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Clinical epidemiology of breast cancer in the elderly

W.J. Louwman[a,*], J.C.M. Vulto[b], R.H.A. Verhoeven[a], G.A.P. Nieuwenhuijzen[c], J.W.W. Coebergh[a,d], A.C. Voogd[e]

[a]Comprehensive Cancer Center South (CCCS), Eindhoven Cancer Registry, P.O. Box 231, 5600 AE Eindhoven, The Netherlands
[b]Department of Radiotherapy, Dr. Bernard Verbeeten Institute, Tilburg, The Netherlands
[c]Department of Surgery, Catharina Hospital, Eindhoven, The Netherlands
[d]Department of Public Health, Erasmus University Medical Centre, Rotterdam, The Netherlands
[e]Department of Epidemiology, Maastricht University, Maastricht, The Netherlands

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ABSTRACT

Breast cancer will increasingly become a disease affecting the lives of older women, especially in more developed countries, the prevalence rising up to 7% over age 70 in the near future. A review of the population-based literature and an analysis of the data of the Eindhoven Cancer Registry and European data regarding the diagnosis, treatment and prognosis showed that the proportion with unstaged and advanced disease (stages III and IV) is higher among elderly patients compared to younger ones and that their treatment is generally less aggressive, although the proportion receiving chemotherapy is increasing since the early 1990s. Disease specific (or relative) survival of elderly breast cancer patients is generally lower and the prevalence of serious (life expectancy affecting) co-morbidity is higher (>50% in patients over age 70).

Because of large individual variations in physical and mental conditions, limited evidence from RCTs and personal preferences prevailing in the decision-making process, treatment of older breast cancer patients seems difficult to fit into guidelines. Therefore, alternative research strategies are needed to understand and improve the care for the elderly breast cancer population, such as descriptive (registry-based) studies and a qualitative, individual-based approach.

1. General introduction: a changing picture

Breast cancer will increasingly affect the lives of older women, especially in developed countries. In the last three decades, women in all age groups have experienced the mortality lowering benefits of earlier diagnosis and more effective treatment of breast cancer. These benefits have been counteracted by the rising incidence, partly also by improved detection. At the same time, demographics are characterised by a large increase of the elderly population, which will become even more pronounced during the next decades. It is thus clear why the most remarkable increase in the absolute number of newly diagnosed breast cancer patients and long-term survivors (at risk for recurrent disease or second breast cancers) will be among the higher age groups, the prevalence doubling from 3.5% in 2000 to 7% in 2015 in the Netherlands.[1] Being confronted with these rising numbers of patients or anticipating them, many doctors and clinical researchers have taken a special interest in the study of breast cancer in older women, whose poorer physical and mental condition and different personal preferences with respect to the available treatment options and the lack of evidence-based guidelines complicate the decision-making process.[2]

* *Corresponding author:* Tel.: +31 40 2971616; fax: +31 40 2971610.
E-mail address: research@ikz.nl (W.J. Louwman).
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This review addresses the most recent trends in diagnosis, treatment and prognosis of breast cancer in older women and provides explanations for these trends. These trends will be illustrated in depth by data of the Eindhoven Cancer Registry, because of its unique clinical data on comorbidity, or by European data. Cancer registry data show actual variations in patterns of staging and treatment by age and therefore offer a scope for improvement of care and for feeding guidelines, in addition to randomised clinical trials (RCTs). However, because of the limitations met in the elderly to perform RCTs, other research strategies also need to be explored, as will be done in this review. But first, an overview will be given of published population-based studies on breast cancer in elderly women during the last five years.

2. Population-based studies on elderly breast cancer patients (Tables 1 and 2)

We searched for population-based studies describing age-related differences in staging, treatment and prognosis of breast cancer. The search was performed in PubMed in June 2007 and was limited to studies written in English and published during the last 5 years. The following combination of search terms was used: *breast cancer AND (cancer registry OR cancer registries OR population based) AND (elderly OR advanced age) AND (stage OR treatment OR survival)*. This resulted in 836 hits from which 30 papers were selected based on their title and abstract. After reading the full text of these 30 papers, it was decided that 22 fulfilled the selection criteria. The results of these population-based studies have been summarised in Table 1.

