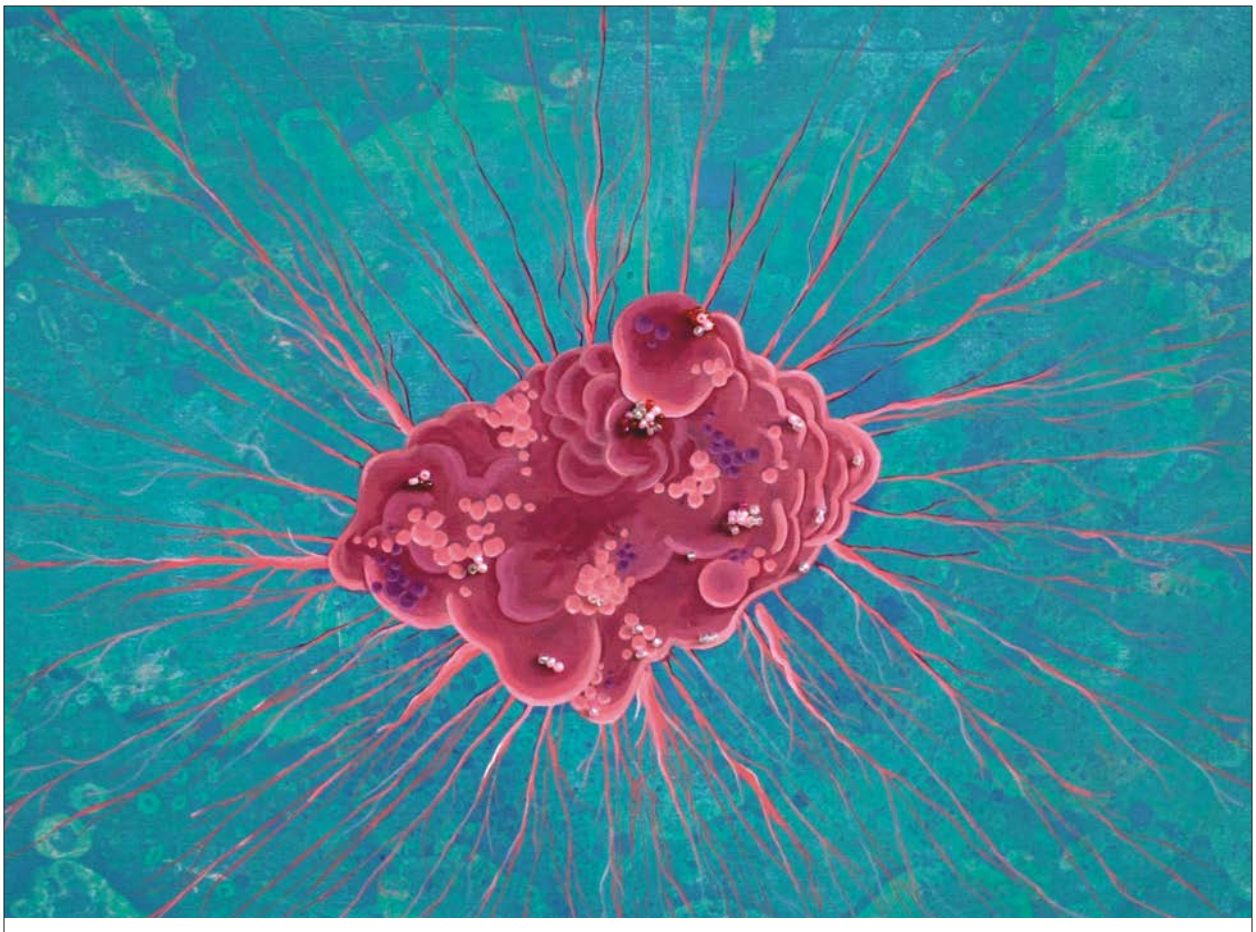

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Disease-free Survival and Metastases Pattern in Breast Cancer Patients after Mastectomy: An Application of Stratified Markov Model

