Journal of the Egyptian National Cancer Institute (2013) **25**, 5–11

Cairo University

Journal of the Egyptian National Cancer Institute

www.nci.cu.adu.eg
www.sciencedirect.com

Original article

Clinico-pathological features of breast carcinoma in elderly Egyptian patients: A comparison with the non-elderly using population-based data

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Received 2 October 2012; accepted 21 October 2012
Available online 22 November 2012

KEYWORDS

Elderly breast cancer;
Incidence;
Epidemiology;
Egypt

Abstract *Background:* Breast cancer (BC) is a major worldwide health care problem that mostly afflicts the elderly population in the more developed countries. It is not known how common is breast cancer among elderly Egyptian patients and whether this differs from the disease in younger patients.

Aims: To study the clinico-pathological features of BC in elderly Egyptian patients ($\geqslant$65 years of age) among the population of an Egyptian Governorate, Gharbiah, and to compare these features with those of younger patients ($<$65 years).

Methods: This is a cross sectional study that compares elderly BC (EBC) and the non-elderly BC (NEBC) using the information from the Gharbiah Population-based Cancer registry (GPCR) during the years 1999–2007.

Results: Out of 6078 BCs, 12% were EBCs and 88% were NEBCs. Between 1999 and 2007, the crude incidence rate (CIR, per 100,000 populations) of EBC increased from 47 to 71 and that of NEBC increased from 16 to 17. Compared to NEBC patients, EBC patients were more likely to have a positive family history and present with a distant disease and less likely to present with a localized disease. EBCs were more likely to have lung metastases and less likely to have liver metastases. Histology, grade, hormone and HER-2 receptor statuses were comparable in both groups.

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Peer review under responsibility of The National Cancer Institute, Cairo University.

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http://dx.doi.org/10.1016/j.jnci.2012.10.003

Apart from hormonal therapies, the elderly were less likely to receive surgery, radiotherapy or chemotherapy.

Conclusion: EBC patients in Egypt present with advanced disease and are less likely to receive surgery, radiotherapy or chemotherapy compared to NEBC patients.

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Introduction

Breast cancer is by far the most common cancer among women of both developed and developing countries accounting for 22.9% of all female cancers. It is also the leading cause of cancer death in females accounting for 13.7% of their cancer-related mortality. The favorable incidence to mortality ratio (3:1) can be attributed to the more favorable survival in developed regions (3.7:1) than the less developed regions (2.7:1) [1]. In Egypt, breast cancer is estimated to be the most common cancer among females accounting for 37.7% of their total with 12,621 new cases in 2008. It is also the leading cause of cancer-related mortality accounting for 29.1% of their total with 6546 deaths. The incidence to mortality ratio is poor (1.9:1) [1]. These estimates are confirmed in many regional Egyptian cancer registries [2,3] as well as in hospital-based frequencies [4].

Breast cancer is an age-related disease. Second to female gender, advancing age is the most important risk factor for breast cancer. Age interactions are frequently reported in studies that examine etiology, prognosis and treatment [5–7]. In USA, approximately 50% of breast cancers occurs in women 65 years of age or older and more than 30% occurs after the age of 70 [8]. Moreover, older women are the fastest growing segment in developed countries [9,10] and they will represent an increasing cohort of patients with newly diagnosed breast cancer as well as cancer survivors [11]. In Egypt, the peak incidence of breast cancer occurs in the age group of 40–59 years [2–4]. Elderly Egyptian population aged 65 years or more increased from 3.4% in 1996 to 3.7% in 2006 [12]. With the improvement of health care systems, life expectancy (LE) of the Egyptians is expected to rise markedly. Currently, LE of Egyptian males and females at birth is 70 years and 76 years, respectively [13]. It is expected that people aged 60 years or more will increase from 4.6 millions in 2000 to 23.7 millions in 2050 [14]. Breast cancer among elderly Egyptians is expected to rise markedly in the future.

These older breast cancer survivors are quite a heterogeneous group especially with respect to multiple co-morbid conditions [15]. Compared with younger women, older women have more ER and PR and less HER-2 expression. Tumor size and nodal involvement increase with age attributable not only to delayed diagnosis but also to aggressiveness [16]. Barriers related to age, functional status, and social support can be associated with less diagnostic activities and less aggressive treatments with poorer survival [17]. EBC patients are underrepresented in clinical trials and their treatments are largely extrapolated from trials in younger patients taking in consideration efficacy, expected tolerance, co-morbidities and patients' preferences. However, the elderly are less likely to undergo surgery, radiotherapy and chemotherapy [17].