Among elderly breast cancer patients, a relatively large proportion of 7–16% remained unstaged.[3–7] Generally the proportion with advanced disease (stages III and IV) was clearly higher among elderly patients compared to younger ones.[5–8] The treatment of elderly breast cancer patients was generally less aggressive than for younger patients.[3,5,9] Although more patients have received chemotherapy since the early 1990s, its use is still less frequent among the elderly.[5,10–15] Moreover, they were less likely to receive radiotherapy[3–5,13,16–18] than younger patients, illustrating the preference for mastectomy without radiotherapy instead of breast conserving treatment (including lumpectomy with axillary dissection and radiotherapy).[13]

Disease specific (or relative) survival of elderly breast cancer patients was generally lower compared to younger patients,[3,13,18] as was also demonstrated in most European cancer registries (Table 2).[19,20] Comorbidity is present more often among elderly patients[13,18,21] and is also related to (sub-optimal) treatment.[5,11,12,16]

3. Recent trends in epidemiology and treatment of breast cancer in the elderly

3.1. Diagnosis

Already in the 70s and early 80s there was a clear tendency towards earlier diagnosis of breast cancer, especially in the younger age groups, as was illustrated by the date of Eindhoven Cancer Registry.[22] The percentage of tumours measuring $\leqslant$2 cm rose from more than 20% to almost 45%. The steadily increasing use of early detection and screening strategies since the early 70s, in combination with the rising public awareness of breast cancer, is considered to be the most likely explanations for this favourable trend. However, no further improvement was observed in the stage distribution for patients aged <50 years, may be because better staging could also have led to more node-positive patients. For patients aged 50–69 years, the stage distribution continued to improve as a result of the introduction of mass mammographic screening, with particularly high attendance rates (85%).[23] A similar improvement was observed for women aged 70–79 years, following the extension of the upper age limit of the screening programme to 75 years in 1998. Recent data show that the stage distribution of patients aged 70–79 years is now almost similar to the stage distribution of all younger age groups (Fig. 1). Women of 80 years and older, however, remained at a higher risk of being diagnosed with more advanced disease.

The detection of small non-palpable lesions by screening has boosted the development and introduction of less invasive staging procedures, such as large core needle biopsy, and localisation procedures.[24] Although not invited for the screening programme, patients aged 75+ years have certainly benefited from these developments as well.

3.2. Prognosis

Relative survival is the preferred way to describe the prognosis of older (breast) cancer patients, because it takes into account the risk of dying from other causes than the disease of interest. An alternative method is to calculate disease-specific survival. However, obtaining reliable information on the cause of death carries the risk of misclassification, especially when the patient has more than one cancer. Retrieving the cause of death may be more difficult for older patients, who are more likely to be admitted to nursing homes and thus disappear from the view of the treating physician or general practitioner. Another complicating factor, also affecting the reliability of relative survival rates of elderly patients and the comparability between populations, is the under-notification of cancer diagnosis in patients with a very bad prognosis, often suffering from other serious co-morbid conditions, whose information may not reach at all the data sources commonly monitored by cancer registries. Fourteen percent of the newly diagnosed patients at age 70–79 and 22% older than age 80 suffered from $\geqslant$2 concomitant conditions. International comparisons of cancer survival estimates, such as in the EUROCARE studies, may also be complicated by the proportion of cases registered purely from death certificate information (DCO cases). A recent analysis of the impact of incomplete ascertainment of cancer cases and the presence of DCO cases concluded that these phenomena should be taken into account when comparing survival estimates between different populations[25] especially for older patients, as incompleteness and DCO registration is associated with increasing age.[26]

Relative survival of breast cancer patients of 70 years is similar to the survival of patients aged 40–70 years, as is indicated by recent data of the Eindhoven Cancer Registry (Fig. 2). Only slightly lower survival rates were observed for patients

Table 1 – Population-based studies of stage, treatment and survival of elderly women with breast cancer, diagnosed since 1990