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Abstract: This study designed and carried out to determine the disease-free survival of breast cancer patients after surgery and to assess its associated factors. The variability in effect of prognostic factors over time was also assessed. For this purpose one hundred seventeen women with breast cancer operated on at three hospitals in Tehran, Iran between 1990 and 2003 were enrolled in study. Since the occurrences of successive metastases in any patient are correlated and the occurrence of one metastasis may make further events more or less likely we used a Stratified Markov model to account for within-subject correlation in event times. This model stratifies data by event so that the baseline hazard is allowed to vary with each metastasis. In this model effect of covariates on the hazard of event is also estimated in each stratum, separately. The variables of age at time of surgery, number of positive lymph nodes, histologic grade, size of tumor, ER status, P53 and Her2 were considered in the model. Median follow up time for patients in study was 26 months after surgery. During the follow up time 44(38%) patients developed metastasis. 20(45%) of those experienced the second metastasis. The median disease-free survival for patients in study was 49.6 month and the median time to experience the second metastasis was 22.5 month. Risk of occurrence of a metastasis in the first year after mastectomy was 12%. Up to the second and fifth years risk of experience a metastasis was 32 and 69%, respectively. The rate of metastasis in our study was higher than some other countries. One reason for highly rate of relapse in patients is the fact that patients sought medical attention when the disease has reached an advanced stage. Stratified Markov model showed that the effect of prognostic factors was different for the first and the second metastasis. Size of tumor and number of positive lymph nodes had a significant effect on the risk of first metastasis. While tumor size was the only factor that affected hazard of the second metastasis. One possible reason for this finding is that the effect of these factors was mixed with the effect of time to first metastasis and we can't separate them in analysis of the second time.

Key words: Breast cancer, metastasis, disease-free survival, recurrent events, stratified Markov models

Introduction

Breast cancer is the most common malignant neoplasm in worldwide (Parkin *et al*., 2005). The annual mortality rate from breast cancer is about 27 death per 100,000 despite improvement in medical management (Marshal, 1993). Breast cancer is one of the most growing and women's health problems

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in Iran. Lack of a cancer registry system makes the number of cancer patient's and annual occurrence of new cases unknown. However, it is estimated that crude incidence rate of disease is about 22.4 new cases per 100,000 women per year (Shamsa and Mohagheghi, 2002). Despite increasing use of breast-conserving therapy; modified radical mastectomy retains an important in primary and salvage treatment; likewise in United States (Marrow *et al*., 1998). Thus, the management of recurrence after mastectomy remains a difficult and challenging problem for oncologists. The most established prognostic factor is the number of positive lymph nodes based on at least level 1 or 2 auxiliary (Carter *et al*., 1989). Traditional prognostic factors consist of tumor size (T), number of positive lymph nodes, grade according to Scraff-Bloom-Richrdson method and lymph vascular invasion; however, controversies exist about biomarkers such as HER2/neu, P53 and ER. It has been recognized that a certain prognostic factors may only be important in the first 5 years after treatment, but not with long-term follow up (Lazovich *et al*., 1999). In other words the effect of some prognostic factors may change over time and the effect of those for the first metastasis and the later metastases is different. This study was carried out to determine the risk of metastasis in breast cancer patients who received surgical treatment followed by adjuvant treatment in three hospitals in Iran and to assess some prognostic factors for the first and the second metastasis separately. We evaluated the effect of significant prognostic factors on the time and sequence of further metastases.

