Chapter 6

Elderly postmenopausal patients with breast cancer are at increased risk for distant recurrence

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Abstract

Background

For postmenopausal patients with hormone receptor positive breast cancer, breast cancer survival decreases with increasing age at diagnosis. The aim of this study was to assess the incidence of breast cancer recurrence, both locoregional and distant recurrence, and contralateral breast cancer, by age at diagnosis.

Methods

Patients enrolled in the Tamoxifen Endocrine Adjuvant Multinational (TEAM) trial were included. Primary endpoints were locoregional recurrence, distant recurrence and contralateral breast cancer. Age at diagnosis was categorized as younger than 65 years, 65-75 years, and 75 years or older.

Results

Overall, 9,766 patients were included, of which 5,349 were younger than 65 years (reference group), 3,060 were 65-75 years, and 1,357 were 75 years or older. With increasing age, a decreased administration of radiotherapy after breast conserving surgery (94%; 92%; 88% respectively) and adjuvant chemotherapy (51%; 23%; 5% respectively) was observed. Risk of distant recurrence increased with age at diagnosis; multivariable hazard ratio for patients aged 65-75 years was 1.20 (95% CI 1.00-1.44), hazard ratio for patients aged 75 years or older was 1.39 (95% CI 1.08-1.79). Risks of locoregional recurrence and contralateral breast cancer were not significantly different across age groups.

Conclusion

Elderly breast cancer patients were at increased risk for distant recurrence. Others have shown that the risk of distant recurrence is mainly affected by adjuvant systemic therapy. All TEAM patients received adjuvant endocrine treatment, however, chemotherapy was administered less often in elderly patients. These findings are suggestive for consideration of chemotherapy in relatively fit elderly breast cancer patients with hormone sensitive disease.

Introduction

Breast cancer is the most common type of cancer in women in Western societies. Worldwide, nearly a third of all breast cancer patients are 65 years or older, and in more developed countries this proportion increases to over 40%[1]. Because of an increasing life expectancy and raised breast cancer incidence with increasing age, the disease will progressively affect the lives of elderly women[2].

Many have published on the worse prognosis of premenopausal compared with postmenopausal breast cancer patients[3-5]. However, evidence is lacking on age specific breast cancer outcome *within* postmenopausal women. Recently, we reported that breast cancer survival in postmenopausal patients decreased with increasing age[6]. To gain further insight in the relation between age at diagnosis and breast cancer outcome, we studied the incidence of breast cancer recurrence, both locoregional and distant recurrence, and contralateral breast cancer, by age at diagnosis in patients included in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) Trial.

Methods

Study population

The TEAM trial has been described extensively in previous reports[6;7]. In short, 9,766 postmenopausal women with estrogen and/or progesterone receptor positive breast cancer, who completed local therapy with curative intent, were randomized to receive either exemestane 25 mg daily for five years or a sequential regimen consisting of tamoxifen 20 mg daily for 2.5–3 years, followed by exemestane 25 mg daily for 2.5–2 years. Adjuvant chemotherapy, if indicated, was given before start of endocrine therapy, and radiotherapy was administered according to local practice. Participants commenced the assigned endocrine study treatment within 10 weeks of completion of surgery and chemotherapy, if indicated. Patients were ineligible if they had a malignancy within five years preceding breast cancer diagnosis, an Eastern Cooperative Oncology Group (ECOG) performance status of more than two, or a significant cardiac disease or other illness interfering with study participation and adequate follow-up. Participants were enrolled in Belgium, The Netherlands, United Kingdom, Ireland, United States of America, Japan, Greece, Germany, and France. Similar protocols were used in the nine countries, with minor differences to accommodate the local treatment guidelines[8]. The trial was registered with ClinicalTrials.gov, NCT00279448, NCT00032136, and NCT00036270; NTR 267; Ethics Commission Trial 27/2001; and UMIN, C000000057.