Authors	Registry (Diagnostic period)	Patients			Outcome		
		No.	Age	Stage	Stage-distribution	Treatment	Survival
Lavelle et al.[9]	North Western Cancer registry (1999)	480	⩾65	Non-metastatic		Less treatment at age ⩾ 80 compared to age 65–69 yrs, unexplained by tumour characteristics	
Doyle et al.[4]	SEER (1992–2000)	48,353	⩾65	I–III	Stage I: 62% Stage II: 31% Stage III: 7%	42% lumpectomy and 55% mastectomy. 45% adjuvant RT, 15% adjuvant CT and 9% adjuvant RT and CT. No increased risk of myocardial infarction after RT	
Aziz et al.[42]	SEER (1990–1995)	20,151	⩾70	I–II	Stage I: 62% Stage II: 38%	75% ALND (No data on systemic therapy and comorbidity)	No survival benefit for ALND treatment over lumpectomy/mastectomy
Gorin et al.[33]	SEER (1992–1999)	49,865	⩾65	All stages	*In situ*: 12% Stage I: 47% Stage II: 30% Stage III: 6% Stage IV: 5%		
Smith et al.[16]	SEER (1992–1999)	11,594	⩾70	T: 1–4 N: 0–3 M: 0		38% of high risk (T3–4 and/or N2–3) patients received PMRT	Adjuvant PMRT has survival benefit for high risk (T3/4 and/or N2/3) women
Punglia et al.[17]	SEER (1991–1999)	19,699	⩾65	I–III	Stage I: 47% Stage II: 45% Stage III: 7%	11% PMRT. More PMRT during 1996 until 1999, compared to 1991	
Elkin et al.[11]	SEER (1992–1999)	5081	⩾66	Hormone receptor-Negative, Stages I–III		Overall 34% adjuvant CT, 52% at age 66–69 years and 5% for 85+. Overall proportion of adjuvant CT from 25% in 1992 to 45% in 1999	15% reduction of mortality through adjuvant CT. Greatest overall survival benefit in node-positive patients and node-negative patients who where likely to receive CT
Giordano et al.[12]	SEER (1991–1999)	41,390	⩾65	I–III		11% CT (from 7% in 1991 to 16% in 1999)	CT decreased breast cancer mortality in N0 and ER-patients
Smith et al.[43]	SEER (1992–1999)	8724	⩾70	N0, ER+		RT decreased risk on second ipsilateral breast cancer or a subsequent mastectomy. An absolute risk reduction of 4.0 events (from 5.1 to 1.1) per 100 women at 5 years	

Eaker et al.[3]	Breast cancer register for the Uppsala/Örebro health-care region (1992–2002)	9059	50–84	I–IV	Stage I: 40% Stage II: 38% Stage III: 5% Stage IV: 2% Unstaged: 16%	Less RT or CT treatment	5-year relative survival of 90%, 89%, 81% and 77% for age 50–69, 70–74, 75–79 and 80–85 years. Relative excess mortality rate of 1.7 among ages 80–84 compared to the 50–69 year old
Doyle et al.[10]	SEER (1992–1999)	31,748	⩾65	I–III	Stage I: 50% Stage II: 32% Stage III: 5% Unknown: 13%	More cardiomyopathy after CT with anthracyclines, (adjusted for baseline heart disease). Less pre-existing heart disease in patients with CT	
Janssen-Heijnen et al.[18]	Eindhoven Cancer Registry (1995–2002)	7978	⩾50	All stages		32%, 52% and 67% in the age-groups 50–64, 65–79 and 80+ had any co-morbidity. Less adjuvant RT and more endocrine therapy for patients with co-morbidity. Less surgery and more endocrine therapy for older patients	81% 5 year relative survival for the 70+ age group, 86% for the age-group <70 years
Louwman et al.[13]	Eindhoven Cancer Registry (1995–2001)	8966	All	All stages		Serious concomitant conditions in 41% and 56% of the age-groups 70–79 and 80+. Less treatment and worse prognosis for patients with comorbidity	5 year survival at age ⩾70 yrs, no comorbidity 93%, cardiovascular disease 77%, diabetes mellitus 69%, ⩾2 concomitant diseases 53%
Adams et al.[7]	The Northern Yorkshire Cancer Registration and Information services (1998–2000)	12,419	All	All stages	More advanced stage in women 65> years compared to <55. Less high grade in elderly	The chances of data on stage and grade at diagnosis being unavailable increased with age. Probably due to less intensive investigation of the tumour	

