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Predictors of the risk of fibrosis at 10 years after breast conserving therapy for early breast cancer – A study based on the EORTC trial 22881–10882 'boost *versus* no boost'

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ABSTRACT

The EORTC 22881-10882 trial in 5178 conservatively treated early breast cancer patients showed that a 16 Gy boost dose significantly improved local control, but increased the risk of breast fibrosis. To investigate predictors for the long-term risk of fibrosis, Cox regression models of the time to moderate or severe fibrosis were developed on a random set of 1797 patients with and 1827 patients without a boost, and validated in the remaining set. The median follow-up was 10.7 years. The risk of fibrosis significantly increased ($P < 0.01$) with increasing maximum whole breast irradiation (WBI) dose and with concomitant chemotherapy, but was independent of age. In the boost arm, the risk further increased ($P < 0.01$) if patients had post-operative breast oedema or haematoma, but it decreased ($P < 0.01$) if

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Nomograms
Early breast cancer

WBI was given with >6 MV photons. The c-index was around 0.62. Nomograms with these factors are proposed to forecast the long-term risk of moderate or severe fibrosis.

1. Introduction

Breast-conserving therapy (BCT) has already demonstrated survival equivalence to mastectomy in many early breast cancer clinical trials.[1–6] BCT is currently considered the standard of care for stages I and II breast cancer. The Early Breast Cancer Trialists' Collaborative Group's meta-analysis[7] showed that radiotherapy (RT) after tumourectomy reduced the 5-year local recurrence rate from 26% to 7%. However, higher irradiation doses increased the risk of fibrosis and worsen cosmetic outcome.[8]

BCT also positively influences the body image of women treated for breast cancer.[9,10] However, longer patient survival may in turn result in increased incidence and/or severity of long-term radiation sequelae that negatively impact on patient's quality of life and body image.

The EORTC 22881-10882 trial investigated the addition of a 16 Gy radiation dose directed to the tumour bed after WBI to 50 Gy. At ten years of follow-up, it showed that the boost dose significantly reduced the risk of local recurrence by 41% in all age groups.[11] However, the absolute benefit was smaller in the patients above 40 years, whose absolute 10-year risk of failure is also the lowest. The rate of moderate to severe fibrosis increased from 13% to 28% with the boost, confirming the worse cosmetic outcome reported at 3 years follow-up.[12]

For women older than 50 years with early breast cancer, for whom the reduction of the 10-year risk of relapse with the boost is relatively modest, the cosmetic result may be particularly relevant to the decision to deliver the boost or not. However, according to Vrieling and colleagues,[12] the boost dose was not the only factor detrimental to the cosmetic outcome.

We now investigate predictors of the long-term risk of fibrosis in this large EORTC database, to develop tools to help clinicians weigh the risks *versus* the expected benefit of delivering a boost dose to an individual patient.

2. Patients and methods

2.1. Design of the 22881-10882 trial

From 1989 to 1996, 5318 early breast cancer patients who had undergone microscopically complete tumour excision and axillary dissection, followed by a 50 Gy breast irradiation, were randomised between no boost (2661 patients) and a 16 Gy boost dose to the tumour bed (2657 patients). Patients were stratified according to age, menopausal status, presence of extensive DCIS (EIC), clinical tumour size, nodal status and centre.

Patients with T1-2, N0-1 and M0 breast cancer were eligible. Patients older than 70 years, with pure carcinoma *in situ* (CIS), multiple tumour foci in more than one quadrant, a history of other malignant disease, an Eastern Cooperative Oncology Group (ECOG) performance score above 2, residual micro-calcifications on mammography or gross residual disease in the breast after lumpectomy (unless re-excision had been performed) were ineligible. Oral informed consent was obtained according to the local and national legislations of the participating institutes. Patients were referred from 31 centres in nine countries. Patients with axillary lymph node involvement received adjuvant systemic therapy: pre-menopausal patients received chemotherapy, post-menopausal patients received tamoxifen. Patients not given adjuvant chemotherapy began RT within nine weeks after lumpectomy. WBI was performed using two tangential megavoltage photon beams (high-energy photons or tele-cobalt). A total dose of 50 Gy in fractions of 2 Gy over five weeks was delivered at the intersection of the central axes of the beams, in agreement with ICRU report 50.[13] The boost dose of 16 Gy had to be delivered in 8 fractions with a direct electron beam, with tangential photon fields, or with an iridium^{192} implant at a dose rate of 0.5 Gy per hour.

2.2. Study population

Patients with major deviations from eligibility criteria ($n = 26$), who received the wrong treatment ($n = 79$), whose tumour was incompletely resected ($n = 12$) or who had insufficient baseline data ($n = 23$) were excluded, leaving 5178 patients in this analysis. Six types of factors were studied: patient characteristics, tumour characteristics, histopathology, post-operative status, WBI and the primary tumour boost (if applicable).

At each visit except baseline, the physician (not blinded for the treatment arm) scored the grade of fibrosis (none/minor/moderate/severe) for the whole breast and for the boost area.

2.3. Statistical methods

For patients who did not receive a boost, we assessed the occurrence of moderate and severe fibrosis in the whole breast, and for patients who received a boost we considered fibrosis only in the boost area. The time to fibrosis was calculated from the day of randomisation to the day moderate or severe fibrosis was first reported.

Patients alive without moderate or severe fibrosis were censored at the last follow-up. Salvage mastectomy and death without fibrosis were considered as competing risks.

Variables with <5% missing data were imputed by the mode or the median. Missing breast irradiation doses were coded as separate variables and were forced in the model whenever the dose itself was included. Variables with more than 20% of missing data were discarded. For oestrogen and progesterone status, 'missing' status was added as a third category.

Radiation quality was coded in four categories: 'Cobalt^{60}', 'X-ray (photons) with energy <6 MV', '=6 MV' and '>6 MV'. Axillary or internal mammary lymph node irradiations were combined into one single indicator variable.

