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Management of Elderly Breast Cancer Patients Referred to the Cancer Institute of Iran during 2000-2014: Call For a National Guideline

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ABSTRACT

Background: About one-third of total breast cancer cases occur in women over 65 years of age. Elderly breast cancer management is a major oncology challenge across the globe. Unlike radical treatment of younger women's mammary tumors, the method used for treatment in elderly breast cancer depends on patient life expectancy. The present study aims to determine the clinical and pathological characteristics of elderly breast cancer in Iranian patients and to identify modal treatment differences compared to developed countries.

Methods: A total of 239 cases of breast cancer patients over 65 years who had been referred to the Cancer Institute of Iran between 2000 and 2014 were studied and their demographic, pathologic, surgical, and adjuvant therapy data were recorded. In addition, the two parameters of recurrence and disease-free survival (DFS) were analyzed statistically.

Results: The mean age of patients was 71.8±6.15 and invasive ductal carcinoma (IDC) was the most commonly occurring tumor among these case. In terms of tumor size, 52.5% of cases were T2, and in terms of axillary lymph node involvement, 53.2% were N1. Stage II had the highest measured rate and metastasis had occurred in 16% of patients, when analyzed during follow up. 74.2% of patients were positive for hormone receptors and 33.1% for HER-2. In terms of treatment, 64.6% of patients underwent modified radical mastectomy (MRM), 76.8% chemotherapy, 75.1% radiotherapy, and 54% hormone therapy. In 54-month follow-ups, local and systemic recurrence occurred in 27 patients, most of which occurred during the first 4 years; 79 patients died of cancer during the same period.

Conclusion: Our results showed that patients' tumor stage was higher than similar studies, and despite the radical regimen strategies in Iran, the risk of recurrence and mortality was higher. Therefore, it is suggested that the study be repeated in other major treatment centers in Iran. We suggest that the treatment of elderly breast cancer be carried out with the help of a multidisciplinary team, and to develop national guidelines for these patients.

Keywords: Elderly breast cancer, Disease-free survival (DFS), Adjuvant therapy, Recurrence

INTRODUCTION:

According to Globocan, 2012, breast cancer constitutes one-fourth of malignant tumors among women and its incidence rate increases with age[1]. In 2010, 10000 new cases of breast cancer were diagnosed in Iran[2-4]. Statistics show that approximately one-third of breast cancer cases are diagnosed among women older than 65 years; these patients are considered cases of elderly breast cancer5. Therapeutic management of this type of breast cancer is always challenging, with multi-organ physiologic functions decrease and an increase underlying diseases that come with advanced age[5]. Additionally, the participation of these patients in clinical trials has some limitations[6,7]. Findings indicate that elderly breast cancer is not always the main cause of death in these patients; underlying diseases also play an important role[5,6].

Many studies show biological behavior differences between elderly breast cancer and its younger counterparts. In elderly patients, the expression of positive estrogen receptor (ER) and progesterone receptor (PR) are is increased and Her-2 gene expression is lower compared to young women[2,5-7]. In these patients, therapeutic management is based on life expectancy and invasive therapies are used less frequently in this group of patients[8]. Breast cancer therapy in young women is carried out according to guidelines, but in older patients, other factors such as cost-benefit, body condition and underlying disease affect therapeutic regimens[9]. Mostly, older cancer patients cannot receive current standard therapeutic protocols and they also receive fewer doses of chemotherapy drugs than younger patients. For example, modified radical mastectomy (MRM) is rarely done in these patients and breast-conserving therapy (BCT) is preferred. In addition, axillary lymph node dissection (ALND) is not common[10].

Chemotherapy and radiotherapy are not strictly performed in older cancer patients, but these patients undergo hormone therapy completely[7,8,10]. This study aims to assess different therapeutic modalities and survival among Iranian breast cancer patients diagnosed at the age of more than 65 years who were referred to the Cancer Institute of Iran according to the demographic and pathological features of elderly breast cancer.

METHODS:

Methodology:

All patients older than 65 years with elderly breast cancer who were referred to the Cancer Institute of Iran, during 2000-2014 were included retrospectively in this project.

Data collection:

A questionnaire was completed for patients in which demographic, pathologic and therapeutic data were collected.

Some parameters were extracted from pathology and immunohistochemistry reports, including HER-2; PR and ER status, and histology type. The results of FISH or CISH for HER-2 evaluation were included if they had been performed. Tumor size and stage were determined according to clinical data and pathology reports. AJCC guideline was used for tumor staging. Therapeutic parameters were included in the study such as: type of surgery (MRM or BCT); neoadjuvant therapy; chemotherapy; radiotherapy; combination therapy; hormone therapy.

