

Breast cancer treatment in high-risk elderly patients: A challenging situation and difficult decisions

Razia Bano,¹ Amina Iqbal Khan,² Waleed Zafar,³ Akif Abbas Zaidi,⁴ Adil Asif Zaidi,⁵ Mohammad Zulqurnain Chaudhry,⁶ Huma Majeed Khan⁷

Abstract

Objective: To assess whether high-risk elderly patients with aggressive tumour biology can be offered standard treatment despite having multiple comorbid conditions.

Methods: This retrospective study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, and comprised data of breast cancer patients aged 65 years or above treated between 2006 and 2012. Data was collected regarding patients' demographics, baseline clinical characteristics, comorbidities, treatment and outcomes. Stata 12 was used for data analysis.

Results: Of the 407 patients in the study, 399(98%) were women and 8(2%) were men. The overall mean age at diagnosis was 70±4.9 years (range: 65-90 years). Overall, 59(14.5%) participants had family history of breast cancer. Bilateral disease was seen in 17(4.2%). Invasive ductal carcinoma was seen in 299(73.5%). Besides, 101(24.8%) patients had no comorbid conditions, while 138(34%) had one, 102(25%) had two and 66(16%) had three or more comorbid conditions.

There was no statistically significant difference between those receiving standard treatment including surgery or other modalities.

Conclusion: Elderly patients of breast cancer may be offered treatment according to the tumour biology and their overall functional status.

Keywords: Elderly, Comorbid, Standard treatment, Chemotherapy. (JPMA 66: 1267; 2016)

Introduction

The incidence of breast cancer increases with age: about 35-40% of women with breast cancer are 65 years or older.¹ The incidence in this age group is put at 50% by other researchers. Elderly breast cancer patients exhibit higher risk of morbidity and mortality compared to younger patients since they may have multiple comorbid conditions. Elderly patients are also often undertreated due to the fear of worsening health during chemotherapy or surgery.² However, age alone should not prevent elderly breast cancer patients from receiving standard aggressive treatment.³ They should receive the same type of surgery as younger patients, which could be either breast-conserving surgery (BCS) with adjuvant radiation therapy or mastectomy based on established treatment criteria. Irrespective of age, surgery offers longer disease-free survival (DFS).⁴ Elderly patients typically have a favourable tumour biology, lower grade, Oestrogen Receptor (ER) and Progesterone Receptor (PR) positive status. Hormonal therapy, therefore, remains the mainstay

of treatment in this age group. Patients with receptor-negative and aggressive tumours or those with lymph node involvement need chemotherapy.⁵

This study was planned to assess whether high-risk elderly patients with aggressive tumour biology can be offered standard treatment despite having multiple comorbid conditions.

Patients and Methods

This retrospective study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH&RC), Lahore, Pakistan, and comprised data of breast cancer patients aged 65 years or above treated between 2006 and 2012. SKMCH&RC is a 187-bed cancer specialist centre where patients' medical records are completely electronic and databases can be searched using key words or International Classification of Diseases version 9 and 10 (ICD-9 and 10) codes.

After approval was obtained from the institutional ethical committee, data was retrieved and that related to patients with incomplete information and those who left before completion of treatment was excluded. Using a data extraction form, information was obtained regarding patients' age, gender, locally-advanced disease (tumour size >5cm, skin involvement, lymph node involvement) at

.....
^{1,2,4-7}Department of Surgical Oncology, ³Department of Cancer Registry & Data Management, Shaukat Khanum Memorial Cancer Hospital & Research Centre, Lahore, Pakistan.

Correspondence: Razia Bano. Email: raazia240@gmail.com

presentation, laterality of tumour, family history of breast cancer amongst first-degree relatives, details of comorbid conditions, histopathology, receptors, metastasis at presentation, stage of tumour, treatment received and the outcome. Patients' medical records were screened for the presence of eight systemic comorbid conditions, including ischaemic heart disease (IHD), coronary artery syndrome (CAD), hypertension (HT), diabetes mellitus (DM), chronic kidney disease (CKD), chronic obstructive airway disease (COAD), asthma and pulmonary tuberculosis (TB). The participants were further divided into four groups: (1) no comorbid condition (2) single comorbid condition (3) two comorbid conditions and (4) three or more comorbid conditions. The patients were divided into five age groups: 65-69 years, 70-74 years, 75-79 years, 80-84 years, and 85 years or more. Depending on the type of treatment received, the patients were further grouped into those receiving standard treatment according to tumour biology and those receiving selective treatment or a portion of the standard therapy omitting either chemotherapy, surgery or radiotherapy, although they were otherwise eligible according to the stage, tumour biology, lymph node status or surgery procedure.