Materials and Methods

The data were obtained from 117 women with breast cancer who underwent adjuvant therapy at three oncology sections (Shohadaye Tagrish, Madaen, Fayazbakhsh Hospital) in Tehran, Iran. The patients were considered since surgery between 1995. Feb and 2003. Jun and continued until a death, emigration or withdrawal for other reason or April 2005. Women with defined breast cancer with no distant metastasis in time of diagnosis who have undergone MRM or BCS were enrolled. Tumors were classified according to the TNM system of the American Joint Committee on Cancer (AJCC) (2002). Grading was performed according to Scarff-Bloom-Richardson method (Le Doussal, 1989). Adjuvant chemotherapy has been categorized to CMF, Doxrubicine-based chemotherapy, Taxen-based therapy and no treatments. ER, HER-2/neu and P53 were measured by Immunohistochemistry (IHC) method (Anonymous, 1999). Paraffin embedded specimens has been stained according to standard IHC method. The colon DO-7 at 1/50 dilution (Dako, catalogue NO:M7001) for P53 and colon 1D5 at 1/50 dilution (Dako, Catalogue NO:M7047) for ER were used.The colon DO-7 at 1/200 dilution (Dako,Catalouge NO:A0485) were used to stain HER-2/neu. 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. According to Canadian guideline, we considered cut off for positivity of 10% cells with moderate /strong complete membranous staining (Hana *et al*., 2001). The patients followed regularly by routine clinical, lab profile, serologic markers (CEA, CA15-3) and Para clinical examinations; furthermore, we followed missing materials by other access such as calling. The patients with poor data on initial meeting and missing materials did not enroll in study. We recorded the first recurrences or metastasis according relevant documentations such as biopsy, X-ray, ultrasound, whole body bone scan and marker rising with physician confirmation. We recorded metastases sites as: liver, lung, bone, brain and other sites. Local recurrence considered for only loc regional relapse. Although, theoretically a metastases aware us about other micro metastases, but we

recorded any site as a separated one and after initial treatment disease -free or time to progression have been recorded. In case we had relevant criteria for more than one site metastasis, we considered other sites as well.

Median follow up time for patients in study was 26 months after surgery, range between less than 1 month (23 days) and 185 months. 80(68%) patients were alive until the end of study. 22(18%) died and status of 15 (13%) was unknown. Median follow up time for live patients was 27 months. Ninteen out of 22 patients who died had experienced metastasis and 3 patients died without metastasis. Because of the only one individual had 3 metastases we focused on up to 2 events only.

Statistical Methods

The occurrences of successive metastases in any patient are correlated. This correlation comes from patient's characteristics and effect of previous metastasis. The occurrence of one metastasis may make further events more or less likely. A Stratified Markov model (Prentice *et al*., 1981) was used to account for within-subject correlation in event times. This model stratifies data by event so that the baseline hazard is allowed to vary with each metastasis. In this model effect of covariates on the hazard of event is also estimated in each stratum, separately. By using this property of model the changes in the effect of factors on the hazard of event can be assessed over the time. The effect of following variables were examined on the hazard of experience a metastasis after surgery: age (at time of surgery), size of tumor, histologic grade, P53, Estrogen Receptor (ER) status, her2/neu, number of positive lymph nodes and lymph node stage. We didn't consider Catapsin because it is unknown for 55% of patients.

In recurrent events data, besides of all covariates, it is expected the time to the previous events is correlated with further events (Cook and Lawless, 2002). We used the time to the first metastasis as a covariate in the model, as well.

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 two or less. 44 patients (38%) developed metastasis within the follow up period. Twenty patients (45%) of those with metastases experienced the second one. 10 (23%) out of 44 patients after first recurrence died without the second metastases, 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, is slightly lower than patients with no metastasis, 49.9, however the difference is not significant ($p = 0.78$). Distribution of characteristics of tumors is shown in Table 1.

105 (89.7%) patients received MRM surgery and 12(10.3%) received BCS. There was no significant difference between occurrences of metastasis in patients underwent MRM or BCS ($p = 0.429$). Sixty patients (51%) had primary tumor in right and 48 (41%) in left breast. Three patients had tumor in both sites.