As the final results of the TEAM trial showed no significant differences in efficacy endpoints between both treatment arms[7], we were able to investigate disease recurrence regardless of

randomized treatment. The database was locked on October 7th 2010; the design of the current post hoc analysis was developed in July 2011.

Patients were categorized in three groups, based on age at diagnosis (younger than 65 years, 65-75 years, and 75 years or older) as discussed at the Meeting of the International Society of Geriatric Oncology (SIOG) in 2009 and in line with other publications[6;9;10]. Study endpoints were 1) locoregional recurrence (recurrence in the ipsilateral breast or chest wall, recurrence in ipsilateral axillary or supraclavicular lymph node(s), or other locoregional localization), 2) distant recurrence (recurrence in bone, skin, liver, lung, brain, or other distant localization), and 3) contralateral breast cancer (new primary invasive tumor in the contralateral breast), whichever came first. In situ carcinoma was not considered to be a recurrence. For 61 patients with synchronously recurrent disease at more than one site, the localization most likely determining the prognosis was used as endpoint.

Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL). Cox proportional hazard models were used to evaluate the association between age at diagnosis and the endpoints. Covariates were included in the multivariable model if they were judged to be clinically relevant. First, estimates were adjusted for country and tumor characteristics (country of residence, histological grade (Bloom Richardson grade I; II; III), T stage (T1; T2; T3,4), nodal stage (negative; positive), estrogen receptor status (negative; positive), and progesterone receptor status (negative; positive)). Next, the fully adjusted model comprised both tumor and treatment characteristics (country, histological grade, T stage, nodal stage, estrogen receptor status, progesterone receptor status, type of surgery (mastectomy; wide local excision), radiotherapy (yes; no), chemotherapy (yes; no), allocated endocrine therapy

Table 1. Distribution of locoregional recurrence and distant recurrence by age at diagnosis.

	<65 years		65-75 years		≥75 years		p
	n	(%)	n	(%)	n	(%)	
Locoregional recurrence							0.24
Ipsilateral breast	55	(49.1)	20	(40.8)	13	(40.6)	
Chest wall	23	(20.5)	16	(32.7)	11	(34.4)	
Ipsilateral lymph node(s)	16	(14.3)	5	(10.2)	6	(18.7)	
Supraclavicular lymph node(s)	8	(7.1)	2	(4.1)	0	(0)	
Other	10	(8.9)	6	(12.2)	2	(6.3)	
Distant recurrence							0.50
Bone	139	(34.0)	95	(38.5)	53	(40.8)	
Liver	144	(35.2)	77	(31.2)	37	(28.5)	
Lung	60	(14.7)	36	(14.6)	22	(16.9)	
Skin	9	(2.2)	7	(2.8)	1	(0.8)	
Brain	11	(2.7)	4	(1.6)	4	(3.1)	
Other	46	(11.3)	28	(11.3)	13	(10.1)	

(tamoxifen followed by exemestane; exemestane) and persistence of endocrine therapy (discontinuation of allocated endocrine therapy because of either adverse events, intercurrent illness, patient refusal or other reasons; continuation of allocated endocrine therapy, or having an event while on study medication)). Patients with missing data were not included in the multivariable model. All statistical tests were two-sided. P values <0.05 were considered to be statistically significant.

Results

Overall, 9,766 patients (range 35-96, median age 64 years) were included; 5,349 were younger than 65 years (median 58 years), 3,060 were 65-75 years (median 69 years), and 1,357 were 75 years or older (median 79 years). Baseline characteristics by age groups were shown in an earlier report[6]; elderly patients presented with larger tumors, without differences in nodal status. With increasing age, the proportion of mastectomy increased significantly, while a marked decrease was observed in the administration of radiotherapy following a wide local excision (94%; 92%; 88% respectively, p<0.001) and administration of chemotherapy (51%; 23%; 5% respectively, p<0.001)[6].

