The access rate to diagnosis and treatment modalities in breast cancer patients in Turkey; Multicenter observational study

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Summary

Purpose: To determine the time elapsed between the first notification of the disease and the access to the diagnosis and treatment modalities and the associated factors in female patients with breast cancer in Turkey.

Methods: Data was acquired from a questionnaire involving 535 patients who applied to 14 various oncology clinics in Turkey between 1st and 28th of February 2010. Analyses were performed by the participating clinics and were divided into 3 groups: centers located in metropolitan areas formed group 1 (n=161), those located in Marmara and central Anatolia region formed group 2 (n=189), and centers located in Karadeniz and East-Southeast Anatolia region formed groups of these centers were formed according to the socioeconomic development of the provinces.

Results: The median patient age was 48 years, 56.1% of patients were less than 50 years of age. Eighty-five percent of the patients detected a mass in their breast by self exami-

Introduction

Breast cancer is the most common type of malignancy and the second most common cause of death by cancer in women, following lung cancer. The incidence of breast cancer in the eastern part of Turkey is 50/100,000 and in the western part is 20/100,000 [1]. According to data from USA, about 1 in 8 women will develop breast cancer during their lives.

The worldwide incidence of breast cancer, espe-

nation and 27% of the patients older than 50 years never had breast imaging until the definite diagnosis was established. The median time elapsed between disease noticed by the patient and application to a health care center was 10 days, between application and biopsy 19 days, between biopsy and surgery 10 days, and between surgery and systemic therapy 31 days. The median time elapsed between patients applying for surgery in groups 1 and 2 centers was 11 and 21 days, respectively (p=0.01). The median time elapsed between biopsy and surgery in groups 1,2 and 3 centers was 14,1.5, and 12 days, respectively (p<0.05).

Conclusion: A high level of awareness regarding breast cancer in our country is related with the time that is defined as 10 days between disease recognition and medical application. The time elapsed between the application and biopsy, surgery and systemic therapy was longer compared with the corresponding figures in developed countries.

Key words: breast cancer, elapsed time to diagnosis and treatment, socioeconomic factors

cially in developing countries, is increasing [2,3]. Besides regular application of screening methods, this may be due to the increase of the obesity rate that is one of the etiologic factors of breast cancer, giving birth to the first child in an older age and also dietary factors. Progression free survival (PFS) and overall survival (OS) rates are affected by delayed access to diagnosis and treatment of breast cancer [4-7]. In advanced-stage tumors, mortality rate increases and more aggressive therapies are needed. Micrometastases and angiogen-

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esis that may exist after removal of the primary tumor and resistance of micrometastatic disease to the chemotherapeutic agents are factors affecting the mortality rate [8].

The purpose of this study was to determine the socioeconomic characteristics of patients with breast cancer, tumor characteristics, the time elapsed between the first notification of the disease and the access to the diagnosis and treatment modalities, reasons of delayed access to diagnosis and treatment modalities and the effects of delay on the disease outcome.

Methods

A total of 535 patients who applied to 14 various oncology clinics in Turkey between 1-28 February 2010 were retrospectively examined. The data was acquired from a questionnaire including 535 patients who applied to 14 various oncology clinics in Turkey.

Table 1 shows the health care centers and the number of participated patients. We primarily aimed to determine the time elapsed between the first notification of the disease and the access to the diagnosis and treatment modalities, to determine the risk factors related to the elapsed time and to determine differences between the different geographic regions in Turkey. Secondarily we aimed to determine the clinicopathologic features of patients with breast cancer and to determine the diagnostic and treatment modalities. The time elapsed to radiotherapy application was not investigated in this study.

Inclusion/exclusion criteria

Patients were only eligible if the diagnosis had been confirmed histologically, and those who had access to all diagnostic and treatment modalities. Exclusion criteria included patients who were male, and women had no access to all diagnostic and treatment modalities.

