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Can patient-, treatment- and pathology-related characteristics explain the high local recurrence rate following breast-conserving therapy in young patients?

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Abstract

The aim of this study was to identify patient-, tumour- or treatment-related factors associated with young age that might explain the higher risk of ipsilateral breast recurrence that occurs after breast-conserving therapy (BCT) in young breast cancer patients. In the 'boost versus no boost trial', 5569 early-stage breast cancer patients were entered. All patients underwent tumorectomy followed by whole breast irradiation of 50 Gy. Patients having a microscopically complete excision were randomised between receiving no boost or a 16-Gy boost, while patients with a microscopically incomplete excision were randomised between receiving a boost dose of 10 or 26 Gy. The 5-year local control rate was 82% for patients $\leqslant 35$ years, 85% for patients aged 36–40 years, 92% for patients 41–50 years, 96% for patients 51–60 years and 97% for patients >60 years of age ($P<0.0001$). In young patients, the tumour was significantly larger and more often oestrogen and progesterone receptor-negative. Invasive carcinoma and the intraductal component were more often of a high grade. The intraductal component was more frequently incompletely resected in young patients. Re-excisions were performed more often (most probably due to a more frequent incomplete excision at the first attempt). The total volume of breast tissue removed at the tumorectomy was smaller in the younger patient group, even after including the volume removed during re-excision. When relating all these parameters (including age itself) to local control, the multivariate analysis stratified by treatment showed that age was the only independent prognostic factor for local control ($P=0.0001$). Including the boost treatment as a separate covariate, the analysis retained age and boost treatment as significant factors related to local control ($P<0.0001$). It was shown that the boost dose significantly reduced the 5-year local recurrence rate from 7 to 4% for patients with a complete excision ($P<0.001$). For patients 40 years of age or younger, the boost dose reduced the local recurrence rate from 20 to 10% ($P=0.002$). This large European Orgnaization for Research and Treatment of Cancer (EORTC) trial demonstrated an increased local recurrence rate in young patients. Although several associations between patient, tumour and treatment factors and age were found, that might explain the high local recurrence rate in the younger patients, it appears that age itself and the boost dose were the only factors that were independently related to local control.

Keywords: Breast cancer; Breast-conserving therapy; Local recurrence; Young age

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1. Introduction

Nowadays, breast-conserving therapy (BCT) (local tumour excision and a sentinel node procedure or axillary lymph node dissection followed by radiotherapy) is a generally accepted treatment option for patients with early-stage breast cancer. A number of trials [1–4] have shown that locoregional control and survival rates achieved with this therapy are comparable to those obtained with mastectomy. This was confirmed by the results of the meta-analysis published by the Early Breast Cancer Trialists' Collaborative Group in 1995 with a follow-up of at least 10 years [5]. Similar survival rates were also achieved in the European Organization for Research and Treatment of Cancer (EORTC) trial 10801 [6], comparing mastectomy with BCT in stage I and II breast cancer patients. Voogd and colleagues [7] combined the results of this study with the results of a similar trial of the Danish Breast Cancer Cooperative Group (protocol DBCG-82TM) in order to investigate prognostic factors for local recurrence and distant failure in BCT versus mastectomy. They concluded that vascular invasion and histological grade were risk factors for local recurrence, irrespective of the primary treatment, and that lobular carcinoma was associated with a higher risk of local recurrence after mastectomy. The presence of an extensive intraductal component (EIC) and especially an age younger than 35 years were highly associated with an increased risk of local recurrence after BCT. Other studies confirmed this influence of age and concluded that young patients with early-stage breast cancer have a worse prognosis than older patients, expressed not only by a higher local recurrence rate, but also by a lower survival rate [8–10].

Many studies have tried to elucidate the relationship between a young age at diagnosis and this poorer prognosis. It was reported that younger patients (the definition of young age ranged from younger than 30 to younger than 45 years of age) present more frequently with factors known to be associated with a poor prognosis, such as large tumours [8,11], high-grade tumours [8–10,12–14], vascular invasion [10,12], lymph node involvement [8,11,15], negative hormone receptors [8,11,12,15–18], and tumours with high S-phase fractions [11,14] and overexpression of p53 [11]. The question of whether a combination of these factors can explain the poor prognosis still remains unresolved. Some studies suggest that age is an independent prognostic factor for local and distant relapse [8,9,12,19], while other authors have concluded that age does not provide additional independent prognostic information [10,11,15]. Some studies not only focused on correlations between tumour factors and age, but also included treatment factors. Only a few of these studies focused on age-related differences in the technique of BCT. However, these studies were limited as some were retrospective studies over a long period of time and some of the relevant treatment parameters were missing (either volume of excision, frequency of re-excision, margin evaluation or radiation dose to the tumour bed) [12,16,18,20].

In the EORTC trial 22881/10882, the effect of the boost dose on local control in patients receiving breast-conserving therapy was evaluated. Since the majority of patients had a microscopically complete excision and were randomised between no further treatment and a 16-Gy boost following whole breast irradiation, the first analyses focused on this group of patients [21]. It was shown that the boost dose significantly reduced the 5-year local recurrence rate from 7 to 4%. Young patients had a significantly higher local recurrence rate compared with older patients. For patients younger than 41 years of age, the boost dose reduced the 5-year local recurrence rate from 20 to 10%. Since the patient population of this trial consists of 5569 early breast cancer patients treated with BCT according to the same protocol, we decided to investigate whether differences in clinical presentation and in the technique of BCT related to age are present. The purpose of this study was to identify patient-, tumour- and treatment-related factors that might explain the higher local recurrence rate in younger patients.

