after surgery was 12%. Risk of experience a metastasis up to the second year was 32% and up to fifth years was 69%. Result of fitting a frailty model to data showed that size of tumor, number of positive lymph nodes and histologic grade had a significant effect on the risk of metastasis ($p<0.05$). Patients with tumor size larger than 5 cm were in higher risk of metastasis compared with others. Increase in the number of positive lymph nodes to more than 10, increased risk of metastasis. Patients with moderate or undifferentiated histologic grade were in higher risk of metastasis to well differentiated patients. Age, family history, lymph node stage, and ER had no significant effect. It was found that there was heterogeneity between patients after adjusting for other covariates because variance of frailty was 0.315. It means that based on the variance of the distribution of frailty, the relative risk of high-risk patients to low-risk patients was 7.2, wherein high-risk group is defined as a cluster at the 95th percentile and low-risk to a cluster of 5th percentile of the frailty distribution.

Conclusion: Known risk factors describe the risk of metastasis partly and other unknown or unmeasured factors, such as genetics or environmental factors are important to describe the risk of metastasis in breast cancer.

Saudi Med J 2006; Vol. 27 (8): 1187-1193

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Received 31st December 2005. Accepted for publication in final form 26th April 2006.

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Breast cancer is the most commonly diagnosed cancer after nonmelanoma skin cancer, and is the second leading cause of cancer deaths in women after lung cancer.[1] Breast cancer accounts for 21.4% of all female malignancies in Iran.[2] A study in Tehran, the capital city of Iran, found that breast cancer accounted for 25.5% of all female cancers with a crude incidence rate of 22.4 in 100,000 women in 1998.[3] One of the essential outcome after breast cancer treatment is recurrence of the disease. It is known that occurrence of metastasis decreases the survival time of patients. It also increases the disability and decreases the quality of life of patients. There are some known prognostic factors for metastasis of breast cancer such as tumor size, histologic grade, estrogen receptor, and axiliary nodes. However, by knowing of these factors we cannot have a reliable prediction for metastasis occurrence. This is due to other unknown, unmeasured or immeasurable factors that affect the risk of metastasis. There are many situations that the cancer metastases cannot be accounted for by known risk factors. Most remaining factors are attributed to patient's characteristics and environmental factors. For this reason, breast cancer is considered a heterogeneous disease. It means that breast cancer is a different disease in different women and natural history of breast cancer is different in different women. The specific characteristics of patients induce a correlation between the time of metastasis occurred for each patient. A patient, with respect to other characteristics, can experience a metastasis in early (or late) time after surgery. In other word, the number of metastasis that a patient experiences in her life depends on her characteristics and environmental factors that are hard to measure. On the other hand, one might expect that a person's actual risk of recurrence be related to the risk of recurrence at former metastases. Using the standard survival techniques on the recurrent events data and ignoring the inter-correlation among events for each subject, the estimate of survival time will be biased and the amount of information contained in the data may be seriously overestimated.[4] This leads to small standard errors for estimated parameters and increases type I error in statistical hypothesis testing. Random effects (frailty) models are an approach to handle this problem in analysis of recurrent events in censored data.[5] In these models, the frailty is a random effect reflecting the individual degree of frailty. Patients with higher frailty have more risk of an event than the others with less value. The aim of this study was to use frailty models to determine the effect of covariates on hazard of recurrence of breast cancer in patients who underwent a surgery at 3 hospitals in Tehran, Iran.

