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Prognostic Factors for Local Control in Breast Cancer After Long-term Follow-up in the EORTC Boost vs No Boost Trial
A Randomized Clinical Trial

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IMPORTANCE Prognostic factors of ipsilateral breast tumor recurrence (IBTR) may change over time following breast-conserving therapy.

OBJECTIVE The EORTC "boost no boost" trial showed that young age and high-grade invasive carcinoma were the most important risk factors for IBTR. This study reanalyses pathological prognostic factors related to IBTR using long-term follow-up.

DESIGN, SETTING, AND PARTICIPANTS Participants included 5569 early-stage breast cancer patients, treated with breast-conserving surgery (BCS) and whole-breast irradiation (WBI), who were randomized between no boost and a 16-Gy boost in the EORTC phase III "boost no boost" trial (1989-1996). A total of 1616 patients with a microscopically complete resection (according to local pathologists), included in the central pathology review, have been analyzed in this study. Median follow-up was 18.2 years.

INTERVENTIONS No further treatment or 16-Gy boost, after BCS and 50-Gy WBI.

MAIN OUTCOMES AND MEASURES Time to ipsilateral breast tumor recurrence (IBTR) as first event.

RESULTS The 20-year cumulative incidence of IBTR in 1616 patients (160 events observed) was 15% (95% CI, 12%-17%). Young age ($P < .001$) and presence of ductal carcinoma in situ (DCIS) (HR, 2.15; 95% CI, 1.36-3.38; $P = .001$) were associated with an increased risk of IBTR in multivariable analysis. The cumulative incidence of IBTR at 20 years was 34% (95% CI, 25%-41%), 14% (95% CI, 10%-18%), and 11% (95% CI, 8%-15%), in patients 40 years or younger, 41 to 50 years and 50 years or older, respectively ($P < .001$). This incidence was 18% (95% CI, 14%-22%) and 9% (95% CI, 6%-12%) for tumors with and without DCIS ($P < .001$). High-grade tumors relapsed more frequently early during follow-up but the relative effect of age and presence of DCIS seemed stable over time. The boost reduced the 20-year IBTR incidence from 31% (95% CI, 22%-39%) to 15% (95% CI, 8%-21%) (HR, 0.37; 95% CI, 0.22-0.62; $P < .001$) in high-risk patients (≤50 years with DCIS present).

CONCLUSIONS AND RELEVANCE The association of high-grade invasive tumor with IBTR diminished during follow-up, while the effect of DCIS adjacent to invasive tumor seemed to remain stable. Therefore, patients with high-grade invasive tumors should be monitored closely, especially in the first 5 years, while additional DCIS is an indication for longer follow-up, emphasizing the importance of long-term trial follow-up to estimate absolute effects accurately.

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Supplemental content

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Since the introduction of breast-conserving therapy (BCT), several retrospective and prospective studies have analyzed clinical and pathological prognostic factors influencing local control. These studies aimed to identify clinical, radiological, and pathological criteria that would guide the individualization of surgery (mastectomy vs breast-conserving surgery [BCS]) and radiotherapy (treatment volume and dose: whole-breast irradiation [WBI] with or without a tumor bed boost vs partial breast radiotherapy or no radiotherapy at all). Well-established risk factors are first of all the conventional staging system (tumor size and nodal presence) followed by several other criteria, such as young age,[1,2] mammographic density,[3] margin status,[4] peritumoral vascular invasion,[5] and molecular subtype.[6]

In the EORTC 10801 study, the long-term follow-up showed a higher local recurrence rate after BCT compared with modified radical mastectomy. Despite this result, the survival was equal in both treatment arms.[7] Risk factors for local recurrence were studied combined with the Danish Breast Cancer Cooperative Group 82TM study. Young age and the presence of an extensive intraductal component (EIC) were associated with an increased risk of local recurrence after BCT. Vascular invasion was a risk factor independent of treatment. The subgroup of patients with a lobular carcinoma fared better with BCT.[5]

More recently, Liu et al[8] showed that the intrinsic subtype of breast cancer was significantly related to the 10-year in-breast recurrence in node-negative early breast cancer patients older than 50 years, treated with tamoxifen and postoperative radiotherapy or tamoxifen alone,[9] varying from 5% for luminal A tumors to 21% for high-risk tumors (Her2 positive or triple negative tumors). The subtype itself was not predictive of benefit from radiotherapy.

