

Declined Guideline Adherence in Older Breast Cancer Patients: A Population-Based Study in The Netherlands

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Abstract: Older women with primary operable breast cancer might receive suboptimal care due to their advanced age. Although several studies reported age as an independent determinant for receiving none or less treatment according to accepted standards, prospective data are lacking. This study evaluates the adherence to a consensus protocol in unselected women aged 80 years and older in the Netherlands. Data were derived from the Dutch population-based Cancer Registry held by the Comprehensive Cancer Centre East. In this study all female patients, 60 years and older, diagnosed with breast cancer TNM stage I–IIIa in the period 2001 until 2006 were selected. Applied treatment according to the Dutch guideline was compared for different age groups. Differences between age groups were evaluated using a chi-square test. In total, 2336 breast cancer patients were studied. Treatment adherence was significantly lower for surgery, radiation therapy and systemic therapy in women aged 80 years and older, and all modalities were applied much less frequently, except for endocrine therapy which was more frequently applied in the oldest old. This study shows a sharp decline in guideline adherence for unselected women aged 80 years and older with primary operable breast cancer, with an observed shift from appropriate locoregional treatment toward endocrine therapy. Whether this approach is justified or not should preferably be tested prospectively. ■

Key Words: breast neoplasms, elderly, guideline adherence, oldest old, treatment

Breast cancer is the most frequently diagnosed cancer among women, with increasing incidence with advancing age. In developed countries, up to 50% of breast cancer cases occur in patients over the age of 65 years and absolute numbers will further increase due to the aging of the western population (1–3).

Breast cancer treatment for the elderly is largely extrapolated from data derived from trials in which elderly are often underrepresented (4). The lack of evidence-based guidelines for elderly, as well as their more vulnerable general condition, complicate the decision-making process (5). Therefore, treatment algorithms are often modified based on a myriad of age-related issues such as co-morbidity, performance status, social

support, mobility, patients or family's preference, quality of life and estimated life expectancy (6–8). Eventually, older women might receive less appropriate care, without prospective studies supporting this strategy (5,9). Indeed, there is evidence that age, among other clinical factors, is an independent determinant for not receiving treatment according to accepted standards, with a reported negative association with breast cancer-related survival (5,10–12).

In the Netherlands, the Dutch Institute for Health Care Improvement (Dutch acronym: CBO), in cooperation with the Dutch Consultative Committee on Breast Cancer (Dutch acronym: NABON), developed the currently used guideline for breast cancer treatment in 2002 (13). The guideline is not age-specific, except for the statement that women aged 70 years or older should not receive adjuvant chemotherapy, in contrast to younger women in certain predefined high-risk cases. Therefore, the assumption could be made that adherence to the Dutch CBO guideline should be

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less age-dependent compared to other international guidelines, like the SIOG recommendations (14), who do not differentiate for age.

For these reasons, we studied the adherence to the generally accepted national guideline in a recent time frame (2001–2006) in unselected series in the Netherlands containing the oldest old (80 years and older) and we compared those results with two arbitrarily chosen younger age cohorts (60–69 and 70–79 years).

PATIENTS AND METHODS

Data were derived from the population-based Cancer Registry held by the Comprehensive Cancer Centre East (CCCE). The CCCE is one of eight CCCs and covers the Eastern part of the Netherlands with 1,3 million inhabitants. The Cancer Registry records all patients diagnosed with cancer since 1989. Demographic, tumor and follow-up data were collected through the medical files by a well-trained registration staff. Follow-up information concerning vital status is collected through a yearly linkage to the Dutch Municipal Personal Records Database (Dutch acronym: GBA).

For this study all female patients diagnosed with breast cancer (ICD-O-3 code C50) in the period 2001 until 2006 were selected. In case of multiple primary breast cancers, only the first tumor was included. Other eligibility criteria were: diagnosed at the age of 60 or older and with TNM (15) stage I, II or IIIa. Patients were divided in three age groups: 60–69, 70–79, and 80 years and older.