2. Patients and methods

2.1. Population and treatment

From 1989 to 1996, 5569 early-stage breast cancer patients were entered in the EORTC 'boost versus no boost' trial. The main objective of this trial was to assess the influence of the boost dose in BCT on treatment outcome in terms of local control, survival and cosmesis. Patients with clinically assessed T1-2, N0-1, M0 breast cancer were eligible for this trial, unless they were older than 70 years, had a histology of pure carcinoma *in situ* (CIS), multiple tumour foci in more than one quadrant, a history of malignant disease, an Eastern Cooperative Oncology Group (ECOG) performance score of more than 2, residual microcalcifications on mammogram or gross residual disease in the breast after tumorectomy (unless re-excision had been performed).

Patients were treated with a tumorectomy and axillary dissection. The whole breast was irradiated by two tangential fields to a dose of 50 Gy in 5 weeks, with a dose per fraction of 2 Gy. After informed consent, patients with a microscopically complete excision were randomised to receive either no boost or a boost of 15 or 16 Gy (15 Gy for interstitial and 16 Gy for external beam therapy). Patients with a microscopically incomplete excision were randomised to receive either a 10-Gy boost or a boost of 25 or 26 Gy (25 Gy for interstitial

and 26 Gy for external beam therapy). A more detailed description of the trial design, characteristics of patients and tumours, surgical and radiation techniques used, has previously been published in Ref. [21].

2.2. Pathology review

The local pathologists were requested to send a set of representative slides of the tumour to one of the authors (HLP) who reviewed all of the available slides. The following items were scored: the largest diameter, histological World Health Organization (WHO) type, histological grade and the aspect of the margin of the dominant lesion, the completeness of excision of the dominant lesion and the minimal microscopic tumour-free margin, the type of CIS (if present), the quantity and histological grade of ductal carcinoma *in situ* (DCIS) as well as the minimal microscopic margin, and the presence of vascular invasion. Slides of 1724 patients (31% of the overall population) were reviewed. No significant differences in patient, tumour and treatment characteristics were found comparing the reviewed patients with the rest of the population. The tumorectomy was considered incomplete for invasive carcinoma when tumour was transected at a margin of the specimen. If the tumour was present at a distance of less than 1 high-power field diameter from the resection plane, the completeness of excision was considered doubtful. Otherwise, the excision was considered complete. The histological grade of all tumours, not withstanding WHO type, was scored according to the Elston/Ellis modification of the Bloom–Richardson system [22]. Since the mitotic activity index (MAI) is considered an important prognostic factor in itself, the MAI was also scored separately [23,24]. The MAI represents the number of mitotic figures in 10 consecutive high power fields of 0.45 mm^2. The tumorectomy was considered incomplete for DCIS when DCIS extended into the margin of the specimen. Otherwise, the excision was considered complete for DCIS. The extent of the DCIS was estimated by counting the number of ducts involved with DCIS in the breast tissue adjacent to the primary tumour. When three or less ducts were involved, the DCIS component was classified as minimal, 4–9 ducts as moderate and when 10 or more ducts were involved, the DCIS component was classified as extensive. Tumours consisting predominantly of DCIS with focal areas of invasion were also classified as infiltrating carcinomas with an EIC. The histological grade of the DCIS component was classified as high, intermediate or low grade [25]. Vascular invasion was considered to be present when distinct tumour emboli were seen in at least three endothelium-lined (blood or lymphatic) vessels in breast tissue surrounding the tumour. When less than three tumour emboli in endothelium-lined vessels were found vascular invasion was considered to be doubtful.

2.3. Statistical methods

For the description of the distribution of patient, tumour and treatment parameters according to the age of the patient, the patients were divided into five age groups based on their age at the time of randomisation: 35 years or younger, 36–40 years, 41–50 years, 51–60 years and older than 60 years of age. However, it appeared that the first two groups were relatively small, therefore, the age categories 35 years or younger and 36–40 years were pooled together for testing the statistical significance of the observed associations. For illustration, these categories are mentioned separately in the tables. Associations between the age categories and ordinal variables were assessed by means of the Jonckheere–Terpstra test for linear by linear association [26]. Associations with an unordered categorical variable of more than two categories were assessed using a Mantel–Haenszel test [27]. For associations with binary variables, a Cochran–Armitage trend test was used [28]. Comparison of the distribution of continuous variables was performed using the Wilcoxon Rank sum test [26]. Accounting for the very large sample size of the overall population and correcting for the multiplicity of testing according to the Bonferroni method [29], a significance level of 0.001 or less was used for claiming significance for any of the comparisons made. Univariate and multivariate logistic regression models [30] of the probability of being 40 years or younger versus being older than 40 years of age were used to assess the statistical significance of the associations. Univariate models are presented at a significance level of 0.01, the multivariate models at 0.001. The results were summarised in odds ratios (OR) with their associated confidence intervals (CIs). $OR < 1$ indicated that the proportion of patients 40 years or younger increased when the variable increased, whereas an $OR < 1$ indicated the opposite. Univariate and multivariate Cox proportional hazard regression models [31] were used to assess the influence of the analysed parameters (including age) on local control. The initial prognostic factor analysis for local control was stratified by treatment arm and included the complete patient population. However, the final model that also included the boost dose as a prognostic factor was done for the patients with a complete excision only (in order to avoid confounding since patients with an incomplete excision all received a boost; the group excluded contained only 251 patients). The results were summarised in hazard ratios (HR) with their associated CIs. $HR > 1$ indicated that the probability of local failure increased with increasing values of the variable, whereas $HR < 1$ indicated the opposite. All patient and treatment variables, associated with age or local control at the 0.05 level, were entered in the first step of the multivariate model selection procedure. Then a backward selection procedure was applied. The analysis was

repeated for the reviewed group, and now the pathology variables, associated with age or local control at the 0.05 level, were added to the model together with the patient and treatment variables. The multivariate models are described at 0.05, 0.01 and 0.001 levels. Time to local recurrence was calculated from the date of randomisation to the date of recurrence. All local recurrences were taken into account. Patients who remained free of local disease were censored at the date of their last visit. Local recurrence rates were estimated using the Kaplan–Meier technique [32].