Methods. The data were obtained from 117 women with breast cancer who underwent surgery at 3 oncology sections (Shohadaye Tagrish, Madaen, Fayyazbakhsh Hospital) in Tehran, Iran. The patients were followed since surgery between 1995 and 2003. Women with defined breast cancer with no distant metastasis at time of diagnosis who have undergone modified radical mastectomy (MRM) or breast-conserving surgery (BCS) were enrolled in the study. Tumors were classified according to the tumor node metastasis (TNM) system of the American Joint Committee on cancer.[6] Grading was performed according to Scarff-Bloom-Richardson method. Adjuvant chemotherapy has been categorized to cyclophosphamide, methotrexate, 5-Fu (CMF), Doxorubicin-based chemotherapy, Taxine-based therapy, and no treatments. Estrogen receptor (ER) was measured by immunohistochemistry (IHC) method.[7] Paraffin embedded specimens have been stained according to standard IHC method.[8] The 1D5 at 1/50 dilution (Dako, catalogue NO:M7047) for ER was used. Scoring system is performed on the basis of the proportion and intensity of the cell showing reactivity by approved laboratories at Tehran and they confirmed by an independent pathologist and the weakly positive specimens ablated from the study. The patients have been followed regularly by routine clinical laboratory profile, serologic markers (CEA, CA15-3) and Para clinical examinations; furthermore, we followed missing materials by other access ways such as calling. Patients with poor data on initial meeting and missing materials did not enroll in the study. We have recorded the first recurrence or metastasis according to relevant documentation such as biopsy, x-ray, ultrasound, whole body bone scan and marker rising with physician confirmation. We have recorded metastases sites as: liver, lung, bone, brain and others. Local recurrence considered for only local regional relapse. Although, theoretically a metastasis makes us aware of other micro metastases, we recorded any site as a separate one. In case when we had relevant criteria for more than one site metastasis, we considered other sites as well. Median follow up time for patients in the study was 26 months after surgery, range between <1 month (23 days) and 185 months. Eighty (68%) patients were alive until the end of study. Twenty-two (18%) died and status of 15 (13%) was unknown. The median follow up time for live patients was 27 months. Nineteen out of 22 patients who died had experienced metastasis and 3 patients died without metastasis. Since only one patient had 3 metastases, so we focused on up to 2 events only.

Table 1 - Distribution of tumor characteristics.

Factor	All patients N* (%)*	Patients with metastasis N (%)	Patients without metastasis N (%)
Size of tumor			
<2 cm	21 (18.6)	5 (11.9)	16 (22.5)
2-5 cm	57 (50.4)	17 (40.5)	40 (56.3)
>5 cm	27 (23.9)	14 (33.3)	13 (18.3)
Skin or chest	8 (7.1)	6 (14.3)	2 (2.8)
Lymph node stage			
Positive	32 (30.5)	8 (20.5)	24 (36.4)
Positive with adhesion	65 (61.9)	27 (69.2)	38 (57.6)
Supraclavicular positive	8 (7.6)	4 (10.3)	4 (6.1)
Histologic grade			
Well differentiated	18 (20.7)	3 (10.7)	15 (25.4)
Moderate differentiated	37 (42.5)	12 (42.9)	25 (42.4)
Non-differentiated	32 (36.8)	13 (46.4)	19 (32.2)
Number of LN+			
<4	68 (59.1)	21 (47.8)	47 (66.2)
(4-10)	26 (22.6)	13 (29.6)	13 (18.3)
>10	21 (18.3)	10 (22.7)	11 (15.5)
Treatment			
Adriamycin or Doxurubicin	40 (47)	18 (62)	22 (39)
Cyclophosphamid,methoterexate,5-Fu	22 (26)	7 (24)	15 (27)
Paclitaxel or Docetaxel	23 (27)	4 (14)	19 (34)
Estrogen receptor status			
Receptor positive	68 (62.4)	22 (55)	46 (66.7)
Receptor negative	41 (37.6)	18 (45)	23 (33.3)

*Numbers and percents are for known values , LN^+ = positive lymph nodes

Table 2 - Location of metastasis.

Location of metastasis	First	Second
Local	6 (10.7*)	1 (5)
Lung	16 (28.6)	4 (20)
Brain	6 (10.7)	6 (30)
Bone	18 (32.1)	3 (15)
Liver	6 (10.7)	4 (20)
Others	4 (7.1)	2 (10)

*Percent in strata

Statistical methods. Frailty models are an extended proportional hazard regression model to account for correlation between observations. In these models, a continuous random effect is introduced into the model to describe excess risk or frailty for different categories, such as individuals or families.[9] In the model, the intensity of recurrence for a given person *i* at time *t* for *k*th metastasis is $\lambda_{ik}(t) = \lambda_0(t)\omega_i \exp(\chi_i^T \beta)$. In this formula ω_i is the frailty for *i*th patient. Patients with a high ω_i value tend to have a high rate of event, and the opposite is true for patients with low ω_i value. The ω_i is assumed to follow a distribution across the population of patients; thus variance of this distribution is a measure of the heterogeneity of the patients.[10] In this study it is assumed the frailty follow a gamma distribution. In the frailty models marginal effect of covariates is not proportional and interpretation of effect of covariates is conditional on the frailty value. The effect of following variables were examined on the hazard of experience a metastasis after surgery: age (at time of surgery), family history, size of tumor, histologic grade, ER status, number of positive lymph nodes and lymph node stage.

