ORIGINAL ARTICLE

Recieved: July 2014
Accepted: October 2014

Estimating Probability of Co-occurrence of Metastasis and Death at Certain Intervals after Surgery in Patients with Breast Cancer

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ABSTRACT

Background: Breast cancer is one of the most prevalent cancers and significant causes of mortality in women. An important problem is the cancer cell metastasis in other organs. Different mechanisms in the beginning, progression, and metastasis of breast cancer makes it difficult to determine patients' ultimate fate (prognosis) and lifespan specifically although events ahead of the patients can be estimated using probabilities. This study was conducted to estimate the probability for the co-occurrence of metastasis and death at certain intervals of 5 years after surgery and 5 years after metastasis in patients with breast cancer.

Methods: In this retrospective study, the data were collected from 608 women having breast cancer and going to the Breast Disease Center of ACECR in 2009-2001. The patients were studied from the time of surgery, and the two events were metastasis and death, respectively. The interval between the surgery and metastasis and that between the metastasis and death caused by cancer or end of follow-ups (for patients who did not die) were measured and analyzed in month. The probability for co-occurrence of the two intervals was estimated using the semiparametric method suggested by Una-Alvarez (2011) and R statistical software.

Results: Median time for the occurrence of metastasis after surgery and duration of follow-up were 34 months and 66 months, respectively. In total, 93 metastases and 46 deaths occurred. The co-occurrence probability interval for all samples was 0.087-0. It was found that the probability for co-occurrence of the two events in patients with more than 50 years old, a tumor larger than 5 cm, lymph node involvement, high stage of the disease, positive HER2, negative ER, and without radiotherapy was greater than that in other groups.

Conclusion: Considering the estimated co-occurrence probabilities, it seemed that factors such as the age over 50 years, tumors larger than 5 cm, lymph node involvement, higher stages, positive HER2, and negative ER increased the probability for the co-occurrence of metastasis and death in breast cancer patients.

Key words: Recurrent events, probability, stage of the disease, lymph node involvement, HER2, ER

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BCCR
2015;7(1):35-49
www.bccrjournal.com

Introduction

Spirituality Breast cancer is one the most prevalent cancers and still a significant cause of death in women despite the progresses made in early diagnosis and treatment of the disease[1]. Every year in the world, 1.15 million people get cancer[2]. Based on the National Cancer Registry's recent report in 2008 in Iran, breast cancer, with a relative frequency of 24.8% of female cancers, was the most frequent cancer among Iranian women. In 2008, 8616 new cases of breast cancer were diagnosed, of which 8424 cases were female, and the age-specific incidence of the cancer was 33.21 years per one thousand people[3].
Mohagheghi (2009) introduced the first five cancers with a high age-specific incidence in Tehran, Iran as breast cancer (31.4 per 100,000), followed with a considerable difference by stomach cancer (10), lung cancer (7), ovarian cancer (6.8), and esophageal cancer (5.3), respectively[4]. The above study showed that breast cancer was a major cancer in Tehran[4]. A significant problem in breast cancer is its metastasis to other organs, and it is actually a main cause of treatment failure, and consequently, over 40000 deaths only in the U.S.A.[2].
Most metastases occur in lungs, with a prevalence of 60%-70%[5], and one of the worst metastases occurs in brain[6]. Some predictors of metastasis are the lymph node involvement , the size of the primary tumor, the time passed after surgery, HER2 oncogene expression rate, estrogen receptors (ER), and even treatment methods and surgery, although metastasis has occurred in people with minimum risk factors[7,8].
Studies of the last two decades showed that different mechanisms influence the incidence and progression of the breast cancer[9], and the clinical course of the disease varies from patient to patient as it is difficult to determine patients' ultimate fate and lifespan clearly. About half of the patients survive disease-free and metastasis-free, and other patients die of rapid recurrence of the disease[8,10]. Therefore, identification of factors predicting patients' fate is useful for clinical decision-making and selecting a treatment[11]. Probabilities can be used to study and determine patients' ultimate fate. The probability of metastasis and death is obtainable using patients' records and might be useful for prediction of patients' status in future. For instance, the probability of co-occurrence of metastasis and death in patients, which was also the objective of this study, indicates in which interval after the surgery the probability of metastasis is higher, and what the probability of death is after the metastasis. The statistical method for measuring those probabilities is the recurrent event statistics. The recurrent events, observed in many longitudinal studies of epidemiology and clinical sciences, refer to the events facing patients during follow-ups in a specific sequence, and sometimes, one or all of them may not occur during follow-ups, and this is called right censoring. These events may be of one type or different types. In recurrent events, the number of events and their time are important, researchers can also pay attention to the interval between events. In the present study, the recurrent events were metastasis and death in breast cancer patients, and the time comprised the intervals of surgery-metastasis and metastasis-death. The objective of studying those events was to estimate the probabilities for co-occurrence intervals of surgery-metastasis and metastasis-death.

