

Treatment of elderly breast cancer: Mansoura Experience

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Abstract

Objectives: There is an observed age related difference in treatment of breast cancer. Elderly women are often not treated in accordance with the current guidelines as far as adjuvant therapy is concerned, and this adversely affects their overall survival.

Patients and methods: We studied 485 women aged 60 years or older diagnosed between 2004 and 2008 treated in Clinical Oncology & Nuclear medicine department, Mansoura University hospital. Data was collected from registry including age, performance status, tumor characters, and treatment was received. Patients were classified into two groups, first aged 60-70 years and second older than 70 years. Data was analysed statistically to detect factors affecting treatment decision.

Results: Median age was 65years old. Mastectomy and conservative breast surgery performed in younger age group, not significant ($P=0.061$). Anthracyclin chemotherapy was less given to the patients >70 years and was highly significant ($P<0.0001$). Chemotherapy was omitted in 58 patients, main cause of omission was the age in age group >70 years ($P<0.0001$). Hormonal treatment was administrated more in older age group ($P=0.026$). Adjuvant treatment offered to younger age group after mastectomy and was significant statistically ($P=0.049$). Radiotherapy after CBS used more in younger age with no significant relation ($P=0.088$). Chemotherapy was administrated to the patients with positive lymph nodes more frequently in younger age group showing high significant relation ($P<0.0001$). Overall (OAS) was shorter in older than younger (24months vs. 37months respectively, $P<0.0001$).

Conclusion: We confirmed that elderly women were substantially undertreated. Geriatric evaluation is recommended when deciding whether and what treatment should be undertaken in older females.

Introduction

Breast cancer is the most common cancer in women in developed western countries (1), and is becoming more significant in many developing countries (2). In Egypt, breast cancer is the most common cancer among women, representing 18.9% of total cancer cases (3) with an age-adjusted rate of 49.6 per 100 000 (4).

Studies had shown that around 50% of patients with breast cancer are those older than 65 years of age and approximately 35% are older than 70 years as increasing age remains the greatest risk factor in developing the disease (5).

Advanced age at diagnosis of breast cancer is considered to be associated with more favourable tumor biology, increased hormonal sensitivity, attenuated human epidermal growth factor receptor 2 (HER2) overexpression, and lower grades and proliferative indexes (6). However, elderly patients are more likely to present with larger and more advanced tumors (7).

Treatment of elderly breast cancer includes consideration of non-breast cancer specific survival, treatment decisions are influenced by patient comorbidities, performance status, less social support, difficulty of transportation, patient or family preference, lower life expectancy and age bias (8, 9).

Therefore, treatment of breast cancer in elderly women often differs from treatment in younger women. So, there is controversy about what is appropriate cancer treatment for older women (10). This controversy is reflected in persistence of age dependent variation in care overtime with older women, being less likely to receive definitive treatment for breast cancer (11,12,13).

Because of lack of adequate scientific evidence, as women aged 65 years or older are less commonly included in randomized clinical trials making the therapeutic impact of new approaches difficult to be assessed in this population (14). Therefore, worldwide only certain proportion of older women with breast cancer are treated in accordance with guide lines (10,15,16).

Life expectancy of older female patients is often underestimated, data from National Vital Statistics report from Disease Control and Prevention Centre released in 2003 shown that female aged 70 years have an average life expectancy of 15 years if they are relatively healthy and 7 years for those over 85 years old (17). However, around 77% of deaths attributed to breast cancer are in women older than 55 years of age (18).

It is truly interesting to know that there is an observed age-related difference in treatment of breast cancer. So, our study was undertaken to determine variations in breast cancer tumor characteristics, initial treatment received and survival among older Women in our hospital.

Patients and Methods

Patient populations

This study is a retrospective study of women aged 60 years and older diagnosed with breast cancer and treated at Clinical oncology & Nuclear Medicine Department, Mansoura University between January 2003 and December 2008. Data was collected from registry of our department. The criteria for inclusion were women proved histologically with invasive ductal and lobular carcinoma, with stage I-III. All patients divided into two groups according to age, 60-70 years and older than 70 years age groups.