Reports on EBC among Egyptians are very scanty, particularly at the population-based level. Accordingly, it is not known whether EBC among Egyptians is similar to EBC in different world regions and how similar it is to NEBC. The aims of the current work were to study the clinico-pathological features of breast cancer among the population of the Gharbiah Governorate, Egypt and to compare these features in the elderly ($\geqslant$65 years of age) with those in younger patients. Information gained would give an accurate estimate and better characterization of this disease in Egypt and this can help in planning its management.

Methods

This is a cross sectional study. The Gharbiah Population-based Cancer registry (GPCR) was approached to study the patterns of elderly and non-elderly breast cancer in the Gharbiah Governorate, Egypt during the years 1999-2007. As of 1st of January 2012, the number of cases retrieved was 6291. We excluded 123 cases because of being non-invasive (i.e. CIS in 43 cases) or being of non-carcinoma histology e.g. NHL (80 case). Five cases were excluded as their ages were not documented and 85 were excluded as they were males. Thus we were left with 6078 cases of primary invasive breast carcinoma The following data were extracted for every case whenever possible: age, year of diagnosis, smoking, family history, laterality, SEER stage [18] and TNM stage [19], metastatic sites if any, histologic type and grade, estrogen, progesterone and Human Epidermal Growth factor receptors-2 (HER-2) receptor status, and treatments employed. Population data were extracted from the website of the Egyptian Central Agency for Public Mobilization and Statistics [12].

Statistical analysis

All statistical analyses were performed using SPSS® software, version 15, Chicago, USA. Differences between the two age groups were explored using independent *t*-test or Mann–Whitney's *U* test (for numerical variables) or using Chi-Squared test or the Fisher's exact method (for categorical variables). A two-sided probability (p) of 0.05 or less was considered statistically significant. The crude incidence rate (CIR) of breast cancer in each age group was calculated by dividing the number of new cases in a particular year by the corresponding number of persons in the population at risk at that particular year. It is expressed as an annual rate per 100,000 persons at risk.

Results

Out of 6078 cases of invasive BCs registered to GPCR between 1999 and 2007, 730 cases (12%) were elderly and 5348 cases (88%) were in the non-elderly group. Between the years 1999 and 2007, the CIR of the total BC (per 100,000 population) of the Gharbiah population increased from 17 to 19 (Fig. 1). During this period, the increase in CIR of EBC was marked

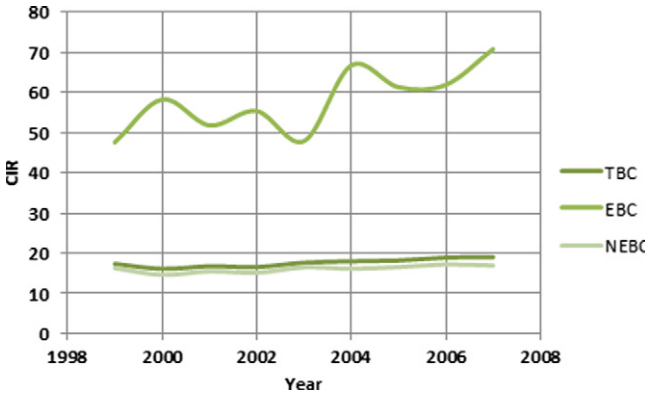

Figure 1 Annual crude incidence rate (CIR) of breast cancer in Gharbiah, Egypt during 1999–2007 (per 100,000 populations). TBC: total breast cancer, EBC: elderly breast cancer, NEBC: non-elderly breast cancer.

(from 47 to 71) while the increase in CIR of NEBC was very mild (from 16 to 17). The EBC to NEBC ratio was almost 1:8. EBC increased from 9.4% of total BC burden in 1999 to 14.5% in 2007 (Table 1). The percentage of the elderly population in Gharbiah showed a small increase from 3.4% in the 1996 census to 3.8% in the 2006 census. The mean age at diagnosis of breast cancer in Egypt increased over the study period; being 49 years in 1999 and 52 years in 2007. This was mostly due to an increase in the mean age of the non-elderly patients (from 47 to 49 years) while that of the elderly was almost stable at 71 years. In both the groups, the mean tumor size was fluctuating around 4 cm. The median tumor size in EBC patients was 3.5 cm (IQR, 3–5 cm) compared to 4.0 cm in NEBC patients (IQR, 3–5 cm, $p = 0.3$).

