Journal of Geriatric Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

Clinical trials

Breast-conserving therapy in older patients with breast cancer over three decades: progress or stagnation

Jan J. Jobsen [a,b,c,*], Judith G. Middelburg [d], Job van der Palen [a,e], Sietske Riemersma [f], Ester Siemerink [g], Henk Struikmans [h], Sabine Siesling [i,j]

[a] Department of Epidemiology, Medisch Spectrum Twente, Enschede, The Netherlands
[b] Department of Radiation Oncology, Medisch Spectrum Twente, Enschede, The Netherlands
[c] Breast Clinic Oost-Nederland, Ziekenhuis Groep Twente, Hengelo, The Netherlands
[d] Department of Radiotherapy, Erasmus Medical Center Rotterdam, The Netherlands
[e] Department of Research Methodology, Measurement, and Data Analysis, Faculty of Behavioral Science, University of Twente, The Netherlands
[f] Laboratory for Pathology Oost Nederland, Hengelo, The Netherlands
[g] Department of Internal Medicine, Ziekenhuis Groep Twente, Hengelo, The Netherlands
[h] Department of Radiation Oncology, Leiden University Medical Centre, Leiden, The Netherlands
[i] Department of Research, Netherlands Comprehensive Cancer Organization, Utrecht, The Netherlands
[j] Department of Health Technology and Services Research, MIRA Institute of Biomedical Technology and Technical Medicine, University of Twente, Enschede, The Netherlands

ARTICLE INFO

Article history:
Received 28 March 2018
Received in revised form 10 May 2018
Accepted 7 August 2018
Available online xxxx

Keywords:
Older adults
Breast neoplasms
Breast-conserving therapy
Survival analyses
Cohort study

ABSTRACT

Background: The aim of this study was to analyze the distant metastases-free survival (DMFS), and disease-specific survival (DSS) after breast-conserving therapy (BCT) in older patients with breast cancer in a large, population-based, single-center cohort study with long-term follow-up.
Material and Methods: Analyses were based on 1,425 women aged 65 years and older with breast cancer treated with BCT. Patients were divided in three age categories: 65 – 70 years, 71 – 75 years, and >75 years. The study period extended over 30 years, divided in three decades. Multivariate survival analysis was carried out using Cox regression analysis.
Results: The two youngest age categories showed significant improvements over time in 12-year DMFS and DSS. For women aged 65 – 70 years, this improvement was noted in stage I and stage II disease, while for women aged 71 – 75 years this was mainly in stage II tumors. Women >75 years of age did not show any improvement over time, regardless of stage.
Conclusion: Among older Dutch women with breast cancer, outcomes with regard to DMFS and DSS after BCT differ between various age categories, showing the least gain in the very old.

1. Introduction

In The Netherlands, the lifetime risk of cancer for women is approximately 1 in 2.6, and for breast cancer 1 in 8. [1] In 2015 over 14,000 women were diagnosed with invasive breast cancer, of whom 28% were 70 years or older at the time of diagnosis. [2] Due to the ageing of the population and the increased life expectancy, the number of newly diagnosed breast cancers is expected to increase by approximately 50% for women over 65 years in the following two decades. [3] Multi-morbidity affects more than half of older adults, and its prevalence increases in very old men and women. Consequently, this coincides with a greater risk of dying of other causes in patients with breast cancer. [4]

In many studies on survival trends, the group of patients with cancer older than 65 years of age is taken as one group without any further stratification. The latter disregards the enormous heterogeneity within this group in terms of frailty, the occurrence of comorbidities, and non-cancer associated mortality. [5, 6]

In a large study of 127,805 patients with breast cancer in The Netherlands, Bastiaannet et al. showed that the relative survival rates for older patients are lower compared to those of younger patients, while the percentage of deaths due to other causes increases with age. [7] In such a heterogeneous group, the problem of inadequate patient selection might potentially result in frail older patients being over-treated and fit older patients being under-treated.

Early breast cancer is usually treated through breast-conserving therapy (BCT) involving lumpectomy (including axillary staging) followed by whole breast irradiation (WBI) with or without a

* Corresponding author: Department of Epidemiology, Medisch Spectrum Twente, Haaksbergerstraat 55, 7513 ER Enschede, The Netherlands.
E-mail address: jjjobsen@hetnet.nl (J.J. Jobsen).

https://doi.org/10.1016/j.jgo.2018.08.007
1879-4068/

boost directed to the primary tumor area and adjuvant systemic therapy on indication. Nowadays, the radiotherapy part is administered with a hypo-fractionation scheme, administered in 16 fractions (WBI) and on indication a boost in five fractions. This scheme of four weeks of daily radiotherapy is often considered too intensive for frail older patients. Studies of new regimens such as accelerated partial breast irradiation (APBI), administered within one or two weeks, might be an alternative option. [8] Intraoperative radiotherapy (IORT), administered the same day as lumpectomy, might be an alternative for older frail patients as well. [9] On the other hand, looking at long-term survival, one could argue whether radiotherapy after lumpectomy is beneficial in older patients with small tumors and clear margins after lumpectomy. Additionally, hormonal therapy after lumpectomy might be an alternative in patients with estrogen positive tumors, but this has to be balanced against the side effects of both treatment modalities. [10]

Considering the arguments above, knowledge on the results and long-term efficacy of lumpectomy (including axillary staging) and WBI for older patients with breast cancer is relevant for future decision-making. In this study, we focus on disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS) of patients with breast cancer aged 65 years and older treated with BCT. We report this outcomes stratified by age groups, using our prospective population-based cohort covering more than 30 years and with long-term follow-up.