The questionnaire

A questionnaire was administered to patients and clinical and pathological information were registered. This questionnaire was explained to the patients orally and in written form to get their permission (Table 2). Six of the questions were related with patient characteristics, 10 with their socioeconomic status, 5 with the date of access to treatment modalities, 6 with pathologic tumor features, 1 with treatment modalities and 2 with prognosis of the disease. The questionnaire was formed by doctors working in the medical oncology clinics. After data analyses, and in order to evaluate the regional differences, the oncology centers were classified in 3 groups according to the socioeconomic development of their provinces [9]. The centers located in metropolitan areas (Istanbul, Izmir and Ankara) formed group 1 (n=161), the centers located in Marmara and Central Anatolia region (Kocaeli, Bursa, Edirne and Kayseri) formed group 2 (n=189) and the centers located in Karadeniz and East-Southeast Anatolia region (Zonguldak, Samsun, Trabzon, Elazig and Divarbakir) formed group 3 (n=185).

Table 1. Health care centers and the number of patients

Center names	Number of patients	%	
Group 1 (n=161)			
Istanbul University Oncology Institute	69	12.9	
Marmara University, Faculty of Medicine	31	5.8	
9 Eylul University, Faculty of Medicine	19	3.6	
Special Bayindir Hospital	30	5.6	
Kartal Resource and Education Hospital	12	2.2	
Group 2 (n=189)			
Kocaeli University Faculty of Medicine	24	4.5	
Erciyes University Faculty of Medicine	118	22.1	
Trakya University Faculty of Medicine	34	6.4	
Uludag University Faculty of Medicine	13	2.4	
Group 3 (n=185)			
Ondokuz Mayis University Faculty of Medicine	54	10.1	
Zonguldak Karaelmas University Faculty of Medicine	33	6.2	
Dicle University Faculty of Medicine	75	14	
Karadeniz Teknik University Faculty of Medicine	16	3	
Elazig Resource and Education Hospital	7	1.3	
Total	535	100	

1. Age

- 2. Menopausal status
- 3. Job
- 4. Educational status
- 5. Marital status
- 6. Working on salary or not
- 7. Monthly income
- 8. Having breast cancer in their family history or not
- 9. Having cancers other than breast in their family history or not
- 10. Number of breast ultrasonographies until diagnosis
- 11. Number of mammographies until diagnosis
- 12. Where they live before and during diagnosis
- 13. Diagnostic methods
- 14. Date of first disease recognition
- 15. Date of first application to a health care center
- 16. First application center
- 17. Treatment center
- 18. Date of biopsy
- 19. Date of surgery
- 20. Having comorbidity or not
- 21. Tumor size
- 22. Axillary lymph node status
- 23. Estrogen receptor status
- 24. Progesterone receptor status
- 25. Human epidermal growth factor receptor status (HER-2)
- 26. Histological grade
- 27. Date of initiation of systemic treatment
- 28. Applied treatments
- 29. Date of local recurrence
- 30. Date of distant metastasis

ER, PR and HER-2 receptors

The American Joint Committee on Cancer system staging (6th edition) was used for staging [10], and the Modified Bloom Richardson system was used for grading [11]. One percent or more staining of estrogen (ER) and progesterone receptors (PR) was considered as positive. HER-2 receptor was evaluated by immunohistochemical methods. One positive result (+/+++) was considered as negative and 3 positive results (+++/+++) as positive. For two positive results (+++/+++), fluorescence *in situ* hybridization (FISH) or chromogenic *in situ* hybridization (CISH) was applied. According to HER-2/Chr 17 ratio, patients with amplification were considered as positive.

Statistical analysis

Data were numerically coded and evaluated with SPSS v.15.0 statistical program. Mann-Whitney U test was used to analyse the access rate to diagnosis and treatment modalities for the 3 oncology centers groups. Kruskal-Wallis test was used for univariate analysis. Cox regression analysis was used for multivariate analysis. P<0.05 was considered as statistically significant.



Figure 1. Age distribution of patients (years, %).