Elderly BC patients were more likely to have a negative family history of breast cancer ($p = 0.07$). Elderly and non-elderly patients had comparable figures for bilateral breast involvement and inflammatory carcinoma features (Table 2). Elderly and non-elderly patients had comparable figures for different histological subtypes ($p = 0.56$). They were also comparable for the favorable histologic subtypes (tubular, modularly or mutinous) being 2.7% and 2.8%, respectively ($p = 0.80$). Elderly patients were more likely to have grade 1 and 4 tumors and less likely to have grade 2 tumors ($p = 0.002$). EBC patients with positive HER-2 status were 16% compared to 30.8% in NEBC patients ($p = 0.189$). Both EBC and NEBC patients had comparable figures for ER and PR.

At diagnosis, Elderly patients were more likely to have advanced breast tumors i.e. T4, distant metastases and hence higher TNM and SEER stages ($p < 0.001$ for all, Table 2). The nodal (N) stage and the number of positive axillary LNs as well as the number of metastatic sites were comparable in both groups ($p = 0.4$, 0.2 and 0.9, respectively). Less than one third of the patients in both groups had N0 disease. The median number (range) of positive axillary LNs in EBC patients was 5 (1–34) compared to 5 (1–47) in NEBC patients. In both the groups, almost 80% of patients with M1 disease had single metastatic sites. Within the M1 category, 39% of elderly patients had visceral metastases compared to 44.5% in the non-elderly patients (p = 0.36, Fig. 2). Compared to NEBC patients, EBC patients were less likely to have liver metastases (13% vs. 25%, $p = 0.02$) and more likely to have lung metastases/malignant effusion (28% vs. 19%, $p = 0.06$). Both groups had comparable figures for bone, brain and other sites of metastases.

The elderly were less likely to undergo surgery, radiotherapy or chemotherapy as part of their treatment plans ($p < 0.001$ for all, Table 3). While the surgical intent was not different in EBC and NEBC patients, the elderly were less likely to undergo breast conservation surgery ($p = 0.02$). When indicated, the elderly were less likely to undergo adjuvant radiotherapy ($p = 0.002$), adjuvant radiotherapy ($p < 0.001$). While hormonal therapy usage was comparable in both the groups, adjuvant hormonal therapy was less likely to be used in elderly patients ($p < 0.001$).

Discussion

This is the first population-based report on EBC in Egypt and the first to report on such a big number of BC cases (>6000). While this report focuses on a single district registry (GPCR), its results can be generalized to the whole country as the population of this region (Gharbiah Governorate) is similar to that of Egypt. Moreover, GPCR is the most mature registry

Table 1 Breast cancer in Gharbiah Governorate, Egypt between 1999 and 2007.

Year	Total Population (×1000)	Elderly population (×1000)		Total BC			Elderly BC				Non-elderly BC			
	N	*N*	%	*N*	Age[a]	Size[a]	*N*	%	Age[a]	Size[a]	*N*	%	Age[a]	Size[a]
1999	3567	122.0	3.40	619	49 ± 11	4.3 ± 2.3	58	9.4	70 ± 5	3.8 ± 1.9	561	90.6	47 ± 9	4.3 ± 2.3
2000	3632	125.3	3.45	585	40 ± 12	4.0 ± 3.4	73	12.5	71 ± 6	3.0 ± 1.4	512	87.5	47 ± 9	4.3 ± 3.7
2001	3696	129.4	3.5	619	50 ± 11	3.8 ± 1.6	67	10.8	71 ± 5	3.6 ± 1.9	552	89.2	47 ± 9	3.8 ± 1.6
2002	3765	133.7	3.55	623	49 ± 12	3.9 ± 1.7	74	11.9	71 ± 5	4.8 ± 2.0	549	88.1	47 ± 10	3.8 ± 1.6
2003	3829	137.8	3.60	675	49 ± 11	4.2 ± 2.3	66	9.8	70 ± 5	4.0 ± 2.2	609	90.2	47 ± 9	4.2 ± 2.3
2004	3899	142.3	3.65	701	51 ± 12	4.0 ± 2.0	95	13.6	71 ± 6	3.9 ± 2.0	606	86.4	48 ± 9	4.0 ± 2.0
2005	3968	146.8	3.70	722	51 ± 12	4.0 ± 2.1	90	12.5	71 ± 6	3.4.0 ± 1.2	632	87.5	48 ± 9	4.0 ± 2.2
2006	4039	153.5	3.80	763	51 ± 11	4.3 ± 2.4	95	12.5	71 ± 5	4.6 ± 2.7	668	87.5	48 ± 9	4.2 ± 2.3
2007	4055	158.1	3.90	771	52 ± 11	4.0 ± 2.0	112	14.5	71 ± 5	3.8 ± 1.5	659	85.5	49 ± 9	4.0 ± 2.0
All years				6078	50 ± 12	4.0 ± 2.0	730	12	71 ± 5	3.9 ± 2.0	5348	88	47 ± 9	4.1 ± 2.2

BC: breast cancer, NA: data not available.
[a] mean ± SD in years.