Table 1 – Characteristics of the patients, the tumours and the treatment: Baseline information (N = 2606)

	Boost		No boost	
	Development (*N* = 1797) *N* (%)	Validation (*N* = 809) *N* (%)	Development (*N* = 1827) *N* (%)	Validation (*N* = 745) *N* (%)
Patients				
Age (years)				
Median	54.8	54.9	55.1	54.2
Range	25.7–78.8	25.6–76.2	22.7–80.2	28.3–78.3
Q25[a]–Q75[b]	47.1–62.3	47.5–63.1	47.6–62.3	46.9–61.0
Menopausal status				
Pre-menopausal	685 (38.1)	302 (37.3)	677 (37.1)	293 (39.3)
Post-menopausal	1,112 (61.9)	507 (62.7)	1,150 (62.9)	452 (60.7)
Oestrogen receptor status				
Negative	363 (20.2)	154 (19.0)	338 (18.5)	168 (22.6)
Positive	978 (54.4)	408 (50.4)	969 (53.0)	387 (51.9)
Unknown	456 (25.4)	247 (30.5)	520 (28.5)	190 (25.5)
Progesterone receptor status				
Negative	426 (23.7)	193 (23.9)	417 (22.8)	164 (22.0)
Positive	822 (45.7)	339 (41.9)	786 (43.0)	350 (47.0)
Unknown	549 (30.6)	277 (34.2)	624 (34.2)	231 (31.0)
Tumour				
Tumour location				
Lateral	904 (50.3)	368 (45.5)	900 (49.3)	352 (47.2)
Central/superior	257 (14.3)	136 (16.8)	294 (16.1)	123 (16.5)
Medial	292 (16.2)	157 (19.4)	292 (16.0)	138 (18.5)
Inferior	344 (19.1)	148 (18.3)	341 (18.7)	132 (17.7)
Clinical T				
T1	931 (51.8)	419 (51.8)	967 (52.9)	370 (49.7)
T2–T3	866 (48.2)	390 (48.2)	860 (47.1)	375 (50.3)
Clinical N				
N0	1602 (89.1)	738 (91.2)	1,664 (91.1)	678 (91.0)
N1–2	153 (8.5)	53 (6.6)	124 (6.8)	52 (7.0)
Nx	42 (2.3)	18 (2.2)	39 (2.1)	15 (2.0)
Histopathology report				
First excision complete				
No	268 (14.9)	115 (14.2)	240 (13.1)	111 (14.9)
Yes	1529 (85.1)	694 (85.8)	1,587 (86.9)	634 (85.1)
Diameter dominant lesion (mm)				
Median	15.0	15.0	15.0	15.0
Range	2.0–53.0	1.0–50.0	1.0–60.0	2.0–50.0
Q25–Q75	11.0–20.0	11.0–20.0	10.0–20.0	10.0–20.0
Histological type				
Invasive ductal carcinoma	1492 (83.0)	666 (82.3)	1478 (80.9)	616 (82.7)
Lobular/mixed invasive	199 (11.1)	98 (12.1)	214 (11.7)	75 (10.1)
Other	106 (5.9)	45 (5.6)	135 (7.4)	54 (7.2)
Number of axillary lymph nodes examined				
None	11 (0.6)	5 (0.6)	12 (0.7)	8 (1.1)
1–5	122 (6.8)	50 (6.2)	116 (6.3)	52 (7.0)
6–10	535 (29.8)	276 (34.1)	566 (31.0)	227 (30.5)
10–15	670 (37.3)	296 (36.6)	638 (34.9)	267 (35.8)
>15	459 (25.5)	182 (22.5)	495 (27.1)	191 (25.6)
Number of positive lymph nodes				
None	1429 (79.5)	636 (78.6)	1443 (79.0)	593 (79.6)
1–3	296 (16.5)	146 (18.0)	316 (17.3)	126 (16.9)
4+	72 (4.0)	27 (3.3)	68 (3.7)	26 (3.5)

(*continued on next page*)

Table 1 – *continued*

	Boost		No boost	
	Development (*N* = 1797) *N* (%)	Validation (*N* = 809) *N* (%)	Development (*N* = 1827) *N* (%)	Validation (*N* = 745) *N* (%)
Post-operative complications				
Haematoma				
No	1596 (88.8)	731 (90.4)	1624 (88.9)	674 (90.5)
Yes	201 (11.2)	78 (9.6)	203 (11.1)	71 (9.5)
Oedema				
No	1734 (96.5)	780 (96.4)	1754 (96.0)	713 (95.7)
Yes	63 (3.5)	29 (3.6)	73 (4.0)	32 (4.3)
Local infection				
No	1756 (97.7)	785 (97.0)	1780 (97.4)	723 (97.0)
Yes	41 (2.3)	24 (3.0)	47 (2.6)	22 (3.0)
Seroma/Lymphocele				
No	1753 (97.6)	787 (97.3)	1784 (97.6)	725 (97.3)
Yes	44 (2.4)	22 (2.7)	43 (2.4)	20 (2.7)
Whole breast irradiation				
Dose range point A (ICRU 50)[13]				
<50 Gy	54 (3.0)	22 (2.7)	59 (3.2)	18 (2.4)
=50 Gy	1593 (88.6)	714 (88.3)	1596 (87.4)	672 (90.2)
>50 Gy	150 (8.3)	73 (9.0)	172 (9.4)	55 (7.4)
Dose Range point B (ICRU 50)[13] *(Gy)*				
Median	50.0	50.0	50.0	50.0
Range	43.5–62.5	40.0–57.0	22.0–58.3	40.0–59.0
Q25–Q75	50.0–51.0	50.0–51.0	50.0–51.0	50.0–51.0
N obs	1716 (95.5)	768 (94.9)	1695 (92.8)	705 (94.6)
Missing	81 (4.5)	41 (5.1)	132 (7.2)	40 (5.4)
Minimum WBI dose (Gy)				
Median	47.7	47.5	47.8	47.5
Range	30.0–53.0	30.0–53.5	20.0–52.2	20.0–54.0
Q25–Q75	47.0–49.0	46.5–49.0	47.0–49.0	47.0–49.0
N obs	1,664 (92.6)	741 (91.6)	1,684 (92.2)	693 (93.0)
Missing	133 (7.4)	68 (8.4)	143 (7.8)	52 (7.0)
Maximum WBI dose at any point (Gy)				
Median	53.0	53.0	53.0	53.0
Range	46.0–64.2	46.0–60.0	47.0–62.5	46.0–60.0
Q25–Q75	52.0–54.5	52.4–55.0	52.0–55.0	52.0–55.0
N obs	1675 (93.2)	749 (92.6)	1702 (93.2)	703 (94.4)
Missing	122 (6.8)	60 (7.4)	125 (6.8)	42 (5.6)
Radiation quality				
$Cobalt^{60}$	538 (29.9)	213 (26.3)	522 (28.6)	203 (27.2)
X-ray < 6 MV	237 (13.2)	106 (13.1)	241 (13.2)	93 (12.5)
X-ray = 6 MV	662 (36.8)	307 (37.9)	706 (38.6)	280 (37.6)
X-ray > 6 MV	360 (20.0)	183 (22.6)	358 (19.6)	169 (22.7)
Primary tumour boost				
Irradiation technique boost				
No boost	0 (0.0)	0 (0.0)	1,827 (100.0)	745 (100.0)
Electron beam (e–)	1126 (62.7)	507 (62.7)	–	–
$Cobalt^{60}$	167 (9.3)	75 (9.3)	–	–
X-ray, not $Cobalt^{60}$	346 (19.3)	162 (20.0)	–	–
Interstitial	158 (8.8)	65 (8.0)	–	–
Energy of boost (MeV), if e–				
Median	10.0	10.0	–	–
Range	4.0–24.0	4.0–27.0	–	–
Q25–Q75	9.0–12.0	9.0–12.0	–	–
N obs	1,126	507	–	–