3. Results

3.1. Local control

Median follow-up was 5.1 years (maximum, 10.2 years). Analysing the influence of young age on local control, it appeared that young patients had an increased probability of ipsilateral breast recurrence (Fig. 1). At 5 years, the actuarial local control rate was 82% for patients $\leqslant 35$ years (95% CI: 75–88), 85% for patients aged 36–40 years (95% CI: 80–89), 92% for patients 41–50 years (95% CI: 91–94), 96% for patients 51–60 years (95% CI: 95–97) and 97% for patients >60 years of age (95% CI: 96–98) ($P<0.0001$).

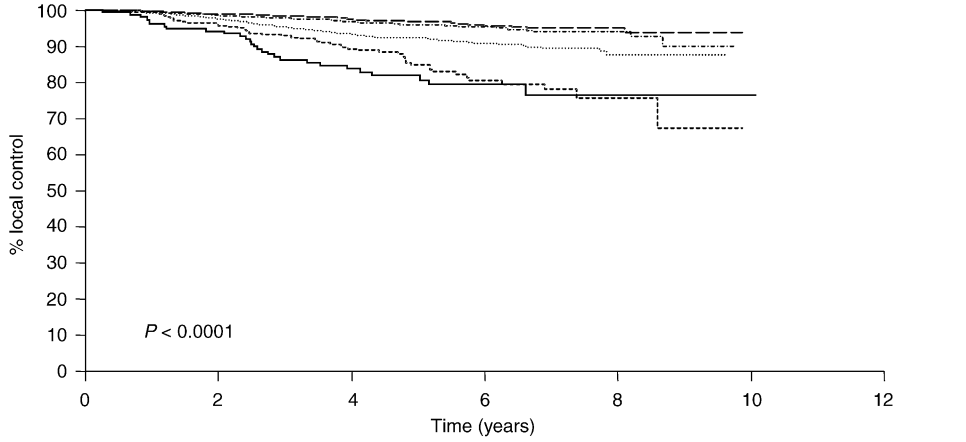
3.2. Patient and tumour characteristics of the overall population per age group ($n=5569$)

156 patients were aged 35 or younger, 314 patients were between the ages of 36 and 40 years, 1407 patients between 41 and 50 years, 1885 patients between 51 and 60 years, and 1807 patients were older than 60 years. Patient and tumour characteristics are described in Table 1. Young women presented more often with palpable tumours (probably due to the screening of patients older than 50 years) and the tumour sizes were larger both clinically and pathologically ($P=0.001$). The pathological tumour size in young patients in particular was more often larger than 20 mm. The percentage of patients with positive axillary lymph nodes and with more than three positive nodes was not significantly different for the various age groups. For those in whom the oestrogen receptor status was known, it was more often negative in the young patients ($P=0.001$). However, this difference was not found for the progesterone receptor distribution.

Univariate logistic regression analysis confirmed that patients 40 years of age or younger had larger palpable tumours, larger pathological tumour sizes, and had less often oestrogen-receptor positive tumours. It also showed that when those patients were compared with patients older than 40 years of age (instead of analysing a trend for the different age groups), young patients had less often progesterone-receptor positive tumours.

3.3. Treatment characteristics of the overall population per age group ($n=5569$)

The treatment characteristics, presented in Table 2, showed that young patients more often had an incomplete first excision, followed by a re-excision ($P=0.001$). However, even though more re-excisions were performed in young patients, the total volume of excision was smaller. Excluding the patients with an *en bloc* excision did not significantly change the outcomes



O	N	Number of patients at risk					Age (years)
28	156	137	95	46	9	1	⩽35
48	314	285	200	90	17	0	36–40
109	1407	1316	912	407	75	0	41–50
75	1885	1768	1220	525	102	0	51–60
58	1807	1694	1237	518	85	0	>60

Fig. 1. Local recurrence rate according to age ([21], with permission of *N Eng J Med*). O, observed; N, number.

Table 1
Patient and tumour characteristics of the overall population by age ($N = 5569$)

	Age (years)					P value[a]	P value[b]
	⩽35	36–40	41–50	51–60	>60		
	$N = 156$	$N = 314$	$N = 1407$	$N = 1885$	$N = 1807$		
	N (%)	N (%)	N (%)	N (%)	N (%)		
T palpation							
Impalpable[c]	3 (2)	11 (4)	153 (11)	502 (27)	520 (29)	0.001[d]	0.0001
⩽10 mm	32 (21)	55 (18)	186 (13)	210 (11)	174 (10)		OR = 1.32
11–20 mm	59 (38)	110 (35)	513 (36)	573 (29)	517 (29)		(99% CI: 1.17–1.48)
>20 mm	34 (22)	76 (24)	353 (25)	381 (20)	398 (22)		
Unknown	28 (18)	62 (20)	202 (14)	219 (12)	198 (11)		
T clinical							
T1[c]	71 (46)	153 (49)	670 (48)	1028 (55)	964 (53)	0.001[e]	0.078
T2	85 (54)	161 (51)	736 (52)	849 (46)	839 (46)		
Unknown	0 (0)	0 (0)	1 (<1)	8 (<1)	4 (<1)		
T pathological							
⩽10 mm[c]	30 (19)	57 (18)	290 (21)	519 (28)	473 (26)	0.001[d]	0.010
11–20 mm	79 (51)	185 (59)	777 (55)	989 (52)	945 (52)		OR = 1.12
>20 mm	44 (28)	64 (20)	310 (22)	344 (18)	344 (19)		(99% CI: 1.00–1.26)
Unknown	3 (2)	8 (3)	30 (2)	33 (2)	45 (2)		
Number of positive nodes							
0[c]	125 (80)	227 (72)	1086 (77)	1447 (77)	1445 (80)	0.004[d]	0.056
1–3	26 (17)	65 (21)	251 (18)	349 (19)	274 (15)		
>3	4 (3)	21 (7)	61 (4)	72 (4)	69 (4)		
Unknown	1 (1)	1 (<1)	9 (1)	17 (1)	19 (1)		
Oestrogen receptor							
Positive	57 (37)	129 (41)	702 (50)	996 (53)	1057 (58)	0.001[e]	0.0001
Negative[c]	51 (33)	91 (29)	342 (24)	342 (18)	269 (15)		OR = 0.45
Unknown	48 (31)	94 (30)	363 (26)	547 (29)	481 (27)		(99% CI: 0.34–0.61)
Progesterone receptor							
Positive	49 (31)	128 (41)	681 (48)	814 (43)	787 (44)	0.65[e]	0.0006
Negative[c]	52 (33)	83 (26)	286 (20)	423 (22)	445 (25)		OR = 0.66
Unknown	55 (35)	103 (33)	440 (31)	648 (34)	575 (32)		(99% CI: 0.49–0.90)