2. Material and Methods

We used information from our prospective longitudinal cohort about all patients diagnosed with invasive breast cancer in the Twente-Achterhoek region between 1985 and 2013 and treated with BCT. All patient data, including demographics, histology, staging information, treatment, and outcome were recorded and were updated regularly. Histological examination was carried out in the Laboratory of Pathology Oost Nederland. Tumors were classified according to the TNM-classification of the UICC, 7th edition 2009.

We defined synchronous bilateral breast cancer as cancer diagnosed in both breasts simultaneously or within three months of diagnosis of the first tumor. Metachronous bilateral breast cancer was defined as breast cancer occurring in the contra-lateral breast more than three months after diagnosis of the tumor in the first affected breast.

Tumors were graded according to the Bloom and Richardson grading system. Presence or absence of lymphovascular space invasion (LVSI) was also recorded. Involvement of the margins of the lumpectomy specimen was considered to indicate the presence of microscopic involvement of invasive carcinoma (IC) or ductal carcinoma in situ (DCIS) in the inked edges of the lumpectomy specimen. The mitotic activity index (MAI) was defined by the number of mitotic figures in an area of 2 mm^2 according to the protocol. [11]

Due to the broad time span, malignancy grading (Table 1) and Her2 receptor status were not available for all tumors.

We divided the cohort into three age categories (65 – 70, 71 – 75, and >75 years old at time of BCT) based on the following considerations: (1) In 1990 the national biannual breast-screening program initially started for women aged 50 – 70 years; (2) In 1998 this program was extended for women aged 70 – 75 years; (3) Adjuvant chemotherapy was initially limited to women ≤70 years, and in the last decade also offered to women >70 years depending on their general condition. In order to analyze changes in recurrence risk and treatment over time, we divided this cohort with a time span of about 30-years into three periods (1985 – 1995, 1996 – 2004, and 2005 – 2013).

To link the number of patients included in this study to the total number of stage I and II invasive breast cancers treated in the Twente – Achterhoek region (the catchment area of the Radiotherapy Department) data was obtained from the Netherlands Cancer Registry (NCR). [2] The NCR is hosted in the Netherlands Comprehensive Cancer Organization and started in 1989, and obtains data by pathology notification in all hospitals in the Netherlands.

Table 1
Patients and tumor characteristics of 1500 breast cancers treated through BCT in 1425 older women according to age categories.

Characteristics	**65 – 70 years** n=793 (%)	**71 – 75 years** n=467 (%)	**> 75 years** n=240 (%)	p-value
Localisation primary				
Lateral upper quadrant	424 (53.5)	254 (54.4)	103 (42.9)	
Lateral lower quadrant	86 (10.8)	53 (11.4)	31 (12.9)	0.016
Medial upper quadrant	173 (21.8)	88 (18.8)	67 (27.9)	
Medial lower quadrant	77 (9.7)	49 (10.5)	19 (7.9)	
Central	33 (4.2)	23 (4.9)	20 (8.4)	
Family history				
Positive	191 (24.1)	129 (27.6)	66 (27.5)	
Negative	602 (75.9)	338 (72.4)	174 (72.5)	ns
Histology				
Ductal carcinoma	616 (77.7)	352 (75.4)	190 (79.2)	
Lobular carcinoma	105 (13.2)	61 (13.1)	27 (11.2)	
Medullar carcinoma	6 (0.8)	4 (0.9)	0	0.044
Tubular carcinoma	41 (5.2)	24 (5.0)	5 (2.1)	
Rest	25 (3.1)	26 (5.6)	18 (7.5)	
Malignancy grading				
Grade 1	229 (28.9)	155 (33.2)	47 (19.6)	
Grade 2	284 (35.8)	216 (46.3)	95 (39.6)	<0.001
Grade 3	135 (17.0)	53 (11.3)	42 (17.5)	
Unknown	145 (18.3)	43 (9.2)	56 (23.3)	
Lymph vascular space invasion				
Positive	63 (7.9)	31 (6.6)	22 (9.2)	
Negative	728 (91.8)	433 (92.7)	215 (89.6)	ns
Unknown	2 (0.3)	3 (0.7)	3 (1.2)	
Presence of CIS				
DCIS	212 (26.7)	129 (27.6)	63 (26.2)	
LCIS	47 (5.9)	19 (4.1)	11 (4.6)	ns
None	534 (67.4)	319 (68.3)	166 (69.2)	
Mitotic Activity Index				
Low (<13 in 2mm^2)	457 (57.6)	316 (67.7)	107 (44.6)	
High (>12 in 2mm^2)	136 (17.2)	70 (15.0)	46 (19.2)	0.009
Unknown	200 (25.2)	81 (17.3)	87 (36.2)	
Hormone receptor status				
ERPR positive	530 (66.8)	335 (71.7)	163 (67.9)	
ERPR negative	82 (10.3)	37 (7.9)	19 (7.9)	
ER pos. PR neg.	124 (15.7)	82 (17.6)	41 (17.1)	ns
ER neg. PR pos.	9 (1.1)	5 (1.1)	3 (1.3)	
Unknown	48 (6.1)	8 (1.7)	14 (5.8)	
Her2neu				
Negative	395 (49.8)	237 (50.8)	109 (45.4)	
Positive	30 (3.8)	9 (1.9)	4 (1.7)	ns
Unknown	368 (46.4)	221 (47.3)	127 (52.9)	
Re-excision				
Yes	40 (5.0)	15 (3.2)	7 (2.9)	
None	750 (94.6)	451 (96.6)	229 (95.4)	ns
Unknown	3 (0.4)	1 (0.2)	4 (1.7)	
Margin Status				
Negative	703 (88.6)	405 (86.7)	199 (82.9)	
Positive IC	56 (7.1)	33 (7.1)	27 (11.3)	0.053
Positive DCIS	30 (3.8)	25 (5.3)	9 (3.7)	
Positive IC+DCIS	4 (0.5)	4 (0.9)	5 (2.1)	
Tumor size				
pT1	648 (81.7)	382 (81.8)	150 (62.5)	
pT2	145 (18.3)	84 (18.0)	88 (36.7)	<0.001
Rest	0	1 (0.2)	2 (0.8)	
Lymph node status				
pN0	608 (76.7)	370 (79.2)	158 (65.8)	
pN1	132 (16.7)	63 (13.5)	52 (21.7)	
pN2	25 (3.1)	10 (2.2)	7 (2.9)	ns
pN3	3 (0.4)	2 (0.4)	1 (0.4)	
Unknown	25 (3.1)	22 (4.7)	22 (9.2)	
Stage				
Stage I	530 (66.8)	320 (68.5)	98 (40.8)	
Stage II	238 (30.0)	125 (26.8)	118 (49.2)	<0.001
Unknown	25 (3.2)	22 (4.7)	24 (10.0)	