Table 1 – *continued*

	Boost		No boost	
	Development (N = 1797) N (%)	Validation (N = 809) N (%)	Development (N = 1827) N (%)	Validation (N = 745) N (%)
Others				
Chemotherapy during radiotherapy?				
No	1724 (95.9)	770 (95.2)	1,749 (95.7)	721 (96.8)
Yes	73 (4.1)	39 (4.8)	78 (4.3)	24 (3.2)
Chemotherapy after radiotherapy?				
No	1615 (89.9)	730 (90.2)	1,656 (90.6)	681 (91.4)
Yes	182 (10.1)	79 (9.8)	171 (9.4)	64 (8.6)
Chemotherapy peri-operative?				
No	1684 (93.7)	761 (94.1)	1,723 (94.3)	693 (93.0)
Yes	113 (6.3)	48 (5.9)	104 (5.7)	52 (7.0)
Tamoxifen given?				
Pre-menopausal (Not asked)	685 (38.1)	302 (37.3)	677 (37.1)	293 (39.3)
Post, No tamoxifen	780 (43.4)	357 (44.1)	827 (45.3)	313 (42.0)
Post, tamoxifen	332 (18.5)	150 (18.5)	323 (17.7)	139 (18.7)
Axillary or internal mammary lymph node irradiation				
No	1377 (76.6)	622 (76.9)	1423 (77.9)	576 (77.3)
Yes	420 (23.4)	187 (23.1)	404 (22.1)	169 (22.7)

a Q25: first quartile, such that 25% of patients have values below or equal to Q25.
b Q75: third quartile or value such that 75% of the patients have a value below or equal to Q75.

The data were randomly divided in two sets: one set for model development (70%) and the rest for independent model validation (30%).

Fractional polynomials were used to relax the linearity assumptions on continuous covariates, but all variables turned out to be linearly related with outcome.

2.3.1. *In the development dataset*

Before developing models, the heterogeneity of the treatment effect between levels of each predictor was tested by Logrank test using meta-analysis methodology.[14] As at least one interaction was significant (haematoma/oedema), separate models were developed for each treatment arm.

All predictors univariately significant at the 0.20 level were included in the initial Cox multivariate model. Independent prognostic factors were then selected by backward elimination at the 0.01 statistical significance level. Because age influences the risk of local recurrence, the models were adjusted by age.

Internal model validation was performed by bootstrap resampling[15] (500 random samples were generated from the original sample on which the model-fitting procedure was independently repeated) and provided a bias-corrected estimate of the area under the receiver operating characteristic curve (c-index) that measures the model's predictive discrimination.[16] Model calibration was assessed using the 500 bootstrap samples by graphically comparing the predicted risk of fibrosis with the actual fibrosis free rates. The final model was then represented in the form of a nomogram.[17]

2.3.2. *In the external validation dataset*

The final multivariate Cox model and the nomogram were applied to the validation dataset. Because this dataset was only half the size of the development dataset, the 0.10 significance level was used.

All analyses were performed using SAS 9.1 and the R package with the Survival, Design and Hmisc libraries.

3. Results

3.1. *Patient characteristics*

There were no marked differences in the distribution of the tested factors between the two arms ('boost' and 'no boost') or between the two datasets (development and validation) (Table 1). The median age was 55 years. Two-third of the patients were post-menopausal and one in three of these received tamoxifen. Only 8.5% of the patients had involved ipsilateral axillary or internal mammary lymph nodes (N1-2). One-third of the patients were irradiated by Cobalt^{60}, all others by photons.

The median follow-up was 10.7 years in both treatment arms. To date, 1079 patients (20.8%) have developed moderate or severe fibrosis, 482 (9.3%) local recurrences and 1013 (19.6%) died.

3.2. *Moderate or severe fibrosis*

In the development dataset, 485 patients (26.9%) in the boost arm had moderate or severe fibrosis *versus* 230 patients (12.6%) in the no boost arm. The risk of moderate or severe fibrosis was significantly increased with the boost (HR = 2.30, CI 95%: 1.97–2.69, $P < 0.0001$). The analysis was performed separately in the two groups because some predictors seemed to impact fibrosis differently in the two treatment arms (e.g. haematoma).

3.3. *Risk of moderate or severe fibrosis in the boost arm*

In the development dataset (N = 1797 patients), the 10-year rate of moderate or severe fibrosis was 26.2% (CI 95%: 24.1–