Earlier analyses of the EORTC boost no boost study found that young age and high-grade tumors were associated with a higher risk of local recurrence after BCT.[10] With a radiotherapy boost dose of 16 Gy following WBI, the local recurrence rate could be reduced by nearly a factor of 2, resulting in the greatest absolute benefit in the youngest patients.[11] In this trial a central pathology review was carried out in a subgroup of patients with a complete resection of the breast tumor according to the local pathologist.

In this article we reanalyze in the centrally reviewed subset the effect of pathological factors on local control with long-term follow-up, with a special focus on assessing the evolution of these effects over time. We also analyze the long-term outcome of subgroups resembling the intrinsic subtypes, and describe the effect of the radiotherapy boost in these subgroups.

Key Points

Question What is the long-term impact of prognostic factors on ipsilateral breast tumor recurrence (IBTR) in patients treated with breast-conserving therapy?

Findings Young age and the presence of ductal carcinoma in situ (DCIS) adjacent to the invasive tumor were associated with an increased incidence of IBTR at long-term follow-up, whereas high-grade tumors relapsed more frequently only during the first 5 years.

Meaning Patients with high-grade invasive tumors should be monitored closely, especially in the first 5 years. The impact of DCIS remained constant over time, indicating that long-term follow-up is necessary. The boost significantly reduced IBTR in these patients.

Methods

Patients and Methods

The trial protocol can be found in Supplement 1. A total of 5569 early breast cancer patients were randomized in the EORTC boost no boost trial from 1989 to 1996. The main aim of the trial was to evaluate the influence of a boost dose in BCT in terms of local control, survival, and cosmetic outcome. The patients were treated with lumpectomy, axillary dissection, and WBI (25 times 2 Gy in 5 weeks). The 5318 patients with a microscopically complete resection according to the local pathologist were randomized between no boost and a 16-Gy boost to the tumor bed. According to the trial protocol, only patients with positive axillary lymph nodes received systemic therapy: chemotherapy for premenopausal patients and tamoxifen for postmenopausal women. Details of the trial have been published previously.[11-13] Oral informed consent was obtained according to EORTC guidelines and the local and national rules of the participating institutes. Ethics committees of the participating institutes approved the protocol. Tissue blocks of 1616 patients from the first years of the accrual period underwent central pathology review, representing 30% of the overall population. Data of this subgroup with a median follow-up of 18.2 years was analyzed.

Pathology Review

The tumor characteristics and margin status were reviewed by the late breast pathologist J.L. Peterse. The extent of ductal carcinoma in situ (DCIS) was estimated by counting the number of ducts involved in the breast tissue adjacent to the primary invasive tumor. The presence of DCIS within the primary tumor was not taken into account. Up to 3 ducts involved was considered a minimal DCIS component; 4 to 9 ducts, a moderate component; and 10 or more ducts involved was considered an extensive DCIS component. Tumors consisting mainly of DCIS with focal areas of invasion were classified as invasive carcinomas with an EIC. The margin status of the invasive tumor as well as the DCIS component was defined as follows: a "positive margin" as tumor on ink, a "very close margin" as tumor seen at 2 mm or less from the inked resection margin, a "close margin" as tumor seen between 3 and 4 mm and a "free margin" as a tumor-free margin of 5 mm or more. The margin status for invasive carcinoma could be scored in 1494 patients and for DCIS in 811 patients. The histologic grade of the invasive tumor was defined according to the Elston/Ellis modification of the Bloom-Richardson system[14] and the histologic grade of DCIS was classified as low, intermediate, or high.[15] The subgroup of hormone-receptor negative, high-grade tumors was analyzed as surrogate for triple-negative tumors, since the Her2 status was unknown for this population. The subgroup of estrogen-receptor positive, low-grade tumors was analyzed as surrogate for luminal A tumors.

