Comparison of Clinical and Pathological Differences of Breast Cancer Patients under 35 and above 55 Years of Age

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ABSTRACT

Objective: In this study, we aimed to evaluate the clinical, pathologic and management differences between breast cancer patients under 35 years of age and postmenopausal patients above 55 years of age.

Materials and Methods: Patients who were operated on for breast cancer between November 2003 and March 2013 in our hospital were retrospectively analyzed. Patients were separated into two Groups according their age; Group 1 (<35 years) and Group 2 (>55 years).

Results: 94 patients with breast cancer, 45 patients in Group 1 and 49 patients in Group 2, were included in the study. The mean follow-up was 51 (19-121) months and 50 (19-120) months in Groups 1 and 2, respectively. Stages of breast cancer at the time of diagnosis were similar between the two groups. The groups were similar in terms of rates of re-excision ($p=0.42$), local recurrence ($p=0.34$) and solid organ metastases ($p=0.182$). The number of oncoplastic and reconstructive procedures were higher in Group 1 ($p=0.04$). Regarding pathological results, the rate of grade 3 tumors, those with Ki-67>12 and triple negative breast cancer were found to be higher in Group 1. In addition, the number of patients receiving chemotherapy was significantly higher in Group 1 ($p=0.03$).

Conclusion: Oncologic results were similar between young patients and postmenopausal patients. Nevertheless, tumor biology was found to be worse in young patients. In addition, oncoplastic and reconstructive approaches were significantly higher in young patients.

Keywords: Breast cancer, young adult, postmenopause

Introduction

Breast cancer is the most common type of cancer in women of all age groups in the world, and is the most common cause of cancer related death. The incidence of breast cancer incidence is eighty per hundred thousand in developed countries, with an incidence of fifty per hundred thousand in west areas of Turkey (1,2). Despite the high prevalence, the average 5-year overall survival for all stages in developing countries is 90% (1). Worse outcome rates are reported for younger patients despite improvements in diagnosis and treatment of breast cancer (1,3). Although the effect of age on prognosis controversial, it has been reported that clinical and pathologic characteristics of young patients differ from those of the elderly (1,4). It has been stated that young patients have more aggressive tumor biology and worse oncologic outcomes than their older counterparts (1,3). In addition, it has been shown that the age of patients with breast cancer influenced the choice of treatment (5). The limit that defines young age is uncertain in one study, it was published that the age limit for young people should be 35 years (6). In 2013 St. Gallen consensus meeting the limit for chemotherapy (CT) was accepted as <35 years of age (7). Some authors classify post-menopausal breast cancer patients aged ≥ 55 as a separate group (8). The incidence of breast cancer under the age of 35 is 1-4% in developed countries, while in our country the national breast cancer registry reported this rate as 7% (1, 9-11). The young aged breast cancer patients who we encounter frequently in daily clinical practice, have specific issues related to fertility, pregnancy, sexuality and aesthetics. Therefore, treatment of these patients should offer an optimal balance between oncologic principles and quality of life. In this study, we aimed to evaluate the clinical, pathologic and management differences between breast cancer patients under 35 years of age and postmenopausal patients above 55 years of age.

Materials and Methods

Patients below 35 years of age and above 55 years of age, who were operated on for breast cancer between November 2003 and March 2013 in our hospital's general surgery clinic Group A were retrospectively analyzed. Local ethics committee approval was obtained. Stage 4, male and recurrent breast cancer patients were excluded from the study. Women who had surgery for breast cancer and who were within the specified age range were enrolled into the study. Patients were separated into two groups according their age at diagnosis: Group 1

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(<35 years) and Group 2 (>55 years). When a patient under 35 years of age was enrolled into the study, another patient 55 years and older who had surgery at the nearest date to the index patient was included in the study.