Clinic-pathological

Data was collected from registry included patients age, performance status according to Karnofsky performance status scale (19), tumor characteristics which included tumor size, regional lymph node involvement, tumor grade (was categorized as well differentiated, moderately differentiated, poorly differentiated, or not determined) histology (invasive duct carcinoma, invasive lobular, or carcinoma in situ), estrogen and progesterone receptors status (categorized as positive, negative, or not stated), HER2-neu status (positive, negative, or not stated).

Treatments

As regards treatment we categorized definitive surgical treatment as mastectomy (modified radical mastectomy (MRM), skin sparing mastectomy, or radical mastectomy) and lumpectomy (breast conserving surgery (BCS)) with axillary lymph node dissection. We determined adjuvant radiation therapy if received after conservative breast surgery (CBS) or as post operative after mastectomy. Adjuvant chemotherapy was defined if given or not, type of chemotherapy in cases of positive lymph nodes. Also reception of adjuvant hormonal was detected.

Overall survival measured from patient's date of diagnosis until death, lost. Disease free survival measured from date of completion of treatment until recurrence, death, or lost.

Statistical analysis

Data was analysed using SPSS (Statistical Package for Social Sciences) version 15. Qualitative data was presented as number and percent. Chi-square test was used for comparison between groups. Non-parametric data was presented as min – max and median. Mann-Whitney test was used for comparison between groups. Kaplan- Meier survival curve was used to estimate survival. P value is considered significant if it is < 0.05.

Results

This retrospective study included 485 patients. Patients' characteristics are listed in table (1). All patients were female. Age ranged from 60 to 85 years with median age 65 years, 346 (71.3%) patients were 60-70 and 139 (28.7%) patients were more than 70 years. Most patients (61.2%) presented with performance status 60-80.

The histological status defined as infiltrating duct carcinoma (IDC) in 88.7%, followed by infiltrating lobular carcinoma (ILC) in 10.7% and only 0.6% diagnosed with carcinoma in situ (CIS). Grade II presented in 294 cases (60.6%), followed by grade III in 90 patients (18.6%). Tumor size ranged from 1 to 7 cm

with median 4 cm. Thirty one patients was T4 and Twenty eight were not assessed with tumor size. Lymph node metastasis presented in 309 (63.7%) and negative in 134 (27.6%), while not assessed in 42 (8.7%). As regards hormone positivity estrogen receptors were positive in 337 patients (69.5%) and only 96 patients (19.8%) were negatives. Epidermal growth factor receptors (EGFR) were positive in only (3.7%) of patients. Status of hormonal receptors and EGFR was not assessed in (10.7%) and (91.1%) respectively. The majority of patients operated by mastectomy (83.3%), and only (9.9%) patients operated with CBS.

Radiotherapy administered to 327 (67.4%) patients, and 158 (32.6%) not received radiotherapy. Adjuvant chemotherapy given to 364 patients, patients received anthracycline containing regimens were 236 (48.7%), Taxine containing regimen were 12 (2.5%) patients, and CMF were 116 (23.9%).

Adjuvant hormonal treatment given to (68.9%), tamofen was the most common hormonal therapy used in (87.4%) of patients who received hormonal therapy. Disease free survival (DFS) ranged from 1 to 84 months with median 26 months. Overall survival (OAS) ranged from 2 to 96 months and the median was 35 months.

Univariate analysis used to compare age with different risk factors. Grade III was in 22% of patients older than 70 years and in 20.6% in those 60-70, but not statistically significant ($P=0.910$). In patients with lymph node examined, it was positive in 240 (69.6%) in patients aged 60-70 years, while was positive in 69 (50.4%) in patients aged > 70 years, and was unknown in 13.1% in the group > 70, this relation was statistically significant (<0.0001).

There was significant relation between hormone positivity and age (<0.0001), as it was positive in 71.9% in older than 70 years and in 68.5% in 60-70 years. Assessment of HERII showed no significant relation with age ($p=0.993$). There was no significant difference in the tumor size between two age groups (median 4 and 5 in group 60-70 & >70 years respectively) ($P=0.179$).