Methods

In this retrospective study, the data were collected from 608 women having breast cancer and going to the Breast Disease Center of ACECR in 2001-2009. The data included time of surgery, time of metastasis, time of death or end of follow-ups, the age at time of surgery, size of the primary tumor, lymph node involvement, stage of the disease, type of the surgery, chemotherapy and radiotherapy, HER2, and ER. As the patients with tumor recurrence in the previous site were few, they were excluded from the study. Moreover, patients who died without metastasis were excluded from the study. The patients were studied from the time of surgery, and the two co-occurrences were metastasis and death, respectively. The interval between the surgery and metastasis and that between the metastasis and death caused by cancer or end of follow-ups (for patients who did not die) were measured in month. The intervals for co-occurrence of the two events and the probability measurement are as follows: months 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60 for the occurrence of metastasis within the first 5 years after surgery; and months 12, 18, 24, 30, 36, 42, 48, 54, and 60 for the occurrence of death within the first 5 years after surgery. The reason for determining an initial interval of 6 months between the surgery and metastasis and 12 months between metastasis and death, that is, eliminating the intervals before 12 months, was that the probability for co-occurrence of the two events at the above intervals was zero in basic analyses and probabilities estimated by the researcher, therefore, those intervals were eliminated. The probability for co-occurrence of the two intervals was estimated using the semiparametric method suggested by Una-Alvarez (2011) and R statistical software[12]. If the time of metastasis and time of death random variables are shown with T1 and T2, respectively, the probability for co-occurrence of the two events would be $P(T1 \leq t1, T2 \leq t2)$. The probability for co-occurrence of the two events was estimated both for all samples and subgroups of some variables.

Results

Mean age of the patients at the time of surgery was 46 years with standard deviation of 10.8 years. Of the patients, 37 people (6%) were single, 496 people (82%) were married, and the remaining people were divorced. The educational level of 310 patients (51%) was below the high school diploma, and that of the others was higher than the high school diploma. The median time for the occurrence of metastasis after surgery was 34 months with confidence interval of 95% (25.4-42.6 months). The median duration of follow-ups was 66 (range:1-312) months. Among the whole population, 93 metastases and 46 deaths occurred. The probabilities were not only estimated for the entire sample but also for subgroups of some important variables (age, size of the primary tumor, lymph node involvement, stage of the disease, type of the surgery, chemotherapy and radiotherapy, HER2, and ER). The data revealed that, of the patients, 66% at stages 0 and I, 82% at stage II, and 91% at stage III underwent modified radical mastectomy (MRM), and rest of the patients underwent breast preservation surgery. The Chi-square test showed that the three percentages for the three stages of the disease differed significantly from one another ($P<0.0001$), and this revealed that most of the patients at stages II and III underwent MRM. Moreover, of the patients, 60% at stage 0, 92% at stage II, and 99% at stage III underwent chemotherapy. In this regard, the Chi-square test showed that the 3% of the three stages of the disease were significantly different from one another ($P<0.0001$), that is, few patients at stages two and three did not undergo chemotherapy. Table 1 shows other information of the groups, including number of samples, number of events, number of censored data, and median and range of surgery-metastasis and metastasis-death intervals. Tables 2 to 7 present probabilities estimated for combined events. Table 2 indicates probabilities estimated for the two events in combination at specific intervals for the entire sample (608 patients). For instance, the value 0.022 in Table 2 means

Table 1: Information related to the time surgery-metastasis and the time metastasis-death in breast cancer patients in each subgroup