Table 2 Demographics and histology of elderly (EBC) and non-elderly breast cancer (NEBC) in Gharbiah, Egypt.

Characteristic	EBC		NEBC		*p*
	N	%	*N*	%	
	730	12.0	5348	88.0	
Smoking	310		2506		
Current or former	3	0.9	7	0.3	
None	307	99.1	2499	99.7	0.156
Positive family history	310		2505		
Yes	9	4.3	138	5.5	
None	301	95.7	2367	94.5	0.070
Laterality	641		5014		
Right	304	47.2	2308	46	
Left	332	51.8	2666	53.2	
Bilateral	5	0.8	40	0.8	0.801
Inflammatory BC					
Yes	2	0.3	21	0.4	
None or unknown	728	99.7	5327	99.6	0.867
Histology	637		5023		
IDC, NOS	593	93.1	4626	92.1	
IDC, special types	16	2.6	139	2.8	
ILC	27	4.3	258	5.1	0.576
Grade	455		4152		
1	29	6.4	195	4.7	
2	324	71.2	3123	75.2	
3	80	17.6	743	17.9	
4	22	4.8	91	2.2	0.002
ER	349		2696		
Negative	138	39.5	1043	38.7	
Positive	211	60.5	1653	61.3	0.758
PR	349		2696		
Negative	134	38.4	1091	40.5	
Positive	215	61.6	1605	59.5	0.458
HER-2	25		237		
Negative	21	84.0	164	69.2	
Positive	4	16.0	73	30.8	0.189
T stage					
1	40	10.9	332	11.3	
2	192	52.5	1763	60.1	
3	36	9.8	425	14.5	
4	98	26.8	412	14.1	<0.001
N stage					
0	123	28.0	1081	27.3	
1	143	32.6	1162	29.4	
2	114	26.0	1083	27.4	
3	59	13.4	627	15.9	0.364
M stage	406		3166		
0	311	76.6	2727	86.1	
1	95	23.4	439	13.9	<0.001
TNM stage	454		3722		
I	23	5.1	158	4.2	
II	141	31.1	1435	38.5	
III	195	43.0	1690	45.4	
IV	95	20.8	439	11.9	<0.001
SEER stage	496		4180		
Localized	122	24.6	1066	25.5	
Regional	279	56.3	2675	64.0	
Distant	95	19.1	439	10.5	<0.001

in the country, being set in the late nineties, and its data are widely used by the International Agency for Research on Cancer (IARC) to reflect cancer incidence in Egypt [3]. Data from other national registries are in line with those of GPCR [2]. On the other hand, the retrospective nature of the present study has its limitations [20]. However, we have done our maximal efforts to have a well conducted study that gives a clear overview of the global situation of BC in the country.

In the current study, the percentage of EBC was 12% of the total BCs. This is comparable to the 10–18% figure in many developing countries including Jordan (10%), Arabs in Israel (18%) [21], Lebanon (14%) [22], and Nigeria (12.3%) [23]. However, the percentage of EBC in the current study is lower that of USA (50%), most of the Western European countries (30–50%) [8,24], Cyprus (34%), and Jews in Israel (42%) [24]. The lower incidence of EBC in Egyptian women and other developing countries may be explained. The population structure is different with younger median population age and lower life expectancy in developing countries [13]. Also, there are variations in life styles and other risk factors including genetic susceptibilities as well as screening practices [17].

Breast cancers in elderly women have some differences from those in younger women. Among others, these differences are related to co-morbidities, tumor extension, nodal involvement, receptor expression (ER, PR & HER-2), and biologic aggressiveness [16]. The current study revealed that BC in elderly Egyptian women differs in some clinico-pathological aspects from that in the non-elderly patients. Compared to NEBC patients, EBC patients were more likely to be smokers (0.4% vs. 0.1%, $p = 0.2$) and to have a negative family history of breast cancer (1.2% vs. 2.6%, $p = 0.03$). The more prevalence of a positive family history in the younger BC patients is similar to a report on a very large number of breast cancer patients [25]. However, due to the retrospective nature of the current study we could not collect data on the number of family members affected or their age at diagnosis or on other breast cancer risk factors.