Twenty nine patients in the first metastasis had one location. Eight with 2 and only one patient had 3 different locations. First metastasis in bone was more likely than the other locations, while rate of occurrence of the second metastasis was the highest in brain (30%). Doxrubicine-based chemotherapy was the most frequent treatment in patients (39.6%). The distribution of treatments is not the same for patients with and without metastasis. However risk of metastasis was not different in treatment categories ($p = 0.08$)

Table 1: Distribution of tumor characteristics

	All patients		Patients with metastasis		Patients without metastasis	
Factor	No*	(%)*	No.	(%)	No.	(%)
Size of tumor						
<2 cm	21	18.58	5	11.90	16	22.54
(2-5) cm	57	50.44	17	40.48	40	56.34
>5 cm	27	23.89	14	33.33	13	18.31
Skin or chest	8	7.08	6	14.29	2	2.82
Lymph node stage						
Positive	32	30.48	8	20.51	24	36.36
Positive with adhesion	65	61.90	27	69.23	38	57.58
Supraclavicular positive	8	7.62	4	10.26	4	6.06
Histologic Grade						
Well differentiated	18	20.69	3	10.71	15	25.42
Moderate differentiated	37	42.53	12	42.86	25	42.37
Non-differentiated	32	36.78	13	46.43	19	32.20
Number of LN+						
<4	68	59.13	21	47.73	47	66.20
(4-10)	26	22.61	13	29.55	13	18.31
>10	21	18.26	10	22.73	11	15.49
Treatment						
ADR	40	47.00	18	62.00	22	39.00
CMF	22	26.00	7	24.00	15	27.00
Tax	23	27.00	4	14.00	19	34.00
ER status						
Receptor Positive	68	62.39	22	55.00	46	66.67
Receptor Negative	41	37.61	18	45.00	23	33.33
P53						
Positive	32	43.84	11	50.00	21	41.18
Negative	41	56.16	11	50.00	30	58.82
Her2						
Positive	47	63.51	10	50.00	37	68.52
Negative	27	36.49	10	50.00	17	31.48

*Numbers and percents are for known values

Table 2 shows the result of a univariate stratified Markov model for describing the effect of the introduced prognostic factors on the first and second metastasis hazard. As seen the effect of factors was different for the first and second one. Age, size of tumor, histologic stage and number of positive lymph nodes were significant on the first metastasis hazard. While lymph node stage, ER status, P53 and Her2 were not significant. Size of tumor was the only significant variable on the risk of the second metastasis and all others were not significant. In other words patients who have experienced the first metastasis had the same risk of getting the second one, regardless of their age, number of positive lymph nodes, histologic grade, ER status Her2 and P53. To account for the effect of time to first metastasis on the second one, the first gap time considered as a covariate in the model. This time showed no significant effect on the second metastasis ($p = 0.9$). However most of the second metastases were occurred in the time intervals shorter than time to first event. Baseline Cumulative Hazard function for each metastasis is shown in Fig. 1. It is seen Cumulative base line hazard for metastasis first and second was different. The risk of the second metastasis was higher over all the time. In other words time to first metastasis was much longer than the second one. Patients in the first year after mastectomy had low risk of metastasis, but for those who developed metastasis in this period hazard of the second one in next one year was much higher. As time increases, difference between two hazards became larger. In the period of between 2 and 5 years after surgery the difference of hazard first and second event got larger.

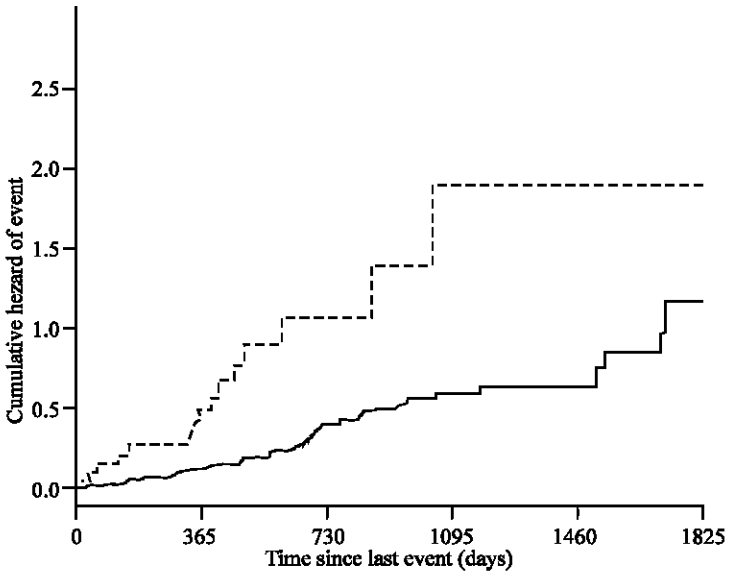

Fig. 1: Cumulative hazard function for two strata, solid: first metastasis, dashed: second metastasis