P-value has been calculated on the known components of the variables. ERPR: ER estrogen receptor and PR progesterone receptor; DCIS: ductal carcinoma in situ; LCIS: lobular carcinoma in situ; IC: invasive carcinoma; ns: not significant

Please cite this article as: Jobsen JJ, et al, Breast-conserving therapy in older patients with breast cancer over three decades: progress or stagnation, J Geriatr Oncol (2018), https://doi.org/10.1016/j.jgo.2018.08.007

2.1. Treatment

BCT initially consisted of lumpectomy with axillary clearance of levels I-III, followed by WBI and a subsequent boost directed to the lumpectomy cavity. After 2001, axillary staging was mainly carried out by sentinel lymph node procedures, and only followed by complete axillary dissection in cases of histologically proven axillary lymph node metastases or if sentinel node biopsy had failed. However, since 2010, those with micro-metastases in axillary lymph nodes could receive irradiation of the axilla instead of axillary dissection. WBI consisted of 50 Gy in 2 Gy fractions, followed by a subsequent boost of 14 Gy to the lumpectomy cavity, irrespective of margin status. Since 2004, the indication to administer a boost dose was determined by age, lymph node status, and margin status: patients with no lymph node metastases, negative margins, and tumor size ≤1,0 cm for age >60 years and ≤2.0 cm for age >70 years no longer received a boost. Since 2010, a hypo-fractionation schedule of 42.56 Gy WBI was administered in 16 fractions. If necessary, a boost of 13.30 Gy in five fractions was given. However, those over 50 years of age with a width of tumor-free margins of >2mm for invasive cancer, and/or >5mm for ductal carcinoma in situ did not receive a boost.

Twelve women included in this study were also enrolled in the IRMA phase-3 trial, in which they were randomized to receive locally external beam APBI administered by 10 fractions in 2 weeks. [8]

Both regional radiotherapy and adjuvant systemic therapy were given in line with existing treatment guidelines. [1] Regional radiotherapy was indicated for patients with four or more axillary lymph node (macro) metastases or if extra-nodal disease was present.

In the late 1980's, adjuvant systemic therapy was usually given to patients with histologically proven axillary lymph node metastasis. Adjuvant hormonal therapy was prescribed to postmenopausal patients who had histologically proven tumor-positive axillary lymph nodes. Since 1999, the indications for adjuvant systemic therapy no longer depended on the axillary lymph node status only but also on the MAI, histological grade, and tumor size. Postmenopausal women could eventually also receive chemotherapy in addition to hormonal therapy, however this was only indicated for patients <70 years.

In late 2004, treatment with trastuzumab in combination with adjuvant chemotherapy was introduced into our region for Her2 positive cases.

2.2. Statistical Methods

Time to recurrence and length of follow-up was calculated from the date of lumpectomy. To test between-group differences for categorical data, the Chi-square test was used. Ipsilateral breast tumor recurrence (IBTR) was defined as failure in the ipsilateral breast.

Survival statistics were obtained in relation to the number of patients and calculated by Log Rank and by applying the method proposed by Kaplan-Meier. The disease-specific survival (DSS), corrected for intercurrent death, was also calculated to the number of patients. This means that data on patients who died of other causes were regarded as censored data. Disease free survival (DFS) was defined as survival without local, regional and/or distant metastases. Univariate analyses were performed on all known histological, treatment, time and age variables. Multivariate survival analysis was carried out using Cox regression analysis. Variables that were univariately related to the outcomes of interest ($p<0.05$) were included in the multivariate analyses.