Most patients included in the current study, whether elderly or non-elderly, had advanced disease at presentation (stage III–IV in 64% and 57%, respectively). This is similar to previous Egyptian reports [26]. Reasons for this may include more genetically aggressive tumors, lack of screening programs, lack of awareness among patients and maybe health care personnel, or patients' negligence [27]. The current study showed that compared with NEBC, EBC patients were more likely to have advanced local (i.e. T4) tumors (27% vs. 14%, $p < 0.001$) and to have M1 disease (23% vs. 14%, $p < 0.001$). This coincides with reports from the SEER registry and San Antonio breast cancer databases [28], European Institute of Oncology in Milan [29], China [30] and Netherlands [31]. The finding that older patients had more advanced tumors than younger patients could be explained by a delay in the diagnosis in older patients because of fewer breast examinations [32] and less frequent screening mammography [33,34]. Contrary to other reports where elderly patients had more N0 disease [28–30], LN involvement was similar in the EBC and NEBC patients of the current study (72% vs. 73%, respectively). This could be related to the late presentation of Egyptian BC patients attributable to many factors [27].

The higher percentages for ILC and favorable IDC subtypes previously reported in EBC patients compared to NEBC patients [28] were not observed in the current study. Contrary to many reports that showed higher ER/PR and lower HER-2

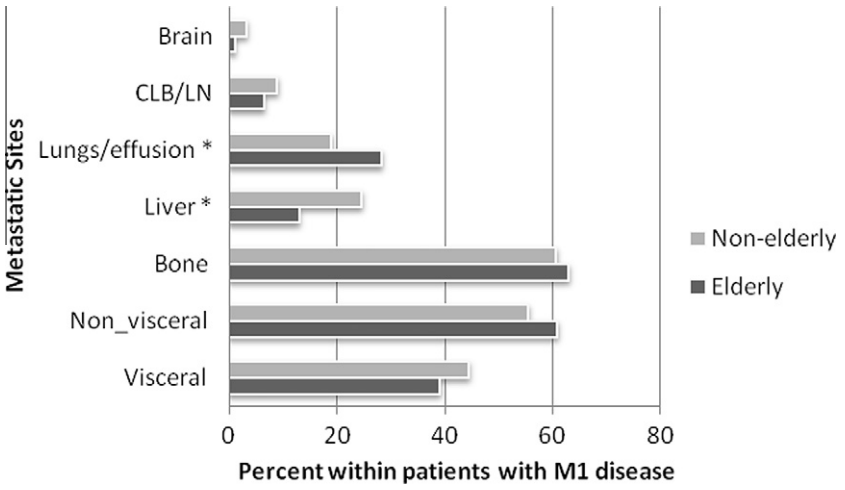

Figure 2 Sites of distant metastases in 92 elderly and 422 non-elderly breast cancer patients (CLB/LN: contra-lateral breast or lymph node metastases).

expressions in the elderly than the younger patients [28–30], there were no statistically significant differences regarding these parameters in the current study. The reasons for this are not known but could be attributed to genetic and biologic differences and variations in risk factors exposure among various populations [26]. However, it should be noted that receptor status, particularly HER-2, was unknown for big proportions in the current study and the impact of this issue cannot be estimated. Thus, these observations need to be verified in prospective studies.

Elderly patients are under-represented in prospective randomized trials and most of their therapeutic strategies are extrapolated from trials of the younger patients taking in consideration factors other than tumor stage and biology [17]. Similar to other reports [35,36], the current study showed that EBC patients are less likely to be offered surgery and when surgery is offered, elderly were less likely to undergo breast conservation. As surgery is the standard of care for the treatment of all early BC patients, elderly patients should be offered the same surgery as younger patients. Alternative therapies should be reserved for those patients too ill or frail for surgery, or for those who refuse it [16]. Fortunately, the sentinel node biopsy procedure has largely solved this problem, allowing an insight of nodal involvement without inducing major side effects [37].