Variable	subgroup	Sample size	Metastasis			Death		
			Number	Median (month)	Range (month)	Number	Median (month)	Range (month)
Total sample		608	93	34	1-233	46	11	1-63
Age	Below 50 years	404	52	38	8-233	27	15	1-63
	50 years and over	204	41	28	1-107	19	8	1-43
Tumor size	Below 2 cm	112	14	42	8-76	3	16	9-17
	2-5 cm	234	33	30	9-111	18	10	1-63
	over 5 cm	59	14	31	10-119	7	11	1-32
Lymph node involvement	No	221	19	48	9-146	4	10	5-27
	Yes	257	54	34	4-119	27	11	1-63
Stage of the disease	0 & 1	118	10	48	9-233	2	5	5-10
	2	302	39	40	14-110	16	16	1-41
	3	156	41	24	1-119	25	9	1-63
Type of surgery	B. preserve	108	14	41	14-110	6	20	1-39
	MRM	474	73	31	4-233	36	11	1-63
Chemotherapy	No	61	4	48	21-233	0	-	-
	Yes	451	84	31	1-146	44	11	1-63
Radiotherapy	No	118	16	41	10-233	4	5	1-35
	Yes	375	69	31	4-146	37	12	1-63
HER2	Negative	102	17	43	4-80	5	11	8-63
	Positive	76	16	34	9-57	8	6	1-29
ER	Negative	137	30	24	4-119	17	8	1-63
	Positive	254	34	42	9-111	13	17	5-32

Table 2: Estimated distribution of the two intervals of surgery-metastasis and metastasis-death in combination for all samples

Surgery-metastasis interval \ Metastasis- death Interval	12	18	24	30	36	42	48	54	60
6	0.001	0.001	0.001	0.002	0.002	0.002	0.003	0.003	0.003
9	0.001	0.003	0.003	0.004	0.004	0.004	0.006	0.006	0.006
12	0.003	0.004	0.004	0.005	0.005	0.005	0.008	0.008	0.008
18	0.010	0.013	0.013	0.014	0.014	0.015	0.018	0.018	0.018
24	0.014	0.018	0.20	0.022	0.022	0.025	0.031	0.031	0.031
30	0.017	0.024	0.026	0.028	0.028	0.033	0.039	0.039	0.039
36	0.018	0.025	0.027	0.030	0.032	0.039	0.045	0.045	0.045
42	0.022	0.033	0.035	0.040	0.042	0.053	0.060	0.060	0.060
48	0.023	0.034	0.037	0.047	0.048	0.060	0.066	0.066	0.066
54	0.030	0.041	0.047	0.056	0.060	0.072	0.078	0.078	0.078
60	0.036	0.056	0.065	0.069	0.069	0.081	0.087	0.087	0.087

that the probability for co-occurrence of metastasis up to 2 years after surgery and that for the occurrence of death up to 3 years after metastasis has been 0.022. In general, the probability for the co-occurrence ranged from 0 to 0.087. The probability for co-occurrence of the two events was also estimated in patients below 50 years old (404 patients) than that in patients with 50 or more years (204 patients). In patients below 50 years old, the probability for co-occurrence of metastasis 6 months after surgery and death 5 years after metastasis was zero. Whereas, the probability for co-occurrence of the two events in patients with 50 or more years appeared during the first months after surgery. The probability for co-occurrence of the two events in patients over 50 years old was higher than that in others and ranged from 0 to 0.06. The probability for co-occurrence of the two events in patients with 50 or more years increased with time faster than that in other patients. In terms of the initial size of tumor, the patients were divided into three groups (below 2 cm, 2-5 cm, and over 5 cm) containing 112, 234, and 59 people, respectively. The probability for co-occurrence of the two events for the patients with a 2 cm tumor was 0-0.12, and there was no probable co-occurrence of the two events in less than 6

Table 3: Estimated co-occurrence of the two intervals of surgery-metastasis and metastasis-death for lymph node involvement