Analyses were performed using the STATA 14.2 statistical software application (StataCorp, College Station, TX, USA). The Medical Ethical Committee Twente approved the analysis on the data

2.3. Results

From 1985 through to 2013 a total of 4,657 BCT in 4,490 women were registered. Analysis was subsequently carried out on 1,500 BCT in 1,425 women aged 65-years and older. The three age categories consisted of 793 women aged 65 – 70 years (52.9%), 467 women aged 71 – 75 years (31.1%), and 240 women older than 75-years (16.0%).

The tumor and patients characteristics at primary diagnosis according to the three age categories are shown in Table 1. Missing data on malignancy grading and MAI occurred mainly in the first period (1985 – 1995).

The incidence of IBTR for the three age categories was 3.9%, 3.8%, and 5.0% respectively. Local failure rate over the studied periods was not significantly different between the different age categories.

The occurrence of contralateral breast cancer (CBC) for the three age categories was 12.1%, 12.0%, and 16.5%, respectively for those aged 65 – 70 years, 71 – 75 years, and > 75 years. The occurrence of second malignancies, other than breast cancer, for the three age categories was 11.1%, 14.1%, and 13.2% respectively.

The total number of invasive stage I and II breast cancers treated either through BCT or mastectomy in the Twente – Achterhoek region is shown in Table 2, and the cohort under study revealed a comparable distribution.

2.4. Time Periods

Table 3 shows the treatment characteristics over the three time periods and the three age categories. Significant changes in the use of surgery as well as type of radiotherapy and of adjuvant systemic therapy were noted over time. The rate of regional surgery changed from 96.6% axillary dissections in the first period to 75.9% sentinel node procedures in the third period. We also noted an increase in the use of radiotherapy of the breast without a boost. This finding was similar for all age categories. The oldest age category also received more adjuvant regional radiotherapy, due to more patients with >3 axillary lymph node metastases.

With respect to the use of adjuvant systemic therapy, we noted a significant increase over time. About 79% of patients did not receive any type of adjuvant systemic therapy in the first period, whereas the use of adjuvant systemic therapy increased to 41.9% in the third period ($p<0.001$). Overall, 36.3% of the patients received adjuvant systemic therapy, of which 88.0% received adjuvant hormonal therapy only, predominantly those with positive ER status. With respect to the three age categories, 80.7% of patients with positive ER status aged 65 – 70 years received adjuvant hormonal therapy alone, compared to 100% of those aged > 75 ($p<0.001$). All three age categories showed a significant increase in the use of adjuvant hormonal therapy for stage II over the three time periods. Nineteen percent of women with stage I disease received adjuvant systemic therapy (17.1% hormonal therapy and 2.2%

Table 2
The occurrence of breast-conserving therapy (BCT) and mastectomy for stage I and II invasive breast cancer in the Twente-Achterhoek region for the different time periods and according to the age categories.

Characteristics	**Total**	**BCT** n (%)	**Mastectomy** n (%)
		1989*– 1995	
Age category			
65 – 70 years	221	149 (67.4)	72 (32.6)
71 – 75 years	100	35 (35.0)	65 (65.0)
> 75 years	157	46 (29.3)	111 (70.7)
		1996 – 2004	
Age category			
65 – 70 years	502	227 (45.2)	275 (54.8)
71 – 75 years	413	188 (45.5)	225 (54.5)
> 75 years	356	73 (20.5)	283 (79.5)
		2005 – 2013	
Age category			
65 – 70 years	672	380 (56.5)	292 (43.5)
71 – 75 years	433	214 (49.4)	219 (50.6)
> 75 years	402	91 (22.6)	310 (77.4)

* Data from the period 1985-1988 were not available in the Netherlands Cancer Registratry.

Please cite this article as: Jobsen JJ, et al, Breast-conserving therapy in older patients with breast cancer over three decades: progress or stagnation, J Geriatr Oncol (2018), https://doi.org/10.1016/j.jgo.2018.08.007

Table 3
Patients and treatment characteristics of 1,500 breast cancers in 1,425 older women, aged ≥ 65-years, treated through breast conserving treatments according to three time periods and the three age categories.