Results

The mean patient age was 48 ± 11.2 years (range 24-89). The number of patients < 40 years was 107 (21.3%) and of those < 50 years 282 (56.1%) (Figure 1). Table 3 shows the patient and sociodemographic characteristics. Forty-five percent of the patients were premenopausal. Most of the patients were housewives (79%), graduated from primary school (41%), married (89%), not working in salaried week (87%), having social insurance (97%), and having 500-1000 Turkish liras monthly income (59%). Thirteen percent of the patients had breast cancer history in their family and 30% had other cancers in their family. Before diagnosis, most of the patients lived in the center of the city. During treatment, the number of patients living in a village and district or borough decreased; on the other hand patients living in metropolitan areas increased (from 22.9 to 30%).

When the factors that contributed to diagnosis were evaluated, it was shown that 85% of the patients applied to a doctor after detecting a breast mass by self examination and after investigation these patients were diagnosed with breast cancer (Table 3, Figure 2).

When the first application centers were evaluated, we determined that 46% of the patients applied to a state hospital, 37% to a university hospital, and 17% to special centers (Table 3). However, 88% of the patients continued their treatment at a university hospital, 8% at a state hospital and 4% at special centers (Table 3).

Sixty-eight percent of patients never had any other disease. Until definite diagnosis was established, the mean number of ultrasound (USG) and/or mammogra-

Table 3. Patient and socioeconomic characteristics

Characteristics	n	%
Age (years)		
≤40 [°]	107	21
>40	396	79
Menopause		
Premenopausal	237	45
Postmenopausal	290	55
Job	411	70
Housewife	411	/9
Employee/elerk	39	8
Worker	29	° 6
Education	2)	0
Illiterate	26	6
Primary school	166	41
Secondary school	82	20
High school	74	18
University	59	15
Marital status		
Married	469	89
Single	25	5
Widow Discover	28	5
Divorced Selemind weath	5	1
Vec	60	13
No	454	87
Social insurance	7,77	07
Yes	440	97
No	14	3
Monthly income (Turkish lira/TL)*		
<500	41	8
500-1000	285	59
1000-3000	149	31
>3000	10	2
Family history of cancer	1.5.5	20
Yes	155	30
NO Project concer in the family	369	70
Ves	72	13
No	460	87
Place of living before treatment	100	0,
Village	19	4
District/borough	149	28
Province	240	45
Metropolitan	121	23
Place of living during treatment		
Village	14	3
District/borough	99	22
Province	202	45
Diagnosis via	135	30
During screening	48	91
Self examination	446	85
Menopause clinics	2	0.4
Routine doctor examination	29	5
First application center		
University hospital	171	37
State hospital	211	46
Special center	80	17
Treatment center		~~
University hospital	443	88
State nospital	43	8
Comorbid disease	19	4
No	328	68
Yes	156	32
	100	22

*1 Euro = 2.4 TL

Table 4. Pathologic tumor characteristics

Characteristics	п	%
T stage		
I	162	34
II	253	52
III	59	12
IV	8	2
N stage		
0	138	37
Ι	110	30
II	73	20
III	49	13
TNM stage		
I	60	16
II	224	61
III	82	22
IV	8	2
TNM stage		
I-II	290	77.5
III-IV	84	22.5
Grade		
1	41	11
2	180	50
3	138	39
ER		
Negative	179	36
Positive	324	64
PR		
Negative	186	37
Positive	318	63
HER-2		
Negative	273	57
Positive	205	43

ER: estrogen receptor, PR: progesterone receptor

phy carried out was 1 ± 1.8 (range 0-17). One hundred and two (26.2%) patients never had breast USG and/ or mammography until having symptoms related with breast disease. Twenty-seven percent of patients > 40 years and 27% of patients > 50 years never had USG and/or mammography done until definite diagnosis was established. Table 4 shows the pathologic tumor features. The mean tumor size was 2.5 ± 3.1 cm (range 0.4-20). The mean positive axillary lymph node number was 1 ± 6.1 (range 0-42). Stage I was found in 16% of patients, stage II in 61%, stage III in 22% and stage IV in 2% of patients. Grade II tumors prevailed (50%). Most patients had positive estrogen (ER) and progesterone receptor (PR) and HER-2 was positive in 43% of the cases (Table 4).