lymph node involvement	Metastasis-death Interval / Surgery-metastasis interval	12	18	24	30	36	42	48	54	60
No Lymph node involvement (221 patients)	6	0	0	0	0	0	0	0	0	0
	9	0	0	0	0	0	0	0.005	0.005	0.005
	12	0	0	0	0	0	0	0.005	0.005	0.005
	18	0.006	0.006	0.006	0.006	0.006	0.006	0.011	0.011	0.011
	24	0.006	0.006	0.010	0.010	0.010	0.010	0.027	0.027	0.027
	30	0.009	0.009	0.013	0.013	0.013	0.013	0.030	0.030	0.030
	36	0.009	0.009	0.013	0.013	0.013	0.013	0.030	0.030	0.030
	42	0.009	0.009	0.013	0.013	0.013	0.013	0.030	0.030	0.030
	48	0.013	0.013	0.017	0.024	0.024	0.024	0.041	0.041	0.041
	54	0.021	0.021	0.032	0.039	0.039	0.039	0.056	0.056	0.056
	60	0.021	0.028	0.038	0.046	0.046	0.046	0.063	0.063	0.063
With lymph node involvement (257 patients)	6	0	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
	9	0.004	0.009	0.009	0.009	0.009	0.009	0.009	0.009	0.009
	12	0.008	0.012	0.012	0.012	0.012	0.012	0.012	0.012	0.012
	18	0.023	0.030	0.030	0.030	0.030	0.030	0.030	0.030	0.030
	24	0.032	0.042	0.042	0.046	0.046	0.005	0.005	0.005	0.005
	30	0.032	0.048	0.048	0.052	0.052	0.056	0.056	0.056	0.056
	36	0.032	0.048	0.048	0.055	0.059	0.069	0.069	0.069	0.069
	42	0.04	0.063	0.063	0.074	0.078	0.094	0.094	0.094	0.094
	48	0.04	0.063	0.067	0.083	0.087	0.102	0.102	0.102	0.102
	54	0.047	0.070	0.073	0.089	0.093	0.109	0.109	0.109	0.109
	60	0.059	0.086	0.09	0106	0.110	0.126	0.126	0.126	0.126

Table 4: Estimated co-occurrence of the two intervals of surgery-metastasis and metastasis-death for stage of the disease

Stage of the disease	Metastasis-death Interval / Surgery-metastasis interval	12	18	24	30	36	42	48	54	60
0 and I (118 patients)	6	0	0	0	0	0	0	0	0	0
	9	0	0	0	0	0	0	0.012	0.012	0.012
	12	0	0	0	0	0	0	0.012	0.012	0.012
	18	0	0	0	0	0	0	0.012	0.012	0.012
	24	0	0	0	0	0	0	0.012	0.012	0.012
	30	0	0	0	0	0	0	0.012	0.012	0.012
	36	0	0	0	0	0	0	0.012	0.012	0.012
	42	0	0	0	0	0	0	0.012	0.012	0.012
	48	0.011	0.011	0.011	0.027	0.027	0.027	0.039	0.039	0.039
	54	0.023	0.023	0.023	0.039	0.039	0.039	0.051	0.051	0.051
	60	0.023	0.038	0.038	0.054	0.054	0.054	0.066	0.066	0.066
II (302 patients)	6	0	0	0	0	0	0	0	0	0
	9	0	0	0	0	0	0	0	0	0
	12	0	0	0	0	0	0	0	0	0
	18	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
	24	0.007	0.007	0.010	0.012	0.012	0.016	0.024	0.024	0.024
	30	0.009	0.011	0.013	0.016	0.016	0.024	0.031	0.031	0.031
	36	0.011	0.013	0.015	0.021	0.021	0.033	0.04	0.04	0.04
	42	0.015	0.023	0.025	0.030	0.030	0.053	0.061	0.061	0.061
	48	0.015	0.023	0.025	0.030	0.030	0.053	0.061	0.061	0.061
	54	0.023	0.030	0.036	0.042	0.048	0.070	0.078	0.078	0.078
	60	0.025	0.037	0.043	0.048	0.054	0.077	0.085	0.085	0.085
III (156 patients)	6	0	0.003	0.003	0.008	0.008	0.008	0.012	0.012	0.012
	9	0.006	0.013	0.013	0.017	0.017	0.017	0.022	0.022	0.022
	12	0.015	0.022	0.022	0.026	0.026	0.026	0.031	0.031	0.031
	18	0.035	0.046	0.046	0.050	0.050	0.050	0.055	0.055	0.055
	24	0.046	0.061	0.065	0.069	0.069	0.069	0.074	0.074	0.074
	30	0.046	0.069	0.074	0.078	0.078	0.078	0.083	0.083	0.083
	36	0.046	0.069	0.074	0.078	0.083	0.083	0.088	0.088	0.088
	42	0.053	0.082	0.086	0.096	0.101	0.101	0.106	0.106	0.106
	48	0.053	0.082	0.092	0.107	0.113	0.113	0.118	0.118	0.118
	54	0.058	0.087	0.096	0.112	0.117	0.117	0.122	0.122	0.122
	60	0.072	0.100	0.110	0.126	0.131	0.131	0.136	0.136	0.136