Figure 1. Trial Population

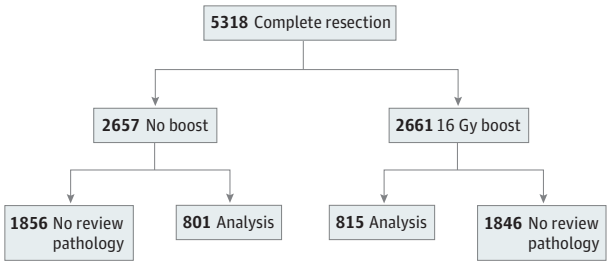


Table 1. Cumulative Incidence of Ipsilateral Breast Tumor Recurrence as First Event at 20 Years of Follow-up (Univariate Effects)

Variable	Subjects	Events	Cumulative Local Recurrence Probability, % (95% CI)	*P* Value
Treatment				<.001
No boost	801	99	17 (13-20)	
16-Gy boost	815	61	12 (9-16)	
Age, y				<.001
27-40	183	49	34 (25-41)	
41-50	442	44	14 (10-18)	
>50	991	67	11 (8-15)	
Presence of DCIS				<.001
No	664	44	9 (6-12)	
Yes	914	110	18 (14-22)	
Histological grade of invasive tumor				.08
Low	784	70	12 (10-15)	
Intermediate	398	35	14 (9-18)	
High	363	42	16 (10-22)	

Abbreviation: DCIS, ductal carcinoma in situ.

Statistical Analysis

Time to ipsilateral breast tumor recurrence (IBTR) as first event was calculated from the date of randomization. Since it is difficult to differentiate between a local recurrence and a new primary tumor in the treated breast, all invasive recurrences found in the ipsilateral breast during follow-up were classified as IBTR. Patients alive without IBTR were censored at the date of last follow-up. Patients who first experienced another event (regional recurrence, new tumor, distant metastasis, or death) were censored at the date of this event. In addition, patients were censored if they experienced any of these other events within 4 months of their IBTR (assuming the other event was already present at the time of local recurrence), except if this concerned a regional recurrence only.

The Cox proportional hazards model was used to analyze the cause-specific hazard of IBTR, where variables included in multivariable analysis were selected based on clinical expertise and supported by univariable analysis. Interactions with time were assessed by the Pearson product-moment correlation between the scaled Schoenfeld residuals of the Cox model and log(time). A global test for interactions was significant ($P = .002$). For a visual inspection of possible interactions with time, the residuals were plotted against time along with a smooth curve.[16] A restricted cubic spline with 3 knots was used for age. Kaplan-Meier estimates of cumulative incidence were reported at 20 years, or at 15 years for subgroups with fewer than 20 subjects at risk at 20 years. Cox models with interactions were used to compare the effect of boost treatment between subgroups. Subjects with missing data necessary for analysis were removed from that particular analysis. Results with a *P* value <0.01 were considered statistically significant.

Results

The median age of the patients was 54 years (eTable 1 in Supplement 2). After lumpectomy and 50-Gy WBI, no boost was given in 801 patients, while 815 patients received a 16-Gy boost (**Figure 1**). The median tumor size was 15 mm, most of the tumors were hormone receptor positive and 78% of patients had negative axillary lymph nodes. Patients with axillary lymph node involvement received adjuvant systemic treatment: 16% of premenopausal patients received chemotherapy and 23% of postmenopausal patients received tamoxifen (20 mg per day for 2 years). The majority of tumors were invasive ductal carcinomas, in 58% of patients associated with a DCIS component (eTable 1 in Supplement 2).