	Time periods			**Age categories**		
Characteristics	**1985 – 1995** n=266 (%)	**1996 – 2004** n=523 (%)	**2005 – 2013** n=711 (%)	**65-70 years** n=793 (%)	**71-75 years** n=467 (%)	**>75 years** n=240 (%)
Age category						
65 – 70 years	165 (62.0)	240 (45.9)	388 (54.6)			
71 – 75 years	44 (16.6)	202 (38.6)	221 (31.1)			
> 75 years	57 (21.4)	81 (15.5)	102 (14.3)			
Surgery						
Lumpectomy	9 (3.4)	32 (6.1)	26 (3.7)	23 (2.9)	22 (4.7)	22 (9.2)
Lump.+ axilla dissection	257 (96.6)	418 (79.9)	145 (20.4)	445 (56.1)	246 (52.7)	129 (53.7)
Lump. + sentinel node	0	73 (14.0)	540 (75.9)	325 (41.0)	199 (42.6)	89 (37.1)
Radiotherapy						
WBI	194 (72.9)	446 (85.3)	623 (87.6)	672 (84.7)	405 (86.7)	186 (77.5)
APBI	0	0	12 (1.7)	9 (1.1)	3 (0.6)	0
WBI + axilla	0	2 (0.4)	32 (4.5)	17 (2.1)	6 (1.3)	11 (4.6)
WBI + parasternal	32 (12.0)	11 (2.1)	0	26 (3.3)	11 (2.4)	6 (2.5)
WBI + regional	40 (15.1)	64 (12.2)	44 (6.2)	69 (8.7)	42 (9.0)	37 (15.4)
Boost to tumour bed						
None	0	30 (5.7)	311 (43.7)	150 (18.9)	137 (29.3)	54 (22.5)
Yes	266 (100)	493 (94.3)	400 (56.3)	643 (81.1)	330 (70.7)	186 (77.5)
Adjuvant systemic therapy						
None	210 (78.9)	333 (63.7)	413 (58.1)	492 (62.0)	323 (69.2)	141 (58.7)
Hormonal therapy	56 (21.1)	181 (34.6)	242 (34.0)	243 (30.6)	137 (29.3)	99 (41.2)
Chemotherapy	0	4 (0.8)	22 (3.1)	21 (2.6)	5 (1.1)	0
Hormonal + chemotherapy	0	5 (0,9)	18 (2.5)	22 (2.8)	1 (0.2)	0
Trastuzumab+Chemo(+horm)	0	0	16 (2.3)	15 (1.9)	1 (0.2)	0

Use adjuvant systemic therapy by time period and tumor size

	Tumor size **pT1**		
1985 – 1995	28 (20.3)	4 (12.5)	7 (16.7)
1996 – 2004	63 (33.5)	40 (24.7)	19 (43.2)
2005 – 2013	113 (35.1)	53 (28.2)	24 (37.5)
	Tumor size **pT2**		
1985 – 1995	10 (37.0)	4 (33.3)	3 (20.0)
1996 – 2004	30 (57.7)	18 (46.2)	18 (50.0)
2005 – 2013	57 (86.4)	24 (72.7)	26 (70.3)

WBI: whole breast irradiation. APBI: accelerated partial breast irradiation, are those from the IRMA-trial. WBI: whole breast irradiation. All variables showed significant differences between the different time periods and age categories.

chemotherapy ± hormonal therapy), compared to 70.9% of women with stage II disease (61.7% hormonal therapy and 9.2% chemotherapy ± hormonal therapy).

We also looked at the impact of tumor size in relation to time and age category. Overall, there was no difference in tumor size over the three periods for the three age categories. Patients aged >75 years had significantly more pT2 tumors compared to the other two categories (Table 1). This difference developed after the first time period Table 5.

2.5. Distant Metastases-free Survival (DMFS)

With a median follow-up of 104 months for all 1,500 tumors, the 12-year DMFS was 82.8%. Overall, we noted a significant ($p<0.001$) improvement over time (Fig. 1). The smoothed hazard estimates in Fig. 2 show the improvement in the first three years. This might be seen due to a significant increase in the use of adjuvant systemic therapy, from 21.1% in the first period to 41.9% in the third period. The use of adjuvant systemic therapy varied between the different age ranges, with 38.0%, 30.8%, and 41.2% of women aged 65-70 years, 71-75 years and >75 years receiving adjuvant therapy ($p=0.009$) (Table 3). However, all age categories showed an increase in use of adjuvant therapies over time (Table 3). The 12-year DMFS was 82.7% for women aged 65 – 70 years, 85.3% for women aged 71 – 75 years, and 77.7% for women > 75 years. Table 4 shows the 12-year DMFS for the different age categories, overall and by stage, over the three time periods. A significant improvement was noted for the first two age categories overall, while, when analyzed by stage, the improvement was limited to women aged 65-70 years with stage I and II tumors and for women aged 71-75 with stage II disease.

In multivariate Cox regression analyses, the following variables were significant: location of the primary tumor in the medial lower quadrant (hazard ratio (HR) 2.1) compared to the upper outer quadrant; positive LVSI (HR 1.7) compared to none; pT2 tumor size (HR 1.8) compared to pT1; and being diagnosed during the second (HR 0.5) or third (HR 0.3) time periods compared to the first time period. For the three age categories, localization of the primary was the only common significant variable. Tumor size and time periods were significant for women aged 65 – 70 years and women >75 years. LVSI showed significance in women 71 – 75 years.

2.6. Disease Specific Survival (DSS)

The 12-year DSS for all women was 85.8%. An overall significant improvement (HR 0.6) was noted over time. The 12-year DSS was 86.6% for women aged 65 – 70 years, 89.2% for women aged 71 – 75 years, and 75.3% for those aged > 75 years.

Table 4 shows the 12-year DSS of the different age categories, overall and by stage, over the three time periods. Only women aged 65 – 70 years showed a significant improvement over time, overall and by stage.

In multivariate Cox regression analysis, age categories, LVSI, tumor size and time periods did show a significant relationship with DSS.