At database lock, median follow-up (interquartile range) from randomization was 5.1 years (4.2-6.0 years), during which 1,062 first events were registered; 193 locoregional recurrences, 786 distant recurrences and 83 contralateral breast cancers. As shown in Table 1, the distribution of locoregional recurrence and distant recurrence was similar across age groups. Figure 1 shows the cumulative incidence of endpoints by age at diagnosis. Cumulative incidence of

Table 2. Breast cancer recurrence by age at diagnosis.

	5-years event		Univariate	p	Multivariable*	p	Multivariable**	p
	n	(%)	HR (95% CI)		HR (95% CI)		HR (95% CI)	
Locoregional recurrence				0.10		0.14		0.10
<65 years	100	(2)	1 (reference)		1 (reference)		1 (reference)	
65-75 years	42	(1)	0.77 (0.55-1.08)		0.71 (0.49-1.04)		0.67 (0.45-0.99)	
≥75 years	27	(3)	1.24 (0.84-1.84)		1.10 (0.71-1.70)		1.00 (0.61-1.63)	
Distant recurrence				**0.006**		0.08		**0.024**
<65 years	378	(8)	1 (reference)		1 (reference)		1 (reference)	
65-75 years	219	(8)	1.06 (0.91-1.24)		1.14 (0.96-1.36)		1.20 (1.00-1.44)	
≥75 years	115	(10)	1.37 (1.13-1.68)		1.26 (1.01-1.57)		1.39 (1.08-1.79)	
Contralateral breast cancer				0.73		0.79		0.75
<65 years	34	(1)	1 (reference)		1 (reference)		1 (reference)	
65-75 years	21	(1)	0.98 (0.60-1.60)		0.99 (0.59-1.66)		1.03 (0.60-1.77)	
≥75 years	11	(2)	1.26 (0.68-2.33)		1.24 (0.64-2.38)		1.31 (0.64-2.68)	

HR: Hazard ratio; CI: confidence interval. * Hazard ratios adjusted for country, histological grade, T stage, nodal stage, estrogen receptor, and progesterone receptor. ** Hazard ratios adjusted for country, histological grade, T stage, nodal stage, estrogen receptor, progesterone receptor, surgery, radiotherapy, chemotherapy, endocrine therapy and persistence of endocrine therapy.