Ipsilateral Breast Tumor Recurrence

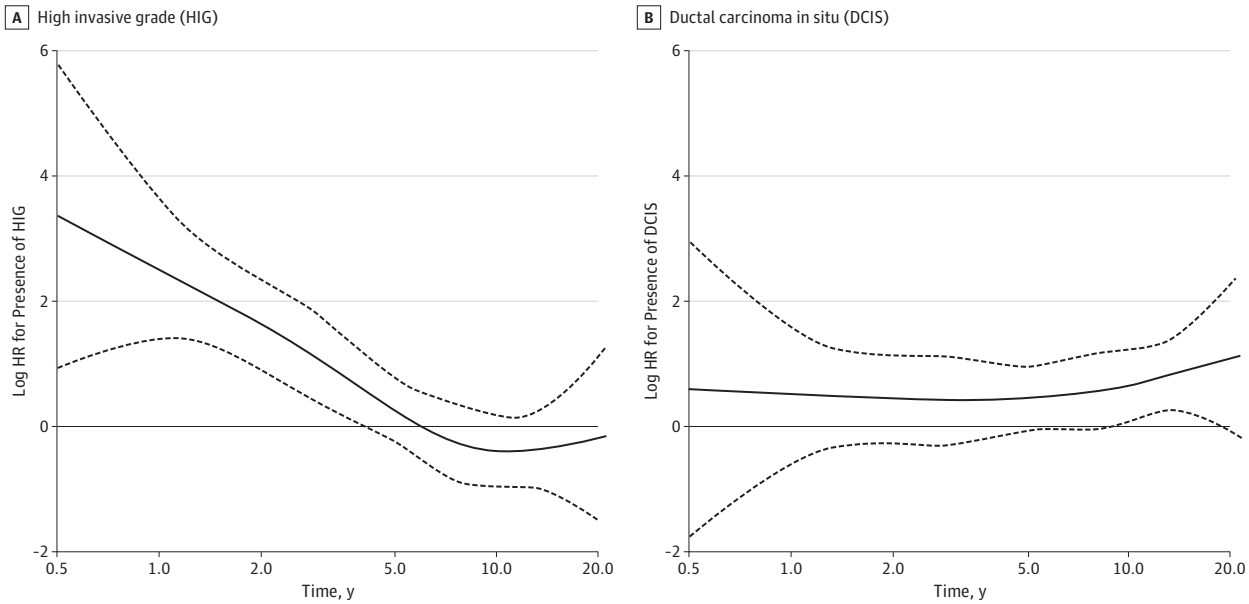
A total of 160 IBTR as first event were found, 99 in the no boost arm and 61 in the boost arm. The 20-year cumulative risk of IBTR was 17% (95% CI, 13%-20%) and 12% (95% CI, 9%-16%), respectively ($P < .001$) (**Table 1**). The patient characteristics of the subgroup with central pathology review did not differ significantly from the population without review,[10] and neither did local control. The cumulative incidence curves of IBTR never reached a plateau and the favorable absolute effect of the boost increased over time as the curves continued to diverge (eFigure 1 in Supplement 2).

In the univariable analysis, the boost treatment and use of tamoxifen were significantly associated with improved local control, whereas young age and the presence of DCIS were prognostic of increased risk of IBTR (eTable 2 in Supplement 2). Patients with high invasive grade were at greater hazard of IBTR in the first 5 years of follow-up, but the effect declined in the course of time (interaction with time $P < .001$, **Figure 2**A), with more than 250 high-grade patients at risk after 5 years (eFigure 2 in Supplement 2). For the presence of additional DCIS no such change in hazard over time was observed (interaction with time $P = .41$, Figure 2B). In patients receiving systemic therapy, the boost still had a significant influence on IBTR (eFigure 3, in Supplement 2). Neither incomplete resection of invasive tumor nor tumor-free margin distance in millimeters for complete resection was significantly related to local control. Also for the additional DCIS component, tumor-free margin in millimeters for complete resection or even incomplete resection did not appear to influence local control.

Risk Factors for Local Recurrence

After adjustment for treatment and known prognostic factors, young age ($P < .001$) and presence of DCIS (HR, 2.15; 95%

Figure 2. Log HR Over Time



Log HR over time for (A) high invasive grade ($P < .001$) and (B) presence of DCIS ($P = .41$) with confidence intervals at 2 standard errors. The time axis has been graduated according to the log scale.