Please cite this article as: Jobsen JJ, et al, Breast-conserving therapy in older patients with breast cancer over three decades: progress or stagnation, J Geriatr Oncol (2018), https://doi.org/10.1016/j.jgo.2018.08.007

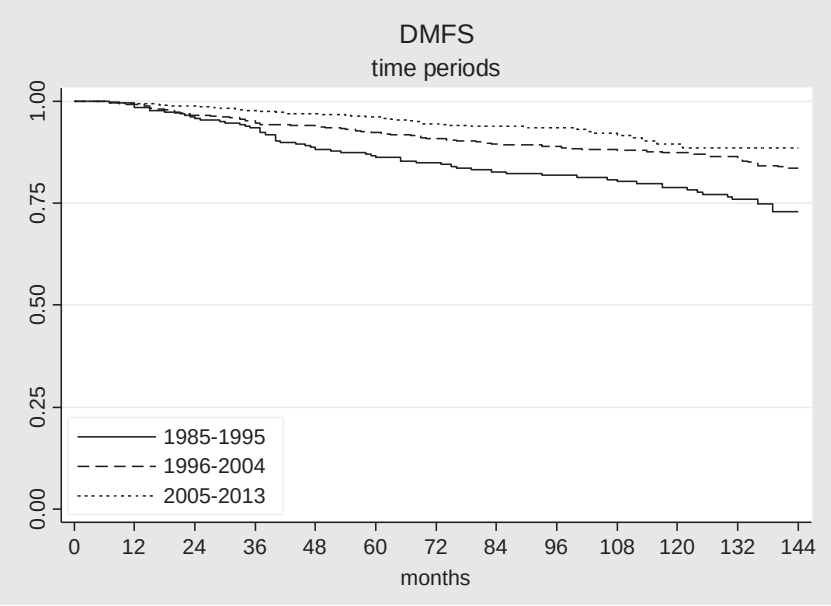

Fig. 1. The distant metastases free survival for 1,500 breast-conserving treatments in 1,425 older women aged ≥ 65 years over three time periods.

2.7. Overall Survival (OS)

The 12-year OS for all included women was 55.4%. The 12-year OS was 65.2%, 54.7%, and 27.2% for women aged 65-70, 71-75 and >75, respectively. These differences were statistically significant. Over time, OS improved significantly for the first two age categories, but did not show any improvement for the oldest age category.

Breast cancer was the cause of death in 31.4%, 20.1%, and 21.3% of women aged 65 – 70 years, 71 – 75 years, and >75 years, respectively.

Table 4
12-year outcome of 1,500 breast cancers in 1,425 older women treated through breast conserving treatments according to three time periods and stage.

Characteristics	**1985 – 1995** n=266	**1996 – 2004** n=523	**2005 – 2013** n=711	p-value
Metastases free survival				
Age category				
65 – 70 years	72.3%	83.3%	88.2%	<0.001
71 – 75 years	73.5%	86.1%	90.6%	0.032
>75 years	74.5%	76.9%	87.9%	0.674
		Stage I		
65 – 70 years	78.6%	89.7%	90.3%	0.003
71 – 75 years	82.8%	91.7%	90.0%	0.442
>75 years	78.0%	87.4%	n a	0.281
		Stage II		
65 – 70 years	60.8%	71.6%	81.5%	0.002
71 – 75 years	58.3%	73.8%	92.3%	0.046
> 75 years	68.7%	72.8%	77.6%	0.790
Disease specific survival				
Age category				
65 – 70 years	78.3%	88.0%	85.4%	<0.001
71 – 75 years	79.4%	90.4%	88.9%	0.089
> 75 years	69.8%	78.1%	85.6%	0.952
		Stage I		
65 – 70 years	87.1%	93.6%	88.1%	0.074
71 – 75 years	82.8%	94.6%	86.2%	0.477
> 75 years	75.6%	83.1%	n a	0.453
		Stage II		
65 – 70 years	62.4%	76.6%	77.5%	0.003
71 – 75 years	73.1%	80.9%	93.7%	0.104
> 75 years	63.2%	76.6%	73.9%	0.470

n a: not available

Occurrence of second malignancies by age category was 11.5%, 15.0%, and 14.2%.

3. Discussion

This study demonstrated an improvement in DMFS and DSS over the last three decades for older women aged 65 years and older with breast cancer treated with BCT. This improvement seems to be limited only to women aged 65 – 75 years, while women >75 years showed no improvement in DMFS and DSS.

This study focused primarily on patients treated with BCT, and it was not our intention to compare these results with mastectomy. As mentioned, our longitudinal long-term cohort allowed for analyses of the effect of time on treatment for older patients. Data on mastectomy use in breast cancer, over the same period, for older patients in our region were not available. The three age categories showed difference in tumor size, which was an independent significant factor in the multivariate analyses for both DMFS and DSS, in particular for women >75 years. The oldest age category had larger tumors, which might be due to the fact that women older than 75 years did not participate in the biannual national breast cancer-screening program. An additional explanatory factor may be worse breast cancer awareness in patients aged >75 years, due to the presence of more cognitive disorders, frailty etc. Looking at tumor size over time, we found that women aged 71-75 years showed a decrease in the incidence of pT2 tumors from 27.3% in the first period to 14.9% in the third, which might be due to the extension of the breast cancer-screening program to women aged up to 75 years in 1998. The latter might also have contributed to the increased survival in this category over time.