(*continued on next page*)

Table 1 – *continued*

Authors	Registry (Diagnostic period)	Patients			Outcome		
		No.	Age	Stage	Stage-distribution	Treatment	Survival
Houterman et al.[21]	Eindhoven Cancer Registry (1995–1999)	549	⩾40	All stages		At least one concurrent disease in 78% and 92% of the age-groups 70–79 and 80+	5-year survival at age ⩾70%, 78%, 73% and 46% for patients with no, low/moderate and high impact comorbidity HR of 3.0 after adjustment for age, nodal status and treatment for high impact versus no comorbidity
Sant et al.[6]	SEER and EUROCARE (1990–1992)	17,650	All	All stages SEER EUROCARE	70–99 years: T1N0M0: 43% T2-3N0M0: 19% T1-3N+M0: 18% T4M0: 7% M1: 6% Not available: 7% T1N0M0: 24% T2-3N0M0: 20% T1-3N+M0: 24% T4M0: 11% M1: 8 Not available: 13%		
Bouchardy et al.[5]	Geneva cancer registry (1989-1999)	407	⩾80	All stages	I (incl. 6 *in situ*): 22% II: 42% III: 15% IV: 9% Unknown: 12%	12% no treatment, 32% tamoxifen, 7% breast-conserving surgery, 33% mastectomy (19% adjuvant therapy), 14% breast-conserving surgery + adjuvant therapy, 2% miscellaneous treatments	Five year specific breast cancer survival: 46%, 51%, 82%, 62% and 90% in cases of no treatment, tamoxifen, mastectomy, mastectomy + adjuvant therapy, breast-conserving therapy + adjuvant therapy
Randolph et al.[8]	SEER (1995–1996)	12,038	⩾69	All stages		Less women aged ⩾75 had mammography in the 2 years before diagnosis than women aged 69–74 and bigger and more high stage tumours (adjusted for confounders)	

	period)	No.	Age	Stage	Stage-distribution	Treatment	Survival
Du et al.[44]	SEER (1991–1996)	35,060	⩾69	All stages		OR for hospitalisation for toxicity (neutropaenia, fever, thrombocytopaenia, adverse effect systemic therapy) 14.4 in women receiving chemotherapy compared to women not receiving chemotherapy. 1.3 OR for 2 or more comorbidities versus no comorbidities	
Vulto et al.[30]	Eindhoven Cancer Registry (1996–2000)	6561	All	All stages		47% of the women aged ⩾70 received primary RT. The OR for receiving secondary RT was 0.4 compared to women aged ⩽49 years. No significant influence by number of concomitant diseases	

SEER, Surveillance Epidemiology, and End Results, a database of 11 population based cancer registries in the USA.
RT, radiotherapy; CT, chemotherapy; PMRT, Post mastectomy radiotherapy; ALND, axillary lymph node dissection; SNB, sentinel node biopsy.

Table 2 – Relative 5-year survival in EUROCARE 3 (19), patients diagnosed 1990–1994

Country	65–74 years		75–99 years	
	n	Survival (%)	*n*	Survival (%)
Austria	395	75	354	73
Czech Republic	400	65	237	57
Denmark	3225	73	3151	66
England	19,532	72	20,781	60
Estonia	466	62	303	58
Finland	2301	80	2213	71
France[a]	1338	82	1178	70
Germany	750	79	623	74
Iceland	77	75	94	80
Italy[b]	6275	81	5256	73
Malta[c]	89	74	60	64
Netherlands (IKA and IKZ-only)	2244	78	1963	72
Norway	2102	80	2481	72
Poland	962	62	629	56
Portugal[d]	285	73	184	74
Scotland	2803	69	3045	60
Slovakia	1380	61	796	50
Slovenia	766	66	504	59
Spain[b]	2426	76	1632	77
Sweden	5989	86	5620	72
Switzerland[a]	417	81	471	67
Wales	2064	68	2409	52
Overall	56,286	76	53,984	69

a Not all registrations of this country registered until 1994.
b Not all registrations of this country registered from 1990 onwards.
c Registered from 1993 until 1994.
d Registered from 1991 until 1993.