Table 2: Estimated effect of covariates on the risk of metastasis by univariate analysis

	First metastasis				Second metastasis			
Factor	Estimate	SE	RR	p-value	Estimate	SE	RR	p-value
Age	-0.03	0.02	0.97	0.04 *	-0.02	0.02	0.98	0.25
Size of tumor								
<2	Reference category							
(2-5)	0.39	0.47	1.48	0.41	1.54	0.87	1.34	0.07
>5	1.39	0.48	4.03	0.004*	1.40	0.86	1.37	0.024*
Lymph node stage								
Positive	Reference category							
Positive with adhesion	0.85	0.41	2.35	0.06	-0.76	0.52	0.47	0.17
Supraclavicular positive	0.63	0.52	1.88	0.22	-1.31	1.31	0.27	0.32
Histologic Grade								
Well differentiated	Reference category							
Moderate differentiated	1.44	0.76	4.22	0.059	0.58	0.36	1.24	0.21
Non-differentiated	2.15	0.824	8.58	0.004 *	0.63	0.31	1.43	0.18
Number of LN+								
<4	Reference category							
≥4	0.80	0.35	2.23	0.023 *	-0.85	0.63	0.43	0.17
ER								
Positive	Reference Category							
Negative	0.35	0.32	1.42	0.27	0.68	0.57	1.98	0.23
P53								
Positive	Reference Category							
Negative	-0.25	0.41	0.78	0.55	0.23	0.60	1.26	0.70
Her2								
Positive	Reference Category							
Negative	0.55	0.44	1.73	0.21	-1.59	1.05	0.20	0.13
Time to first metastasis					0.09	0.063	1.09	0.9

*Significant at level 0.05

Table 3: Estimated effect of covariates on the risk of metastasis by multivariate analysis

	First metastasis				Second metastasis			
Factor	Estimate	SE	RR	p-value	Estimate	SE	RR	p-value
Size of tumor								
<2	Reference category							
(2-5)	0.49	1.13	1.06	0.67	2.08	1.05	8.02	0.048*
>5	1.18	0.36	3.17	0.047*	2.19	0.91	8.93	0.016*
Number of LN+								
<4	Reference category							
≥4	2.92	1.19	8.58	0.015*	-0.05	0.64	0.57	0.39

*Significant at level 0.05

A multivariate stratified Markov model was used to examine the independent effect of prognostic factors after adjusting for potential confounding effects of other variables (Table 3). For the first metastasis size of tumor and number of positive lymph nodes were significant in the model. All other covariates were eliminated from the model. Risk of first metastasis for patients with number of positive lymph node equal or grater than four is 8.Fifty eight fold risk of patients with less than four positive lymph nodes. There was no significant difference between patients with tumor size less than 2 cm and those with tumor size up to 5cm ($p = 0.67$). However patients who had tumor size larger than 5 cm had risk of 3.17 times more than patients with small tumor (Table 3).

The prognostic factor for the second metastasis was tumor size. Risk of second metastasis for patients with tumor size greater than 2 cm was 8 folds of patients with tumor size less than 2 cm. The risk increased to 8.9 fold for patient with tumor size greater than 5cm.

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 is occurred, on average, about half time of the first one.

Risk of occurrence of metastasis in the first year after mastectomy for study group was 12%. In the second and fifth years after mastectomy, risk of experience a metastasis was 32 and 69%, respectively.

Discussion

Mean age of patients in this study was 48.5 years that show in Iran, breast cancer affects women at least one decade younger than their counterparts in developed countries (Sant *et al*., 1998).

