RESEARCH ARTICLE

Survival Analysis of Breast Cancer Patients in Northwest Iran

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Abstract

Background: Breast cancer is the most frequently occurring cancer among Iranian women; however limited studies have been conducted to address survival rates. **Objective:** The objective was to examine survival rates in Tabriz (Northwest of Iran) and comparing with those of data reported from other cities and countries. **Methods:** Survival rates were calculated for one, three, five, seven and ten years for 271 breast cancer patients referred to one university clinic during 1997-2008. **Results:** Survival analysis demonstrated a lower survival rate compared to western countries. **Conclusions:** Survival rates for our patients are similar/better than other cities in Iran, but lower than certain European countries and the US. Further studies with a higher number of patients are now required.

Keywords: Breast cancer - survival - Tabriz, Iran

Introduction

Breast cancer (BC) is estimated as the most frequently occurring cancer (estimated as 23% of all cancers) as well as the most fatal form of malignancy among women accounting for 16% of cancer deaths. Therefore, BC is considered as a major health issue worldwide (Harirchi et al., 2011).

According to Iranian Centre for the Prevention and Control of Disease (Ministry of Health and Medical Education, 2000, Iran), breast cancer has been reported to be the most prevalent cancer among Iranian women and accounts for 21.4% of all malignancies. The incidence of breast cancer in Europe and the USA is estimated between 8-10% while the lowest prevalence is observed in Asian countries at roughly 1%. In Iran, the incidence of breast cancer was reported as 6.7/1,000 in 2002, which was even lesser than other countries (Rezaianzadeh et al., 2009). Later on, BC was ranked number one malignancy among Iranian women, comprising 24.4% of all neoplasms with a crude incidence rate of 17.8 and an ASR of 23.65 in the year of 2006. However, since specific studies describing the clinicopathologic features, stages, and age distributions of BC in Iran are limited, it is difficult to predict the present and future patterns of BC and carry out the most appropriate preventive and therapeutic measures to decrease the burden of the disease (Harirchi et al., 2011). It appears that the survival rate in Iranian breast cancer patients is poor (Vahdaninia et al., 2004).

In this study, we analyzed the survival rate of breast cancer patients who referred to our university clinic in Tabriz, a city in the northwest of Iran and compared it with data reported from other parts of Iran or countries around the world.

Materials and Methods

A cohort study on 271 breast cancer patients was conducted in oncology clinic of university hospital between 1997 and 2008. Data were gathered from medical records including age, tumor diameter, number of involved nodes, histopathological type, estrogen receptor (ER) and progesterone receptor (PR) expression, c-erbB2 status, menopausal status and administered chemotherapy protocol.

Metastatic disease was investigated by clinical symptoms or signs and assessed in the bones, chest, brain and liver. Primarily plane radiographs were used to assess the chest and bones. When the diagnosis was uncertain or equivocal, bone scan and computed tomography (CT) were used. Ultrasound or less frequently CT was used to rule out the presence of liver metastasis. Primary metastatic disease was disregarded in this study.

Tumor markers were evaluated at the first visit of the patients. Carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3) were routinely measured; CEA and CA15-3 were said to be elevated when above a value of 10 ng/ml and 25 U/ml respectively.

Pathological reports were collected from the patients' previous mastectomy or wide local excision specimens. Pathological grade, lymph node status, tumor size, ER, PR, Her 2, P53, KI67, and tumor type were recorded for each patient where possible. Lymph node involvements were assessed on the pathologic reports when it was

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available and were grouped on the amount of involved nodes. Overall survival was assessed by calculating the time from first visit of the patient to the last contact with poor performance status or death.

Recurrences were defined as skeletal or non-skeletal (brain, liver, lung or other sites). Sites of recurrences were detected by physical examination, X- rays, and or other imaging techniques. Patients were classified with skeletal metastases if these were the only sites of involvement; otherwise, they were classified with non-skeletal metastases. Data were analyzed by SPSS 16 software and survivals were determined at intervals of one, three, five, seven and ten years.