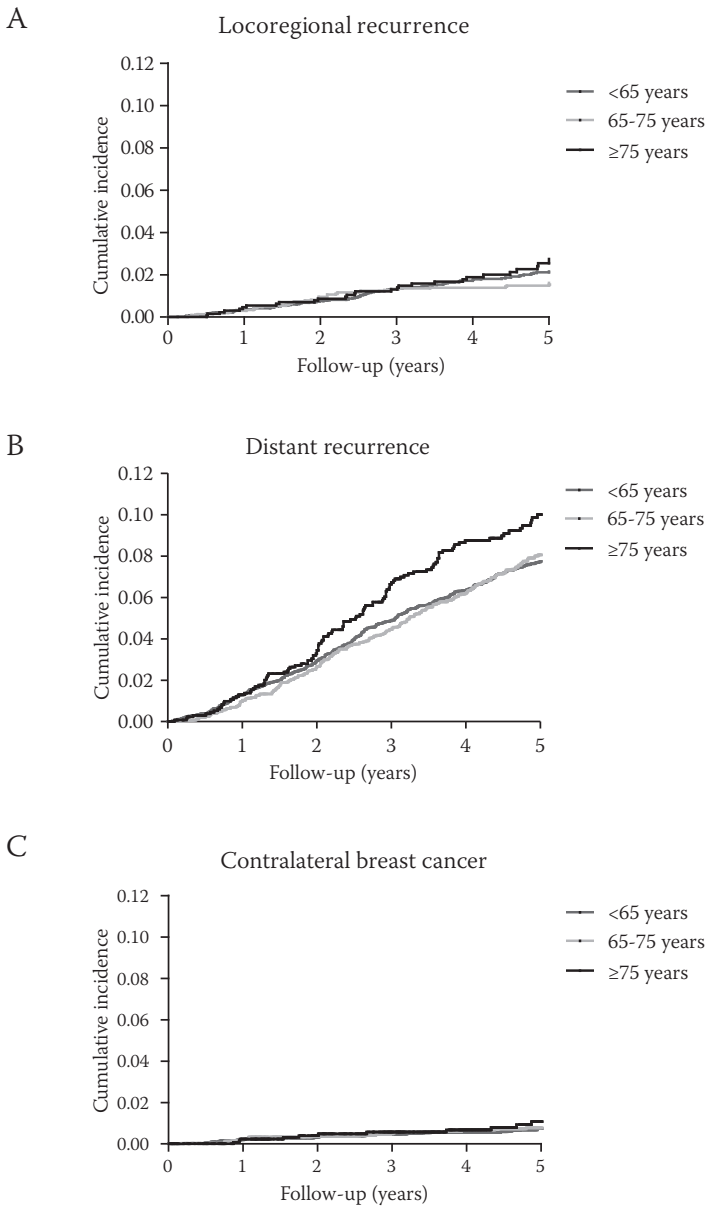

Figure 1. Cumulative incidence of A) locoregional recurrence, B) distant recurrence C) and contralateral breast cancer by age at diagnosis.

locoregional recurrence was 2.1%, 1.6%, and 2.4% respectively; cumulative incidence of distant recurrence increased from 7.6% in patients younger than 65 years, 8.1% in patients aged 65-75 years of age, to 9.6% in patients aged 75 years or older. Cumulative incidence of contralateral breast cancer was 0.8%, 0.8%, and 1.0% respectively.

Table 2 shows the results of Cox regression analyses. In both univariate and multivariable analyses, the risk of locoregional recurrence was similar across age categories. Contrary, the risk of distant recurrence increased with increasing age at diagnosis. Patients aged younger than 65 years functioned as a reference, univariate hazard ratio (HR) for patients aged 65-75 was 1.06 (95% confidence interval (CI) 0.91-1.24) and HR for patients aged 75 years or older was 1.37 (95% CI 1.13-1.68). Both the partly and fully adjusted model showed comparable results; the fully adjusted HR for patients aged 65-75 was 1.20 (95% CI 1.00-1.44); HR for patients aged 75 years or older was 1.39 (95% CI 1.08-1.79), p=0.024. The risk of contralateral breast cancer was not significantly different across age categories.

To test the sensitivity of the endpoints, three alternative analyses were performed. The results of these alternative analyses were similar to the main results. First, survival analyses were repeated without restriction to the *first* site of recurrence, i.e. all events irrespective of the sequence of occurrence were included in the analysis. Multivariable HR for locoregional recurrence was 0.79 (95% CI 0.57-1.09) for patients aged 65-75 years, and 0.94 (95% CI 0.62-1.43) for patients aged 75 years or older; multivariable HR for distant recurrence was 1.17 (95% CI 0.98-1.40) for patients aged 65-75 years, and 1.39 (95% CI 1.09-1.76) for patients aged 75 years or older; and multivariable HR for contralateral breast cancer was 0.90 (95% CI 0.53-1.52) for patients aged 65-75 years, and 0.92 (95% CI 0.46-1.83) for patients aged 75 years or older.

Second, synchronous endpoints (n=61) were recoded as locoregional recurrence, and contralateral breast cancer, respectively. Multivariable HR for locoregional recurrence, for patients aged 65-75 years was 0.76 (95% CI 0.54-1.06), HR for patients aged 75 years or older was 0.92 (95% CI 0.59-1.42), p=0.260; multivariable HR for distant recurrence, for patients aged 65-75 years was 1.20 (95% CI 0.99-1.46); HR for patients aged 75 years or older was 1.45 (95% CI 1.12-1.88), p=0.015; and multivariable HR for contralateral breast cancer, for patients aged 65-75 years was 1.05 (95% CI 0.62-1.80); HR for patients aged 75 years or older was 1.46 (95% CI 0.73-2.94), p=0.546.