Concerning systemic therapies 91% of the patients were treated with chemotherapy, 8% with hormonal therapy, while 1% of patients were followed up without treatment. When chemotherapy regimens were evaluated, we determined that 32% of the patients were treated with 6 cycles of FEC/FAC (fluorouracil, doxorubicin/epirubicin, cyclophosphamide), 20% with 4



Figure 2. The diagnostic methods of patients with breast cancer (%).

cycles of AC (doxorubicin, cyclophosphamide), 20% with 4 cycles of AC followed by 4 cycles of docetaxel, 23% with 3 cycles of FEC/FAC followed by 3 cycles of docetaxel, nearly 3% with TAC (docetaxel, doxorubicin, cyclophosphamide), and nearly 1% with CMF (cyclophosphamide, methotrexate, fluorouracil).

After a mean follow up of 17 ± 29 months (range 1-209) 19 (4%) patients developed local recurrence and 49 (10%) distant metastasis. The mean time elapsed between surgery and local recurrence and between surgery and distant metastasis was 34.3 ± 20.7 months (range 5.2-84.5) and 27.1 ± 28.4 months (range 1-138), respectively. For patients with local recurrence, the mean time elapsed between the recognition of the disease by the patients and initiation of systemic treatment was 110 days and for those without it was 92 days (p=0.4). The mean time elapsed for patients with distant metastasis and for those without was 119 days and 92 days, respectively (p=0.3).

The date of the first recognition of the disease, application to a health care center, biopsy time, surgery time, and initiation of systemic treatment were evaluated to determine the access rate to diagnosis and treatment modality analysis. When all patients were evaluated (n=535), we determined that the mean time elapsed between the first recognition of the disease by the patients and patients applying to a health care center was 10 days (range 0-731) and the mean time elapsed between application to a health care center and histopathologic diagnosis was 19 days (range 0-881) (Figure 3). The mean time elapsed between biopsy and surgery was 10 days (range 0-182), and surgery and systemic therapy 31 days (range 0-253). The mean time elapsed between the first recognition of the disease by patients and systemic treatment was 91 days (range 14-860). The mean time elapsed between biopsy and systemic treatment was 45 days (range 2-296).

Figure 4 shows the evaluated data of access rate to diagnosis and treatment modalities according to the groups of centers. The median time elapsed between first recognition of the disease by the patients and the patients applying to a health care center was statistically different between groups (p<0.05). The median time elapsed between patients applying for biopsy in group 1 and group 2 centers was 11 and 21 days, respectively (p=0.01). The median time elapsed between biopsy and surgery in group 1, 2 and 3 centers was 14, 1.5 and 12 days, respectively, and was statistically significantly shorter in group 2. The median time elapsed between surgery and systemic treatment was not different among groups.

Univariate analysis showed that the time elapsed between the first recognition of the disease by patients and application to a health care center for patients >40years, patients graduated from secondary school or higher, patients having family history of breast cancer or other cancers, patients living in a village and district, patients diagnosed in menopause clinic and routine medical examination was statistically significantly shorter (p < 0.05). The time elapsed between applying to a health care center and surgery for patients > 40 years, patients graduated from university, employees or clerks, and retired patients and patients treated in special centers was shorter than in other patients (p<0.05). The time elapsed between surgery and initiation of systemic treatment for premenopausal patients, patients graduated from university, living in city centers and metropolitan areas, those first applying to a university hospital, patients treated in special center and patients having comorbid diseases was shorter than in other patients (p < 0.05).



Figure 3. Elapsed time to diagnosis and treatment modalities in Turkey; days, median (range).



Figure 4. Differences of elapsed time between group centers (days, range).