CI, 1.36-3.38; $P = .001$) were statistically significant predictors of IBTR (**Table 2**). The histological grade of the invasive tumor did not significantly influence long-term local control. The association between age at randomization and IBTR was nonlinear (eFigure 4 in Supplement 2), but similar in both treatment arms. The risk of IBTR decreased from age 30 to about 50 from 34% (95% CI, 25%-41%) to 11% (95% CI, 8%-15%) (Table 1). As of the age of 50, the risk more or less stabilized. In tumors with and without additional DCIS, the cumulative incidence of IBTR at 20 years was 18% (95% CI, 14-22) and 9% (95% CI, 6%-12%), respectively ($P < .001$) (Table 1).

A total of 124 patients had estrogen receptor (ER) and progesterone receptor-negative, high-grade tumors. In this group were 16 events. The 15-year cumulative incidence of IBTR in this population was 16% (95% CI, 8%-23%). The IBTR incidence related to age showed the following trend: 15-year cumulative incidence of IBTR was 34% (95% CI, 9%-53%) in patients younger than 40 years of age, 19% (95% CI, 2%-32%) in patients aged 41 to 50, compared with 6% (95% CI, 0%-12%) for patients older than 50 years ($P = .04$). The presence of additional DCIS did not influence local control in this population.

464 patients had ER-positive, low-grade tumors. In this group were 43 events. The 15-year cumulative incidence of IBTR in this subgroup was 11% (95% CI, 8%-14%). Age had a significant influence also in this population: patients younger than 40 years had a 15-year IBTR incidence of 34% (95% CI, 14%-49%) compared with 10% (95% CI, 5%-15%) for patients 40 years or older ($P < .001$). The presence of DCIS in this population showed a trend in 15-year IBTR incidence: 14% (95% CI, 9%-19%) for patients with additional DCIS vs 7% (95% CI, 3%-11%) for patients without ($P = .02$).

Effect of the Boost Treatment in High-Risk Patients

The influence of the radiotherapy boost on the different subgroups is shown in **Figure 3**.

For patients younger than 50 years, the 16-Gy boost dose reduced the 20-year cumulative incidence of IBTR from 24% (95% CI, 18%-30%) to 15% (95% CI, 10%-20%) (HR, 0.51; 95% CI, 0.33-0.77; $P = .002$). In patients with additional DCIS, the boost dose reduced the 20-year cumulative incidence of IBTR from 22% (95% CI, 17%-27%) to 14% (95% CI, 9%-19%) (HR, 0.47; 95% CI, 0.31-0.69; $P < .001$). In the population with both risks combined, the boost dose reduced the 20-year cumulative incidence of IBTR from 31% (95% CI, 22%-39%) to 15% (95% CI, 8%-21%) (HR, 0.37; 95% CI, 0.22-0.62; $P < .001$). The influence of the boost in the older patients with DCIS (545 patients with 45 events) was not significant: a 20-year cumulative incidence of IBTR of 15% (95% CI, 9%-21%) without vs 14% (95% CI, 5%-23%) with the boost ($P = .11$).

For the subgroup of patients with hormone receptor-negative, high-grade tumors, the 16-Gy boost dose reduced the 15-year cumulative incidence of IBTR from 31% (95% CI, 14%-44%) to 5% (95% CI, 0%-9%) (HR, 0.23; 95% CI, 0.07-0.70; $P = .01$).

For patients with ER-positive, low-grade tumors, the 16-Gy boost dose did not change the IBTR rate. Neither was this the case for patients with ER positive, low-grade tumors and additional DCIS.

Discussion

This long-term analysis of randomized BCT patients with a central pathology review showed that 2 factors had a significant

Table 2. Multivariable Analysis for Ipsilateral Breast Tumor Recurrence as First Event

Variable	HR (95% CIs)	*P* Value
Treatment		
No Boost vs 16 Gy Boost	0.62 (0.41-0.92)	.02
Age		
Per year[a]		<.001
Positive nodes		
No vs yes	0.82 (0.43-1.56)	.55
Systemic therapy[b]		
No vs yes	0.76 (0.44-1.29)	.31
Diameter		
Per mm	1.03 (1.00-1.06)	.05
Grade invasive tumor		
Intermediate/low vs high	0.87 (0.52-1.46)	.60
DCIS		
No vs yes	2.15 (1.36-3.38)	.001
Estrogen		
Negative vs positive	1.11 (0.67-1.85)	.67
Progesterone		
Negative vs positive	0.79 (0.48-1.29)	.34

Abbreviations: DCIS, ductal carcinoma in situ; mm, millimeter.