N, number of patients; T, tumour size; OR, odds ratio; CI, Confidence Interval.
[a] The age categories ⩽35 and 36–40 years have been lumped together for testing.
[b] Logistic regression model of patients ⩽40 versus patients >40 years of age.
[c] Reference category.
[d] Jonckheere–Terpstra test.
[e] Cochran–Armitage trend test.

described in Table 2. Therefore, the data are given for the overall population. Significantly less postoperative breast and axilla complications were present in the younger patients ($P = 0.001$).

Median time span between tumorectomy and the start of radiotherapy, median total dose to the tumour bed, and the proportion of patients receiving axillary node irradiation were not significantly related to age. Irradiation of internal mammary chain (IMC) was performed more frequently in the younger patients ($P = 0.001$; again for testing, the two youngest age groups were combined). If the axillary node-negative and node-positive patients were considered separately, no specific trend appeared for the node-positive patients, but IMC irradiation was performed more often in the younger node-negative patients ($P = 0.001$). Considering adjuvant treatment overall (chemotherapy or tamoxifen or both), it appeared that older patients received adjuvant treatment more frequently ($P = 0.001$). Analysed according to the axillary node status, this difference remained significant for the node-negative patients ($P = 0.001$), but lost significance for the node-positive patients. This difference might be explained by the fact that older node-negative patients received hormonal therapy more frequently than younger node-negative patients received chemotherapy.

Univariate logistic regression analysis showed that patients aged 40 years or younger had more re-excisions, more incomplete first excisions for invasive

Table 2
Treatment characteristics of the overall population by age ($N = 5569$)

	Age (years)					P value[a]	P value[b]
	⩽35	36–40	41–50	51–60	>60		
	$N = 156$	$N = 314$	$N = 1407$	$N = 1885$	$N = 1807$		
	N (%)	N (%)	N (%)	N (%)	N (%)		
Re-excision							
Yes	55 (35)	108 (34)	387 (28)	426 (23)	368 (20)	0.001[e]	0.0001
No[c]	100 (64)	205 (65)	1016 (72)	1455 (77)	1431 (79)		OR = 1.77
Unknown	1 (1)	1 (<1)	4 (<1)	4 (<1)	8 (<1)		(99% CI: 1.36–2.30)
First excision complete for invasive carcinoma							
Yes	118 (76)	230 (73)	1107 (79)	1572 (83)	1538 (85)	0.001[e]	0.0001
No[c]	37 (24)	83 (26)	292 (21)	308 (16)	261 (14)		OR = 0.59
Unknown	1 (1)	1 (<1)	8 (<1)	5 (<1)	8 (<1)		(99% CI: 0.44–0.79)
Volume of excision							
⩽100 cm^3[c]	68 (44)	141 (45)	550 (39)	666 (35)	567 (31)	0.001[d]	0.0001
101–200 cm^3	32 (21)	50 (16)	311 (22)	473 (25)	457 (25)		OR = 0.77
201–300 cm^3	10 (6)	18 (6)	117 (8)	180 (10)	212 (12)		(99% CI: 0.66–0.89)
>300 cm^3	12 (8)	24 (8)	111 (8)	202 (11)	229 (13)		
Unknown	34 (22)	81 (26)	318 (23)	364 (19)	342 (19)		
Breast complications							
Present	7 (4)	27 (9)	150 (11)	253 (13)	258 (14)	0.001[e]	0.0004
Absent[c]	147 (94)	286 (91)	1251 (89)	1628 (86)	1539 (85)		OR = 0.53
Unknown	2 (1)	1 (<1)	6 (<1)	4 (<1)	10 (1)		(99% CI: 0.33–0.84)
Axilla complications							
Present	20 (13)	31 (10)	225 (16)	334 (18)	328 (18)	0.001[e]	0.0004
Absent[c]	134 (86)	282 (90)	1177 (84)	1547 (82)	1469 (81)		OR = 0.58
Unknown	2 (1)	1 (<1)	5 (<1)	4 (<1)	10 (1)		(99% CI: 0.39–0.86)
Timespan between tumorectomy and start RT median in days (range)	39 (17–196)	40 (14–227)	40 (13–298)	41 (12–469)	40 (3–244)	0.23[f]	0.34
Total dose to tumour bed median in Gy (range)	64 (2–76)	61 (26–80)	63 (40–82)	60 (38–80)	64 (22–79)	0.13[f]	0.59
Axillary irradiation							
Yes	6 (4)	18 (6)	76 (5)	101 (5)	96 (5)	0.94[e]	0.82
No[c]	149 (96)	293 (93)	1318 (94)	1772 (94)	1688 (93)		
Unknown	1 (1)	3 (1)	13 (1)	12 (1)	23 (1)		
IMC irradiation							
Yes	32 (21)	76 (24)	328 (23)	387 (21)	335 (19)	0.001[e]	0.23
No[c]	123 (79)	235 (75)	1067 (76)	1485 (79)	1450 (80)		
Unknown	1 (1)	3 (1)	12 (1)	13 (1)	22 (1)		
Chemotherapy and/or tamoxifen							
Yes	42 (27)	95 (30)	335 (24)	590 (31)	581 (32)	0.001[e]	0.86
No[c]	114 (73)	219 (70)	1072 (76)	1295 (69)	1226 (68)		