Results. A total of 65 metastases were detected in the 3490 person-month of follow-up. Only one patient had 3 metastases and all others had <2. Forty-four patients (38%) developed metastasis within the follow up period. Twenty patients (45%) of those with metastasis experienced the second one. Ten (23%) out of 44 patients after first recurrence died without the second metastasis, while 9 (20%) died after second one. Ages of patients in the study were between 26 and 75 years with mean 48.5 years. Mean age of patients with metastasis (45.9), was slightly lower than patients with no metastasis, (49.9); however the difference was not significant (p=0.78). Seventy-seven (66%) had no history of breast cancer in their family. Most of patients received MRM surgery (89.7%). There was no significant difference between occurrences of metastasis in patients who underwent MRM or BCS (p=0.429). Sixty patients (51%) had primary tumor in the right and 48 (41%) in the left breast. Only 3 patients had tumor in both

Table 3 - Estimated effect of covariates by frailty model.

Factor	Estimate	SE	RR	*P*-value
Age	-.08	.04	.92	.09
Family history				
No	Reference category	Reference category	Reference category	
Yes	-.5	.79	.6	.56
Histologic grade				
Well differentiated	Reference category	Reference category	Reference category	
Moderate differentiated	2.25	.78	9.2	.008*
Non-differentiated	2.07	.99	4.3	.058
Size of tumor				
<2 cm	Reference category	Reference category	Reference category	
2-5 cm	.99	1.02	2.7	.39
>5 cm	1.9	.95	6.6	.007*
Estrogen receptor				
Positive	Reference category	Reference category	Reference category	
Negative	.13	.53	1.14	.83
Number of LN+				
<4	Reference category	Reference category	Reference category	
4-10	1.63	.93	4.13	.13
>10	2.2	.99	9.04	.049*
Lymph node stage				
Positive	Reference category	Reference category	Reference category	
Positive with adhesion	-2.26	1.11	.1	.06
Supraclavicular positive	-1.37	1.32	.25	.37
Frailty	.32			.05

*Significant at .05 level, SE - standard error, RR - relative risk, LN+ = positive lymph nodes

sites. Distribution of tumor characteristics is shown in **Table 1**. Twenty-nine patients in the first metastasis had one location. Eight patients had 2 and one patient had 3 different locations. Location of metastases was summarized in **Table 2**. The first metastasis in bone was more likely than the other locations. Rate of occurrence of the second metastasis was the highest in brain (30%). **Table 3** shows the result of a frailty model for describing the effect of the introduced prognostic factors on metastasis hazard. Risk of metastasis for patients with moderate-differentiated tumors, with known value of frailty, was 9.2-fold of patients with well-differentiated tumor. Patients with non-differentiated tumors patients had 4.3-fold higher risk to well differentiated groups, however this effect is not significant in 0.05 level. Patients with tumor size larger than 5 cm were in higher risk of metastasis compared with others (**Table 3**). Increase in the number of positive lymph nodes to more than 10, increased risk of metastasis. Variance of frailty was found 0.315. This variance showed heterogeneity among patients even with the same covariates. However, a test that the frailty variance is zero is not rejected by the available data, based on the variance of the distribution of frailty, the relative risk of high-risk patients to low-risk patients, regardless of the value of the prognostic factors was 7.2, wherein high-risk group is defined as a cluster at the 95th percentile and low-risk to a cluster of 5th percentile of the frailty distribution. The median disease-free survival for patients in study was 49.6 month. For patients who had one metastasis median time to experience the second one was 22.5 month. The second metastasis occurred, on average, in about half time of the first one. Risk of occurrence of metastasis in the first year after surgery was 12%. Up to the second and fifth years after mastectomy, risk of experience a metastasis was 32% and 69%. Cumulative intensity of metastasis adjusted by significant factors is shown in **Figure 1**. Hazard curves were shown only for the first 5 years because of inadequate observation. Hazard of happening a metastasis for patients with different positive lymph nodes were crossover the time (**Figure 1a**). In **Figure 1b** it was observed that the hazard for patients with larger tumor size was higher than smaller ones over the study time. In **Figure 1c** it was observed that patients with undifferentiated tumors experienced metastasis from the early time after surgery and continued until 2 years, else than one event that occurred after 3 years. However, in 2 other groups metastasis developed after 2 years and the last metastasis was observed at 172 month after surgery in well differentiated group. During the first 5 years risk of moderate group is always higher than well-differentiated patients.