[a] See eFigure 5 in Supplement 2.

[b] Systemic therapy indicates tamoxifen or chemotherapy.

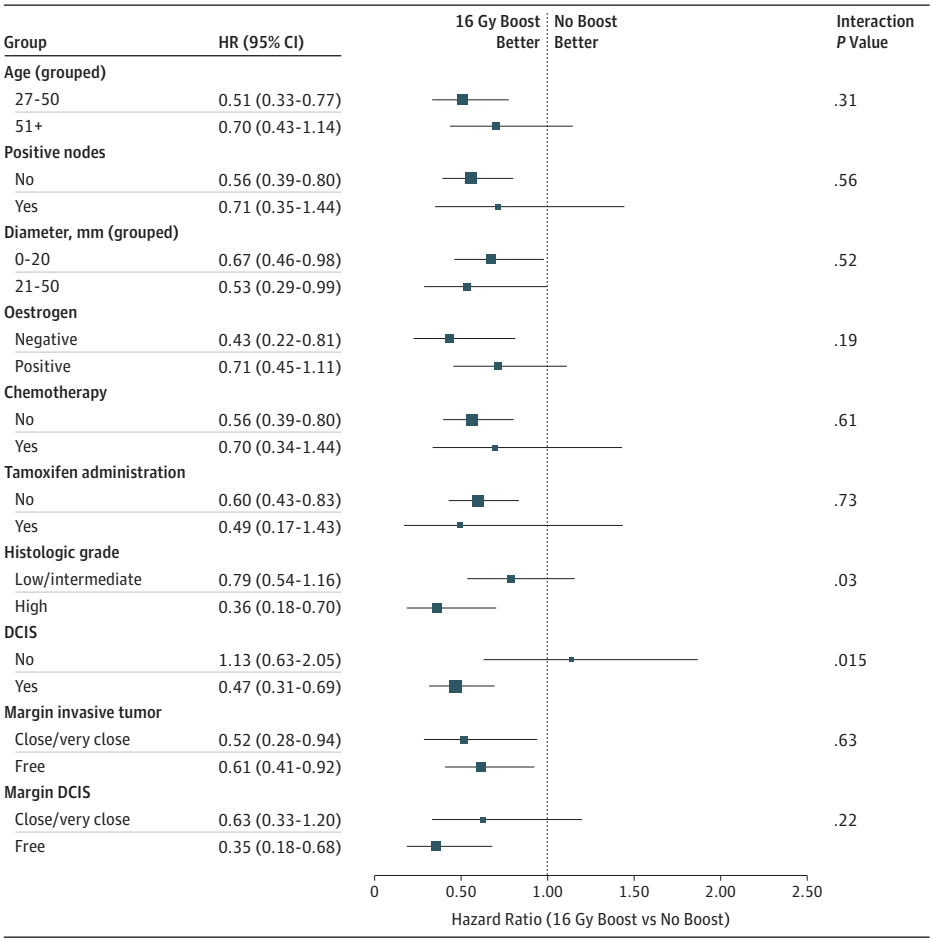
negative impact on local control: young age and the presence of an additional DCIS component adjacent to the primary tumor.

The negative impact of young age on local control could be reduced by the boost in radiation therapy dose. Bartelink et al[11] showed that the relative improvement in local control by the boost was similar for the different age groups; however, the absolute risk reduction in local recurrence was the largest in the younger patients. Younger patients were not at higher risk for adverse effects of the boost dose in terms of cosmetic outcome or fibrosis development, which remained independent from age.[17]

In our previous analysis,[10] we showed that the grade of invasive cancer, together with boost and age, remained significant in the final multivariable analysis. With longer follow-up, the relative effect of invasive tumor grade decreased rapidly within the first 5 years, losing its significance with longer follow-up, whereas the relative effect of presence of DCIS did not diminish over time (Figure 2), doubling the IBTR incidence at 20 years. This factor has a constant relative effect on local control over time, meaning that the absolute difference between the cumulative incidence curves continues to widen, emphasizing the importance of long-term follow-up.[18]