months after surgery. In patients with a 2-5 cm tumor, the probability for co-occurrence of the two events was 0-0.07, lower than that in the other two groups, and similar to the first group with a tumor below 2 cm, there was no probable co-occurrence of the two events in less than 6 months after surgery. In patients with a tumor over 5 cm, the probability was 0-0.14, higher than that in two other groups, and the probability for co-occurrence of the two events in less than 9 months after surgery was zero although the probability increased with time more rapidly. Table 3 shows the co-occurrence probabilities for the lymph node involvement in two groups of patients (with involvement and without involvement). Number of samples in these two groups was 221 and 257 patients, respectively. In the group without lymph node involvement, the co-occurrence probabilities were estimated 0-0.06, as they were 0 within 12 months after surgery and 42 months after metastasis. Whereas, in the group with lymph node involvement, the co-occurrence probabilities appeared in initial months in the range of 0-0.13 and increased more rapidly. In terms of the stage of the disease, the patients were divided into three groups; stages 0 and I (118 patients), stage II (302 patients), and stage III (156 patients). Table 4 shows the co-occurrence probabilities. The range of the co-occurrence probabilities in patients at stages 0 and I, patients at stage II, and patients at stage III was 0-0.07, 0-0.09, and 0-0.14, respectively. As shown in the above ranges, the co-occurrence probabilities increased with the stage of the disease. The co-occurrence probabilities were also estimated in terms of the type of surgery. In this regard, patients were divided into two groups, including 108 patients with B. Preserve and 474 patients with MRM. Ranges of the co-occurrence probabilities in the two groups were almost the same in 0-0.09. In the group with B. preserve, the co-occurrence probability of metastasis up to 12 months after surgery and death up to 5 years after metastasis was zero, while it increased by 0.09 more rapidly after these intervals. However, in the group with MRM, the probabilities appeared after surgery. Furthermore, the co-occurrence probabilities were estimated for two groups of patients undergoing chemotherapy (451 patients) and patients not undergoing chemotherapy (61 patients). The co-occurrence probability for metastasis and death in patients who did not receive chemotherapy after surgery was lower than that in another group.

Based on the estimations, in the group without chemotherapy, the co-occurrence probability of metastasis and death within 18 months after surgery was zero, as it appeared 18 months after surgery and 36 months after metastasis. In this regard, the range of the probability was 0-0.05. In the group with chemotherapy, the co-occurrence probability was 0-0.1 and appeared within first months after surgery. Table 5 shows the co-occurrence probabilities for two groups of patients undergoing radiotherapy (375 patients) and patients not undergoing radiotherapy (118 patients). The co-occurrence probabilities for patients without radiotherapy and patients with radiotherapy were 0-0.099 and 0-0.092, respectively. Generally, the co-occurrence probabilities for the patients without radiotherapy, except for the first 9 months after surgery, were higher than that for the other group. In other words, the probability for co-occurrence of the two events in patients without radiotherapy appeared later than that in the other group but increased over time more rapidly. Table 6 presents co-occurrence probabilities estimated for groups with positive HER2 (76 patients) and negative HER2 (102 patients). Ranges of the probabilities in the group with positive HER2 and the group with negative HER2 were 0-0.2 and 0-0.14, respectively. The co-occurrence probabilities in the group with positive HER2 were higher than those inthe group with negthe group with negative HER2 and increased with time more rapidly.

Table 5: Estimated co-occurrence of the two intervals of surgery-metastasis and metastasis-death for radiotherapy

Radiotherapy	Metastasis-death Interval / Surgery-metastasis interval	12	18	24	30	36	42	48	54	60
Without (118 patients)	6	0	0	0	0	0	0	0	0	0
	9	0	0	0	0	0	0	0	0	0
	12	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003
	18	0.011	0.011	0.011	0.011	0.011	0.011	0.011	0.011	0.011
	24	0.011	0.011	0.011	0.011	0.011	0.019	0.019	0.019	0.019
	30	0.016	0.023	0.023	0.023	0.032	0.032	0.032	0.032	0.032
	36	0.016	0.023	0.023	0.032	0.032	0.040	0.040	0.040	0.040
	42	0.024	0.031	0.031	0.040	0.040	0.048	0.048	0.048	0.048
	48	0.024	0.031	0.031	0.052	0.052	0.061	0.061	0.061	0.061
	54	0.024	0.031	0.042	0.063	0.079	0.087	0.087	0.087	0.087
	60	0.024	0.043	0.054	0.063	0.079	0.087	0.087	0.087	0.087
With (375 patients)	6	0	0.001	0.001	0.003	0.003	0.003	0.003	0.003	0.003
	9	0.002	0.004	0.004	0.006	0.006	0.006	0.008	0.008	0.008
	12	0.004	0.006	0.006	0.008	0.008	0.008	0.010	0.010	0.010
	18	0.012	0.016	0.016	0.018	0.018	0.018	0.020	0.020	0.020
	24	0.018	0.024	0.027	0.031	0.031	0.031	0.039	0.039	0.039
	30	0.019	0.028	0.032	0.035	0.035	0.038	0.046	0.046	0.046
	36	0.021	0.029	0.033	0.036	0.039	0.045	0.053	0.053	0.053
	42	0.025	0.038	0.041	0.047	0.050	0.063	0.071	0.071	0.071
	48	0.025	0.038	0.041	0.050	0.052	0.066	0.074	0.074	0.074
	54	0.033	0.046	0.049	0.058	0.061	0.074	0.082	0.082	0.082
	60	0.040	0.055	0.059	0.068	0.070	0.084	0.092	0.092	0.092