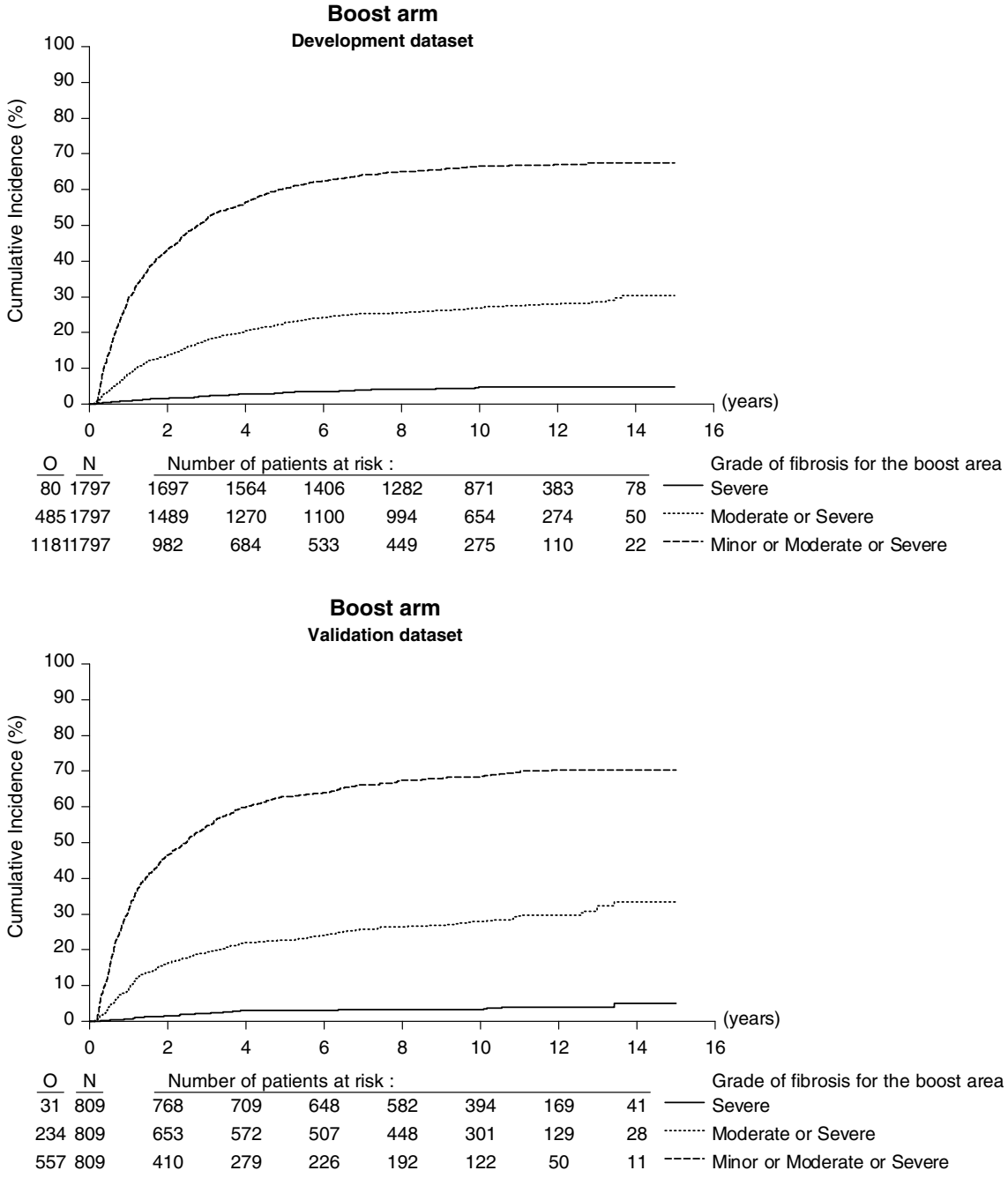

Fig. 1 – Cumulative incidences of the different grade of fibrosis for the boost area in the boost arm, applied to the development and validation datasets.

26.3) and it was 26.9% (CI 95%: 23.8–30.0) in the validation dataset ($N = 809$ patients) (Fig. 1).

In the univariate analysis, the following variables were associated with the risk of moderate or severe fibrosis ($P < 0.20$): largest diameter of dominant lesion, clinical N+, progesterone receptor status, tamoxifen treatment for post-menopausal women, breast complications after surgery (haematoma, oedema, seroma/lymphocele and local infection), axillary or internal mammary node irradiation, chemotherapy during RT, chemotherapy after RT, peri-operative chemotherapy, time between tumourectomy and RT (with and without peri-operative chemotherapy), radiation quality, total dose to point A (intersection of the beam axes),[13] minimum and maximum dose at any point, boost technique and beam energy for electron boost and external boost target volume.

After the backward multivariate selection, the independent prognostic factors of moderate or severe fibrosis ($P < 0.01$) were adjuvant tamoxifen for post-menopausal women, haematoma or oedema after surgery, radiation quality, maximum irradiation dose, concomitant chemotherapy, irradiation boost technique and energy of electron boost (Table 2A).

Table 2A – Final multivariate Cox model in the boost arm for each dataset (N = 2,606)

	Development (n = 1797)		Validation (n = 809)	
	HR/99% CL[a]	P-value	HR/90% CL[b]	P-value
Age (by 10 years)	1.10 (0.90; 1.34)	0.2273	1.24 (1.03; 1.50)	0.0507
Tamoxifen:		0.0011 (2df)		0.5365 (2df)
• *Post-menopausal versus Pre-menopausal*	0.80 (0.53; 1.21)	0.1633	0.77 (0.52; 1.14)	0.2723
• *Tamoxifen versus No tamoxifen*	1.55 (1.14; 2.12)	0.0003	1.01 (0.74; 1.37)	0.9494
Haematoma	1.80 (1.32; 2.47)	<0.0001	1.83 (1.34; 2.51)	0.0016
Oedema	2.23 (1.38; 3.61)	<0.0001	0.94 (0.53; 1.68)	0.8654
Radiation quality:		<0.0001(3df)		<0.0001(3df)
• *X-ray versus Cobalt*^{60}	0.88 (0.63; 1.23)	0.3183	0.80 (0.58; 1.11)	0.2690
• *X-ray > 6 MV versus X-ray = 6 MV*	1.41 (1.00; 1.98)	0.0101	2.19 (1.61; 2.99)	<0.0001
• *X-ray < 6 MV versus X-ray = 6 MV*	0.50 (0.33; 0.76)	<0.0001	0.95 (0.67; 1.34)	0.7987
Maximum WBI dose				
• *No missing value versus missing*	0.51 (0.22; 1.16)	0.0341	0.42 (0.20; 0.89)	0.0576
• *Dose (Gy)*	1.12 (1.05; 1.20)	<0.0001	1.14 (1.07; 1.20)	0.0004
Chemotherapy during RT	2.40 (1.48; 3.91)	<0.0001	1.79 (1.12; 2.84)	0.0400
Irradiation technique boost		<0.0001 (3df)		0.5179 (3df)
• *Electron beam versus X-rayy*	0.29 (0.14; 0.59)	<0.0001	0.61 (0.33; 1.15)	0.1979
• *Cobalt*^{60} *versus X-ray*	0.78 (0.46; 1.34)	0.2355	1.01 (0.62; 1.65)	0.9751
• *Interstitial versus X-ra*	1.07 (0.67; 1.73)	0.7051	1.06 (0.66; 1.70)	0.8478
If electron beam, energy (MeV)	1.08 (1.03; 1.14)	<0.0001	1.05 (1.00; 1.09)	0.0965

a Development dataset: alpha-significance level = 0.01, Hazard Ratio (HR) and 99% Confidence Limits (CL).
b Validation dataset: alpha-significance level = 0.10, Hazard Ratio (HR) and 90% Confidence Limits (CL).