Multivariate analysis showed that the independent variables detecting the time elapsed between the first recognition of the disease by the patients and application to a health care center were job, their living place during treatment, lymph node stage and PR (p<0.05) (Table 5). Also, independent variables were the first ap-

Period	Factor	Group 1 days, mean±SD	Group 2 days, mean±SD	Group 3 days, mean±SD	Hazard ratio	95% CI	p-value
First recognition- application	Job (housewife vs. other*)	20±5 vs. 13±2	10±0.2 vs. 9±1	20±3 vs. 9±2	0.57	0.38-0.86	0.007
	Place of living during treatment (province +metropolitan vs. vil- lage + district/borough)	15±3 vs. 1±1	10±0.2 vs. 9±0.2	31±9 vs. 9±1	0.48	0.31-0.74	0.001
	Lymph node stage (N0 vs. N1 + N2 + N3)	21±9 vs. 14±3	10±1 vs. 10±2	9±2 vs. 10±4	1.55	1.05-2.28	0.028
	PR (negative vs. positive)	10±2 vs. 16±4	10±0.3 vs. 10±1	14±4 vs. 10±2	1.60	1.08-2.39	0.019
Applica- tion - Surgery	Application center (University vs. State hospital)	14±2 vs. 16±5	0 vs. 16±6	9±5 vs. 10±2	3.57	2.01-6.33	< 0.001
	Application center (University vs. special center)	14±2 vs. 11±4	0 vs. 13±6	9±5 vs. 20±8	2.89	1.69-4.93	< 0.001
	Treatment center (University vs. State hospital)	16±2 vs. 10±1	0 vs. 31±11	12±1 vs. 20±9	0.15	0.07-0.33	< 0.001
	Treatment center (University vs. Special Center)	16±2 vs. 10±2	$0 \text{ vs. } 7 \pm 4.3$	12±1 vs. 0±1.2	0.19	0.08-0.45	< 0.001
	Additional disease (not present vs. present)	11±2 vs. 15±3	0 vs. 7±5	14±1 vs. 10±2	0.56	0.38-0.82	0.003
Surgery- Systemic treatment	Job (housewife vs. other)	34±2 vs. 30±2	33±2 vs. 31±10	31±1 vs. 28±5	0.45	0.29-0.71	< 0.001
	Place of living during treatment (province + metropolitan vs. village + district/borough)	31±1 vs. 45±11	32±3 vs. 36±4	28±2 vs. 44±8	2.15	1.31-3.51	0.002
	Lymph node stage (N0 vs. N1 + N2 + N3)	30±3 vs. 31±2	42±6 vs. 42±6	22±7 vs. 31±1	0.48	0.31-0.73	0.001
	PR (positive vs. negative)	28±4 vs. 32±2	33±2 vs. 32±3	31±1 vs. 31±2	1.64	1.06-2.55	0.028

Table 5. Factors affecting the access rate to diagnosis and treatment modalities (Cox regression analysis)

*student, retired, employee/clerk, worker

PR: progesterone receptor, CI: confidence interval

plication center, the treatment center for surgery and whether patients had non cancerous diseases or not.

Discussion

Breast cancer is the most common type of cancer in women and it is the second leading cause of death by cancer in women. In most countries, screening programs for breast cancer are initiated at the age of 40. In some countries, mammography is applied once a year until the age of 70, but in some countries it is applied once a year during their lifetime. In Turkey, although the survival rates increase, the age of first diagnosis of breast cancer does not change [12-15]. The median patient age with breast cancer in Turkey is less than in Europe and America [1]. Aksoy et al. evaluated 1038 patients and determined that 11.1% of the patients were at the age of 35 or less [16]. In line with this study, Ozmen et al. evaluated 1492 patients and found that the rate of patients under 35 years old was 5.5% [17]. Our study demonstrated that 21.3% of the patients were 40 or less, and 56.1% were 50 or less.

In our national health policy, the Turkish Ministry of Health recommends breast cancer screening programs. According to recommendations, patients who are between the age of 20 and 55 should examine themselves once a month and should be examined by a doctor once a year. Patients who are between 55 and 70 years should have mammography once every 2 years [18]. However, there is no randomized study to determine the age of initiation to breast cancer screening in Turkey. In our study, we determined that 27.8% of the patients with breast cancer were between the age of 55 or over and they had never had mammography/breast USG done in their lifetime (data not shown in Tables). There are studies that evaluated the role of breast self-examination on the early detection of cancer. Thomas et al. randomly examined 266064 patients to evaluate the effects of breast self-examination regarding breast cancer mortality and found that breast self-examination never decreased the mortality rate [19]. Green et al. also demonstrated that self-examination of the breast never increased the diagnostic rate or never decreased breast cancer mortality [20].