Age of patients at time of surgery is not a significant factor in the final model neither for the first metastasis nor for the second. This may be because of patients below 35 years with breast cancer had tumors with a poorer prognostic profile. However, this did not translate into a poorer overall survival and this might be attributable to more aggressive adjuvant treatment of younger patients (Gruber *et al*., 2005; Foo *et al*., 2005).

In this study we found there was no difference in terms of recurrence after MRM or BCS. This finding agreed with some other studies (van Tienhoven, 1999). The risk of metastasis in the first year for patients underwent MRM was 12% and for BCS was 14%. In the second year after surgery this rate was 36 and 34% for MRM and BCS, respectively. These rates are higher than some other countries, such as United States (Carlo, 2005), Netherland (van Tienhoven, 1999), Korea (Lee, 1997) and Japan (Sonno, 1995). One possible reason for this is the small sample size, especially for BCS patients, because the number of patients who received BCS was few and only three of those developed metastasis over the study time. Another 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 smaller. 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 disease.

Apparently, bone is the most frequent site of systemic progression of breast cancer (Campo McKnight, 2005). 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. Thirty percent of patients developed the second metastasis in the brain.

As we expected, in the present study, hazard of experience a metastasis after surgery was found to be associated with size of tumor and number of positive lymph nodes. Increase in the number positive lymph node increased the hazard of metastasis. A study performed in the Switzerland revealed that number of positive lymph nodes was solely significant for regional metastasis (Sant, 1998). This effect has been verified by studies in United States (Grills, 2003), Brazil (Megale Costa, 2004) and Korea (Kim, 2005) as well. Tumor size was shown as another prognostics factor in 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 (Lerouge, 2004; Megale Costa, 2004; Chia *et al*., 2004).

In this study we find the tumor size is the only factor affect the hazard of the second metastasis. Other variables that are significant for first metastasis are no longer significant for the second metastasis. One possible reason for this is the number of patients who developed the second metastasis was only 20 patients that seems we need more to find more reliable result for the second metastasis. Another reason for this finding is that the effect of these factors was mixed with the effect of time to first metastasis and we can't separate them in analysis of the second time and the point estimates of some of those are of opposite signs.

In the univariate analysis it is found that histologic grade is a significant variable. Patients who were well-differentiated had relapse time from 774 days after surgery. The first metastasis in patients with moderate grade observed at the same time, while patients in undifferentiated group developed metastasis from 44 until 655 days after surgery. We can see that undifferentiated patients developed metastasis in the range time that two other groups showed no metastasis. Thus there was a significant effect for grade in univariate analysis. In multivariate analysis histologic grade was not a significant variable. One cause for this is that there was a high association between grade and number of positive nodes. Only 18% of well-differentiated patients had Number of positive lymph nodes greater than 4, while 71% undifferentiated patients had equal or greater than 4. This positive association was found between histologic grade and size of tumor, as well.

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References

American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 2002. Springer Verlag, New York-Berlin-Heidelberg.

Anonymous, 1999. New York. Memorial Sloan Kettering Cancer Center.

Campo McKnight, D.A., D.M. Sosnoski, J.E. Koblinski and C.V. Gay, 2005. Roles of osteonectin in the migration of breast cancer cells into bone. J. Cell Biochem. Sep. 19; (In Press).

Carlo, J.T., 2005. Survival analysis following sentinel lymph node biopsy: A validation trial demonstrating its accuracy in staging early breast cancer. Proc. Bayl Univ . Med. Cent., 18: 103-107.

Carter, C., C. Allen and D. Henson, 1989. Relation of tumor size, lymph node status and survival in 24,740 breast cancer. Cancer, 63: 181-187.

Chia, S.K., C.H. Speers, C.J. Bryce, M.M. Hayes and I.A. Olivotto, 2004. Ten-year outcomes in a population-based cohort of node-negative, lymphatic and vascular invasion-negative early breast cancers without adjuvant systemic therapies. J. Clin. Oncol., 22: 1630-1637.

Cook, R.J. and J.F. Lawless, 2002. Analysis of repeated events. Statistical Methods in Med. Res., 11: 141-166.