Table 6: Estimated co-occurrence of the two intervals of surgery-metastasis and metastasis-death for positive and negative HER2

HER2	Metastasis-death Interval / Surgery-metastasis interval	12	18	24	30	36	42	48	54	60
Negative (102 patients)	6	0	0.010	0.010	0.010	0.010	0.010	0.010	0.010	0.010
	9	0	0.010	0.010	0.010	0.010	0.010	0.022	0.022	0.022
	12	0	0.010	0.010	0.010	0.010	0.010	0.022	0.022	0.022
	18	0.019	0.028	0.028	0.028	0.028	0.028	0.041	0.041	0.041
	24	0.019	0.028	0.028	0.028	0.028	0.028	0.055	0.055	0.055
	30	0.019	0.028	0.028	0.028	0.028	0.028	0.055	0.055	0.055
	36	0.019	0.028	0.028	0.028	0.028	0.028	0.055	0.055	0.055
	42	0.019	0.028	0.028	0.028	0.028	0.051	0.078	0.078	0.078
	48	0.019	0.028	0.028	0.061	0.061	0.084	0.110	0.110	0.110
	54	0.029	0.039	0.039	0.072	0.072	0.094	0.121	0.121	0.121
	60	0.051	0.061	0.061	0.093	0.093	0.116	0.143	0.143	0.143
Positive (76 patients)	6	0	0	0	0	0	0	0	0	0
	9	0	0.007	0.007	0.007	0.007	0.007	0.007	0.007	0.007
	12	0	0.007	0.007	0.007	0.007	0.007	0.007	0.007	0.007
	18	0.011	0.018	0.018	0.018	0.018	0.018	0.018	0.018	0.018
	24	0.015	0.022	0.033	0.033	0.033	0.033	0.033	0.033	0.033
	30	0.020	0.037	0.048	0.048	0.048	0.048	0.048	0.048	0.048
	36	0.020	0.037	0.048	0.062	0.062	0.088	0.088	0.088	0.088
	42	0.020	0.050	0.061	0.093	0.093	0.015 4	0.015 4	0.015 4	0.015 4
	48	0.020	0.050	0.061	0.093	0.093	0.015 4	0.015 4	0.015 4	0.015 4
	54	0.020	0.050	0.077	0.110	0.110	0.170	0.170	0.170	0.170
	60	0.035	0.081	0.108	0.141	0.141	0.202	0.202	0.202	0.202

Table 7: Estimated co-occurrence of the two intervals of surgery-metastasis and metastasis-death for ER results