Stata 12 was used for data analysis. Standard descriptive summary statistics were used to characterise the sample. Time to death analyses were done by fitting a Cox Proportional Hazards Model. Patients were assumed to be censored at the time of last follow-up. The hazard ratios of death were adjusted for key variables suggested by the literature.¹⁻⁶ All tests were two-sided, with a type 1 error level of 0.05. Survival was calculated using Kaplan-Meier survival curve.

Results

Of the 685 patients identified, data of 407(59.4%) patients was included. Of them, 399(98%) patients were women and 8(2%) were men. The overall mean age at diagnosis was 70±4.9 years (range: 65-90 years). Moreover, 208(51.1%) patients were aged between 65-69 years, 129(31.7%) 70-74 years, 45(11%) 75-79 years, 19(4.7%) 80-84 years and 6(1.5%) were aged 85 years or more (Table-1). Overall, 59(14.5%) participants had family history of breast cancer. Bilateral disease was seen in 17(4.2%) patients, while the remaining had it in either the left or the right breast. Invasive ductal carcinoma (IDCa) was seen in 299(73.5%) patients. Besides, 101(24.8%) patients had no comorbid conditions, while 138(34%) had one, 102(25%) had two, and 66(16%) had three or more comorbid conditions. Of the total, 288(71%) patients were strongly positive for both ER and PR receptors. As far as stage of the disease was concerned, 211(50%) patients were in stage II,

Table-1: Demographic characteristics and details of surgery procedures of breast cancer patients (n=407).

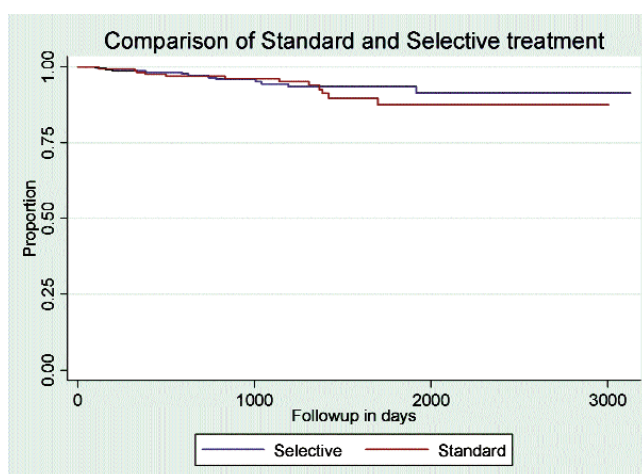
Characteristic	N	%
Age Groups		
65-69	208	51.1
70-74	129	31.7
75-79	45	11.0
80-84	19	4.7
85 or older	6	1.5
Primary diagnosis		
DCIS	12	2.9
IDCa	301	73.7
ILCa	19	4.7
ILCa + IDCa	9	2.2
Papillary	7	1.7
Papillary + DCIS	2	0.5
Mucinous	10	2.5
Malignant phalloides	2	0.5
Metaplastic carcinoma	1	0.2
Neuroendocrine	2	0.5
Comorbid Groups		
No comorbid conditions	101	24.8
One comorbid condition only	138	33.9
Two comorbid conditions	102	25.1
Three or more comorbid conditions	66	16.2
Molecular subtypes		
Luminal A	242	59.5
Luminal B	63	15.5
Triple negative	44	10.8
H2N type	25	6.1
Others	33	8.1
Surgery procedure		
Modified radical mastectomy	171	42.0
Simple Mastectomy	55	13.5
Wide Local Excision + Axillary Lymph Node Dissection	58	14.2
Wide Local Excision + Sentinel Lymph Node		
Biopsy + Frozen Negative	59	14.5
Wide Local Excision only	17	4.2
Axillary Lymph Node Dissection for occult cancer	1	0.2
No surgery	46	11.3

DCIS: Ductal carcinoma in situ
 IDCa: Invasive ductal carcinoma
 ILCa: Invasive lobular carcinoma
 ER: Oestrogen receptors
 PR: Progesterone receptors
 H2N: Her 2 neu receptors.

99(24.4%) in stage III, 52(12.7%) in stage I, 23(5.6%) in stage IV and 4(1%) at unknown stage. Locally advanced disease was present in 118(29%) patients. Furthermore, 55(13.5%) patients received simple mastectomy and 171(42%) received modified radical mastectomy. Chemotherapy was received by 177(43.5%) patients, radiation therapy by 288(70.8%) and adjuvant hormonal therapy by 322(81.6%). Overall, 165(40.5%) patients

Table-2: Treatment stratified by age groups and status of comorbidity.