Finally, according to patients' file and follow up, time of tumor recurrence (local and systemic) and patient deaths were determined.

Statistical analysis:

The outcome parameter, described as recurrence and/or

patient death after therapy was determined. Data were analyzed using SPSS 18 software. Disease-free survival (DFS) was calculated based on the Kaplan Mayer Model.

RESULTS:

239 patients were included in this study. The average age was 71.8 ± 6.15 and all patients were between 65 to 97 years old. As shown in Table-1, the maximum frequency was related to age group 65-69 (%43.9 of patients)

According to pathological reports, invasive ductal carcinoma (IDC) was the most common cancer type, accounting for 85.5% of cases (**Table 1**).

Only 179 cases presented clinical data in relation to tumor size. A size of 2-5 cm which corresponded to T2 was seen in the majority of patients presenting relevant clinical data (52.5%) and T1 and in situ, with 16.8% and 3.9% were second and third, respectively..

According to pathologic reports, only 171 patients had data on lymph node status with 46.8 % of patients having lymph nodes that were free from the tumor, and in node-positive patients, 53.2% of them showed signs of involvement of only 1 to 3 lymph nodes (N1).

In this study, only 39(16.3%) cases had cancer metastasis (16.3%). (**Table 1)**

Out of 193 cases, stage II comprising 48.2% and stage IV with 20.2% were the first and second most common clinical stages.

74.2% of patients were ER-positive, 60.9% were PR positive, and 33.1 % were HER2- test positive.

In 86.6% of patients "surgery" was considered as the first therapeutic intervention, with Modified Radical Mastectomy being the most commonly used method (64.6%) (**Table 2**).

As shown in Table 2, 76.8%, 75.1% and 54% of cases had received chemotherapy, radiotherapy and hormone therapy, respectively. Table 2 shows adjuvant therapy

Table 1. Clinicopathological characteristics of 239 Elderly Breast Cancer Patients

Parameter	Category	Percentage
Age (65-97) n=239	65-69	105 (43.9%)
	70-74	65 (27.1%)
	75-79	40 (16.7%)
	80-84	21 (8.7%)
	85-89	3 (1.2%)
	90-94	3 (1.2%)
	≥95	2 (0.8%)
Histology n=228	IDC	14.07
	ILC	12.66
	DCIS	12.37
	Others	10.10
Tumor size n=179	T in situ	7(3.9%)
	T1	30 (16.8%)
	T2	94 (52.5)
	T3	15 (8.4%)
	T4	33 (18.4%)
Axillary lymph node n=171	N0	80 (46.8%)
	N1	65 (38%)
	N2	25 (14.6%)
	N3	1 (0.6%)
Metastasis n=236	Not present	197 (83.5%)
	Present	39 (16.3%)
Tumor staging n=193	0	4 (2.1%)
	I	26 (13.5%)
	II	93 (48.2%)
	III	31 (16.1%)
	IV	39 (20.2%)
ER status n=143	Positive	106 (74.1%)
	Negative	37 (25.9%)
PR status n=138	Positive	84 (60.9%)
	Negative	54 (39.1%)
HER-2 status n=124	Positive	41 (33.1%)
	Negative	83 (66.9%)

in more details.

Clinical data of patients regarding recurrence parameters were incomplete. 96 cases were followed up during 62±43.1 months. Twenty-seven cases of patients who had undergone surgery displayed recurrence with a local to systemic proportion of 15:12. It is noteworthy that 74% of recurrences occurred within the first four years (**Table 3**). In addition, more than 80% of deaths occurred during the first four years (**Table 4**). **Table 5-6** and **Figure 1** display disease-free survival (DFS) rate based on Kaplan Mayer Analysis. Average and standard deviation of recurrence time was 50.2±12.1 months for patients, and the mean and SD were calculated to be 20±50.1. Our results showed that DFS rate for six months, one year, two years, three years and four years was 77%, 59%, 44%, 29% and 25%, respectively.

Additionally, **Table 6** shows data on tumor recurrence based on type of adjuvant therapy in patients who had undergone surgery. As shown, 6 out of 8 patients who had only received hormone therapy, showed no recurrence and 11 out of 29 patients who had received both chemotherapy and radiotherapy, showed tumor recurrence.

Only 1 out of 7 cases who received hormone therapy and 4 of 22 cases who received concurrent chemotherapy and radiotherapy died during follow-up.