Results

Mean age was 48 (26-82), five patients were below 30, and 14 below 40 years old. 109 patients were premenopause, 83 postmenopause, 3 perimenopause and 43 unknown. 36.1% had tumor >4 cm and 9.5% <2 cm.

18.6% had N1, 14.4% N2, 12.8% N3, 16.7% unknown, and 27.5% negative. 51.1% with metastasis, (26.6% nonskeletal, 24.5% skeletal and 1.4% both).

116 were ER and PR positive, 104 and 103 were negative, 36 and 37 were unknown. In fifteen years follow up 52 patients died.

Life table analysis showed one, three, five, seven and ten years overall survival of about 96, 86, 81, 79, and 76% respectively. It showed significant correlation of survival with age less or above 40 years. Patients less than 40 years old had one, three and five years survival (82, 74, and 65 %) while patients over 40 had survivals of 95%, 86%, and 83% respectively (log rank=0.22). Sites

Table 1. Characteristics of the Patients

Menstrual state	Pre menopausal	109
	Post menopausal	83
	Peri menopausal	3
	Unknown	43
Tumor diameter	1-1.9 cm	23 (8.5%)
	2-2.9 cm	41 (15.1%)
	3-3.9 cm	47 (17.3%)
	>4	87 (32.1%)
	T4	7 (2.6%)
	Unknown	36 (13.3%)
Nodes	<3	48 (22.4%)
	4-9	37 (13.7%)
	>10	33 (12.2%)
	Positive	25 (9.2%)
	Negative	71 (26.2%)
	Unknown	43 (15.9%)
ER	Positive	116 (42.8%)
	Negative	104 (38.4%)
	Unknown	36 (13.3%)
PR	Positive	116 (42.8%)
	Negative	103 (38.0%)
	Unknown	37 (13.7%)
Metastatis	nonskeletal	38 (26.6%)
	skeletal	35 (24.5%)
	no	68 (47.6%)
	both	2 (1.4%)
Age	Mean (26-82) 48.07	95%CI(46.74-49.4)
Survival	Mean (5-216 month) 74.38	95%CI(68.86-78.9)

of metastasis were another parameters that had significant correlation with survival (skeletal metastasis had better survival) while diameter of the tumor had minimal effect to survival (T>4 cm had lower survival, P=0.08). Hormone receptor-positive patients did not provide survival benefit.

Discussion

This is a report about survival pattern of breast cancer from northwest of Iran. Despite the extensive knowledge about incidence and survival rates for cancer in the western world, present information in developing countries is insignificant. International comparisons with developing countries are too limited. Where conducted, differences in survival have been mainly focused in differences of patient's age, stage of disease at diagnosis, and the presence of metastasis. Patterns in survival can provide information regarding the impact and severity of cancer. Recognizing the differences in survival rate among populations could assist uncovering failures in systemic policy and inappropriate program delivery, and furthermore support the planning of systems for enhanced cancer control (Sadjadi et al., 2009).

Various studies have provided conflicting data from Iran (Faradmal et al., 2012).

We have in overall unveiled one, three, five, seven and ten years survival of about 96, 86, 81, 79, and 76% respectively which is similar to other studies from Iran.

In a retrospective study of breast cancer patients, Fouladi and coworkers (2011) in Ardabil and Rezaianzadeh, (2009) in southern Iran reported overall five year relative survival rate of 51% and 58% respectively. The three-year overall survival was 76% (95%CI; 73-79%) in later study. Fouladi and coworkers (2011) reported that patients who received no surgery had lesser survival compared to those who underwent mastectomy or lumpectomy.

Because primary metastatic patients may require any breast surgery, they have poor prognosis. Patients who had undergone lumpectomy correspondingly have smaller tumor size and are diagnosed with lower stage. Therefore, they observed higher survival rate compared to mastectomy patients. Overall, our study provided higher survival rate. This may be correspond with inclusion of higher number of patients in our study compared to cross sectional study of Ardabil (only patients of year 2003), as well as health promotion during the previous years.