Table 2B – Final multivariate Cox model in the no boost arm for each dataset (N = 2572)

	Development (n = 1827)		Validation (n = 745)	
	HR/99% CL[a]	P-value	HR/90% CL[b]	P-value
Age (by 10 years)	1.06 (0.88; 1.28)	0.3822	1.07 (0.91; 1.29)	0.5359
Maximum WBI dose				
• *No missing value versus missing*	0.21 (0.07; 0.63)	0.0003	0.32 (0.11; 0.91)	0.0739
• *Dose (Gy)*	1.24 (1.14; 1.35)	<0.0001	1.17 (1.08; 1.29)	0.0009
Chemotherapy during RT	2.52 (1.38; 4.62)	<0.0001	2.23 (1.11; 4.56)	0.0620

a Development dataset: alpha-significance level = 0.01, Hazard Ratio (HR) and 99% Confidence Limits (CL).
b Validation dataset: alpha-significance level = 0.10, Hazard Ratio (HR) and 90% Confidence Limits (CL).

The bootstrap resampling and the re-modelling of the final multivariate model in the validation dataset confirmed the above findings. Four prognostic factors were clearly validated (selected in ⩾95% of the boostrap models, Table 3A): the presence of haematoma, the radiation quality, the maximum irradiation dose and the delivery of chemotherapy during RT (Table 2A). However, the four other variables were not firmly validated (selected in >50% of the bootstrap models but not firmly statistically significant in the validation dataset). Nevertheless, we kept them in the final multivariate model with the hope to improve precision.

Table 3A – Bootstrap resampling in the boost development dataset

	N inclusion	Bootstrap	Percent inclusion
Age (by 10 years)	Forced	500	–
Tamoxifen	356	500	71.2
Haematoma	494	500	98.8
Oedema	453	500	90.6
Radiation quality	496	500	99.2
Maximum WBI dose (Missing value)	Forced	500	–
Maximum WBI dose (Gy)	477	500	95.4
Chemotherapy during RT	479	500	95.8
Irradiation technique boost	329	500	65.8
If electron beam, energy (MeV)	294	500	58.8

Table 3B – Bootstrap resampling in the no boost development dataset

	N inclusion	Bootstrap	Percent inclusion
Age (by 10 years)	Forced	500	–
Maximum WBI dose (Missing value)	Forced	500	–
Maximum WBI dose (Gy)	500	500	100.0
Chemotherapy during RT	436	500	87.2

Calibration plots in the development dataset suggested that the final model was well calibrated (Fig. 3A). The c-index[16] for the final multivariate model was 0.66 in the development set and 0.62 in the validation set. When excluding WBI treatments with Cobalt^{60} or <6 MV X-rays, the c-index was 0.67 in the development set and 0.59 in the validation set.

3.4. *Risk of moderate or severe fibrosis in the no boost arm*

In the development dataset ($N = 1827$ patients), the 10-year rate of moderate or severe fibrosis was 12.2% (CI 95%: 10.7–13.8) and in the validation dataset ($N = 745$ patients) it was 14.3% (CI 95%: 11.8–16.9) (Fig. 2).

In the univariate analysis, the following factors were significantly associated with the risk of moderate or severe fibrosis ($P < 0.20$): chemotherapy given during, after RT or peri-operatively, time span between tumourectomy and RT with peri-operative chemotherapy, tamoxifen in post-menopausal women, radiation quality, diameter of dominant lesion, total dose given to point B (centre of the tumour excision area),[13] maximum dose at any point, the number of nodes examined.

After the backward multivariate selection, only the maximum irradiation dose and the giving of concomitant chemotherapy were independent prognostic factors for moderate or severe fibrosis ($P < 0.01$, Table 2B). The internal and external

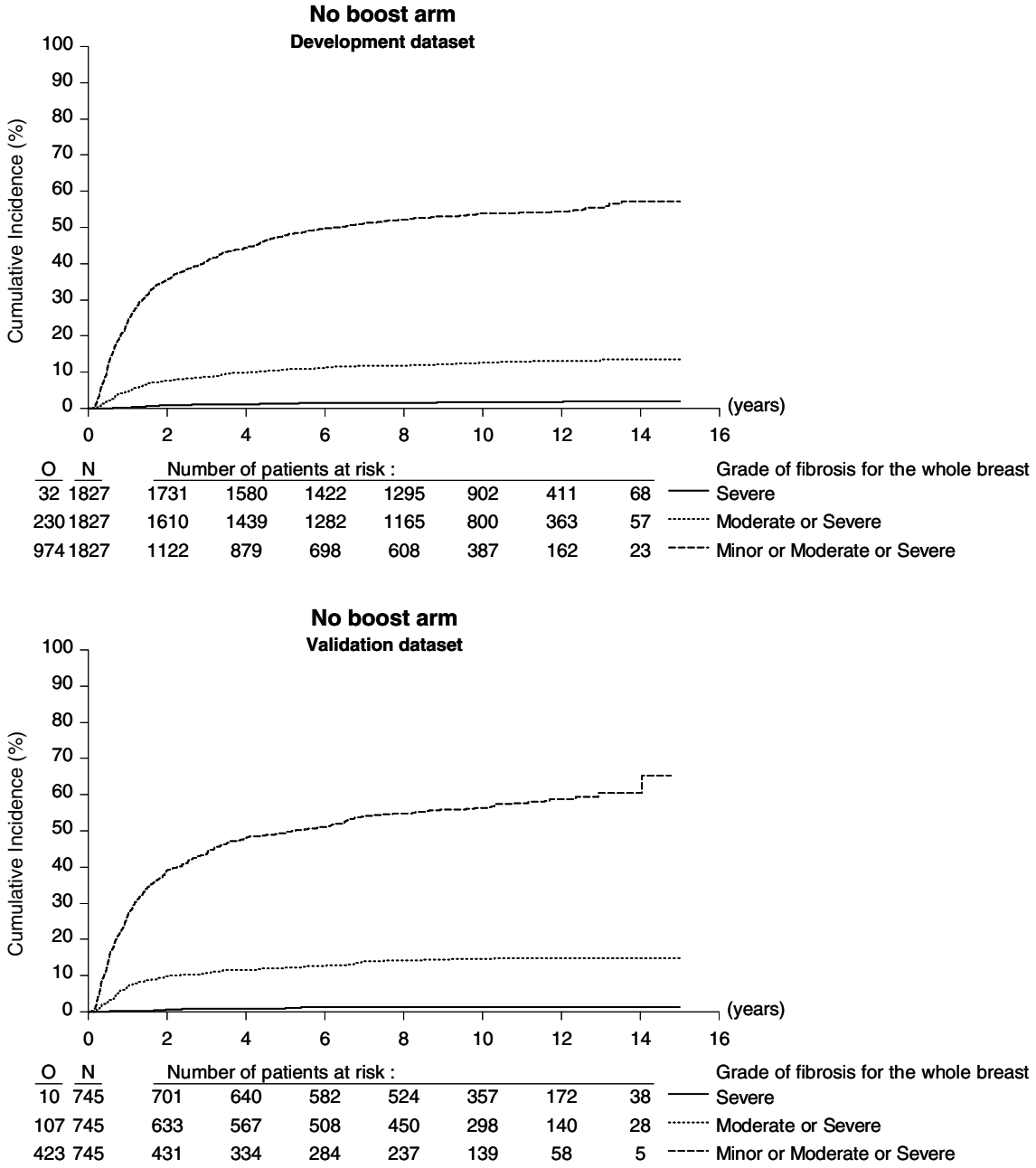

Fig. 2 – Cumulative incidences of the different grade of fibrosis for the whole breast in the no boost arm, applied to the development and validation datasets.