N, number of patients; RT, radiotherapy; Gy, gray; IMC, internal mammary chain.
[a] The age categories ⩽35 and 36–40 have been lumped together for testing.
[b] Logistic regression model of patients ⩽40 versus patients >40 years of age.
[c] Reference category.
[d] Jonckheere–Terpstra test.
[e] Cochran–Armitage trend test.
[f] Wilcoxon Rank sum test.

carcinoma, smaller excision volumes, and had fewer breast and axillary complications. Multivariate analysis for patient and treatment characteristics showed that the following factors were independently related to age: palpable tumour size ($P = 0.0001$; OR = 1.41 (99% CI: 1.18–1.69)), re-excision ($P = 0.0001$; OR = 1.80 (99% CI: 1.12–2.90)), and excision volume ($P = 0.0001$; OR = 0.70 (99% CI: 0.56–0.87)). The model indicated that, while correcting for the fact that younger patients tended to have larger palpable tumours and re-excisions were

performed more frequently, the total excision volume was smaller in the younger patients.

3.4. Tumour characteristics according to the pathology review per age group ($n = 1724$)

The excision was complete for invasive carcinoma in 94% of patients (clearly in 82% and doubtfully in 12%) and incomplete in 6%. If the invasive tumour was accompanied by DCIS, the DCIS component was incompletely excised in 15%. The results of the pathology review analysed per age group (presented in Table 3) showed no significant differences in the distribution of the histological tumour types. Although not significant, the proportion of invasive lobular carcinoma increased with age and in the youngest patient category relatively more medullary carcinomas were found (scored as 'other': 12% for patients $\leqslant 35$ years, 4% for patients 36–40 years and 2% for patients >40 years of age). Young patients had significantly more often high grade carcinomas, with a high MAI, and with well outlined, round tumour margins (indicating a fast, expansive growth). The completeness of excision of invasive carcinoma was not different for the different age groups, and for all groups, the median tumour-free margin for invasive tumour was 5 mm. The distribution of CIS was not significantly different for the age groups. Young patients had more incomplete excisions of DCIS (35% for patients $\leqslant 35$ years, 21% for patients 36–40 years and 14% for patients >40 years of age), resulting in a borderline significant difference ($P = 0.008$); however, the median tumour-free margin was not significantly different for the different age groups, with a median margin of 4 mm. DCIS was more often high grade and present in moderate or extensive quantities in the young patients ($P = 0.001$). A trend was found for EIC being more often high grade in young patients (data not shown): if present, EIC was high grade in 72% in patients $\leqslant 40$ years and 44% in patients >40 years of age ($P = 0.13$). The presence of vascular invasion was not significantly related to age.

Univariate logistic regression analysis indicated that tumours in patients aged 40 years or younger more often had well outlined, round margins, and less often had well outlined, stellate margins. Tumours in younger patients were of a higher histological grade and MAI and if DCIS was present, they were less often completely resected, whereas the DCIS was more often of a high grade. Multivariate logistic regression analysis with the variables defined for the whole group retained only histological grade ($P = 0.0001$; OR = 1.93 (99% CI: 1.48–2.51)). Adding the variables specific to the presence of (D)CIS, the model retained only the grade of DCIS as an independent prognostic factor ($P = 0.0001$; OR = 2.27 (99% CI: 1.52–3.45)). This indicated that in patients with DCIS, it was more often high grade in the young patients.

3.5. Uni- and multivariate prognostic factor analysis for local control

The results of the univariate Cox regression analysis for local control stratified by treatment arm are shown in Table 4. The patient and treatment variables that reached 0.05 significance in association with age or local control for the overall population were entered in the first step of the multivariate model. Multivariate Cox regression analysis showed that three variables were significant at 0.05: age ($P = 0.0001$; HR = 0.59 (95% CI: 0.48–0.71)), T palpation ($P = 0.007$; HR = 2.14 (95% CI: 1.23–3.72)), and progesterone receptor ($P = 0.004$; HR = 0.66 (95% CI: 0.49–0.87)). This result indicated that a higher local recurrence rate was observed in young patients, an in patients with palpable tumours and progesterone-receptor negative tumours. At a significance level of 0.01, the model retained the same parameters. Finally, the model at the 0.001 level retained only age ($P = 0.0001$; HR = 0.56 (99% CI: 0.51–0.68)).

All variables that reached 0.05 significance in association with age or local control for the reviewed population were entered in the first step of the multivariate model. The afore-mentioned patient and treatment variables were also entered. Multivariate Cox regression analysis showed that two variables were significant at 0.05: age ($P = 0.0001$; HR = 0.52 (95% CI: 0.41–0.67)) and histological grade of DCIS ($P = 0.03$; HR = 1.49 (95% CI: 1.04–2.11)). A higher local recurrence rate was observed in the younger patients and in tumours with a high grade *in situ* carcinoma. At significance levels of 0.01 and 0.001, the model retained only age ($P = 0.0001$; HR = 0.45 (99% CI: 0.35–0.59)).