Mastectomy performed in 84.1% and 81.3% in age groups 60-70 and > 70 years respectively, on the other hand CBS was performed in 10.7% and 7.9% in less and more than 70 years respectively and not significant ($p=0.061$). Adjuvant chemotherapy was given in 80.3% of patients 60-70 years and in 61.9% of those more than 70 years, but did not show significant relation ($P=0.062$). The type of chemotherapy showed significant relation with age group (<0.0001), the patients with age 60-70 received anthracycline were 61% while only 18% of the patients >70 received same chemotherapy, and on the other hand CMF protocol given in 43.2% and 16.2% in patients > 70 & 60-70 years respectively.

Chemotherapy was omitted in 58 patients because of age (22 patients), comorbidity (19 patients), patients refusal (13 patients), and in 4 patients because of other causes. The cause of omission showed statistically significant relation with age (<0.0001), as 37.9% was because of age all was in patients aged >70 years, and 32.8% because of morbidity 63.2% of them was in patients aged 60-70 years. Also radiotherapy showed high significant relation (<0.0001), the patients with age > 70 years 51.1% received radiotherapy, while 74% of patients aged 60-70 years received radiotherapy. We found also that 76.3% and 65.9% of age group >70 and 60-70 years received hormonal respectively, this relation was statistically significant (0.026). Overall survival median was longer in younger age group (37 vs. 24) (<0.0001). Overall five-year survival was about 18% for patients aged 60-70 years, while was < 5% in patients >70 years age group. (Fig 1).

The type of therapy presented in table (3). For patients who underwent mastectomy, there was a trend to offer adjuvant treatment to the younger group (60-70 versus >70) (97.2% vs. 92.9%) respectively, and was significant (P=0.049). Chemotherapy and radiation therapy were given more to the younger group 82.5%, and 72.9% than older group (62.8%, and 47.8%) respectively, and both associated with high statistically significant relation (<0.0001).

For the patients who underwent lumpectomy, patients who were (86.5%) younger were given more radiation therapy than older (63.6%) patients, but not significant (0.088).

The results showed that 84.5% of patients found to have positive lymph nodes received chemotherapy. About 88.8% of patients in the 60-70 years age group received chemotherapy as opposed to 69.6% in those >70years group, and this difference was highly significant (<0.0001). In patients with hormone receptor positive status, 98% received hormone therapy in the >70 years age group and about 92% in the 60-70 age groups, and this difference was statistically significant (P=0.037).

In the patients who received chemotherapy, median OAS was 43 months in the patients 60-70years age group, while was 29 months in the patients >70 years age group, and this was highly significant (<0.0001).

Table 1: Patients Characteristics

Characters	Number (NO)	Perecent (%)
-Performance status(PS):		
*80-100	188	38.8
*60-80	297	61.2
-Histology:		
*IDC	430	88.7
*ILC	52	10.7
*CIS	3	0.6
-Grade:		
*grade I	45	9.3
*grade II	295	60.8
*grade III	90	18.6
-Lymph node status:		
*positive	309	63.7
*negative	134	27.6
*not assessed	42	8.7
-Hormonal receptors:		
*positive	337	69.5
*negative	96	19.8
*unknown	52	10.7
-HERII status:		
*positive	18	3.7
*negative	25	5.2
*unknown	442	91.1
-Surgical procedure:		
*mastectomy	404	83.3
*lumpectomy	48	9.9
*no surgery	33	6.8
-Chemotherapy:		
*yes	364	75.1
*No	121	24.9
-Type of chemotherapy:		
*Anthracycline	236	48.7
*Taxane	12	2.5
*CMF	116	23.9

Characters	Number (NO)	Perecent (%)
-Radiation therapy:		
*yes	327	67.4
*No	158	32.6
-Hormonal therapy:		
*yes	334	68.9
*No	151	31.1