Many elderly women are denied postoperative radiotherapy or receive it with some delay [38,39]. The current study showed that almost 55% of EBC did not receive radiotherapy compared to 27% in NEBC patients. The same pattern was also reported in elderly BC studies [40]. Reasons like chronic illnesses, long distance to radiotherapy facilities, protracted radiotherapy course, frailty, limited social support and psychological and economic factors and patients' or family's preference, all contribute to the underutilization of radiation therapy and hence the preference of mastectomy over conserving surgeries in elderly patients. As adjuvant radiotherapy in the elderly reduces recurrences and increases breast cancer-specific survival [41,42], the elderly should not be denied this treatment modality easily. Rather, the decision has to be tailored taking in cosideration the individual fitness and co-morbidities. It is also important to evaluate alternative schedules such as partial breast irradiation [43], intra-operative radiotherapy [44], and hypo-fractionated schedules [16].

Poly-chemotherapy may induce a significant benefit in terms of relapse and survival rates up to 70 years of age [45]. However, tolerability is also reduced among elderly patients [46]. In line with previous reports [28,47], EBC patients in the current study were less likely to receive chemotherapy than the NEBC patients particularly in the adjuvant setting. Chemotherapy should be individualized taken into account the estimated absolute benefit, life expectancy, treatment tolerance, and patient preference [16]. It is recommended that adjuvant chemotherapy should not be age-based [16] as older patients within ER-negative or node-positive disease derive large benefits of this modality [48,49]. Four cycles of AC are preferred over CMF and both are superior to capecitabine. Taxanes can also replace anthracylines to reduce cardiac risks [16]. Use of myeloid growth factors is advisable [50]. In the metastatic setting, preference should be given to chemotherapeutic agents with safer profiles. This entails choosing single rather than drug combinations and those with minimal toxicities and in an adjusted dose. These can include weekly taxanes and oral regimens as capecitabine or vinorelbine [17].

There is no age-dependent efficacy of tamoxifen or aromatase inhibitors [16]. With good tolerability, ease of use and documented benefit, endocrine treatments have been commonly used in ER/PR positive elderly patients both in the adjuvant and metastatic settings [17]. Similar to other reports [30], there were no significant differences in hormonal therapy use between EBC and NEBC patients. Aromatase inhibitors have a slightly greater efficacy than tamoxifen and the choice of either agent should consider their possible toxicities relevant to the elderly e.g. cardiovascular and skeletal adverse events with aromatase inhibitors and thrombo–embolic events or endometrial carcinoma with tamoxifen [17].

In conclusion, the Egyptian EBC patients present with a more advanced disease and are less likely to receive curative therapies as surgery, radiotherapy or chemotherapy than younger patients. Increasing awareness among patients and

Table 3 Treatments of elderly (EBC) and non-elderly breast cancer (NEBC) in Gharbiah, Egypt.

	EBC		NEBC		*p*
	N	%	*N*	%	
Surgery	399		3036		
None	83	20.8	291	9.6	
Yes	316	79.2	2745	90.4	<0.001
Surgery intent					
Curative	306	96.8	2662	97.0	
Palliative	10	3.2	83	3.0	0.890
Surgical procedure					
BCS	16	5.0	245	8.9	
Mastectomy	300	95.0	2500	91.1	0.019
Radiotherapy	310		2618		
None	169	54.5	701	26.8	
Yes	141	45.5	1917	73.2	<0.001
Radiotherapy intent					
Adjuvant	125	88.7	1819	94.9	
Palliative	16	11.3	98	5.1	0.002
Adjuvant radiotherapy	247		2328		
None	122	49.4	509	21.9	
Yes	125	50.6	1810	78.1	<0.001
Chemotherapy	315		2637		
None	115	36.5	205	7.8	
Yes	200	63.5	2432	92.2	<0.001
Chemotherapy intent	250		2349		
(Neo) adjuvant	162	81.0	2180	89.6	
Palliative	38	19.0	252	10.4	<0.001
Adjuvant chemotherapy					
None	88	35.2	169	7.2	
Yes	162	64.8	2180	92.8	<0.001
Hormonal therapy	312		2480		
None	129	41.3	1068	43.1	
Yes	183	58.7	1412	56.9	0.563
Hormonal therapy intent					
Adjuvant	158	86.3	1337	94.7	
Palliative	25	13.7	75	5.3	<0.001
Adjuvant hormonal therapy	248		2200		
None	90	36.3	863	39.2	
Yes	158	63.7	1337	60.8	0.368

BCS: breast conservation surgery, MRM: modified radical mastectomy.

health care professionals and adopting a screening policy can lead to earlier detection and lower cancer-stage at diagnosis. Treatment of elderly patients should not differ from the younger patients solely because they are ''older''.

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