Data regarding tumor biology, patient characteristics, treatment and outcome were obtained from the Medulla (Probel Inc.) database and patient files. The diagnosis was verified by fine needle biopsy prior to surgery in all cases. The treatment was decided after multidisciplinary assessment. Patients were informed about the possible aesthetic problems after surgery. Breast conserving surgery (BCS) or mastectomy was performed along with oncoplastic and reconstructive techniques in case of possible aesthetic problems due to surgery. Surgical margins were evaluated by frozen-section during surgery, and specimen mammography was obtained in cases with microcalcifications. Sentinel lymph node biopsy (SLNB) and/or level 1.2 axillary dissection (AD) was performed in patients with clinically (physical examination and mammography + breast ultrasonography (US)) negative axilla.

Patient characteristics included age, history of breast cancer in the 1st and 2nd degree relatives (family history). The American Joint Committee on Cancer Staging (AJCC-2010) TNM classification was used for staging. Stage, lymph node status, histologic type, grade, lymphovascular invasion (vascular invasion), Ki-67 levels, hormone receptor status, and molecular subtypes were recorded as part of tumor biology. The types of treatment were identified as surgical treatments, chemotherapy (CT), hormonal therapy (HT), and radiotherapy (RT). The outcome data were rate of re-excision, local and regional recurrence, and distant metastasis.

The follow-up protocol consisted of physical examination by a general surgeon and radiological evaluations (mammography and/or breast ultrasound (US)) every 4 months for the first 3 years, every 6 months for the next 2 years, and annual visits from the 5th year on. All patient data were recorded.

Statistical analysis

SPSS 15.0 (SPSS Inc, Chicago, Illinois, USA) was used for statistical analysis of data. Chi-square test was used for the comparison of categorical data between groups. Data were analyzed by two-sided tests, and $p < 0.05$ was considered as significant.

Results

Ninety-four breast cancer patients with 45 patients in Group 1 and 49 patients in Group 2 were included in the study. The median follow-up period was 51 (19-121) months in Group 1 and 50 (19-120) months in Group 2. The median age was 33 (24-35) years in Group 1, and 61 (55-74) years in Group 2. Table 1 summarizes patient and tumor biology characteristics, and table 2 depicts treatment methods and outcome data. During the study period, 728 women were operated on for breast cancer, and 59 (8.2%) of them were under 35 years of age. 45 patients who could be contacted and had complete data were included in the study. Intraoperative frozen section examination of surgical margins was performed in 83 patients (42 patients in Group 1 and 41 patients in Group 2), and specimen mammography was obtained in 47 cases.

Five patients who received neoadjuvant chemotherapy (NAC) in Group 1 (5/11), and three such patients in Group 2 (3/5) underwent BCS. All patients with NAC in Group 1 and 2 underwent level 1.2 axillary dissection. Axillary dissection was performed in 34 patients

in Group 1 and in 33 patients in Group 2. Sentinel lymph node biopsy (BLDB) was done in 15 patients in Group 1 and in 19 patients in Group 2.

There was a difference between surgical techniques within the two groups. BSC rate was higher in postmenopausal women while mastectomy rate was higher in younger patients. In the younger aged patient group oncoplastic breast surgery (OBS) techniques were used in 4 patients, including glandular flap in 2 cases, oncoplastic breast reduction in one case, and round block skin incision in 1 patient. In addition, 19 cases underwent delayed reconstruction in this group with 9 silicone implants, 3 transverse rectus abdominis myocutaneous flap (TRAM), 2 latissimus dorsi (LD) flap + implant, and only LD flap in 1 case. Six patients in the postmenopausal group underwent simultaneous OMC techniques; 3 oncoplastic breast reduction, 2 glandular flap and one round block technique. Two patients with mastectomy had reconstruction; one simultaneous TRAM, and one delayed LD + implant.