All information concerning tumor site, histology, age at diagnosis, treatment and stage was retrieved from the Cancer Registry. The TNM classification was used for staging all patients. In case the pathological TNM was unknown, the staging was complemented with the information from the clinical TNM. Information concerning the estrogen receptor (ER) status and progesterone receptor (PR) are routinely collected by the Cancer Registry since 2005. In order to complete the information on ER and PR receptor status for the patients diagnosed in earlier years, a linkage with PALGA (The nationwide network and registry of histo- and cytopathology in the Netherlands) was performed to complete the information concerning the ER and PR status of the tumors.

Information on applied treatment modalities was retrieved and compliance with the Dutch CBO guide-

line of 2002 was assessed (13). Since this guideline was not yet available in 2001, we used the generally accepted consensus protocol for the studied time period. For surgery, treatment should have been mastectomy or lumpectomy and axillary staging (sentinel node biopsy and/or axillary lymph node dissection). Adjuvant systemic therapy should have been applied in case of positive axillary lymph nodes or in case of a high risk node negative tumor (Bloom and Richardson grade 3 or size >3 cm) and should consist 5-year adjuvant endocrine therapy (in case of a hormone positive tumor) or adjuvant chemotherapy in case of a hormone negative tumor for women aged under 70 years. Radiation therapy should have been applied following lumpectomy, in case of more than three positive lymph nodes and in case of a high-risk/TNM T3 tumor. In case of nonadherence, a subdivision was made into “no treatment performed,” which implies not having received this treatment, and “treatment performed,” which implies having received treatment which should not have been the case.

Descriptive analyzes were performed in order to characterize the studied population. Different applied treatment modalities (surgery, radiation therapy, and systemic therapy) were compared for the different age groups using a chi-square test (80 years and older versus 60–79 years). Similarly, guideline adherence was compared for the three age groups. Calculations on the performed treatment strategies were performed by including only those patients that fulfilled the criteria on that specific treatment modality. All analyzes were performed using the statistical software package SAS 8.29 (SAS Institute Inc., Cary, NC, USA)

RESULTS

Tumor characteristics

In total, 2336 women were studied: 1044 (45%) aged 60–69 years, 806 (35%) aged 70–79 years, and 486 (21%) aged 80 years and older, respectively. Tumor characteristics and therapy according to the different age groups are shown in Table 1. Overall stage distribution in the oldest age group appears to be less favorable compared to the younger age groups. Concerning the estrogen and progesterone receptor status, no significant difference was found between the two younger age groups and the oldest age group. However, the hormone receptor status was more frequently unknown in the 80 plus group (21% com-

Table 1. Tumor and Therapy Characteristics

	60–69 years (n = 1044)	70–79 years (n = 806)	≥80 years (n = 486)	Total (n = 2336)	Chi-square (p-value*)
Stage					
Stage 1	553 (53.0)	401 (49.8)	140 (28.8)	1094 (46.8)	<0.001
Stage 2a	335 (32.1)	235 (29.2)	180 (37.0)	750 (32.1)	
Stage 2b	101 (9.7)	120 (14.9)	131 (27.0)	352 (15.1)	
Stage 3a	55 (5.3)	50 (6.2)	35 (7.2)	140 (6.0)	
WHO differentiation grade					
Grade 1	193 (18.5)	158 (19.6)	86 (17.7)	437 (18.7)	<0.001
Grade 2	443 (42.4)	338 (41.9)	174 (35.8)	955 (40.9)	
Grade 3	279 (26.7)	190 (23.6)	123 (25.3)	592 (25.3)	
Unknown	129 (12.4)	120 (14.9)	103 (21.2)	352 (15.1)	
ER and/or PR					
Negative	126 (12.1)	105 (13.0)	54 (11.1)	285 (12.2)	0.817
Positive	761 (72.9)	590 (73.2)	328 (67.5)	1679 (71.9)	
Unknown	157 (15.0)	111 (13.8)	104 (21.4)	372 (15.9)	
Surgery					
Yes	1035 (99.1)	786 (97.5)	403 (82.9)	2224 (95.2)	<0.001
No	9 (0.9)	20 (2.5)	83 (17.1)	112 (4.8)	
Lymph node dissection					
Yes	1020 (97.7)	770 (95.5)	348 (71.6)	2138 (91.5)	<0.001
No	24 (2.3)	36 (4.5)	138 (28.4)	198 (8.5)	
Radiation therapy					
Yes	646 (61.9)	429 (53.2)	94 (19.3)	1169 (50.0)	<0.001
No	398 (38.1)	377 (46.8)	392 (80.7)	1167 (50.0)	
Endocrine therapy					
Yes	388 (37.2)	292 (36.2)	262 (53.9)	942 (40.3)	<0.001
No	656 (62.8)	514 (63.8)	224 (46.1)	1394 (59.7)	
Chemotherapy					
Yes	145 (13.9)	18 (2.2)	3 (0.6)	166 (7.1)	<0.001
No	899 (86.1)	788 (97.8)	483 (99.4)	2170 (92.9)	

Source: Comprehensive Cancer Centre East.