Foo, C.S. *et al*., 2005. Breast cancer in young Asian women: Study on survival. ANZ J. Surg., 75: 566-572.

Grills, I.S., 2003. Risk factors for regional nodal failure after breast-conserving therapy: Regional nodal irradiation reduces rate of axillary failure in patients with four or more positive lymph nodes. Intl. J. Radiat. Oncol. Biol. Phys., 56: 658-670.

Gruber, G., S. Menzi, A. Forster, G. Berclaz, H.J. Altermatt and R.H. Greiner, 2005. Sites of Failure in Breast Cancer Patients with Extracapsular Invasion of Axillary Lymph Node Metastases No Need for Axillary Irradiation?! Strahlenther Onkol, 181: 574-579.

Hana, M.W., H.J. Kahn and M. Ienkowska *et al*., 2001. Definig a test for HER-2/neu evaluation in Breast cancer in the diagnostic setting. Mod. Pathol., 14: 677-14681.

Kim, K.J., 2005. Treatment results and prognostic factors of early breast cancer treated with a breast conserving operation and radiotherapy Jpn. J. Clin. Oncol., 35: 126-133.

Lazovich, D., C.C. Solomon and D.B. Thomas *et al*., 1999. Breast-conserving therapy in the United States following the 1990 national institute of Health Consensus Development Conference on the Treatment of patient with early stage breast cancer. Cancer, 86: 628-637.

Le Doussal, V., 1989. Prognostic value of histologic grade nuclear components of Scarff-Bloom-Richardson (SBR): An improved score modification based on a multivariate analysis of 1262 invasive ductal breast carcinoma. Cancer, 64: 1914-1921.

Lee, H.D., 1997. Breast conserving therapy in stage I and II breast cancer in Korea. Breast Cancer Res. Treat., 44: 193-199.

Lerouge, D., 2004. Locally advanced non inflammatory breast cancer treated by combined chemotherapy and preoperative irradiation: Updated results in a series of 120 patients. Cancer Radiother., 8: 155-167.

Marrow, M., D.P. Winchester and J.S. Chieml *et al*., 1998. Factor responsible for the under utilization of breast-conserving therapy. Proc. Am. Soc. Clin. Oncol., 1998.

Marshal, E., 1993.The Politics of breast cancer. Science, 259: 616-617.

Megale Costa, L.J., 2004. Ratio between positive lymph nodes and total dissected axillaries lymph nodes as an independent prognostic factor for disease-free survival in patients with breast cancer. Am. J. Clin. Oncol., 27: 304-306.

Parkin, D.M., F. Bray, J. Ferlay and P. Pisani, 2005. Global Cancer Statistics 2002. CA Cancer J. Clin., 55: 74-108.

Prentice, R.L., B.J. Williams and A.V. Peterson, 1981. On the regression analysis of multivariate failure time data. Biometrika, 68: 373-379.

Sant, M. *et al*., 1998. Survival of women with breast cancer in Europe: Variation with age, year of diagnosis and country. The EURO CARE Working Group. Intl. J. Cancer, 77: 679-683.

Shamsa, A.Z. and M.H. Mohagheghi, 2002. National Project for cancer registry. Proposing a Model by the National Center for Cancer Registry. Final Report of the Project. Sponsored by Cancer Institute of Tehran University of Medical Sciences and Deputy of Research, Ministry of Health, Treatment and Education. Islamic Republic of Iran: Tehran.

Sonoo, H., 1995. Comparison of Modified Radical Mastectomy with Quadrantectomy, Axillary Dissection and Radiation Therapy in Early Breast Cancer in Japanese Women. Breast Cancer, 2: 119-125.

Van Tienhoven, 1999. Prognosis after treatment for loco-regional recurrence after mastectomy or breast conserving therapy in two randomized trials (EORTC 10801 and DBCG-82TM). EORTC Breast Cancer Cooperative Group and the Danish Breast Cancer Cooperative Group. Eur. J. Cancer, 35: 32-38.