Age Groups	Surgery				Chemotherapy				Radiotherapy			
	Yes		No		Yes		No		Yes		No	
	N	%	N	%	N	%	N	%	N	%	N	%
65-69 years	187	89.9	21	10.1	128	61.5	80	38.5	165	79.3	43	20.7
70-74 years	108	83.7	21	16.3	36	27.9	93	72.1	76	58.9	53	41.1
75-79 years	31	68.9	14	31.1	11	24.4	34	75.6	32	71.1	13	28.9
80-84 years	14	73.7	5	26.3	2	10.5	17	89.5	11	57.9	8	42.1
85 or older	3	50.0	3	50.0	0	0	6	100.0	4	66.7	2	33.3
Comorbidity												
Single Comorbid	120	87.0	18	13.0	67	48.5	71	51.4	97	70.3	41	29.7
Two Comorbid	85	83.3	17	16.7	39	38.2	63	61.8	74	72.5	28	27.4
Three or more Comorbid	52	78.8	14	21.2	20	30.3	46	69.7	42	63.6	24	36.4

**Figure:** Kaplan-Meier survival comparison between patients who received standard treatment and those who received selective treatment.

received standard treatment, while 242(59.5%) received selective treatment. Until last follow-up, 383(94.1%) patients were alive, whereas 24(5.9%) died; 21(87.5%) of these death were cancer related.

Treatment stratified by age groups and comorbidity was also compared (Table-2). There was no statistically significant difference in mortality between those who received standard treatment (including surgery, chemotherapy, hormonal therapy and radiation therapy according to the tumour biology) and those who received part of the treatment (Figure-1).

Discussion

Breast cancer is the second-biggest cause of cancer-specific deaths among women. Breast cancer in patients above the age of 65 years is increasing. Its incidence is about 30% to 50% in those above the age of 70 years; as the life expectancy in this age group is increasing, so is the

incidence of breast cancer.^{6,7} Since elderly patients have multiple comorbid conditions and decreased functional status, decision-making regarding aggressive treatment depends on the overall functional status of the patient.⁸ Still, there is no consensus on treatment of breast cancer among the elderly, and they are often undertreated due to fear of increased morbidity and mortality in the presence of comorbid conditions.⁹ The assessment of cardiac patients with breast cancer was done by echocardiography. The patients were optimised by internal medicine and were examined by a senior anaesthetist, cardiologist and pulmonologists before the start of treatment.

Moreover, 395(91%) patients in our study underwent surgery successfully, whereas 39(8.98%) either refused surgery or were at very high risk for anaesthesia. Axillary dissection was carried out in 257(59.29%) patients. Breast surgery is considered to have lower morbidity; however, postoperative complications regarding wound infections can occur.¹⁰ Three of our patients needed ventilator support, but recovered. One patient developed myocardial infarction (MI) immediately after operation, delayed wound healing was observed in 15 patients with uncontrolled diabetes or post neoadjuvant chemotherapy, and one patient developed partial mastectomy wound dehiscence. Rocco N. et al. studied postoperative complications in 449 patients and observed that morbidity was higher in patients with comorbid conditions but mortality was not higher. Therefore, surgery can be done in elderly patients with comorbid, whereas only fragile patients can be excluded.¹¹

Since the trends in breast surgery are more towards the breast conservation, and suitable patients can undergo wide local excision or wire localisation surgery after down staging the tumour, intra-operative time is less while

post-operative complications are even lesser compared to mastectomy. In very high-risk patients, BCS can be performed under local anaesthesia or regional blocks. Three patients in our study who were not considered fit for general anaesthesia underwent mastectomy under regional block, 2 mastectomies were done under local anaesthesia as these patients had severe COAD, whereas 19(4.4%) underwent lumpectomy under local anaesthesia, axilla was radiated in these patients along with breast. Elderly patients should receive the same type of surgery as the younger patients, either BCS with adjuvant radiation therapy or mastectomy depending upon the criteria irrespective of age.¹² Swaminathan et al. studied the choice of surgery in older women with breast cancer, and emphasised that surgery offers longer DFS.¹³