Values within parenthesis are expressed in percentage. ER/PR positive if >10% of the biopsy was positive for at least one of the receptors.

*Women with age ≥80 years versus women with age 60–79 years.

ER, estrogen receptor; PR, progesterone receptor.

pared to 15% and 14% for the 60–69 and 70–79 groups, respectively).

Treatment

Applied treatment is shown in Table 1. A total of 2224 patients received surgical treatment, as is according to the guideline. The proportion of patients undergoing surgery decreased with increasing age: 99% for patients aged 60–69 years, 98% for 70–79 years, with a sharp decline toward 83% for patients aged 80 and older ($p < 0.001$). Likewise, a similar decline was observed concerning the proportion of patients undergoing axillary lymph node dissection and/or a sentinel node procedure: 98%, 96%, and 72% ($p < 0.001$). Also, radiation therapy after primary surgery was performed less frequently in the oldest age group. A small minority (7%) of all patients received chemotherapy. However, for systemic endocrine therapy an inverse relation was observed: patients diagnosed at 80 years or older received endocrine therapy more frequently (54%) as compared with patients in the younger age groups.

In Table 2, the three different treatment modalities are shown. First the number of patients in whom the specific modality was applicable (according to the guideline) is presented, followed by the number of patients who indeed did receive this modality. Since all patients qualify for surgery this modality corresponds with Table 1. For radiation therapy, the decrease is mainly due to a sharp decreased application following lumpectomy: 95% for patients aged 60–69 years, 91% for patients aged 70–79 years and only to 63% for patients aged 80 and older.

Table 3 shows whether therapy was performed according to the guideline or not, with distinguishment between no treatment performed (although it was recommended by the guideline) and indeed performed treatment (where it was not recommended by the guideline). What shows is that adherence to the guideline for all three modalities decreased with increasing age. Surgery was applied in only 72% of patients of 80 years and older, whereas for younger

Table 2. Applied Locoregional and Systemic Therapy

	60–69 years, n (%)	70–79 years, n (%)	≥80 years, n (%)	chi-square, (p-value [‡])
<i>Locoregional surgical therapy</i>				
Surgery (mastectomy or lumpectomy): applicable for all patients				
No	9 (0.9)	20 (2.5)	83 (17.1)	<0.001
Yes	1035 (99.1)	786 (97.5)	403 (82.9)	
Axillary staging (SNB and/or ALND): applicable for all patients				
No	24 (2.3)	36 (4.5)	138 (28.4)	<0.001
Yes	1020 (97.7)	770 (95.5)	348 (71.6)	
<i>Locoregional radiation therapy (RT)</i>				
Radiotherapy after lumpectomy				
Patients without a lumpectomy: 1271 (54.4%)				
Patients with a lumpectomy: 1065 (45.6%)				
No	32 (5.3)	35 (9.2)	30 (37.0)	<0.001
Yes	571 (94.7)	346 (90.8)	51 (63.0)	
Radiotherapy after a T3 tumor				
Patients without a T3 tumor: 2272 (97.3%)				
Patients with a T3 tumor: 64 (2.7%)				
No	4 (21.1)	6 (23.1)	8 (42.1)	0.106
Yes	15 (78.9)	20 (76.9)	11 (57.9)	
Axillary radiotherapy for ≥3 ± LN				
Patients without >3 LN+: 2174 (93.1%)				
Patients with >3 LN+: 162 (6.9%)				
No	7 (11.5)	13 (20.0)	14 (38.9)	0.003
Yes	54 (88.5)	52 (80.0)	22 (61.1)	
<i>Systemic therapy</i>				
Chemotherapy for LN± and HR–				
Patients without LN+ and HR–: 2245 (96.1%)				
Patients with LN+ and HR–: 91 (3.9%)				
No	7 (17.1)	25 (83.3)	20 (100)	<0.001
Yes	34 (82.9)	5 (16.7)	0 (0)	
Chemotherapy for high-risk tumor [†]				
Patients without high-risk tumor: 2224 (95.2%)				
Patients with high risk tumor: 112 (4.8%)				
No	17 (34.0)	48 (96.0)	11 (91.7)	0.062
Yes	33 (66.0)	2 (4.0)	1 (8.3)	
Endocrine therapy for LN± and HR±				
Patients without LN+ and HR+: 1822 (78.0%)				
Patients with LN+ and HR+: 514 (22.0%)				
No	50 (21.1)	32 (18.5)	19 (18.3)	0.692
Yes	187 (78.9)	141 (81.5)	85 (81.7)	
Endocrine therapy for high risk tumor and HR±				
Patients without high risk tumor and HR+: 2183 (93.5%)				
Patients with high risk tumor and HR+: 153 (6.5%)				
No	21 (25.9)	21 (40.4)	3 (15.0)	0.129
Yes	60 (74.1)	31 (59.6)	17 (85.0)	