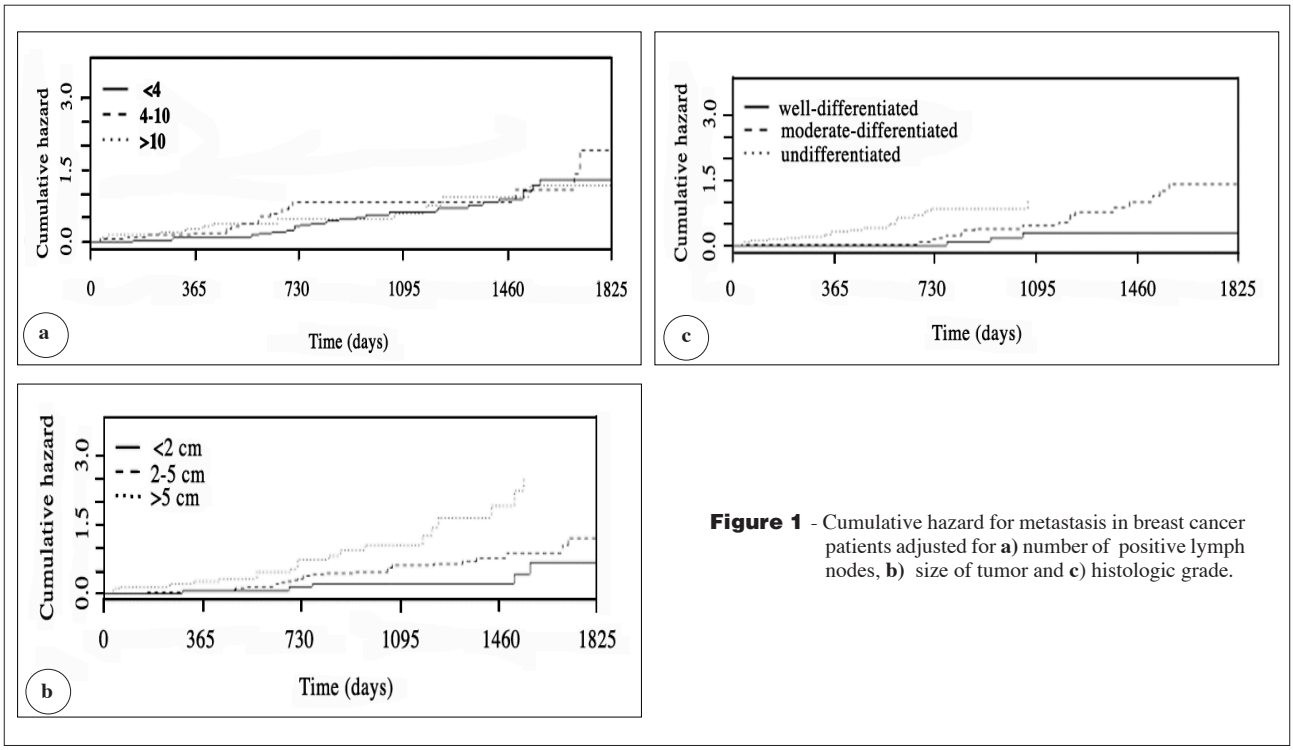

Figure 1 - Cumulative hazard for metastasis in breast cancer patients adjusted for **a)** number of positive lymph nodes, **b)** size of tumor and **c)** histologic grade.