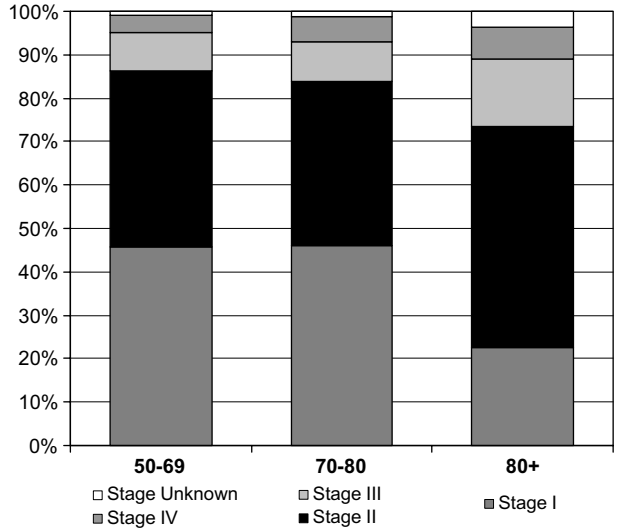

Fig. 1 – Stage distribution among patients with invasive breast cancer aged 50 years or older, according to age group. Period of diagnosis 2000–2005. (*Source:* Eindhoven Cancer Registry).

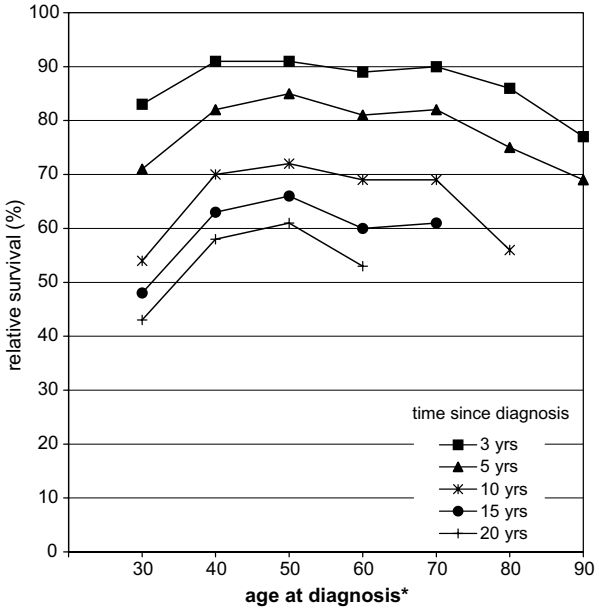

Fig. 2 – Relative survival of breast cancer patients diagnosed between 1990 and 2002 in Southeastern Netherlands, according to age at diagnosis (*midpoint of 10 year age interval) and time since diagnosis.

of 80 years and older, despite their poorer stage distribution and under-treatment, indicating that tumours behave less aggressively in older patients. Support for this hypothesis comes from Italy, where it was also found that the tumours of elderly women were larger with a higher risk of positive lymph nodes, but at the same time were more likely to be c-ERBB2 positive and have positive oestrogen- and progesterone receptors, a lower grade and lower proliferation indices.[27]

There is likely to be much variability in aggressiveness of the disease in this age group, stressing the need for a better understanding of the biology in older women to improve prognostication and choice of therapy.[28]