The increase in the use of adjuvant systemic therapy in the oldest age category, when compared to that of the other two categories, is in contrast to an absence of improvement in DMFS and DSS for this age group. The use of the different treatment strategies also changed for surgery and radiotherapy. Surgery became less invasive, with more sentinel node procedures compared to axillary dissections. Radiotherapy changed to more local treatment with more WBI only and less boost irradiation. However, this less aggressive primary treatment with surgery and radiotherapy did not result in a worse outcome over the years.

Women >75 years did not show an improvement in DMFS and DSS. In the extensive analyses we noted that the latter was particularly due to stage II tumors showing a trend for a worse outcome. Tumor size

Please cite this article as: Jobsen JJ, et al, Breast-conserving therapy in older patients with breast cancer over three decades: progress or stagnation, J Geriatr Oncol (2018), https://doi.org/10.1016/j.jgo.2018.08.007

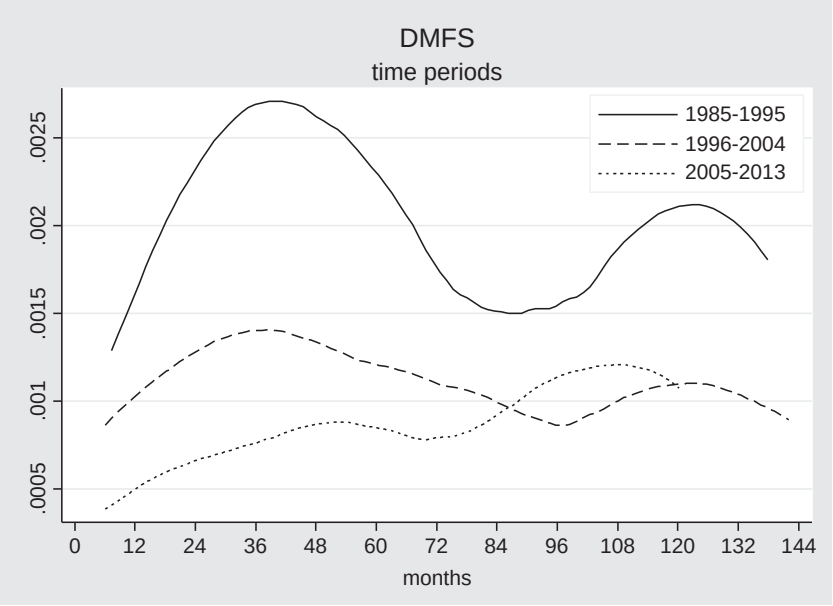

Fig. 2. The smoothed hazard estimates of the distant metastases free survival for 1,500 breast-conserving treatments in 1,425 older women aged ≥ 65 years over three time periods.

was, for this age category, an independent significant factor in the multivariate analyses, which may be due to the fact that for women aged >75 years, the use of adjuvant hormonal therapy was lower that among women aged 65-75. OS did not show improvement for all age categories, which might be related to a higher rate of non-breast cancer-related deaths for the oldest age category.

In early stage breast cancer, discussions regarding different adjuvant treatment options involve balancing the reduction in risk of recurrence gained against the potential for increased treatment-related toxicity. A key component of the care of the older adult is the recognition that chronologic age alone cannot guide the management of an individual with breast cancer; rather, treatment decisions must also take into account an individual's functional status, estimated life expectancy, the risk and benefits of the therapy, potential barriers to treatment, and patient preference. [12] Unfortunately, a lack of specific literature relating to primary treatment in early breast cancer in older women means formulating evidence –based approaches to treatment is difficult. Randomized studies on adjuvant hormonal and chemotherapy have been performed, but women ≥70 years have rarely been included in such trials. In a recent paper, Kiderlen et al. found that the risk of loco-regional recurrence and distant metastases was similar between women aged 65 – 74 years and ≥ 75 years. [13] In a large population-based study of older breast cancer patients over three decades, Kanapuru et al found that relative survival gains increased for all age groups: 65 – 74, 75 – 84, and >85 years. [14] Although these results likely indicate that the benefit from advances in therapy and supportive care also extend to older women with breast cancer patients, we could not confirm this for women aged >75 years in our study.

The present study has some potential limitations, such as the inclusion of a relatively small number of women aged >75 years, lack of data on comorbidities and geriatric assessment results, and missing data on malignancy grading and Her-2 receptor status. However, our study also has several strengths, including the large sample size, a time span of about 30-years, a prospectively population-based design, high quality clinical data, long-term follow-up, and nearly no loss to follow-up (0.5%).

Table 5
10-year disease-free survival and disease-specific survival for 1,502 breast cancers in 1,428 older women treated through breast conserving treatments by stage and age category and according to three time periods.