ER	Metastasis-death Interval / Surgery-metastasis interval	12	18	24	30	36	42	48	54	60
Negative (137 patients)	6	0	0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.004
	9	0	0.006	0.013	0.013	0.013	0.013	0.013	0.013	0.013
	12	0.012	0.020	0.020	0.020	0.020	0.020	0.020	0.020	0.020
	18	0.038	0.045	0.045	0.045	0.045	0.045	0.045	0.045	0.045
	24	0.042	0.049	0.054	0.054	0.054	0.054	0.061	0.061	0.061
	30	0.050	0.062	0.067	0.067	0.067	0.074	0.081	0.081	0.081
	36	0.050	0.062	0.067	0.067	0.067	0.082	0.089	0.089	0.089
	42	0.050	0.067	0.072	0.079	0.079	0.104	0.111	0.111	0.111
	48	0.050	0.067	0.072	0.079	0.079	0.104	0.111	0.111	0.111
	54	0.050	0.067	0.079	0.086	0.086	0.112	0.119	0.119	0.119
	60	0.067	0.079	0.091	0.098	0.098	0.124	0.131	0.131	0.131
Positive (254 patients)	6	0	0	0	0	0	0	0	0	0
	9	0	0	0	0	0	0	0.004	0.004	0.004
	12	0.002	0.002	0.002	0.002	0.002	0.002	0.006	0.006	0.006
	18	0.004	0.010	0.010	0.010	0.010	0.006	0.010	0.010	0.010
	24	0.008	0.010	0.014	0.014	0.014	0.018	0.027	0.027	0.027
	30	0.008	0.013	0.016	0.016	0.016	0.021	0.030	0.030	0.030
	36	0.08	0.013	0.016	0.020	0.025	0.029	0.038	0.038	0.038
	42	0.008	0.020	0.024	0.027	0.032	0.043	0.052	0.052	0.052
	48	0.008	0.020	0.024	0.038	0.043	0.043	0.052	0.052	0.052
	54	0.016	0.029	0.032	0.047	0.051	0.063	0.072	0.072	0.072
	60	0.023	0.045	0.048	0.063	0.068	0.079	0.088	0.088	0.088

Table 7 indicates co-occurrence probabilities for groups with positive ER (254 patients) and negative ER (137 patients). As shown in the table, the probabilities in the group with negative ER and the group with positive ER ranged 0-0.13 and 0-0.09, respectively, that is, co-occurrence probabilities for the negative ER were higher than those for the positive ER. In the group with positive ER, the combined probability for metastasis and death was zero up to 9 months after surgery and up to 42 months after metastasis.

Discussion:

According to previous studies, patients' survival is expected to increase with improved treatments for the breast cancer, while the occurrence of metastasis often fails the treatment, and subsequently, the survival decreases[13, 14]. The present study also obtained similar results for the co-occurrence probabilities of metastasis and death in all samples.

The co-occurrence probabilities in the two age groups showed that metastasis and death were more likely to happen in patients with 50 or more years. Most of researchers have found that the age below 50 years was a factor predicting low survival of patients[14]. However, Kuru et al. (2008) who studied the survival and its predictors in breast cancer patients after surgery and after metastasis, separately, confirmed that patients' survival after surgery and after metastasis decreased with age[15]. Nam (2008) also introduced the increase in age as a risk factor for patients' survival relevant to the increased probability of metastasis and decreased patients' survival[16]. The difference between results of the present study and those of the above study might be due to the different design of the present study that examined the probability of the co-occurrence of metastasis and death and did not examine other underlying causes of death in older ages.

The effect of tumor size on the co-occurrence probabilities of metastasis and death was another factor examined in this study. The co-occurrence probabilities of the two events for patients with a tumor smaller than 5 cm were almost equal, and those for patients with a 5 cm tumor were higher than those of two other groups. In a study performed on 1148 women with breast cancer in Shiraz, Iran, tumors larger than 5 cm increased the probability for death during the first 5 years after diagnosis by 2.07 as that by tumors smaller than 2 cm ($P<0.001$)[17].

Harputluoglu (2008) performed a retrospective study on 144 breast cancer patients with metastatic brain and examined the interval between the incidence of cancer and metastasis (only brain) and the interval between metastasis and death, separately[18]. However, Harputluoglu did not find any correlation between tumor size and survival[18]. The reason for the difference between this result and that of the present study might be that Harputluoglu examined only metastasis of brain. Kuru (2008) also found a significant correlation between tumor size and median survival after surgery ($P=0.99$), while there was no such a correlation between tumor size and survival after the first distant metastasis (osseous or visceral) ($P=0.79$). Kwon et al. (2010) studied the survival in 66 breast cancer patients with metastatic brain and did not find any relationship between tumor size and survival[15, 19]. The difference in results of various studies might be due to their different design and population. It must be mentioned that the present study examined the co-occurrence probability of the two events that was not considered in other studies.

In the present study, the co-occurrence probabilities of metastasis and death in the group with lymph node involvement was higher than those in the other group. Observational and retrospective studies have shown that occult lymph node involvement was an important predictor of recurrence and survival of breast cancer patients. Weaver (2011) showed that the survival time in the group with lymph node involvement was shorter than that in the other group, as there was a significant difference between survival times of the two groups[20]. Kuru (2008) also revealed a significant correlation between lymph node involvement and survival time after surgery and after metastasis[15]. Rezaeian et al. also introduced the number of involved lymph nodes as a factor affecting breast cancer patient survival[17].