3.3. *Treatment*

Like their younger counterparts, older breast cancer patients have benefited from the development and introduction of less invasive staging and treatment procedures, and new drugs. Still, age continues to play an important role in the use of these and other procedures, which are considered standard care for younger women. Data from the Netherlands Cancer Registry indicate that there was not much difference between patients younger than 70 and those aged 70–80 years with respect to the use of breast-conserving surgery and the use of radiotherapy following BCS (Figs. 3–5).[29] However, the picture was completely different for women of 80 years and older, which constituted 8% of the total group. After adjustment for stage, grade and the presence of co-morbidity, age appeared to be a stronger factor for receiving radiotherapy than co-morbidity.[30] In fact, after BCS, patients aged 80 years or older were 10 times less likely to receive radiotherapy than those of 50–64 years of age (OR 0.1; 95% CI 0.1–0.2). These results seem to imply that older age tends to be confused with chronic illness. Other factors, such as the distance to radiotherapy facilities, and the protracted radiotherapy course, frailty, limited social support and psychological and economic factors and patients' or family's preference are also mentioned as explanatory factors.

The same age-related pattern was observed with respect to axillary lymph node staging. In 1997, just before the introduction of sentinel node biopsy in the south-east Netherlands 23% of the women of 70–80 years did not undergo an axillary staging procedure (i.e., axillary dissection), compared to 42% of the patients of 80 years and older (Fig. 6). Considering the limited morbidity associated with sentinel node biopsy and the valuable prognostic information resulting from it, one would expect the introduction of this procedure to lead to a substantial decrease in the proportion of elderly patients not undergoing axillary staging. This was only true for women of 70–80 years, where this proportion decreased to 13%. In 2005, only 33% of the patients of 80 years and older underwent a sentinel node procedure and 41% did not undergo any axillary staging.

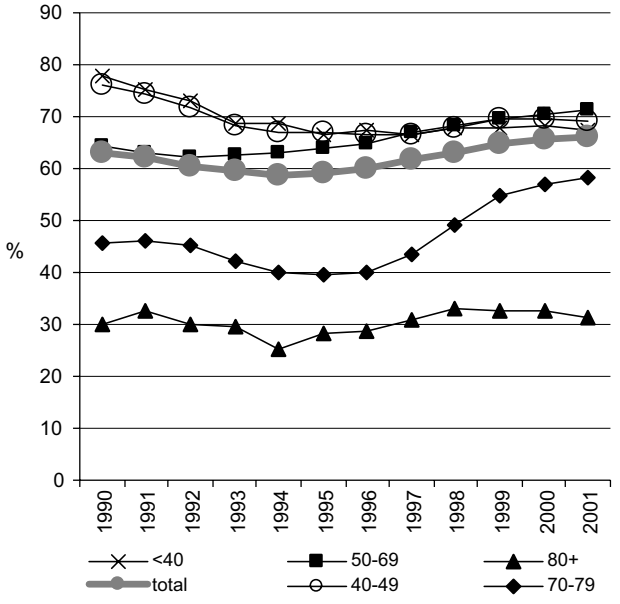

Fig. 3 – Proportion of patients with invasive breast cancer ⩽2 cm (pT1) undergoing breast-conserving surgery. (*Source:* Netherlands Cancer Registry).

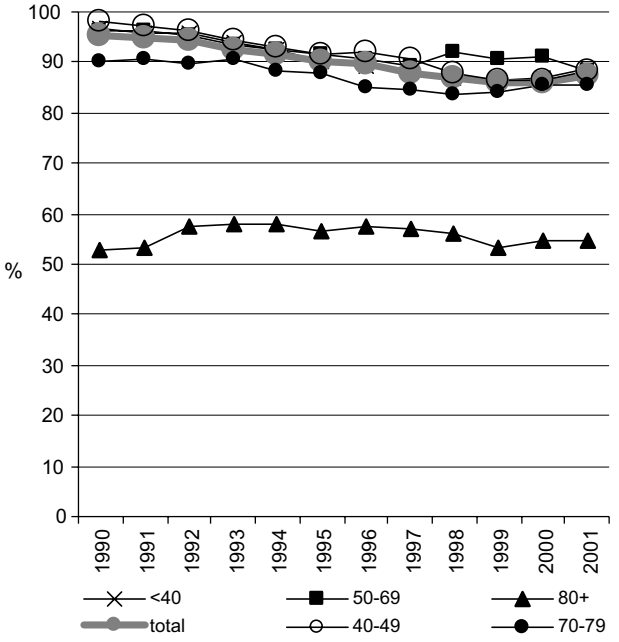

Fig. 4 – Proportion of patients with invasive breast cancer ⩽2 cm (pT1) receiving radiotherapy following breast-conserving surgery. (*Source:* Netherlands Cancer Registry).