Source: Comprehensive Cancer Centre East.

[‡]Women with age ≥80 years versus women with age 60–79 years.

[†]High risk tumor: Bloom and Richardson grade 3 tumor or tumor >3 cm.

LN, lymph node; SNB, sentinel node biopsy; ALND, axillary lymph node dissection; HR, hormone receptor.

patients the guideline adherence was nearly perfect (97% and 96%). The same pattern, although less pronounced, was seen for the guideline adherence concerning radiotherapy: 94% for patients aged 60–69 years, 89% for 70–79 years, and 87% for 80 years and older. The majority of those patients not treated in accordance with the guideline received less treatment than recommended by the guideline, implying no radiotherapy at all despite a positive indication. Guideline adherence concerning systemic therapy was even lower: 83% for patients aged 60–69 years, 79%

for 70–79 years, and 63% for 80 years and older. Most of those patients who were not treated according to the guideline did receive systemic treatment (mainly endocrine therapy) although this was not recommended.

Details of the applied endocrine therapy of the 486 patients aged 80 years and older is shown in Table 4. A total of 83 patients did receive neither surgery nor radiation therapy. In this group the application of endocrine therapy was markedly higher (81%) as compared for those who received either or both

Table 3. Locoregional and Systemic Therapy (Divided into Chemo- and Endocrine Therapy) According to the Guideline

Age groups	60–69 years, n (%)	70–79 years, n (%)	≥80 years, n (%)	Chi-square (p-value [*])
Surgical treatment				
According to guideline				
Yes	1017 (97.4)	770 (95.5)	348 (71.6)	<0.001
No	27 (2.6)	36 (4.5)	138 (28.4)	
Radiation therapy				
According to guideline				
Yes	978 (93.7)	720 (89.3)	421 (86.6)	<0.001
No	66 (6.3)	86 (10.7)	65 (13.4)	
No treatment performed	42	52	51	
Treatment performed	24	34	14	
Systemic therapy				
According to guideline				
Yes	867 (83.0)	633 (78.5)	304 (62.6)	<0.001
No	177 (17.0)	173 (21.5)	182 (37.4)	
No treatment performed	37	53	22	
Treatment performed	140	120	160	
Chemotherapy				
According to guideline				
Yes	942 (90.2)			
No	102 (9.8)			
No treatment performed	24			
Treatment performed	78			
Endocrine therapy				
According to guideline				
Yes	832 (79.7)	633 (78.5)	304 (62.6)	<0.001
No	212 (20.3)	173 (21.5)	182 (37.4)	
No treatment performed	71	53	22	
Treatment performed	141	120	160	

Source: Comprehensive Cancer Centre East.

*Women with age ≥80 years versus women with age 60–79 years.

Table 4. Endocrine Therapy in Women 80+

	Surgery and RT performed	Surgery or RT performed	No surgery no RT performed
No endocrine therapy	45 (47.9)	159 (52.3)	16 (19.3)
Endocrine therapy	49 (52.1)	145 (47.7)	67 (80.7)

Source: Comprehensive Cancer Centre East
RT, radiation therapy.

modalities (48% and 52%, respectively), suggesting a shift from locoregional toward endocrine therapy.