Age categories	**65 – 70 year** **% HR (95% CI)** n=530 (stage I) n=238 (stage II)	**71 – 75 year** **% HR (95% CI)** n=320 (stage I) n=125 (stage II)	**>75 year** **% HR (95% CI)** n=98 (stage I) n=119 (stage II)
Time periods	**Disease free survival** **Stage I**		
1985 - 1995	81.5% 1	72.2% 1	90.3% 1
1996 - 2004	92.1% 0.4 (0.2-0.9)*	89.1% 0.4 (0.1-1.0)*	90.1% 0.9 (0.1-6.1)
2005 - 2013	91.6% 0.3 (0.1-0.7)*	83.2% 0.5 (0.2-1.2)	97.1% 0.4 (0.1-4.8)
	Stage II		
1985 - 1995	66.4% 1	75.0% 1	75.5% 1
1996 - 2004	73.8% 0.7 (0.4-1.4)	79.2% 0.7 (0.2-2.2)	76.2% 1.0 (0.4-3.1)
2005 - 2013	85.2% 0.3 (0.1-0.7)*	92.0% 0.4 (0.1-1.5)	70.7% 1.5 (0.5-4.5)
Time periods	**Disease specific survival** **Stage I**		
1985 - 1995	88.1% 1	82.8% 1	89.1% 1
1996 - 2004	95.2% 0.4 (0.1-1.1)	95.7% 0.2 (0.1-0.9)*	n.a
2005 - 2013	90.4% 0.3 (0.1-1.0)	85.8% 0.4 (0.1-1.3)	97.1% 0.4 (0.1-4.9)
	Stage II		
1985 - 1995	68.0% 1	73.1% 1	86.1% 1
1996 - 2004	78.8% 0.6 (0.3-1.2)	88.2% 0.4 (0.1-1.5)	78.3% 1.6 (0.4-6.2)
2005 - 2013	89.7% 0.2 (0.1-0.6)*	93.3% 0.3 (0.1-1.3)	78.6% 2.0 (0.5-7.8)

n.a: not available due to small number and events
* statistically significant; HR: hazard ratio; CI: confidence interval

4. Conclusion

We noted a clear improvement in DMFS and DSS for women age 65 – 75 years, in spite of a less aggressive primary treatment with surgery and radiotherapy over time, but related to an increase in the use of adjuvant systemic therapy. No improvement in survival was seen for women over 75 years of age, particularly for those with stage II disease.

Acknowledgements

We would like to thank Marissa van Maaren, researcher at the Netherlands Comprehensive Cancer Centre for providing the data of the NCR.

Please cite this article as: Jobsen JJ, et al, Breast-conserving therapy in older patients with breast cancer over three decades: progress or stagnation, J Geriatr Oncol (2018), https://doi.org/10.1016/j.jgo.2018.08.007

Conflict of interest

The authors declare that they have no conflict of interest

Author contributions

Conception and design: J.Jobsen, H.Struikmans, J.vanderPalen, J.Middelburg, S.Riemersma, E.Siemerink

Data collection: J.Jobsen, S.Siesling

Analysis and interpretation: J.Jobsen, H.Struikmans, J.vanderPalen, J.Middelburg

Manuscript writing: J.Jobsen, H.Struikmans, J.vanderPalen, J.Middelburg, S.Riemersma, E.Siemerink, S.Siesling

Approval of final article: J.Jobsen, H.Struikmans, J.vanderPalen, J.Middelburg, S.Riemersma, E.Siemerink, S.Siesling

All authors read and approved the final manuscript.

References

[1] NABON. Breast Cancer Guideline [Internet]. 2012. Available from: http://www.oncoline.nl/uploaded/docs/mammacarcinoom/Dutch Breast Cancer Guideline 2012.pdf (accessed September 2016)

[2] Intergraal Kancer centrum Nederland (IKNL). www.cijfersoverkanker.nl.

[3] Smith BD, Smith GL, Hurrita A, et al. Future of cancer incidence in the United States: burdens upon an ageing, changing nation. J Clin Oncol 2009;27:2758–65.

[4] Marengoni A, Angleman S, Melis R, et al. Ageing with multimorbidity: a systematic review of the literature. Ageing Res Rev 2011;10:430–9.

[5] Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–56.

[6] Yancik R, Wesley MN, Ries LA, et al. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 year and older. JAMA 2001;285:885–92.

[7] Bastiaannet E, Liefers GJ, de Craen AJM, 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.

[8] Breast cancer with low risk of local recurrence: partial and accelerated radiation with three –dimensional conformal radiotherapy vs. standard radiotherapy after conserving surgery. (phase III study) https://clinical**trials**.gov/ct2/show/NCT01803958.

[9] Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomized controlled equivalence trial. Lancet Oncol 2013;14:1269–77.

[10] Hughes K, Schnaper L, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. New Engl J Medicine 2004;351:971–7.

[11] Baak JPA, van Diest PJ, Voorhorst FJ, et al. Prospective multicenter validation of the independent prognostic value of the mitotic activity index in lymph node-negative breast cancer patients younger than 55 years. J Clin Oncol 2005;23:5993–6001.

[12] O'Conner T, Shinde A, Doan C, et al. Managing breast cancer in the older patient. Clin Adv Hematol Oncol 2013;11:341–7.

[13] Kiderlen M, van de Water W, Bastiaannet E, et al. Survival and relapse free period of 2926 unselected older breast cancer patients: a focus cohort study. Cancer Epidemiol 2015;39:42–7.

[14] Kanpuru B, Ershler WB, Hesdorffer C, et al. Long-term survival of older breast cancer patients: population-based estimates over three decades. Breast Cancer Res Treat 2012;134:853–7.

Please cite this article as: Jobsen JJ, et al, Breast-conserving therapy in older patients with breast cancer over three decades: progress or stagnation, J Geriatr Oncol (2018), https://doi.org/10.1016/j.jgo.2018.08.007