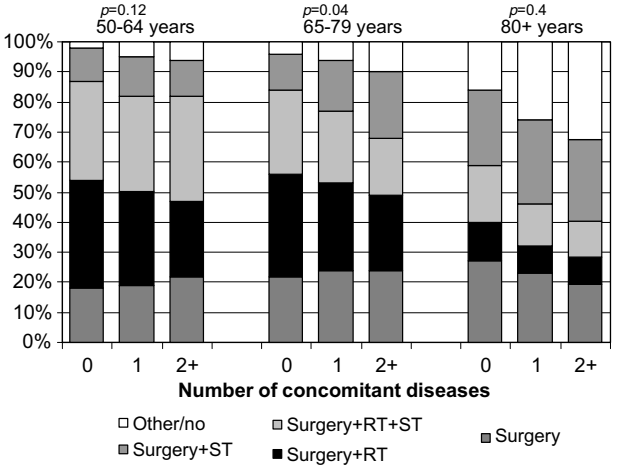

Fig. 5 – Primary treatment of patients with invasive breast cancer from 1995 to 2002, according to age and concomitant disease. RT: radiotherapy. (*Source:* Eindhoven Cancer Registry).

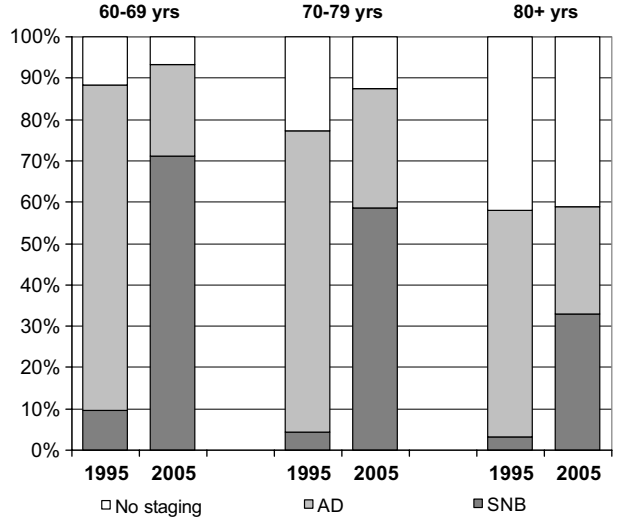

Fig. 6 – The proportion of patients undergoing axillary dissection (AD), sentinel node biopsy (SNB) or no axillary staging procedure in 1995 and 2005. (*Source:* Eindhoven Cancer Registry).

The previous data illustrate that special efforts should be put in studying the safety of less aggravating treatment plans, such as intra-operative radiotherapy as well as the implementation of such alternatives. In effect, omitting axillary staging, restricted use of breast-conserving surgery and omitting post-operative radiotherapy have remained a rather common practice among elderly patients, especially in those of 80 years and older, and these differences are only partly explained by the presence of concurrent diseases in these patients. Similar deviations from practice guidelines in the elderly have been observed in other studies,[31,32] but still little is known about the possible reasons; it is up to the attending physicians to weigh the benefits of a breast cancer specific intervention against the (short-term) harms and competing risk of dying from other causes in each individual patient.[33]

4. Current dilemmas and directions for future research (Table 3)

Clinical trials are credited for a large proportion of the improvements in cancer therapy. The major thread for the implementation and reproducibility of trial results is the selective uptake of older patients in RCTs, related to their co-morbidity, lack of understanding of the consent procedure and deficient social support. If still desirable, RCTs testing less aggressive and arduous treatment strategies and aiming at the majority of the elderly will be much more likely to be successful in entering a sufficient number of patients and provide widely applicable results than trials designed exclusively for patients without functional limitations[34] (see Table 3).