All excisions were complete according to local pathologists, but resection margin width was analyzed from central review data. Neither the margin for the invasive tumor nor for the

Figure 3. Effect of the Radiotherapy Boost Dose on IBTR for the Different Subgroups



DCIS indicates ductal carcinoma in situ; IBTR, ipsilateral breast tumor recurrence.

associated DCIS component was associated with IBTR. These results confirm the Society of Surgical Oncology–American Society for Radiation Oncology consensus guidelines on margins in BCS for invasive cancer.[4] These guidelines concluded that positive margins (ink on tumor) were associated with a 2-fold increase in the risk of local recurrence, but if the margins were negative (no ink on tumor) an increase in margin width did not significantly decrease the risk of local recurrence.

Based on the risk factors for local control, we defined high- and low-risk populations. The high-risk group consisted of patients 50 years or younger with DCIS in addition to the invasive tumor, in which the boost dose reduced the incidence of IBTR with a HR of 0.37 (95% CI, 0.22-0.62) translating in an absolute decrease of 16% at 20 years.

A low-risk group was defined as patients having ER-positive, low-grade tumors (as an approach for the selection of luminal A tumors). The radiotherapy boost did not appear to modify the risk of local relapse in this subgroup. We know that overall the percentage of local recurrences in early breast cancer patients is decreasing.[19,20] In this favorable population, the question is whether they need any radiotherapy at all.[6,21] Three different studies randomized postmenopausal women with low-risk hormone receptor-positive early-breast cancer treated with BCS and endocrine therapy between WBI and no further treatment.[22-24] The 5-year results show an IBTR incidence of 0.6% to 1.3% in the WBI group compared with 4.0% to 7.7% in case of no RT. Only Hughes et al[25] published the long-term follow-up results: a 10-year loco-regional recurrence rate of 2% in the WBI group compared with 10% in the no RT patients. This result underlines the need for long-term follow-up given the pattern of late recurrences in these favorable tumors.[26] Liu et al[8] concluded that patients older than 60 years with T1 luminal A tumors, treated with lumpectomy and tamoxifen alone, had a 10-year IBTR of only 3.1%. Currently, several single-arm trials of BCS and endocrine therapy without radiotherapy in post-menopausal patients with small luminal A tumors are initiated (Clinicaltrials.gov NCT01791829, NCT02400190, NCT02653755). The development of gene-expression signatures related to local control in breast cancer is another important tool in the selection of patients benefiting from postoperative radiotherapy,[27] but a reliable and validated profile predicting the need for postoperative radiotherapy is currently not yet available.

Limitations

There are limitations to this study. The pathology review population was limited to less than one-third of the whole trial population. Therefore, the subgroup analysis does not have much power, and although the forest plot indicates homogeneity of the effect of radiotherapy boost treatment, the nonsignificance of interactions should be interpreted with caution. Furthermore, the IBTR rates have fallen greatly in the past years, so the absolute risk reduction caused by the boost is currently probably smaller. Owing to the absence of a treatment arm without radiotherapy we could not study the possibilities of omitting radiotherapy for favorable subgroups. As the measurement of HER2/neu was not standard during the course of the trial, we were unable to fully assess the impact of subtyping on local control.

Conclusions

The long-term follow-up analysis of pathological prognostic factors associated with local control in the EORTC boost no boost trial showed that young age and the presence of associated DCIS increase the risk of IBTR. In patients with both factors the radiotherapy boost dose reduced the IBTR risk with an HR of 0.37, leading to an absolute risk reduction of 16% at 20 years. The proportional hazards assumption of a constant hazard was valid for almost all variables, except for the effect of high histologic grade, which diminished over time. The fact that the relative impact of additional DCIS on local control seemed to remain constant over time, whereas the impact of high grade decreased over time, underlines the importance of long-term trial follow-up to correctly estimate absolute effects. Patients with high-grade invasive tumors need to be monitored closely especially in the first 5 years, whereas patients with invasive tumors with associated DCIS need long-term follow-up, at least 20 years.

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