DISCUSSION

This study shows that a large part of elderly women in the Netherlands with primary operable

breast cancer did not receive care according to the national guideline. The adherence to the guideline steeply declined for women aged 80 years and older for all modalities: surgery, radiation therapy, and systemic therapy. Interestingly, women aged 80 years and older more frequently received endocrine therapy although this was not recommended.

One of the strengths of our study is the population-based character covering a complete region in the Netherlands with good access to health care, thereby giving a good representation of the general health care environment without bias of referral patterns or selection criteria. Furthermore, this sampling frame allowed us to study a large number of patients (2336 patients of whom 486 patients of 80 years or older). The time period (2001–2006) we analyzed is another strength of our study, since in this period a consensus protocol based on the National (CBO) guideline was used. In the studied time period, therapeutic decisions on the majority of newly diagnosed breast cancer patients were made in multidisciplinary meetings. Since this multidisciplinary setting treatment proposals are expected to be optimal, also for elderly, it is suggestive that doctor's preference might have played a large role in the observed decline in guideline adherence. Also other factors not studied like general condition of the patient, the presence of significant co-morbidity, specific geriatric syndromes, and patients' preference might have played an important role in those decisions.

Adherence to the guideline concerning both surgery and radiotherapy was lowest in the oldest age group. This is in accordance with the literature reporting less locoregional surgery and frequent omission of radiation therapy in elderly (5,6,9–12,16–18). Reported factors for not performing surgery are comorbidity (closely related to the surgeons' judgment), patients' preference, and advanced age itself (10–12). It is unclear why radiation therapy is applied less frequently in elderly, since it reduces local recurrence rate irrespective of age or tumor characteristics with subsequent reduction in breast cancer-related mortality (19). Probably, the decreased mobility of elderly and the reluctance to embark on long-lasting treatment might have played a role. Unfortunately, this patient-specific information which might have played a role in the individual decision making is not recorded in the CCCE database.

The application of endocrine therapy for women 80 years and older shows an interesting pattern: increased application of systemic therapy. Of note,

concerning the percentage of receptor positivity the application of endocrine treatment should have been even higher not only in the oldest but also in the younger age groups. Probably, the less invasive and not very toxic endocrine therapy was an attractive alternative for surgery resulting in a shift from loco-regional toward endocrine treatment. This observation is in line with a study reporting primary endocrine therapy might be superior to surgery in elderly with hormone receptor positive tumors and significant comorbid disease who were unfit for other forms of therapy (20). Although it is uncertain that primary surgery improves overall survival in this age group in comparison with initial endocrine therapy, primary surgery improves the progression-free survival, and thereby certainly has a role in local-regional disease control (20–21). Thereby elderly have been underrepresented in breast cancer trials for guidelines, so the optimal therapy remains uncertain (4).

This study also showed that axillary staging was performed less frequently in 80+ patients, which is in accordance with other reports (5,16). Obviously, this improper staging will have negative impact on both loco-regional disease control as well as balanced treatment decision making.

In the oldest age group we more frequently found a higher stage at presentation, which may (partly) be due to the Dutch screening program. In the Netherlands, women between the age of 50–75 (in former years age 50–70) are screened for breast cancer and therefore these age groups may have a more favourable stage distribution compared to the oldest group. Furthermore, the higher stage at presentation might also be a reflection of different disease biology in elderly and/or the result of patients and/or doctors delay.

In conclusion, in the general health care environment the adherence to the current Dutch treatment guideline for primary operable breast cancer sharply declines with advancing age. Since prospective data are lacking it remains to be disputed whether the existing guidelines, derived from trials performed in younger patients, can be extrapolated to the oldest old. Several questions remain to be answered: Which patient- and doctor-related factors play a role in non-adherence? What effect will nonadherence have on disease control, quality of life and overall survival? Should frail elderly be treated the same as fit elderly? Are the existing guidelines appropriate for the oldest old? These questions should preferably be addressed in future prospective studies.

CONFLICT OF INTEREST STATEMENT

None declared.

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