Pathological evaluation showed 6 patients with grade 1, 16 cases with grade 2, 23 cases with grade 3 tumors in Group 1, and 11 patients with grade 1, 20 cases with grade 2, 18 cases with grade 3 tumors in Group 2. There were 10 triple-negative (ER, PR, HER2) patients in Group

Table 1. Patient and tumor biology characteristics

	Group 1 ≤35 age (%)	Group 2 ≥55 age (%)	p value
Total	45	49	
Age (years)	33	61	
Family history	5 (11.1)	2 (4.1)	0.154
TNM Stage 0	1 (2.1)	2 (4.1)	
Stage 1	10 (22.2)	14 (28.6)	
Stage 2	25 (56.2)	27 (55.1)	
Stage 3	9 (20.1)	6 (12.2)	
Total early stage	36 (80.0)	43 (87.8)	0.305
Lymph node involvement	31 (68.9)	26 (53.1)	0.116
Histologic type			
Ductal	37 (82.2)	36 (73.5)	
Lobular	3 (6.7)	7 (13.3)	
Other	5 (11.1)	6 (12.2)	
Lymphovascular involvement	31 (68.1)	26 (53.1)	0.116
Grade 1+2	22 (48.9)	31 (63.3)	0.035
3	23 (51.1)	18 (36.7)	0.035
Ki 67 ≤12	18 (40.0)	30 (61.2)	0.020
>12	22 (48.9)	13 (26.5)	0.022
Unknown	5	6	
Molecular subtypes			
Luminal A	13 (28.9)	26 (53.1)	0.01
Luminal B	17 (37.8)	17 (34.7)	0.59
HER2 (+)	5 (11.1)	3 (6.1)	0.38
Triple negative	10 (22.2)	3 (6.1)	0.02

Table 2. Treatment type and outcome data

	Group 1 ≤35 age (%)	Group 2 ≥55 age (%)	p value
Surgical treatment			
BCS	23 (51.1)	34 (69.4)	0.02
Mastectomy	22 (48.9)	13 (26.5)	0.02
OBS+Reconstruction	19 (42.2)	8 (16.3)	0.04
Axillary dissection	34 (75.6)	33 (67.3)	0.28
SLNB	15 (33.3)	19 (38.8)	
Adjuvant treatment			
CT+RT+HT	29 (64.4)	25 (51.0)	
CT	13 (28.9)	6 (12.2)	
RT+HT	2 (4.4)	11 (22.3)	
HT	1 (2.2)	7 (15.6)	
Neoadjuvant CT	11 (24.4)	5 (10.2)	
Total CT	40 (88.8)	34 (69.4)	0.03
Total RT	31 (68.1)	36 (73.5)	0.30
Co-morbidity	2 (4.4)	19 (38.8)	0.05
Postoperative Complication	7 (15.6)	3 (6.1)	0.14
Re-excision	5 (11.1)	4 (8.1)	0.42
Local recurrence	5 (11.1)	3 (6.1)	0.34
Distant metastases	9 (20.0)	5 (10.2)	0.18
BCS: breast conserving surgery; OBS: oncoplastic breast surgery; CT: chemotherapy; RT: radiotherapy; HT: hormonotherapy; SLNB: sentinel lymph node biopsy			

1 and 6 cases in Group 2. There were 22 patients with Ki 67 > 12 in Group 1 and 13 patients in Group 2.

Re-excision was performed in five cases in Group 1 and four patients in Group 2 due to positive surgical margins on frozen section evaluation. Simultaneous LD flap was used in a young patient with re-excision to close the large parenchyma defect. In Group 1, axillary recurrence was identified in one patient in 21 months, and total excision was performed. Within the same group, three patients with BCS developed local recurrence at 22nd, 48th, and 69th months, as well as an incisional recurrence in one patient with mastectomy. These lesions were all re-excised. One postmenopausal patient with NAC had axillary recurrence at 19th month, and an excision was performed. Local recurrences in one patient with BCS on 59 months (postoperative pathology revealed in situ cancer), and one patient with mastectomy who did not comply with RT protocol (she further completed RT after excision) were locally excised with frozen section evaluation. Appropriate systemic chemotherapy was implemented after local recurrence. There were nine distant metastases in Group 1; three bone and liver, two bone and lung, one liver, one lung, and one bilateral ovary metastases. The five distant metastases in Group 2 were two patients with bone and liver, one bone and lung, one liver, and one right adrenal lesion. These cases received additional systemic chemotherapy.