The multivariate analysis of factors associated with local control was repeated with the boost dose as a separate covariate for patients with a complete excision. This analysis demonstrated that only age ($P < 0.0001$; HR = 0.60 (99% CI: 0.51–0.70)) and the use of an additional dose of radiation ($P < 0.0001$; HR = 0.51 (99% CI: 0.37–0.70)) remained significant at a level of 0.001.

4. Discussion

In this large prospective study, it was shown that young age is an important prognostic factor for local control following BCT. Analysis of patient and tumour characteristics of the overall population revealed that tumours in young patients were both clinically and pathologically larger and more often oestrogen and progesterone receptor-negative. More re-excisions were performed (most probably due to the fact that the first excision was more often incomplete) and a smaller total volume was excised (volume of excision plus subsequent re-excision) in young women. The small excisions in

Table 3
Tumour characteristics according to pathology review by age ($N = 1724$)

	Age (years)					P value[a]	P value[b]
	⩽35	36–40	41–50	51–60	>60		
	$N = 49$	$N = 111$	$N = 448$	$N = 558$	$N = 558$		
	N (%)	N (%)	N (%)	N (%)	N (%)		
Histology							
Invasive ductal carcinoma[c]	38 (78)	85 (77)	312 (70)	381 (68)	384 (69)	0.062[e]	0.013
Invasive lobular carcinoma	0 (0)	3 (3)	29 (6)	42 (8)	52 (9)		(invasive ductal versus others)
Mixed invasive pattern	2 (4)	9 (8)	43 (10)	65 (12)	55 (10)		
Other	8 (16)	9 (8)	56 (13)	60 (11)	55 (10)		
Unknown	1 (2)	5 (5)	8 (2)	10 (2)	12 (2)		
Tumour margin							
Well outlined, round	16 (33)	26 (23)	92 (21)	90 (16)	75 (13)	0.001[e]	0.005[h]
Well outlined, stellate	29 (59)	66 (59)	287 (64)	403 (72)	413 (74)		
Poorly outlined, diffuse[c]	1 (2)	7 (6)	24 (5)	20 (4)	17 (3)		
Poorly outlined, multinodular[c]	2 (4)	8 (7)	40 (9)	30 (5)	43 (8)		
Unknown	1 (2)	4 (4)	5 (1)	15 (3)	10 (2)		
Histological grade							
Low[c]	10 (20)	35 (32)	201 (45)	277 (50)	304 (54)	0.001[d]	0.0001
Intermediate	8 (16)	28 (25)	107 (24)	150 (27)	132 (24)		OR = 1.93
High	29 (59)	39 (35)	121 (27)	104 (19)	98 (18)		(99% CI: 1.48–2.51)
Unknown	2 (4)	9 (8)	19 (4)	27 (5)	24 (4)		
MAI							
<10[c]	17 (35)	50 (45)	243 (54)	342 (61)	368 (66)	0.001[d]	0.0001
10–19	7 (14)	15 (13)	62 (14)	74 (13)	72 (13)		OR = 1.50
⩾20	16 (33)	23 (21)	79 (18)	64 (11)	57 (10)		(99% CI: 1.16–1.95)
Unknown	9 (18)	23 (21)	64 (14)	78 (14)	61 (11)		
Excision microscopically complete for invasive carcinoma							
Yes[c]	40 (82)	87 (78)	345 (77)	449 (80)	440 (79)	0.92[e]	0.71
No	2 (4)	5 (5)	29 (6)	32 (6)	34 (6)		
Doubtful	5 (10)	13 (12)	57 (13)	62 (11)	61 (11)		
Unknown	2 (4)	6 (5)	17 (4)	15 (3)	23 (4)		
Tumour-free margin from invasive carcinoma							
Median in mm (range)	5 (0–15)	5 (0–20)	5 (0–20)	5 (0–25)	5 (0–30)	0.059[g]	0.32
Presence and type of CIS							
None[c]	22 (45)	29 (26)	157 (35)	186 (33)	232 (42)	0.01[e]	0.14
Ductal	26 (53)	71 (64)	238 (53)	319 (57)	273 (49)		
Lobular	0 (0)	3 (3)	24 (5)	23 (4)	27 (5)		
Mixed	0 (0)	4 (4)	20 (4)	18 (3)	12 (2)		
Unknown	1 (2)	4 (4)	9 (2)	12 (2)	14 (3)		
Excision microscopically complete for DCIS							
Yes	16 (62)	54 (72)	185 (72)	255 (76)	219 (77)	0.008[f]	0.008
No[c]	9 (35)	16 (21)	39 (15)	47 (14)	34 (12)		OR = 0.51
Unknown	1 (4)	5 (7)	34 (13)	35 (10)	32 (11)		(99% CI: 0.27–0.98)
Tumour-free margin from DCIS							
Median in mm (range)	4 (0–10)	3 (0–20)	3 (0–20)	4 (0–25)	5 (0–15)	0.023[g]	0.52
Quantity of DCIS							
Minimal[c]	10 (38)	30 (40)	112 (43)	166 (49)	167 (59)	0.001[d]	0.060
Moderate	8 (31)	24 (32)	71 (28)	75 (22)	56 (20)		
Extensive	6 (23)	19 (25)	59 (23)	76 (23)	46 (16)		
Unknown	2 (8)	2 (3)	16 (6)	20 (6)	16 (6)		

(*Continued on next page*)

Table 3 (*continued*)

	Age (years)					*P* value[a]	*P* value[b]
	⩽35	36–40	41–50	51–60	>60		
	N = 49	*N* = 111	*N* = 448	*N* = 558	*N* = 558		
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)		
Histological grade of DCIS							
Low	1 (4)	10 (13)	54 (21)	89 (26)	75 (26)	0.001[d]	0.0001
Intermediate	7 (27)	26 (35)	122 (47)	145 (43)	132 (46)		OR = 2.27
High	18 (69)	39 (52)	81 (31)	103 (31)	76 (27)		(99% CI: 1.52–3.45)
Unknown	0 (0)	0 (0)	1 (<1)	0 (0)	2 (1)		
Presence of vascular invasion							
Yes	8 (16)	21 (19)	79 (18)	78 (14)	64 (11)	0.01[e]	0.31
No[c]	31 (63)	80 (72)	320 (71)	409 (73)	424 (76)		
Doubtful	8 (16)	5 (5)	41 (9)	59 (11)	53 (10)		
Unknown	2 (4)	5 (5)	8 (2)	12 (2)	17 (3)		

N, number of patients; MAI, mitotic activity index; CIS, carcinoma *in situ*; DCIS, ductal carcinoma *in situ*.