Discussion. The mean age of patients in this study was 48.5 years, breast cancer affects women at least one decade younger than their counterparts in developed countries.[11] In this study, we found there was no difference in terms of recurrence after MRM or BCS. That is agreed with some other studies.[12] The risk of metastasis in the first year for patients underwent MRM was 12% and for patients underwent BCS was 14%. Up to the second year after surgery, this rate was 36% and 34% for MRM and BCS. These rates are higher than many other countries, such as United States,[13] Netherland,[8] Korea[14] and Japan.[15] One possible reason for this is the sample size, especially for BCS patients, as the number of patients who received BCS was few and only 3 of those developed metastasis over the study time. More probable reason for highly rate of relapse in patients is the fact that Iranian patients generally seek medical attention when the disease has reached an advanced stage. Therefore, diagnosis is made when the chance of a full cure is impossible. Many patients referred to cancer centers at T2-3N2 and it means they were not detected at early stage and they will meet more risk for recurrence of the disease. It is known that bone is the most frequent site of systemic progression of breast cancer.[16,17] In our study, bone is the preferred site of metastasis and 32% of first metastasis developed in bone. The second metastasis was more likely in brain that is the most probably cause of death for these patients. Family history showed no effect on metastasis and it was not significant. However, the coefficient for family history in frailty model found negative. It means that the patients who had a knowledge regarding breast cancer had less risk of experiencing a metastasis. This could be due to more information that those patients knew regarding the disease. This is guess because the data showed that 20% of patients with positive family history were with tumor size greater than 10 cm, while 30% of patients with no family history had large tumor size. A study performed in Iran showed that patients with a negative family history of breast cancer waited shorter than others before seeking care.[18] As we expected, in the present study, hazard of experience a metastasis after surgery was found to be associated with size of tumor, number of positive lymph nodes and histologic grade. Increase in the number of positive lymph nodes increased the hazard of metastasis. A study performed in the Switzerland revealed that number of positive lymph nodes was solely significant for regional metastasis.[6] This effect has been verified by studies in the United States, Brazil[19] and Korea[20] as well. Tumor size was shown as another prognostics factor in the study. Patients with greater tumor had more chance of developing metastasis. This result is the same as many other studies were performed

in other countries.[21-23] The starting time to develop a metastasis was very different in histologic groups. Patients who had undifferentiated tumors developed metastasis from 44 until 655 days after surgery, while well-differentiated group had recurrence time from 774 days after surgery. The first metastasis in patients with moderate grade was started after 2 years. We can see that undifferentiated patients developed metastasis in the time interval in which 2 other groups showed no metastasis. Variance of frailty distribution showed risk of metastasis for patients was related to the patient-specific effects. With existence of this effect, hazard of an event for a patient is hard to predict. Effect of all prognostic or risk factors is marginally depending on the frailty value. An alternative to frailty models could be a stratified Cox regression model that used the individual patient as stratum. This approach is proper when most of the subjects in study experience more than one event. In the present study, since the large number of patients had no metastasis and a few patients had only one metastasis this approach should be considered less suitable. In general, this frailty study showed, as expected, that was considerable individual heterogeneity in the hazard of recurrence; thus the gap times within patients were mutually dependent. This means that the effect of covariates has no proportional interpretation and the effect of each covariate is conditional on the frailty value. In recurrent events data the informative censoring could be cause a bias in the results. The informative censoring can be due to a terminating event that affects the number of later recurrence.[24] This effect is more considerable when those patients experiencing events at highest rate are typically observed for shorter periods of observation due to mortality. In our analysis death was a terminate event. When death occurred no further metastasis was possible. Then there were an association between death and developing metastasis. However, the number of death in study patients was not a lot and most of death occurred after the second years of surgery. Our study concerned only those patients we had enough information from their medical records and information to follow them. Thus the result may not reflect the absolute figure of patients. The limitations of current study were the number of the specimen, case selection process, variations of the adjuvant therapy and missing value for some cases; however, all the physicians have performed similar guideline.

Acknowledgment. The authors are very grateful to Professor Jerry F. Lawless from the Department of Statistics and Actuarial Sciences, University of Waterloo for his helpful comments. We are also grateful to Dr. Mortazavi, Dr. Yahyazadeh, Dr. Sadrolhefazi and Dr. Moradi for kindly preparing the data. This research was supported by a grant from Tehran University of Medical Sciences, Tehran, Iran.

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