A high level of awareness regarding breast cancer in our country is related to the time that is defined as 10 days (range 0-731) between the recognition of disease and the medical application. The relationship between stage and the time elapsed between the first recognition of disease by the patients and the medical application were evaluated and the results showed that patients with stage I-II (13 days) had applied to a health care center earlier than patients with stage III-IV (20 days) (p=0.2). This could be attributed to the difficulty of applying to a health care center. And also, as shown in our study, patients with advanced disease stage are mostly seen at a younger age and the mass in the breast may be attributed to non cancerous reasons.

The diagnosis and treatment of breast cancer requires multidisciplinary approach. In Turkey, the number of pathologists, general surgeons, and radiation oncologists are sufficient but according to the data from Medical Oncology Society in Turkey, the number of medical oncologists is 355 only [21]. According to 2009 census, in Turkey the number of patients aged of 15 years or over is 54 million. The number of patients who are treated/followed by a medical oncologist is nearly 150,000 [22]. In addition, due to the increase of cancer incidence in our country, the number of medical oncologists is not sufficient. Most of the medical oncologists work in Istanbul, Ankara and Izmir (228/355 doctors, 64%) which are the 3 biggest cities in Turkey, and considering the population of these cities, the number of medical oncologists is not sufficient. Regarding these cities, the number of patients who are at the age of 15 or older, and who are treated/followed by a medical oncologist is 72,287.

Rayson et al. evaluated data from Canada in 2004 [23]. They determined that the time elapsed between the first recognition of disease and biopsy was 14 days, the time between biopsy and surgery 21 days and the time between surgery and systemic treatment 41 days. When these data were compared with the data in Turkey, the corresponding figures of our study were 34, 10 and 31 days, respectively. Reed et al. from Canada evaluated 6,418 patients and they found that the median time elapsed between the first recognition of disease and biopsy was 17 days and also the related factors for the time elapsed from diagnosis and treatment were determined as young age, not having a mass in breast, location of the mass, ethnicity and not having a family history [24]. Mayo et al. from Canada found that the time elapsed between the first recognition of disease and surgery was 34 days. This time was 29 days in 1992, and increased to 42 in 1998 [25].

The estimated median time elapsed between the first recognition of disease and systemic treatment was 91 days in our series, which was similar to the literature. In 2 different studies from Canada the median time elapsed between the first diagnosis of disease and the initiation of adjuvant treatment were 91 and 96 days [26,27]. A study from Denmark found that the time elapsed for 352 patients treated with classic CMF given on days 1-14 was 31 days, for 6,065 patients treated with i.v. CMF (on day 1) 28 days and for 1,084 patients treated with FEC 30 days [28]. However, patients whose chemotherapy initiation exceeded 89 days after surgery were excluded from this study.

Different studies evaluated the effects of delay regarding adjuvant treatment. Richards et al. evaluated 101,954 patients and indicated that delay of diagnosis for 3 months or more causes the patients to be diagnosed at advance disease stage and the survival rate to decrease [5]. In our study, we estimated that any delay to diagnosis longer than 3 months or more caused T I+T II disease rate to decrease from 89 to 74% (p=0.003) and also caused axillary lymph node rate to increase from 25 to 40% (p=0.029; data not shown in Tables). Arndt et al. found that delay to diagnosis of more than 3 months causes an increase of poorly differentiated tumors by 3.4 times [29].

As a result, a high level of awareness regarding breast cancer in our country is related with the time that is defined as 10 days between the recognition of the disease and medical application. Compared with developed countries, the time elapsed between the application and biopsy, surgery and systemic treatment are longer than expected and these differences were markedly differently between different regions in Turkey. Important factors effecting the time elapsed are related to the patient's occupation, whether she is a housewife or not, diagnosis and treatment center, the patient living place, and whether the patient has an additional comorbid disease or not.

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