[a] The age categories ⩽35 and 36–40 have been lumped together for testing.

[b] Logistic regression model of patients ⩽40 versus patients 40 years of age.

[c] Reference category.

[d] Jonckheere–Terpstra test.

[e] Mantel–Haenszel test.

[f] Cochran–Armitage trend test.

[g] Wilcoxon Rank sum test.

[h] OR = 1.58 (99% CI: 0.73–3.41) for well outlined, round, versus poorly outlined, OR = 0.83 (99% CI: 0.42–1.67) for well outlined, stellate, versus poorly outlined.

young patients might be explained by a combination of the following factors: young patients have smaller breasts, benign lesions are more common, and the surgeon will aim at an excellent cosmetic result in these young women. Only a few other studies have looked at age-related differences in treatment parameters in patients treated with BCT and at the influence of these differences on local control. Fowble and colleagues [18] showed that young women were more likely to undergo tumour bed re-excision. However, they found that even with a higher frequency of re-excisions in the young age group, the percentage of patients with a final negative margin status was not different among the various age groups. Thus, it is plausible that re-excisions in young patients were performed more often to achieve a tumour-free margin rather than to enlarge the already tumour-free margin. This might also explain their observation that re-excision was not associated with a decreased risk of breast recurrence in young women; a decrease that was reported for example in the series of Vicini and colleagues [33]. The data of Fowble and colleagues confirm our finding that re-excisions are performed more frequently in young patients due to the fact that the margins of the first excision are more often positive. In light of this observation, the question posed by Regine and Kramer [34] is interesting: "Is there a difference between the patient whose margins are clearly negative after the initial excision and the patient who requires a re-excision to ultimately clear initially microscopically-involved margins?" For tumour locations other than the breast, it has been shown that the risk of local recurrence was significantly greater if the margin of the first excision showed microscopic cut-through (even if the margin was negative after re-excision) than if the margin was negative after the initial excision [35]. These results highlight the difficulties encountered when trying to excise the correct layer of additional tissue in an attempt to achieve negative margins, after the first excision resulted in positive margins. This is illustrated by the fact that in breast cancer patients, when the entire new margin specimen was examined, no tumour was found in 40–45% of patients who had a previously positive margin [36,37]. An analysis of risk factors for local control after BCT performed by Kemperman at The Netherlands Cancer Institute showed that the presence of residual tumour in the specimen of a re-excision was independently predictive for ipsilateral breast recurrence, even after correcting for age, margin involvement and the presence of angio-invasion [38]. This might indicate that there is indeed a difference in terms of local control between these two groups of patients as suggested by Regine and Kramer. Further study is therefore indicated to identify this possible risk factor for local recurrence.

The results of the pathology review showed that invasive tumour was more often of a high grade in young patients. This indicated that aggressive tumours occurred more frequently in young patients. Univariate analysis of invasive tumour grade and local control showed a significant correlation. However, tumour

Table 4
Univariate model for local control stratified by treatment ($N = 5569$)

	Hazard Ratio estimate	99% Confidence Interval	*P* value
All patients ($N = 5569$)			
Age (years)			
$\leqslant 40$[a] versus 41–50 versus 51–60 versus > 60	0.56	0.48–0.65	0.0001
Menopausal status			
Premenopausal[a] versus postmenopausal	0.41	0.30–0.55	0.0001
T palpation			
Impalpable[a] versus palpable	2.06	1.30–3.27	0.0001
T mammography (mm)			
$\leqslant 10$[a] versus 11–20 versus 21–30 versus > 30	1.09	0.89–1.33	0.28
T clinical			
T1[a] versus T2	1.22	0.92–1.63	0.073
T pathological (mm)			
$\leqslant 10$[a] versus 11–20 versus > 20	1.30	1.04–1.61	0.002
Re-excision			
Yes versus no[a]	1.18	0.85–1.63	0.20
Volume of excision (cm^3)			
$\leqslant 100$[a] versus > 100	0.86	0.69–1.06	0.067
First excision complete for invasive carcinoma			
Yes versus no[a]	0.78	0.53–1.14	0.089
Number of positive axillary lymph nodes			
None[a] versus 1–3 versus > 3	1.06	0.80–1.39	0.61
Oestrogen receptor			
Positive versus negative[a]	0.61	0.43–0.88	0.0004
Progesterone receptor			
Positive versus negative[a]	0.66	0.46–0.95	0.003
Breast complications			
Present versus absent[a]	0.84	0.53–1.36	0.36
Axilla complications			
Present versus absent[a]	0.77	0.50–1.17	0.11
Timespan between tumorectomy and start RT (weeks)			
$\leqslant 4$[a] versus 5 versus 6 versus 7 versus 8 versus > 8	1.06	0.97–1.17	0.090
Total dose to tumour bed			
per Gy	1.01	0.95–1.06	0.79
Axillary irradiation			
Yes versus no[a]	0.72	0.35–1.49	0.24
IMC irradiation			
Yes versus no[a]	0.25	0.90–1.75	0.080
Chemotherapy and/or tamoxifen			
Yes versus no[a]	0.75	0.53–1.06	0.033
Review patients ($N = 1724$)			
Histology			
Invasive ductal carcinoma[a] versus other	0.73	0.40–1.33	0.18
Tumour margin			
Well outlined, round versus poorly outlined[a]	1.04	0.43–2.51	
Well outlined, stellate versus poorly outline[a]	0.77	0.36–1.63	0.39
Histological grade			
Low[a] versus intermediate versus high	1.68	1.24–2.28	0.0001
MAI			
< 10[a] versus 10–19 versus $\geqslant 20$	1.38	1.01–1.89	0.007
Excision complete for invasive carcinoma			
Yes versus no[a]	0.98	0.31–3.13	0.99
Microscopic margin from invasive carcinoma			
per mm	0.97	0.91–1.05	0.35
Presence of CIS			
Yes versus no[a]	1.52	0.85–2.70	0.063
Excision complete for DCIS			
Yes versus no[a]	0.77	0.34–1.72	0.40