Elderly patients usually have favourable tumour biology, lower grade tumours and strongly ER, PR positive. Therefore, hormonal therapy remains the mainstay of systemic treatment in this age group. However, receptor negative, aggressive tumours and lymph node positive patients still need chemotherapy.¹⁴ Elderly patients usually have a number of comorbid issues like HT, IHD, COAD, DM, CKD and, therefore, are not offered the standard treatment. Age itself is not the contraindication to receive the treatment, neither are the comorbid conditions, but it is the functional status of the patient, which should be assessed prior to the start of the treatment. Sonmez et al. suggested that complete functional evaluation is necessary and comorbid conditions itself are risk factors for overall survival.¹⁵ Elderly patients, who are otherwise healthy, can receive standard chemotherapy. Muss et al. compared standard chemotherapy with capecitabine in elderly population and found that capecitabine was inferior.¹⁶ Bernard et al. found that adjuvant chemotherapy does benefit the elderly, however, ER, PR positive patients can be offered hormonal therapy thus omitting chemotherapy.¹⁷ Anthracycline-based chemotherapy has better outcome in terms of local recurrence over CMF (cyclophosphamide, methotrexate, 5-fluorouracil) in elderly population.¹⁸

Radiation therapy plays an important role in irradiation of subclinical disease after surgery to decrease local recurrence, and improves DFS, especially in patients with BCS and high-risk patients undergoing mastectomy. In this study, 70.8% patients received radiation therapy. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) carried out a meta-analysis of 10,801 women in 17 randomised trials of comparison of radiotherapy versus no radiotherapy in BCS.¹⁹ Hughes et al. carried out a study involving inpatients over the age of 70 years and

randomised the cases into tamoxifen alone vs tamoxifen and radiation therapy. After a follow-up period of 10.5 years, they found that radiation plus tamoxifen group had lower local recurrence (2%) as compared to tamoxifen alone (9%) ($p=0.001$).²⁰

Elderly patients are usually ER/ PR positive and are more likely to receive hormonal treatment in the form of tamoxifen and aromatase inhibitors. Tamoxifen has a favourable toxicity profile and reduces distant relapse, which is why older women can benefit from the endocrine treatment as can the younger.²¹ Elderly postmenopausal women are likely to receive aromatase inhibitors. The Breast International Group (BIG) 1-98 Trial included 4,922 breast cancer patients; one group was allocated to tamoxifen and the other to letrozole (an aromatase inhibitor). After a five-year follow-up period, letrozole was considered superior to tamoxifen, and it was observed that older women hormone receptor positive patients should not be deprived of hormonal therapy.²²

Trastuzumab is known for cardiac toxicity. Elderly Her 2 Neu (H2N) positive patients with multiple comorbid are less likely to get targeted therapy. However, older patients with good functional status can receive this therapy.²³ Only 4 patients in our study with age below 70 years received targeted therapy. Elmorani et al. found that clinical trials are required to establish guidelines for breast cancer treatment in elderly population.²⁴

We observed that most of our patients with single or two comorbid tolerated surgery, chemotherapy, radiation and hormonal therapy. Chemotherapy was offered to patients with locally advanced disease, inflammatory breast cancer, lymph node positive, receptor-negative tumours and stage IV disease. Chemotherapy was omitted in very fragile and receptor-positive patients.

Conclusion

About 40.5% of our patients tolerated standard treatment including surgery, chemotherapy, radiation and hormonal therapy, depending upon the tumour biology. There was no statistically significant difference in mortality between patients who received standard treatment or selective treatment (omitting chemotherapy or radiation therapy). Triple negative, node positive, advanced stage high-risk elderly patients with multiple comorbid conditions but overall good functional status may tolerate and are likely to benefit from standard therapy. Therefore, they may not be deprived of chemotherapy or radiation therapy if they present with aggressive disease and are otherwise healthy.

Acknowledgments

We are grateful to Ainul Quader, Dr. Anam Arif and Dr.

Warda Riaz for assistance in data collection.

Disclosure: No.

Conflict of Interest: No.

Funding Sources: No.