Table 2: Patients and tumor characters in relation to age group

Factors	60-70 years(346)	>70 years(139)	P value
Histology:			
* IDC	312(90.2%)	118(84.9%)	0.248
*ILC	32(9.2%)	20(14.4%)	
*CIS	2(0.6%)	1(0.7%)	
Grade:			
*grade1	32(9.3%)	13(9.4%)	0.910
*grade2	215(62.1%)	79(56.8%)	
*grade3	64(18.5%)	26(18.7%)	
* unknown	35(10.1)	21(15.1%)	
Estrogen receptor:			
*Positive	237(68.5%)	100(71.9%)	<0.0001
*Negative	81(23.4%)	15(10.8%)	
* Unknown	28(8.1%)	24(17.3%)	
HER2 amplification:			
*Positive	13(3.8%)	5(3.6%)	0.993
*Negative	18(5.2%)	7(5%)	
* Unknown	315(91%)	127(91.4%)	
Median tumor size: (range, median)	1-7(4)	2-7(5)	0.179
Axillary lymph node metasta-sis			
*Positive	240(69.6%)	69(50.4%)	<0.0001
* Negative	84(24.3%)	50(36.5%)	
* Unknown	21(6.1%)	18(13.1%)	
Surgery:			
*Mastectomy	291(84.1%)	113(81.3%)	0.061
*Lumpectomy	37(10.7%)	11(7.9%)	
*No surgery	18(5.2%)	15(10.8%)	
Chemotherapy:			
*Positive	278(80.3%)	86(61.9%)	0.062
*Negative	68(19.7%)	53(38.1%)	
Type of chemotherapy:			
* Anthracycline	211(61%)	25(18%)	<0.0001
*Taxane	10(2.9%)	2(1.4%)	
*Taxane	56(16.2%)	60(43.2%)	
*CMF			
Radiotherapy:			
*Negative	90(26%)	68(48.9%)	<0.0001
*Positive	256(74%)	71(51.1%)	

Factors	60-70 years(346)	>70 years(139)	P value
Hormonal: *Negative *Positive	118(34.1%) 228(65.9%)	33(23.7%) 106(76.3%)	0.026
OAS (median): In months	37	24	<0.0001

Table 3: Indication for adjuvant therapy:

Factors	60-70 years	>70 years	P value
Positive lymph nodes (NO): * chemotherapy;	240	69	<0.0001
Yes			
No	213(88.8%) 27(11.3%)	48(69.6%) 21(30.4%)	
Positive hormonal receptors (NO): *received hormonal therapy;	237	100	0.037
Yes	218(92%)	98(98%)	
No	19(8%)	2(2%)	0.049
Mastectomy(No): *any adjuvant	291	113	<0.0001
Yes	281(96.6%)	105(92.9%)	
No	10(3.4%)	8(7.1%)	
*chemotherapy	291	113	<0.0001
Yes	240(82.5%)	71(62.8%)	
No	51(17.5%)	42(37.2%)	
* radiotherapy	291	113	<0.0001
Yes	212(72.9%)	54(47.8%)	
No	79(27.1%)	59(52.2%)	
*hormonal	291	113	0.035
Yes	197(67.7%)	88(77.9%)	
No	94(32.3%)	25(22.1%)	
Lumpectomy (No): *received radiotherapy;	37	11	0.088
Yes	32(86.5%)	7(63.6%)	
No	5(13.5%)	4(36.4%)	

Table 4: Cause of omission of chemotherapy

Cause	60-70 years	>70 years	P value
Age	0(0%)	22(73.3%)	<0.0001
Comorbidity	12(42.9%)	7(23.3%)	
Patient refuse	12(42.9%)	1(3.3%)	
Others	4(14.2%)	0(0%)	
Total	28	30	58

Survival Functions

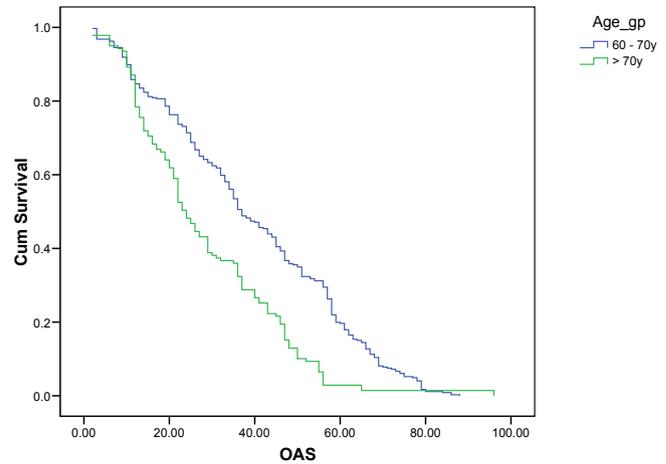


Fig 1: Overall survival as a function of age.