(*Continued on next page*)

Table 4 (*continued*)

	Hazard Ratio estimate	99% Confidence Interval	*P* value
Microscopic margin from DCIS			
per mm	0.95	0.86–1.05	0.18
Quantity of DCIS			
Minimal[a] versus moderate versus extensive	1.22	0.83–1.80	0.18
Histological grade of DCIS			
Low[a] versus intermediate versus high	1.72	1.10–2.70	0.002
Presence of vascular invasion			
Yes versus no[a]	1.31	0.67–2.52	0.30

T, tumour size; RT, radiotherapy; IMC, internal mammary chain; MAI, mitotic activity index; CIS, carcinoma *in situ*; DCIS, ductal carcinoma *in situ*.

[a] Reference category.

grade appeared not to be an independent prognostic factor for local control. These results confirmed the outcome of previous studies that found a correlation between high grade and local control [39,40], but concluded that it was not an independent prognostic factor for local control when analysed in a multivariate analysis together with factors such as age, margin involvement and vascular invasion [41–43]. The invasive component of the tumours was not more often incompletely excised in the young patients (despite the smaller overall excision volume). This might be due to patient selection since in this trial relatively few patients with a microscopically incompletely excised tumour were entered (only 5% according to the randomisation) [44]. It was more surprising, considering the difference in excision volume, that the microscopic tumour-free margin was not different for the age groups as well. We would expect this margin to be smaller in young patients. DCIS appeared to be more often of a high grade and incompletely excised in young patients. These observations led to the conclusion that high-grade DCIS is left behind more frequently in young women. Thus, young patients are left with a greater tumour burden, that is possibly not controllable by moderate doses of radiation. It was not possible to analyse the patients with EIC separately (due to the small numbers involved), but the presence of EIC is a well-established risk factor for ipsilateral breast recurrence after BCT [20,45,46]. Holland and colleagues [47] concluded that patients whose tumours contain EIC more often have a large subclinical tumour burden left in the breast following lumpectomy compared with patients without EIC. Wazer and colleagues [48] showed that young age and EIC were associated with an increased probability of residual tumour on re-excision; and in patients with EIC, margin status was less predictive for the incidence of residual tumour. Vicini and colleagues [49] showed that EIC is an important risk factor for local control, and that in cases of EIC-positive tumours, large excisions were associated with a significant decrease in the risk of recurrence.

We found several associations between patient, tumour and treatment factors and age that might partly explain why young patients have such a high local recurrence rate. However, the multivariate analysis showed that the only factors independently related to local control were young age itself and the boost dose. The boost dose significantly reduced the 5-year local recurrence rate from 7 to 4% for patients with a complete excision as reported by Bartelink and colleagues ($P<0.001$) [21]. In patients aged 40 years or younger, the local recurrence rate was reduced from 20 to 10% by the boost ($P=0.002$). In patients aged 41–50 years, the local recurrence rate was reduced from 10 to 6% ($P=0.02$) and, in patients older than 50 years of age, from 4 to 3% ($P=0.10$).

Based on the results of this analysis, it is not possible to explain the worse prognosis in terms of local control for young patients. Since tumours in young patients more often have pathological parameters that are associated with poor prognosis, it might be possible that breast tumours in young patients have a different natural history, occurring in a different biological and genetic background. Further research is needed to elucidate the possible differences in genetic alterations in tumours of young patients compared with older patients. DNA microarray analyses will play an important role in identifying genetic alterations in the tumours of young patients as well in helping to identify a prognostic profile that selects high-risk patients that would benefit from adjuvant therapy [50].

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Appendix. Trial participants and responsible physicians

Tilburg, NL (Poortmans), Utrecht, NL (Struikmans), Leuven, B (Van den Bogaert), Dijon, F (Horiot), Paris, F (Fourquet), Amsterdam, NL (Borger), Heerlen, NL (Jager), Nijmegen, NL (Hoogenraad), Cologne, D (Müller), Geneva, CH (Kurtz), Nottingham, GB (Morgan), Montpellier, F (Dubois), Namur, B (Salamon), Lausanne, CH (Mirimanoff), Leiden, NL (Leer), Grenoble, F (Bolla), Haifa, I (Kuten), La Louviere, B (Renaud), Krefeld, D (Schulz), Rotterdam, NL (Koper), Antwerp, B (Van den Weyngaert), Brussels, B (Storme), Creteil, F (Calitchi), Berlin, D (Budach), Dusseldorf, D (Roth), Brisbane, A (Poulsen), Pamplona, E (Dominguez), Vannes, F (Monpetit), Tel Aviv, I (Kovner), Barcelona, E (Biete Sola), Madrid, E (Calvo).

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