Third, contralateral breast cancer was recoded as locoregional recurrence. Multivariable HR for locoregional recurrence, for patients aged 65-75 years was 0.77 (95% CI 0.56-1.06); HR for patients aged 75 years or older was 1.08 (95% CI 0.72-1.62), p=0.164.

Also, two additional analyses were performed to diminish selection bias. First, survival analyses for distant recurrence were stratified by T stage since increasing age was associated with larger tumors (Supplementary table 1). Although not significant, estimates were comparable to the main analysis. Second, survival analyses for locoregional recurrence were stratified by most extensive surgery since elderly patients more frequently underwent a mastectomy (Supplementary table 2). Again, the results remained similar.

Discussion

To summarize, we found that elderly breast cancer patients had a higher risk of distant recurrence, while the risks of locoregional recurrence and contralateral breast cancer did not significantly differ across age groups. Additional analyses were performed to test the robustness of the endpoints and to explore whether our findings may have been biased. Inclusion of three alternative definitions of endpoints did not alter the results. Moreover, stratified analyses by T stage and most extensive surgery revealed comparable estimates.

Many have published on predictors of breast cancer recurrence in premenopausal compared to postmenopausal patients. Virtually all studies observed a higher risk of locoregional breast cancer recurrence in premenopausal compared to postmenopausal women[4;5;11-14]. Few studies addressed breast cancer recurrence *within* postmenopausal patients, and again most focused on locoregional recurrence[15-18]. It is tempting to speculate on the possible mechanisms which may explain our findings. Based on the literature, we hypothesize that locoregional recurrence may reflect suboptimal local[19] and/or systemic[20] treatment, while distant recurrence and contralateral breast cancer more likely reflect suboptimal systemic treatment[20-23]. As all TEAM patients received endocrine treatment, the decreased administration of chemotherapy with increasing age may have contributed to a higher distant breast cancer recurrence in elderly patients. Of note, the hazard ratio for contralateral breast cancer for patients aged 75 years or older was comparable with the hazard ratio for distant recurrence, but the distribution of contralateral breast cancer was not statistically different across age groups, possibly due to a low number of events.

Few have studied chemotherapy efficacy in elderly breast cancer patients. In the Early Breast Cancer Trialists' Collaborative Group meta-analysis, not enough women older than 70 years were included to be able to draw conclusions about chemotherapy efficacy in this age group[20]. However, a review of randomized clinical trials on chemotherapy in node positive breast cancer patients revealed that older patients derived similar reductions in breast cancer mortality and recurrence compared to younger patients[24]. Recently, Muss et al evaluated the efficacy of two regimens of adjuvant chemotherapy in older women with early stage breast cancer. Standard chemotherapy showed to be superior to oral capecitabine, especially in patients with hormone receptor negative tumors. Two studies aimed to evaluate the benefit of chemotherapy in elderly breast cancer patients, in which chemotherapy was compared with a no treatment arm[25;26]. Both trials failed to recruit and were closed early. The investigators suggested that a recruitment failure was due to the inability to convince patients to accept randomization in which a no treatment arm was incorporated[25]. Our findings suggest that addition of chemotherapy might be of benefit in relatively fit breast cancer patients with hormone receptor positive breast tumors. This needs to be evaluated in future studies.

As the association between age and distant recurrence was not eliminated by adjustment for both tumor and treatment characteristics, additional mechanisms may play a role, such as different tumor biology resulting in worse breast cancer outcome[27]; or interplay between tumor and patient characteristics including immunosenescence, which may result in a higher risk of disease progression[28;29]; or a different response to anti-cancer therapy due to interactions with comorbidity and polypharmacy[30].