The other studies from Tehran have previously reported 5-year overall breast cancer survival rates of 60% (Mousavi et al., 2011) and 62% (Vahdaninia et al., 2004). These studies were conducted on records of patients during 1998-2001 and 1997 respectively. Although the former study had recruited numerous patients in the study, it denoted the survival of a cross sectional study in the past 10 years. Higher survival rate of our patients may correspond with 10 years advancement in health system as well as with early detection of patients and their referral to only one clinic. This data requires further clarification by multicenter study and higher number of patients.

Iran has considerably poor survival rates compared to European countries and the United States when 5-year overall survival rates in Tabriz were compared with those

of 46% in India, 64% in Oman, 65% in Greece, 71% in Germany, 78% in Belgium, 89% in the USA, and 84% in the UK. Because cultural barriers prevent Iranian women from comfortably communicating with a physician for sensitive female-specific health problems; even highly educated women are reluctant to seek treatment for breast tumors. In addition, cancer treatment units are not readily accessible which delays diagnosis and screening mammography is not commonly practiced (Rezaianzadeh et al., 2009).

In the study conducted by Harirchi and colleagues (2011), the age distribution analysis of BC showed the highest incidence among women aged 40-49 years [mean age (±SD): 48.4 years (±12.5)], followed by the women in sixties and seventies. This age distribution differs from that of western countries but is similar to that of developing nations (Hemminki et al., 2011).

This finding indicates that the peak incidence of age for BC is 10 years lower in Iran, which is consistent with previous studies (Harirchi et al., 2011).

Age distribution in our study like data reported by Paula Curado (2011) shows high incidence among women 40-49, this could correspond with cultural, behavioral, genetic or geographical diversities seen in Asian patients.

Breast cancer in Asian patients is characterized by early tumor occurrence along with relatively younger median age at diagnosis. The peak age of BC in Asian countries is between 40 and 50 years, whereas in the Western countries it has been reported to be between 60 and 70 years. As matter of fact, the incidence of BC is rising in Asia and it is consistent with increased mortality (Paula, 2011).

In the study conducted by Vahdaninia and colleagues (2004), 167 women were screened from 1997 for 5 years. The mean age of the patients at diagnosis was 47.2 years, who were presented with stages III (33%) and IV (28%). The mean survival time was 47.3 months with relative survival rate of 62%. In respect with disease stage, the mean survival time for stage I, II, III, IV was 56, 51, 46, and 42 months respectively.

Mean age of our patients was 48 years which is similar to above data. As we excluded primary metastatic or stage IV patients from our study, we observed higher survival findings (81%), if it was not in fact due to the progression in health system during the past ten years.

Although some findings (Vostakolaei et al., 2012) did not show significant association between survival and age, our results showed otherwise. Patients younger than 40 years old had lower survival compared to patients older than 40 years. This data is similar to those of other countries that consider age below 40 is a poor prognostic factor. Almost in all studies dealing with breast cancer survival, it is indicated that age and stage are predictors of prognosis (Ugnat et al., 2004).

We could not find any relationship between stage and survival. This may be due to smaller number of patients or poor reports of lymph nodes involvement which was the major shortcoming of this study.

In many studies premenopausal and younger age at breast cancer diagnosis were poor prognostic factors for locoregional control and survival. In report made by

Mansell (2009) and coworkers, large tumour size, high grade, involvement of more than 3 axillary nodes and the presence of lymphovascular invasion were highly significant and independent predictors of recurrence within 2.5 years.

The correlation between tumor diameter and survival was minimal in our study; this is in contrast with Mansell (2009) or other studies such as BIG 1-98 trial with significant relation and may correspond with inadequate pathological report.

Other factors reported to be independent predictors of early recurrence include low ER positivity and human epidermal growth factor receptor 2 (HER2) over-expression/amplification. But no significant difference was found in their group of patients. (Kheradmand et al., 2010)

We also did not find any correlation between hormone receptors and survival. This is in contrast with our earlier report on only metastatic breast cancer patients (Eivazi-Ziaei et al., 2012), from northwest Iran where receptor positive patients provided significantly good survival.