Discussion

There is no accepted definition of older female patients. We adopted 60 years as cut off for inclusion in the current study because 60 years is age of menopause according to NCCN guide Lines 2007 and also it is the age of retirement in Egypt. The age 70 years was selected because of increasing fragility of patients and majority of studies excluded women aged 70 years or older in randomized clinical trials.

Regardless of age, infiltrating ductal carcinoma is the most common histologic subtype as demonstrated in our study. Older patients have been noted to have a greater frequency of tumors with more indolent histology and favorable biologic tumor profile as older patients are likely to express estrogen and progesterone receptors which improve prognosis and also they are candidates for adjuvant hormonal treatment (20, 21).

In current study majority of patients with positive hormonal receptors as suggested by prior studies. Hormonal therapy which carries less risks and toxicity compared to chemotherapy is more likely to be offered and given to elderly patients with breast cancer

Surgery is the mainstay treatment for patients with early stage of breast cancer. It has been found that breast conservation Surgery followed irradiation has equal efficacy to more extensive surgical procedures such as mastectomy. However, current data suggested that elderly women less likely to perform breast conservation surgery than their younger counterparts (22, 23). Similarly to the result of our study, in contrary a recent study had shown that mastectomy and lumpectomy were performed at almost the same frequency (24).

Radiation therapy is well tolerated in the elderly. Postoperative radiotherapy decreases ipsilateral breast cancer recurrence after breast conservation surgery and chest wall recurrence after mastectomy. Current study showed that radiation therapy was given less than in patients 70 years old or older. 52.2% of them did not receive adjuvant radiotherapy. Numerous data showed that adjuvant postoperative radiotherapy decreases local recurrence but had no effect on

survival (25,26,27,28). So, it may be reasonable that to offer radiation therapy to patients who may benefit such as those with life expectancy more than 5 years, with large tumors, positive lymph nodes or negative hormone receptors.

Our study had shown that chemotherapy was generally given in both age groups and there was no statistical difference. There was note of a trend to give less toxic chemotherapy as the patient gets older. Non anthracycline containing regimens were thought to be preferable because of the fear of cardiac toxicity in older patients, but regimens such as CMF showed no significant advantage over tamoxifen in different trials involving older Women (29,30,31).

Doxorubicin based chemotherapy seems to be more effective as was reported in the NSABPB-16 trial, short course (four cycles) of doxorubicin and cyclophosphamide combined with tamoxifen being superior to tamoxifen alone (32).

There is an urgent need of less toxic and more efficacious chemotherapy regimens. Although not specifically aimed at elderly patients, a recent study showed that docetaxel and cyclophosphamide were superior to doxorubicin and cyclophosphamide in terms of overall and disease free survival. In a subgroup analysis, the combination of docetaxel and cyclophosphamide was active and tolerable even in elderly patients and could be a reasonable alternative for elderly patients with cardiac risk for anthracycline toxicity (33).

Another alternative regimen was mainly a fluorouracil agent. A recently reported randomized trial with oral agent capecitabine in breast cancer patients 65 years old or older in an adjuvant setting showed significantly reduced relapse free survival and overall survival in the capecitabine group (34).

Our study demonstrated that chemotherapy was significantly more often omitted from high elderly patients (70 years or older) mainly because of age as shown in table (4). So, we still consider that there could be somewhat of under treatment similarly, to previous studies suggested that the age was the strongest predictor of lesser treatment (35, 36).

Significant survival differences were noted between the 70 and older age group and 60-70 age group (24 m versus 37 m) $p=0.0001$. However besides age, survival is affected by other parameters such as tumor and patient's characteristic and perhaps functional status and comorbidities may play a role. It is true that breast cancer increases with age. At the same time as the age increases, the risk of death from causes besides breast cancer also increases (37). Therefore, geriatric evaluation is recommended when deciding whether and what treatment should be undertaken in older female as geriatric evaluation includes not only the relevant comorbidities but also the patient cognitive status and social environment (38, 39).

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