References

- Cappellani A, Di Vita M, Zanghi A, Cavallaro A, Piccolo G, Majorana M, et al. Prognostic factors in elderly patients with breast cancer. *BMC Surgery*. 2013; 13:S2.
- Boer K. Effective treatment strategy in elderly breast cancer patients. *OryHetil*. 2005;146:15-21.
- Bastiaannet E, Liefers GJ, de Craen AJ, Kuppen PJ, Van De Water W, Portielje JE, et al. Breast cancer in elderly compared to younger patients in the Netherlands: stage at diagnosis, treatment and survival in 127,805 unselected patients. *Breast Cancer Res Treat*. 2010; 124:801-7.
- Besic N, Besic H, Peric B, Gasper P, Petric R, Zumuc J, et al. Surgical treatment of breast cancer in patients aged 80 years or older-how much is enough? *BMC Cancer*. 2014; 14:700.
- Oran ES, Yankol Y, Soybir GR, Karsidag T, Sakatalli O, Gecgel U, et al. Distinct postsurgical management in younger and elderly breast cancer patients results in equal survival rates. *Asian Pac J Cancer Prev*. 2014; 15:7843-7.
- Binder-Foucard F, Bossard N, Delafosse P, Belot A, Woronoff AS, Remontet L. Incidence and mortality of cancer in France during the period 1980-2012: solid tumors. *J Epidemiol Publ Health*. 2013;62:95-108.
- Wildiers H, Kunkler I, Biganzoli L, Fracheboud J, Valstos G, Barnard Mary C, et al. Management of breast cancer in elderly individuals: recommendations of the international Society of Geriatric Oncology. *Lancet Oncol*. 2007; 8:1101-15.
- Braithwaite D, Satariano WA, Sternfield B, Hiatt RA, Ganz PA, Kerlikowske K, et al. Long term prognostic role of functional limitations among women with breast cancer. *J Natl Cancer Inst*. 2010;102:1468-77.
- Lavelle K, Todd C, Moran A, Howell A, Bundred N, Campbell M. Non standard management of breast cancer increases with age in the UK: a population based cohort of women > or = 65 years. *Br J Cancer*. 2007; 96:1197-203.
- Vitug AF, Newman LA. Complications in breast surgery. *Surg Clin North Am*. 2007; 87:431-51.
- Rocco N, Rispoli C, Pagano G, Rengo G, Compagna R, Danzi M, et al. Breast cancer surgery in elderly patients: postoperative complications and survival. *BMC Surgery*. 2013; 13: S25.
- Reed MWR, Wyld L, Audisio RA. The surgical management of breast cancer in elderly; Springer. 2010; 197-211.
- Swaminathan V, Spiliopoulos MK, Audisio RA. Choice of Surgery for Older Women with Breast Cancer. *Breast Care*. 2012;7:445-51.
- Mustacchi G, Gazzaniga ME, Pronzato P, De Matties A, Di Costanzo F, Foriani I. Breast cancer in elderly women: a different reality. Results from NORA study. *Ann Oncol*. 2007;18:991-6.
- Sonmez OU, Arslan UY, Esbah O, Helvacı K, Turker I, Ummugul U, et al. Effects of comorbidities and functional living activities on survival in geriatric breast cancer patients. *Contemp Oncol*. 2014; 18:204-10.
- Muss HB, Berry DA, Cirincione CT, Theodoulou M, Mauer AM, Kornblith AB. Adjuvant Chemotherapy in Older Women with Early-Stage Breast Cancer. *N Engl J Med*. 2009; 360: 2055-65.
- Bernard D, Errante D, Galligioni E, Crivellari D, Bianco A, Salvagnol L, et al. Treatment of breast cancer in older women. *Acta Oncol*. 2008;47: 187-98.
- Fisher B, Redmond C, Legault-Poisson S, Dimitrov NV, Brown AM, Wickerham DL, et al. Postoperative chemotherapy and tamoxifen compared with tamoxifen alone in the treatment of positive-node breast cancer patients aged 50 years and older with tumors responsive to tamoxifen: results from the National Surgical Adjuvant Breast and Bowel Project B-16. *J Clin Oncol*. 1990;8:1005-18.
- Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, Correa C, Taylor C, Arriagada R, et al. Early Breast Cancer Trialists Collaborative Group. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. *Lancet*. 2011; 378:1707-16.
- Hughes KS, Schnaper LA, Cirincione C, Berry DA, McCormick B, Muss HB, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 or older with early breast cancer. *J Clin Oncol*. 2010; 28:507.
- Muss HB, Woolf S, Berry D, Cirincione C, Weiss RB, Budman D, et al. Adjuvant chemotherapy in older and younger women with lymphnode positive breast cancer. *JAMA*. 2005; 293:1073-81.
- Crivellari D, Sun Z, Coates AS, Price KN, Thürlimann B, Mouridsen H, et al. Letrozole compared with Tamoxifen -For Elderly Patients with Endocrine -Responsive Early Breast Cancer : The BIG 1-98 Trial. *J Clin Oncol*. 2008; 26:1972-9.
- Ring A, Reed M, Leonard R, Kunkler I, Muss H, Wildiers H, et al. The treatment of Early breast cancer in women over the age of 70. *Br J Cancer*. 2011; 105:189-93.
- Elomrani F, Zine M, Afif M, Lannaz S, Ouziane I, Mrabti H, et al. Management of Early Breast Cancer in older women: from screening to Treatment. *Breast Cancer : Targets & Therapy*. 2015; 7:165-70.
- Kimmick GG, Muss HB. Systemic therapy for older women with breast cancer. *Oncology (Williston Park)* 2001;15:280-291.