As shown above, the co-occurrence probabilities of metastasis and death increased with the stage of the disease (survival decreased), and this disagreed with results obtained by Kwon (2010) and Harputluoglu (2008) and agreed with results obtained by Kuru (2008) and Li (2010)[14, 15, 18, 19]. Different results in this regard might be due to application of different definitions and methods for staging the disease or different frequency distributions of patients. There was not any significant correlation between the type of surgery and the co-occurrence probability for patient survival after surgery and after metastasis. A randomized clinical trial with 20 years of follow-up has shown that the overall survival of the patients undergoing B. Preserve and radiotherapy did not significantly differ from that of patients undergoing MRM[14]. This result might confirm the importance of B. preserve and the probable survival of the disease, similar to MRM, which has been often focused and discussed by the relevant specialists and breast cancer patients. However, it should be noted that the stage of the disease played an important role in selecting the type of surgery. In this regard, the data showed that patients with B. preserve (34%) in the group at stages 0 and I were more than other patients, while at higher stages of the disease, patients with MRM (86%) were more than others. Therefore, different stages of the disease should be taken into account when examining the effect of the type of surgery. However, in this study, low number of patients with B. preserve in stages II and II made the estimated probabilities less accurate. In this regard, another problem for the effectiveness of B. preserve was its different local recurrence with that of MRM, which could not be examined with data of the present study. The probabilities estimated for groups with/out chemotherapy revealed that patients without chemotherapy were more likely to survive, and this disagreed with the result obtained by Kuru (2008), Harputluoglu (2008), and Kwon (2010)[15, 18, 19].

It is noteworthy that chemotherapy is certainly applied with regard to the stage of the disease by specialists and surgeons. In this study, 59% of the patients at stages 0 and I and 95% of the patients at higher stages had received chemotherapy. In this respect, less probability of survival in patients with chemotherapy might be due to the patients' higher stages of the disease, and this result could not deny the effect of chemotherapy on increased survival of patients. If the co-occurrence probabilities of the two events in the groups with/out chemotherapy had been estimated in terms of the stage of the disease, more accurate results would have been obtained. However, this was not applicable due to the low number of patients at stages II and III. Radiotherapy increased the probability of survival after surgery and metastasis in combination. Most major clinical trials have proved the effect of radiotherapy on reduced local recurrence and death of the breast cancer[14]. The present study showed that the co-occurrence probabilities of metastasis and death in patients with positive HER2 were higher than those in patients with negative HER2. This result conformed to that of studies introducing the higher expression of HER2 oncogene as a predictor of early recurrence and incidence of worse outcomes of the disease[14]. However, Harputluoglu et al. (2008) did not find a significant correlation between the expression of HER2 and patients' survival[18]. Today, trastuzumab is known as an effective drug for increasing survival of patients with positive HER2 although it is not widely used in most countries due to its high cost and not being covered by insurance companies. It should be noted that the years when this study was being performed, most of the studied patients did not receive trastuzumab due to its high cost. Therefore, results of this study could emphasize on the necessity for further studies on cost-effectiveness of trastuzumab as an effective factor in breast cancer patients' survival. Numerous studies have proved the role of higher expression of estrogen and progesterone receptors in improved disease-free survival and overall survival of breast cancer patients[14, 15, 18]. This study also showed that the co-occurrence probabilities of metastasis and death after diagnosis of the breast cancer in the group with negative ER were higher than those in the other group. Detection of this prognostic factor for survival can help specialists to choose the appropriate therapeutic protocol for breast cancer patients. Based on the estimated co-occurrence probabilities, it could be concluded that factors, such as the age over 50 years, tumors larger than 5 cm, lymph node involvement, higher stages of the disease, failure to undergo radiotherapy, positive HER2, and negative ER in metastasis and the subsequent death were important predictors of the breast cancer patients' survival and should be particularly considered by specialists and surgeons. Finally, it must be noted that the probabilities mentioned in this study were estimated with some limitations of which a major limitation was the incomplete information of patients about predictive variables. The reason was that the study was retrospective making the co-occurrence probabilities less accurate. Moreover, numbers of patients having complete information about the studied variables decreased due to the above reason, thus, only univariate co-occurrence probabilities were estimated for each variable, as it was not possible to estimate the multivariate probabilities for two or more variables in combination. In this regard, prospective studies are suggested to be performed in Iran in order to collect more accurate information. Furthermore, estimated peripheral probabilities of the two events may be effective in decision-makings.

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