Table 2. Treatment of 239 Elderly Breast Cancer Patien

Parameter	Category	Percentage
Surgery type n=201	MRM	130 (64.6%)
	BCT	62 (30.9%)
	Missing	9 (4.4%)
Chemotherapy (Ch) n=185	Received	142 (76.8%)
	Not received	43 (23.2%)
Radiotherapy (RT) n=169	Received	127 (75.1%)
	Not received	42 (24.9%)
Hormone therapy (H) n=161	Received	87 (54%)
	Not Received	74 (46%)
Combination adjuvant therapy n=239	Not Received	10 (4.2%)
	Ch	29 (12.1%)
	H	20 (8.4%)
	RT	10 (4.2%)
	RT+Ch	58 (24.3%)
	Ch+H	8 (3.3%)
	RT+H	12 (5%)
	RT+Ch+H	47 (19.7%)
	missing	45 (18.8%)

DISCUSSION:

TOur findings showed 86% of elderly breast cancer is IDC which is corresponded to Bastiannet et al. and Mustachi et al.[11,12].

In this study, T2 was the most common tumor size, even though in similar studies carried out in Italy and the US, more than half of patients were T1[12,13]. This difference is probably due to breast cancer screening programs and higher awareness among western women. Approximately 47% of patients were N0 and most of those who had positive axillary lymph nodes were N1. This result is compatible with other studies[12,14].

Regarding tumor staging, our findings displayed higher stages of cancer than Western counterparts. About 48% of patients in this study were stage II, but other studies reported stage I as being most frequent[15,16]. This difference is probably due to lack of appropriate screening programs and delays in diagnosis and treatment.

Regarding IHC, there are similarities and differences with other studies. In our study, 74% and 61% of cases were ER positive and PR positive, respectively. In a study in Italy, approximately 83% of 1024 cases were

Table 3. Recurrence rate mong patients included in the study

Parameter	Category	Percentage
Recurrence status n=96	Not present	69 (71.9%)
	Present	27 (28.1%)
Type of recurrence n=27	Local	15 (55.6%)
	Systemic	12 (44.4%)
Recurrence time n=27	Under 6 months	6 (22.2%)
	6-12 months	5 (18.5%)
	12-24 months	4 (14.8%)
	24-36 months	4 (14.8%)
	36-48 months	1 (3.7%)
	48-54 months	0 (0%)
	Over 54 months	7 (25.9%)

Table 4. Mortality rate among patients included in the study

Parameter	Category	Percentage
Death status n=79	Not present	69 (87.3%)
	Present	10 (12.7%)
Recurrence time n=10	Under 6 months	1 (10%)
	6-12 months	2 (20%)
	12-24 months	3 (30%)
	24-36 months	1 (10%)
	36-48 months	1 (10%)
	48-54 months	0 (0%)
	Over 54 months	2 (20%)

ER positive[12]. Cyr and et al. showed similar results[13]. Our work showed that 33% of patients were HER-2 positive. Although we had no information about the use of trastuzumab, there are differences between these results and that of studies in the US and the Netherlands[16,17]. Some authors believe that the rate of HER-2 positive reports was higher in Iran during recent years for reasons such as lack of high-quality laboratory equipment and diagnostic protocols. In 2012, Keyhani et al. performed a systematic review and found that more than 44% of patients in 22 studies were HER-2 positive, a result which is higher than the global average statistics[18].

Our results showed that MRM is the selected surgery procedure in 64% of cases. On the other hand, tumor staging showed that approximately 63% of patients could be candidates for BCT procedures. It seems that radical surgery procedures are preferred in Iran compared to Western countries. This is a while a study conducted in Italy and another study by Rocco et al. showed rates of conservative breast treatment being 45% and 37% respectively[13,19]. It is probable that the lower use of BCT in Iran is related to cultural differences compared to Western societies.

Our study showed that chemotherapy was used more than in other countries. Approximately 77% of patients received chemotherapy. Radiotherapy was also more common than result from similar studies[20]. In this study 54% of patients received hormone therapy, which is less than other studies with 84% receiving hormonal therapy in Italy[13]. This may be due to more invasive therapy and surgery treatments for this group of women in Iran.

Unfortunately, in this study due to lack of patient files and inaccessibility to patients, assessing survival posed considerable problems. Nevertheless, from the 96 patients who were followed, only 28% displayed local or

Table 5. Recurrence rate mong patients included in the study

Median			Mean		
Standard error±	Confidence interval		Standard error±	Confidence interval	
	Upper limits	Lower limits		Upper limits	Lower limits
20±5.1	30.1	9.8	50.2±12.1	74.0	26.5

Table 6. Disease-free survival rate in the population studied

Time (Month)	Status	Cumulative Proportion Surviving at the Time	N of Cumulative Events	N of Cumulative Events	N of Remaining Cases
		Standard error	Estimate		
6	Recurrence	0.778	0.080	6	21
12	Recurrence	0.593	0.095	11	16
24	Recurrence	0.444	0.096	15	12
36	Recurrence	0.296	0.088	19	8
48	Recurrence	0.259	0.084	20	7
70	Recurrence	0.222	0.080	21	6

systemic recurrence. In a US study, local and systemic recurrence was reported to be less than 8%13. In another study in France, 7-year survival was estimated as more than 86% 14. Our results revealed that despite strict therapeutic regimens in Iran, tumor recurrence is high, therefore revisions in treatment methods are necessary.