model validations clearly validated these two predictors (Table 3B).

Calibration plots in the development dataset suggested that the final model was not well calibrated for all predictions (Fig. 3B) as the confidence intervals were large. The c-index was 0.65 in the development dataset and decreased to 0.59 in the validation dataset.

3.5. *Nomograms of risk of moderate or severe fibrosis by treatment arm*

The two final multivariate models are displayed as nomograms (Fig. 4). For illustration, patients were classified according to the total points derived from the respective nomogram into four equally sized subgroups in the boost arm, and into three groups in the no boost arm. The cumulative incidence of moderate or severe fibrosis in each subgroup was calculated in the development and in the validation dataset (Fig. 5).

The models did not discriminate well between the patient subgroups with a low risk of fibrosis (less than 125 points in the boost arm and all patients in the no boost arm): the confidence limits for the rate of fibrosis of the various subgroups overlapped (Table 4). However, the high risk subgroups (more than 125 points in the boost arm) were well discriminated: the nomogram for the boost arm is able to identify patients at high risk (>20%) of moderate or severe fibrosis at 10 years.

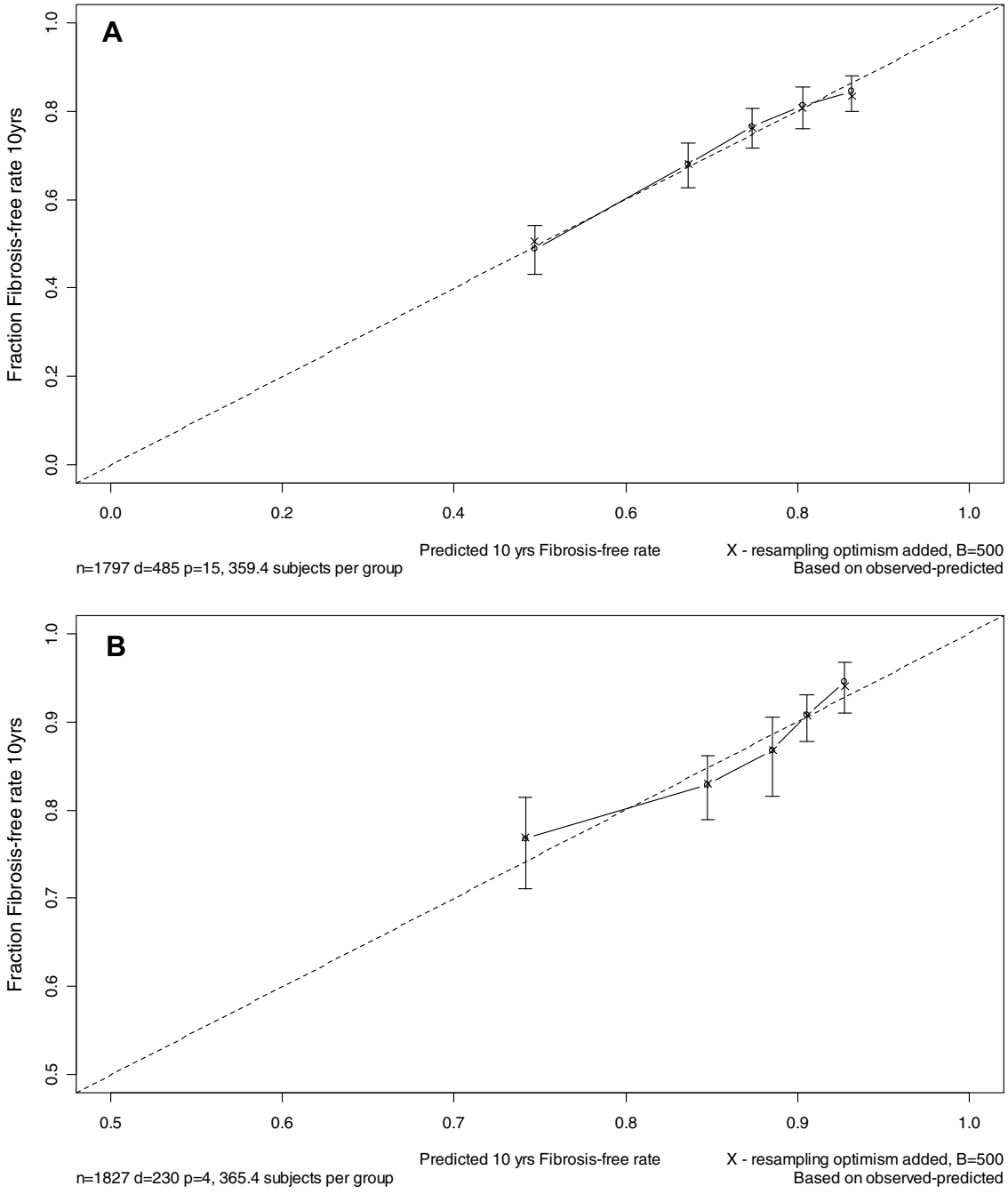

Fig. 3 – Calibration plots: comparison of predicted (y-axis) with observed (x-axis) 10-year moderate or severe fibrosis free rate in the development dataset, for the boost arm (A) and for the no boost arm (B). Vertical lines represent 95% confidence limits.