One may argue that increasing age may be associated with a lower adherence to endocrine therapy and consequently may result in a higher rate of recurrence. No data were available on adherence by pill count. However, multivariable analyses were adjusted for nonpersistence, which was defined as discontinuing the assigned endocrine treatment because of adverse events, intercurrent illness, patient refusal, or other reasons. Previously, we reported a higher rate of nonpersistence of endocrine therapy with increasing age, in the Dutch and Belgian patients included in the TEAM study. However, both in patients aged 65-75 years as well as in patients aged 75 years or older, survival was not affected by nonpersistence[31]. The absence of a consistent association between nonpersistence and outcome suggests that the current findings cannot adequately be explained by age specific adherence.

Strengths and limitations

A major strength of this study is the ability to study a large group of breast cancer patients followed as part of a clinical trial on endocrine therapy. Trial data comprise highly standardized treatment algorithms and virtually complete follow-up. The TEAM trial had very few exclusion criteria, among which there was no upper age limitation. This enabled us to study age specific breast cancer recurrence. However, although eligibility criteria of the TEAM trial were quite broad, it is known that trial populations generally comprise relatively healthy patients compared to the general population[32]. Additionally, as enrollment in the TEAM trial was restricted to postmenopausal patients with hormone receptor positive disease, these results may not necessarily be extrapolated to all breast cancer patients.

Conclusion

In conclusion, elderly breast cancer patients included in the TEAM trial had a higher risk of distant recurrence. This risk may be due to underuse of chemotherapy, which therefore might be considered in relatively fit elderly patients.

Supplementary table 1. Distant recurrence of breast cancer by age at diagnosis, stratified by T stage.

	5-years event n	(%)	Univariate HR (95% CI)	p	Multivariable* HR (95% CI)	p
T1				0.12		0.11
<65 years	130	(4)	1 (reference)		1 (reference)	
65-75 years	70	(4)	0.93 (0.71-1.23)		1.03 (0.74-1.42)	
≥75 years	26	(5)	1.41 (0.97-2.05)		1.60 (1.01-2.51)	
T2				0.54		0.14
<65 years	199	(12)	1 (reference)		1 (reference)	
65-75 years	126	(13)	1.11 (0.90-1.37)		1.26 (0.98-1.62)	
≥75 years	76	(13)	1.12 (0.87-1.44)		1.29 (0.93-1.80)	
T3, T4				0.76		0.70
<65 years	46	(21)	1 (reference)		1 (reference)	
65-75 years	23	(21)	1.11 (0.69-1.78)		1.22 (0.70-2.12)	
≥75 years	13	(17)	0.86 (0.48-1.57)		1.30 (0.63-2.69)	

HR: Hazard ratio; CI: confidence interval. * Hazard ratios adjusted for country, histological grade, nodal stage, estrogen receptor, progesterone receptor, most extensive surgery, radiotherapy, chemotherapy, endocrine therapy and persistence of endocrine therapy.

Supplementary table 2. Locoregional recurrence by age at diagnosis, stratified by most extensive surgery.

	5-years event n	(%)	Univariate HR (95% CI)	p	Multivariable* HR (95% CI)	p
Mastectomy				0.61		0.57
<65 years	54	(3)	1 (reference)		1 (reference)	
65-75 years	32	(3)	0.84 (0.55-1.29)		0.80 (0.49-1.31)	
≥75 years	21	(3)	1.08 (0.67-1.74)		1.06 (0.58-1.92)	
Wide local excision				0.19		0.11
<65 years	46	(2)	1 (reference)		1 (reference)	
65-75 years	10	(1)	0.60 (0.34-1.06)		0.49 (0.24-0.99)	
≥75 years	6	(1)	1.06 (0.51-2.24)		1.07 (0.45-2.52)	

HR: Hazard ratio; CI: confidence interval. * Hazard ratios adjusted for country, histological grade, T stage, nodal stage, estrogen receptor, progesterone receptor, radiotherapy, chemotherapy, endocrine therapy and persistence of endocrine therapy.

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