Patients with ER/PR positive tumors have demonstrated improved disease free survival compared to similarly staged patients with ER/PR negative tumors in 5 years, but the difference is not significant on patients in 10 years (Devita et al., 2011). Since our patients were in different stages in follow up and we determined 10 years survival, the expected results were shown to be different from our previous report dealing with only stage IV patients with low survival.

Breast cancer patients in British Columbia (B.C.) had greater one-year survival rates than patients in Ardabil for each age group under 60.

Table 2 describes the results of this study with age related survival of patients. As of this data, the relative one year survival in B.C. (total= 0.95) is greater than Ardabil (0.92). Our patients' one year survival (0.96) is similar to B.C., but we have prominent decline in survival of patients below 40 years old (0.82 versus 0.99).

We should conduct more studies with high number of patients for detection of different age groups and survival.

The median age of breast cancer diagnosis was 61 years (range 24-104 years) in B.C. and 44 years (range 21-86 years) in Ardabil. About 23% of B.C. patients and 64% of Ardabil patients were younger than age 50 at the time of diagnosis (Sadjadi et al., 2009). The median age of our patients was 47 years (range 26-82 years) and 61.6% were 50 or younger than 50.

Reports show variable survival rates in patients

Table 2. One-year Survival Rates for Female Invasive Breast Cancer Cases Diagnosed in 2003 in Ardabil (Iran) and British Columbia, Canada by Age Group

Age	Ardabil		British Columbia	
	No. of Cases	One-year Survival rate	No. of Cases	One-year Survival rate
20-39	39	0.92	124	0.99
40-49	36	0.92	430	0.99
50-59	27	0.89	597	0.97
60+	16	1.00	1290	0.92
Total	118	0.92	2441	0.95

affected with breast cancer considering different ethnic populations. Asian Americans have demonstrated better survival compared to other major ethnic groups in the US. Inconsistent reports have been made regarding South Asians having better survival than others in England and California while lower rate of survival observed in British Colombia (Sadjadi et al., 2009).

Hislop (2007) reported distinguished differences in BC survival among general populations of China, South Asia and B.C. Survival rate was the highest among Chinese women. This is interesting data where the proportions screened were similar among the three ethnic groups. South Asian women showed the poorest survival. This difference was speculated that differences in treatment practices as well as possibility of cancer biology affecting tumor progression may interfere among these ethnic groups.

Biological differences at the genetic or molecular levels may result in more aggressive disease symptoms along with higher speed of invasion in some native women as compared to the other ethnic groups. Thorough understanding of breast cancer and its specificities at molecular level will enable us to further explore these interactions. Needless to say, public education and awareness regarding early detection of breast cancer is a basic requirement (Rastad, 2012).

Utilizing news and communication media with sufficient coverage for announcements and educational programs are critically efficient. It is also important to educate health care providers who will come in contact with BC patients and relatives. It is necessary to establish screening programs for breast cancer including periodic breast examination and mammography where early lesions can be detected with appropriate survival and overcoming to corresponding mortality. (Sadjadi et al., 2009). Further studies are required to address the differences among the Asian countries in respect with diagnosis, screening activities, lifestyle, genetic susceptibility, in order to clarify the reasons for these dissimilarities (Curado, 2011).

The improvement in detection of early BC in Iran may be explained by increased awareness among Iranian women with respect to the methods of BC screening especially mammography, increased medical advice and availability of mammography devices. It is important to note that regular screening mammography is not available through BC screening programs in Iran, so privately operated screening mammography has been increased due to public demand.

Furthermore, some basic characteristics of BC, such as age at the time of diagnosis or referral, are different among nations that demand unique, specific, simple, cost-effective, evidence-based, and culturally appropriate screening programs based on their needs and the priorities of health care system (Harirchi et al., 2011).

In conclusion, while substantial amount of international researches and publication have been devoted to risk and prognostic factors of breast cancer, specific research corresponding with Iranian patients is non-significant. Furthermore, the association between survival rate of patients suffering breast cancer and socio-demographic and pathologic factors has been widely studied in developed countries. We may conclude here that survival rate of our breast cancer patients is significantly lower than European countries and the US. Other studies with high number of patients should be conducted for survival analysis of patients particularly below 40 years.

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