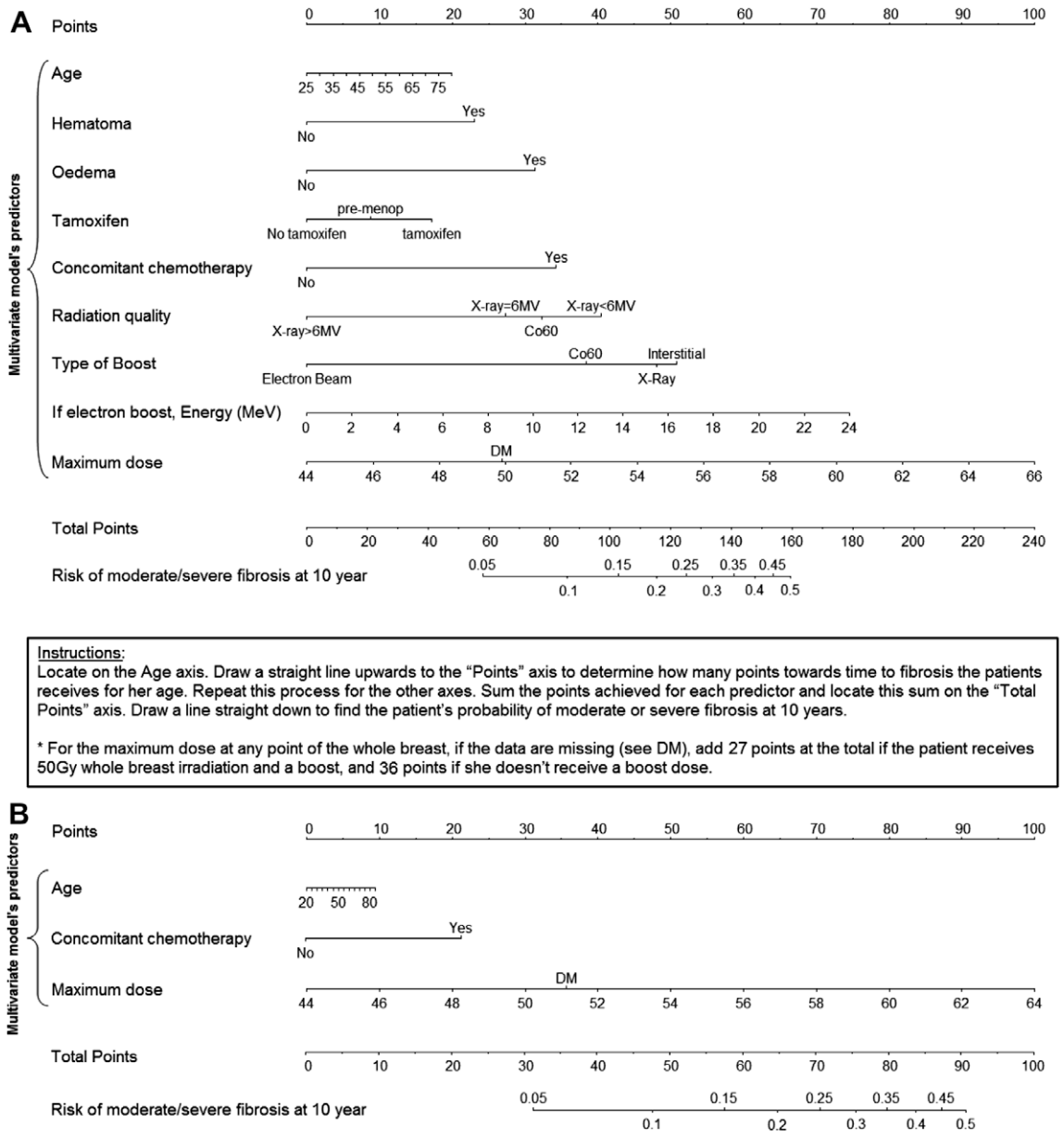

Fig. 4 – Nomograms to predict the 10-year risk of moderate or severe fibrosis in the boost arm (A) and in the no boost arm (B) (see instructions).

4. Discussion

In this trial, an extra boost dose of 16 Gy significantly improved local control, but did not improve survival at 10 years of follow-up.[18] Age was the strongest prognostic factor of local recurrence at 10 years adjusted to the treatment arm but in the present analysis, the risk of moderate or severe fibrosis was not influenced by the patient's age. In this study, fibrosis was scored by the treating physician on a 4-point ordinal scale and was therefore assessed in a rather subjective manner.

The interaction analysis revealed that a breast complication (haematoma and/or oedema) after surgery was predictive for the risk of moderate or severe fibrosis in relation to the giving of an irradiation boost: the incidence of breast complications was similar in both treatment arms, but in case of post-surgical breast complication, the risk of fibrosis was higher with the boost than without. Therefore, predictors of the risk of fibrosis differ in the two treatment arms and should be studied separately.

The multivariate prognostic factor analysis for the risk of fibrosis was adjusted by the only significant predictor of local recurrence and age. Our analyses identified several factors significantly associated with the risk of moderate or severe fibrosis. In both arms, the risk of moderate or severe fibrosis significantly increased with increasing maximum WBI dose. It also increased with an extra boost dose, as was expected from previous studies.[19,20] Like Toledano and colleagues,[21] we also found that peri-operative chemotherapy was associated with an increased long-term risk of fibrosis. However,