In the postmenopausal group 19 patients had co-morbidities; 9 diabetes mellitus (DM), 8 hypertension, 5 cardiac disease, and 2 pulmo-

nary diseases. There were 7 postoperative complications within young patients; 2 seroma formation, 2 delayed wound healing (7-10 days), 1 bleeding, 1 partial flap necrosis (treated with debridement), and breast asymmetry in one case. Adjuvant therapy was delayed for 2-3 weeks in the patient requiring debridement. There were 3 patients with postoperative complications in Group 2 including 1 seroma, wound separation in an obese patient with DM, and 1 hematoma.

The groups were similar in terms of oncologic outcomes such as re-excision rate ($p=0.42$), local recurrence rate ($p=0.34$), and distant metastasis rate ($p=0.182$).

Discussion and Conclusions

The age groups are oncologically similar in terms of re-excision, local recurrence and distant metastases rates. Surgeries that are more extensive are preferred in the younger patients, with a higher proportion of oncoplastic and reconstructive procedures. This group of patients had worse tumor biology characteristics. More patients received chemotherapy in the younger group as compared to postmenopausal patients. Young and postmenopausal women with breast cancer had similar stages on initial diagnosis.

Local oncologic control and distant metastasis rates were found to be similar in young and postmenopausal patients with breast cancer. Young age is reported to be an independent risk factor for local recurrence for breast cancer patients (12). The European Organization for Research and Treatment of Cancer (EORTC) reported that patients under 35 years of age are at risk for local recurrence (13). The local recurrence rates were reported to be higher in patients younger than 35 years of age as compared to those between 35-40 years (14, 15). In addition, it has been stated that local recurrence increased parallel with each year of decrease in age (16). Acceptable local control may be achieved with appropriate treatment in this age group. Problematic surgical margin rate was indicated as 19% in younger breast cancer patients (17). Achieving a safe margin is extremely important for local control in breast cancer. In our series, the rates of re-excision and local recurrence were higher in the younger group as compared to postmenopausal group; however, this difference was not statistically significant. Performing more mastectomies, and ensuring wide excision in breast conserving surgery by using oncoplastic techniques have led to similar local control rates in young patients. Nixon et al. (4) reported being less than 35 years of age as a risk factor for local recurrence and distant metastases. Breast tumors with aggressive biological properties are known to result in distant metastases more frequently. In our series, there was no statistically significant difference between young and postmenopausal patients in terms of distant metastases. This finding is thought to be related to the high percentage of young patients receiving chemotherapy, the limitations on patient volume and short follow-up period in this study.

It was determined that there was a difference between the groups in terms of surgical treatment. Our study showed that more aggressive treatment methods and aesthetic and reconstructive oncoplastic surgical techniques have been used more commonly in young breast cancer patients. Breast cancer causes more physical and psychological disturbance in young women. Age is not a contraindication for breast conserving surgery in the treatment of breast cancer. BCS has been shown to provide local control similar to mastectomy in young patients (18). Nevertheless, it has been published that the most frequently performed surgical procedure for breast cancer in patients under 35 years of age