CONCLUSION:

Patients in this study were mostly at stage II, and hormone receptors were positive in most cases. Among surgical procedures, MRM was more routine than BCT, and radiotherapy and chemotherapy were used more than other studies.

This work is probably the first study of elderly breast cancer in Iran. It seems that therapeutic protocols for these patients are the same as those of breast cancer in younger women. The authors offer three distinct suggestions as follows:

1. Similar studies should be carried out in other medical centers in Iran to determine the similarities and differences with this work.
2. In cases of elderly breast cancer, therapeutic principals should be managed with the help of a multidisciplinary board, so patients can receive better and optimized surgery, chemotherapy, radiotherapy and

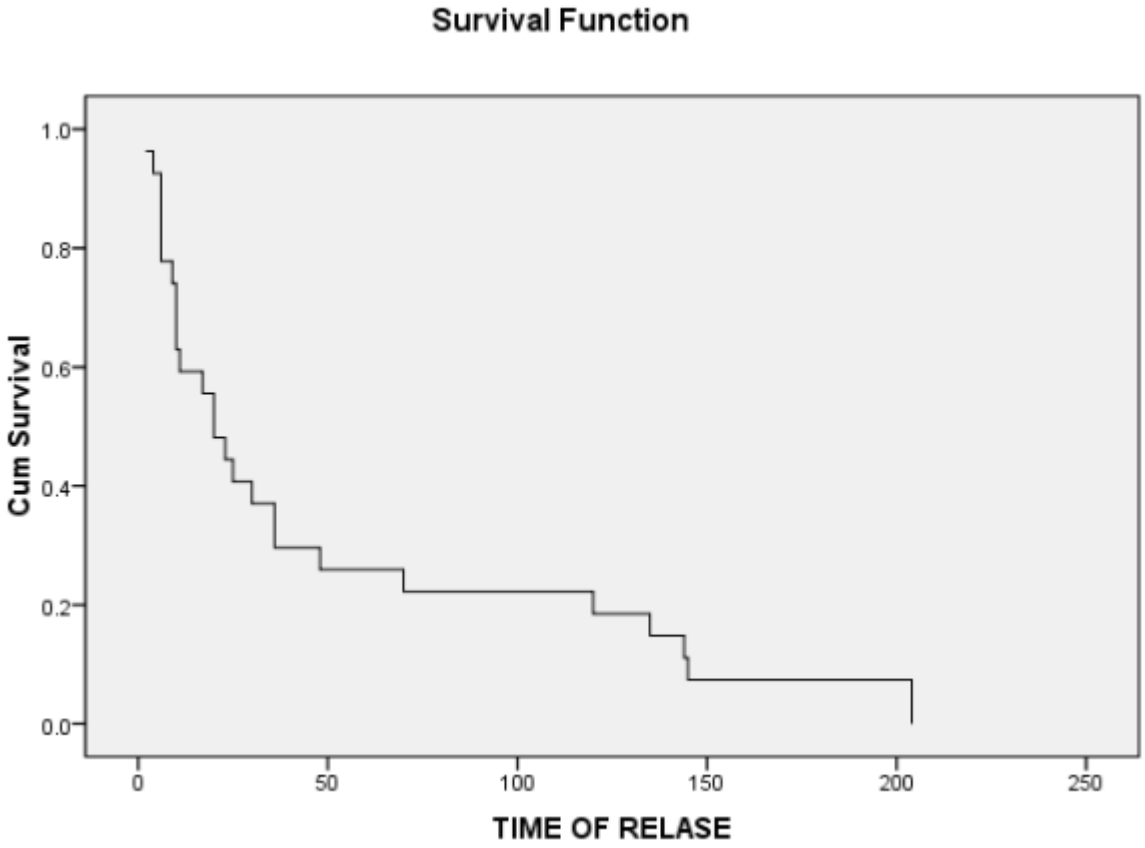

Figure 1. Time of Relapse

hormone therapy.

3. With clarification of therapeutic differences between Iran and other countries, national guidelines for better therapeutic management of elderly breast cancer should be developed.

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