There is evidence that selection of patients may explain differences in outcome between randomised patients and patients not entering a trial[35] and there is a lack of effective strategies for trial enrolment, especially for elderly cancer patients.[3,36] To enable valid generalisation of trial results, a thorough administration of the total number of eligible patients in each participating centre is needed, as well as the reasons why patients were not entered into the trial. In most academic and general hospitals, the annual number of patients older than 75 years will vary between 5 and 30, depending on the size of the hospital. Considering this relatively small number of patients and the large inter-individual differences in physical and mental health, increasing the need for individualised treatment plans, it is clear that sufficient patient

Table 3 – Research strategies to understand and improve care for elderly patients

Strategy	Strengths	Limitations
Randomised controlled trials (RCTs)	Controlled conditions of the trial provide strong conclusive evidence of cause-and-effect relationships	Problems with implementation and reproducibility because of selective uptake of older patients (related to co-morbidity, lack of understanding of the consent procedure and deficient social support)
Descriptive studies (cancer registry or hospital-based registry)	Collecting standard data on tumour stage, disease characteristics and treatment will be sufficient to monitor adherence to guidelines or the implementation of new guidelines. Adding co-morbid conditions to the database will help to find some explanations for non-compliance with guidelines	Documentation of data for the very elderly patients is as good as practice delivers and that is likely to be variable
	Collection of follow-up data will give an impression of outcome (such as loco-regional control, quality of life, treatment-related complications and health care utilisation)	Completeness and quality of the data is dependent on the accuracy and discipline of doctors to document information in their clinical files
Qualitatively oriented (accurate documentation of steps preceding diagnosis and treatment for each individual patient)	Recognising patterns in the structure or organisation of breast cancer care underlying suboptimal care and unfavourable treatment outcomes, which would otherwise have remained undetected	Documentation for a considerable period of time is needed
	Enables evaluation of new concepts such as the role of shared decision making and the assessment of patient and doctor preferences in improving the quality of care	Completeness and quality of the data is dependent on the accuracy and discipline of doctors to document information in their clinical files

accrual will remain a threat for the success of future trials in the elderly.

The difficulty of developing and performing RCTs for the elderly and the uncertainties about the applicability of the results to general practice leave ample room for descriptive studies,[37] based on data of cancer registries or hospital-based registries. Collecting standard data on tumour stage, disease characteristics (i.e., grade, steroid receptor status) and treatment (i.e., surgery, radiotherapy and adjuvant systemic treatment) will be sufficient to monitor adherence to guidelines or the implementation of new guidelines. Adding co-morbid conditions to the database will help to find some explanations for non-compliance with guidelines. Moreover, cancer registries should also consider to collect follow-up data to evaluate treatment outcome. Loco-regional control of disease may be such a parameter, but also the assessment of quality of life, treatment-related complications and health care utilisation at certain points during follow-up in a random sample of the patients should be relatively easy to organise by a cancer registry. But even then cancer-registry based studies have their limitations. Documentation of data for the very elderly patients is as good as practice delivers and that is likely to be variable. Completeness and quality of the data is dependent on the accuracy and discipline of doctors to document information in their clinical files. Electronic patient records with predefined data fields may increase the completeness of the data and may be used by the cancer registry to link with other relevant clinical data and follow-up data. But it is possible that even these extra efforts to increase the accuracy and the completeness of the data will be insufficient to visualise and analyse the complexity of the decision-making process.

A more qualitatively oriented strategy would be to analyse the decision-making process in each individual patient by an accurate documentation of the steps preceding diagnosis and treatment. For example, which clinical information was available when a clinical decision was made and what information was taken into account? Which disciplines were involved in the decision-making process? In combination with a structured evaluation and discussion of the data, this method may result in recognising patterns in the structure or organisation of breast cancer care underlying suboptimal care and unfavourable treatment outcomes and which would otherwise have remained undetected. Such a strategy may also be useful to evaluate the potential contribution of a comprehensive geriatric assessment[38] and of new concepts such as shared decision making[28] and the assessment of patients and doctor preferences[39–41] to the improvement of quality of care in older patients.

Conflict of interest statement

None declared.

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