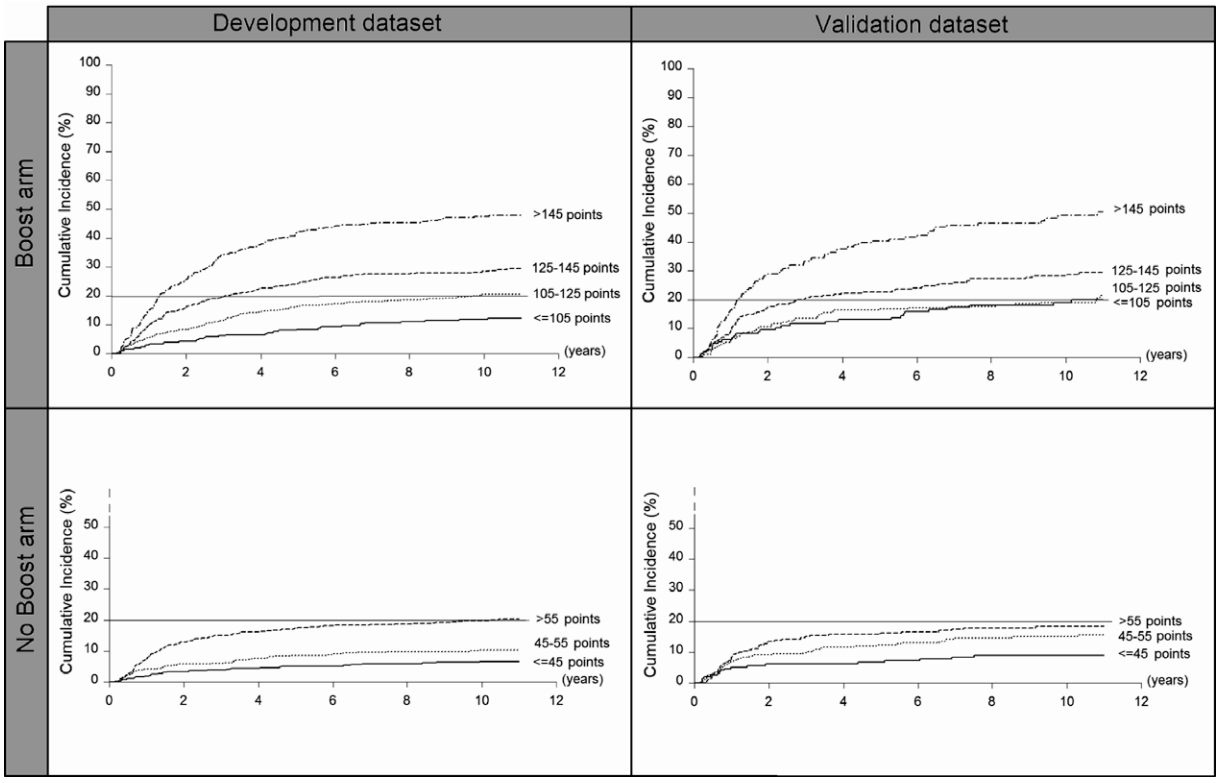

Fig. 5 – Cumulative incidence of moderate or severe fibrosis in the boost arm and in the no boost arm according to the total prognostic score derived from nomograms, applied to the development and validation datasets, respectively (the horizontal line indicates 20% cumulative incidence of moderate or severe fibrosis).

Table 4 – 10-year rate of moderate or severe fibrosis by treatment arm and by total prognostic points for each dataset (N = 5178)

	Total points	Development		Validation	
		N (%)	Rate of fibrosis[a] (95% CL[b])	N (%)	Rate of fibrosis[a] (95% CL[b])
Boost arm	<=105	312 (17.4%)	11.4 (7.8; 14.9)	145 (17.9%)	18.1 (11.8; 24.4)
	105–125	563 (31.3%)	19.3 (16.0; 22.6)	245 (30.3%)	18.5 (13.6; 23.4)
	125–145	553 (30.8%)	27.9 (24.2; 31.7)	256 (31.6%)	27.7 (22.2; 33.3)
	>145	369 (20.5%)	47.1 (41.9; 52.2)	163 (20.1%)	46.5 (38.7; 54.4)
No boost arm	<=45	502 (27.5%)	6.3 (4.2; 8.5)	196 (26.3%)	8.8 (4.8; 12.8)
	45–55	663 (36.3%)	9.9 (7.6; 12.2)	287 (38.5%)	14.9 (10.8; 19.1)
	>55	662 (36.2%)	19.1 (16.1; 22.2)	262 (35.2%)	17.8 (13.1; 22.5)

a Rate of moderate or severe fibrosis.
b 95% CL: 95% Confidence Limits.

some factors were prognostic only in the boost arm: adjuvant tamoxifen treatment, a breast complication after surgery (haematoma and oedema) and the WBI radiation quality (no significant difference between Cobalt^{60} and photons, but the risk of fibrosis decreased significantly with increasing photon energy). Some technical parameters were also prognostic: the boost technique and the energy of boost electron beam (the fibrosis rate was lowest with low energy electrons and highest with Cobalt^{60} or interstitial boost).

During the internal validation of the prognostic model by bootstrap re-sampling in the boost arm, the tamoxifen treatment, the boost technique and the beam energy of the boost were not firmly confirmed as prognostic factors (these variables were selected in <75% of the models). The selection of these variables in the final multivariate model seems influenced by small variations in the data and may thus be specific to the database at hand. This was also suggested in the independent validation, where tamoxifen and boost technique were no longer significantly associated with an increased risk of fibrosis. These three variables may therefore not be extremely important for predicting the development of fibrosis. It would be interesting to validate our results on another trial's data, to elucidate if these three variables really are associated with the risk of fibrosis. In women who underwent BCT,

tamoxifen was reported to be associated with worse cosmetic outcome in some trials[22,23] but not in others.[24,25] We could not confirm either of these findings. Nevertheless, we decided to keep these variables in the model as they may still improve the precision of the predictions.

There was also an issue with the statistical power in the validation dataset. Because the validation set is smaller than the development set, we adjusted the significance level to maintain similar power. However, the power remained limited by the relatively low number of events especially for factors that have a relatively low prevalence. Only few patients had oedema after surgery (3.5% of patients in the development dataset and 3.6% in the validation dataset) so its effect on fibrosis could be unstable. The predictive power of the models was relatively modest. The c-index was between 0.60 and 0.65 (when 0.50 represents chance prediction). The model in the boost arm was well validated for patients with a high risk of fibrosis (>20%) but less for patients with a low risk (<20%). This could explain why the prognostic model in the no boost arm was not very powerful: in this arm, the risk of fibrosis was always low (in majority under 20%). However, to the best of our knowledge this is the first time that an attempt was undertaken to build a nomogram to predict the risk of fibrosis, based on a very large and well-documented study population in a randomised trial.

An important limitation of our analysis is that many patients were treated with $Cobalt^{60}$ or low energy X-rays and that only non-conformal techniques were used. The model's predictive accuracy seemed only modestly reduced when restricted to the patients treated with $\geqslant 6$ MV X-rays. However, we cannot forecast the model validity for newer conformal techniques which will hopefully cause much less late fibrosis.

In the absence of better tools, our results may help the clinician in providing a basis for decision making (whether to deliver a boost or not to an individual patient): using the baseline characteristics of the patients, the clinician could on one hand estimate the expected age-adjusted benefit in local control and on the other hand estimate the risk of fibrosis, both with or without the boost by using the two nomograms. Based on this, an informed decision regarding the expected risks and benefits of delivering a boost to the particular patient could be made. The nomograms could be especially useful for patients older than 50, in whom the increase in local control resulting from an extra boost dose remains rather marginal: the nomograms would indeed predict whether the patient would be at high risk (>20%) of developing moderate or severe fibrosis if the extra boost dose was delivered. Obviously, other critical factors for the risk of fibrosis, such as dose homogeneity in the target volume must also be optimised as much as possible.[26]

These findings are clinically relevant because, from now on, the age-dependent expected benefit can be objectively weighted against the risk of long term fibrosis (>20% or not) in the decision to deliver a boost or not.

Conflict of interest statement

None declared.

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