was mastectomy (19). The mastectomy rate in our study was found to be higher in young patients as compared to the postmenopausal group. Younger patients could have undergone extensive surgery to provide better local control, due to increased anxiety at younger ages and socio-economic reasons. It was also thought that the younger patients probably consulted a physician for the first time and had their first surgery, thus they preferred a more extensive surgical operation with fear of death. In 2013, St. Gallen consensus meeting stated that extensive surgery did not provide better local control (7). It is well known that breast surgeons have favored extensive surgery until this consensus statement. Emotional and psychological problems in young women have been stated to be higher than the older group after breast cancer surgery (20). It was identified that efforts to provide physical integrity and aesthetics was more important after both BCS and mastectomy in young patients as compared to the post-menopausal group. With the advances in adjuvant treatment, life-expectancy in patients with breast cancer has prolonged. Oncoplastic and reconstructive techniques, which improve the quality of life, are used more in younger patients. This high rate is thought to result from higher demand by the young patients, and higher rates of reconstruction suggestion by surgeons. Co-morbidities are more in postmenopausal women. Although there were more postoperative complications in the younger patients due to additional oncoplastic and reconstructive techniques, this difference did not reach statistical significance.

According to our study results, young breast cancer patients have worse biologic tumor features than postmenopausal group. Grade, Ki-67, and molecular subtypes are important prognostic factors for breast cancer (21). Young patients with breast cancer have been reported to have a higher proliferation rate, more grade 3 tumors, and worse molecular subtypes (3, 22, 23). Breast cancer has different biological properties that vary from person to person. In our study, significantly higher rates of grade 3 tumors and Ki-67 rates were identified in the younger patients. Göksu et al. (19) reported that luminal B was the most common molecular subtype in breast cancer patients 35 years of age and younger. In addition, triple negative breast cancer rates have been reported to be high in this group of patients. Collins et al. (24) stated luminal B is the most common type of breast cancer in younger patients. In our series, luminal B and triple-negative molecular subtypes were the most frequent types. These findings indicate that breast cancer has aggressive biological and clinical tumor characteristics in the young. For this purpose, it is thought that all treatment planning and evaluation should be personalized.

According to our study, disease stage at the time of diagnosis does not depend on the patient's age. It has been reported that younger patients are diagnosed at more advanced stages due to lack of screening mammography, dense breast parenchymal structure, and low awareness of patients (19, 23, 25). Reviews indicating that younger patients present with advanced staged breast cancer have also been published (26). Age is thought to be an independent prognostic factor in breast cancer (4). However, this issue is controversial due to limitation of studies on age and delay in diagnosis of breast cancer. It has been reported that patients under 40 years of age were not diagnosed at more advanced stages of breast cancer, and age was not an independent risk factor (27). Screening mammography is not performed under forty years of age, and young patients consult a doctor with a mass in their breast. Regardless of age, patients who present with a breast lump tend to have a more advanced disease stage on diagnosis. Screening mammography for breast cancer program began in 2010 in Turkey. According to the breast cancer registry, 90% of patients in all age groups presented with

a palpable mass (1). In our region, majority of patients are diagnosed due to a breast mass, therefore, stage at diagnosis are similar. Age is not considered as a factor influencing stage, when breast cancer is diagnosed with evaluation of presence of symptoms.

The rate of breast cancer in Western countries under the age of 40 years has been reported as 4-7% (1,9). Andreas et al. (28) noted the rate of breast cancer in patients aged ≤ 35 as 2.4%. According to the Turkish national cancer registry data, rate of breast cancer under the age of 40 is 17.6% (18). In another study from our country, the rate of breast cancer in patients aged 35 or below was reported as 16.9% (29). This rate was determined as 8.2% in our series. Unlike Western countries, our country has a high incidence of breast cancer in young women. We believe that the high proportion of younger population in our country may explain this finding.

There are some limitations of this study. Some differences could have been undetected due to the limited number of cases.

Breast cancer in young patients and postmenopausal women are similar in terms of oncologic results. Breast cancer in young age has worse biological properties than those in postmenopausal women. Oncoplastic and reconstructive approaches are more common in the young. Due to symptomatic admission, tumor stage at the time of diagnosis does not differ in different ages. The results of large, prospective, multicenter studies are awaited to clarify tumor biology, treatment, and outcome in breast cancer in young patients.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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