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Clinical Trial

Endocrine therapy with or without whole breast irradiation in low-risk breast cancer patients after breast-conserving surgery: 10-year results of the Austrian Breast and Colorectal Cancer Study Group 8A trial

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KEYWORDS
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Abstract ***Purpose:*** To investigate long-term results of patients with hormonal receptor−positive breast cancer treated with breast-conserving surgery (BCS) and consecutive endocrine therapy (ET) with or without whole breast irradiation (WBI).
Methods and materials: Within the 8 A trial of the Austrian Breast and Colorectal Cancer Study Group, a total of 869 patients received ET after BCS which was randomly followed by WBI (n = 439, group 1) or observation (n = 430, group 2). WBI was applied up to a mean total dosage of 50 Gy (+/− 10 Gy boost) in conventional fractionation.
Results: After a median follow-up of 9.89 years, 10 in-breast recurrences (IBRs) were observed in group 1 and 31 in group 2, resulting in a 10-year local recurrence−free survival (LRFS) of 97.5% and 92.4%, respectively (p = 0.004). This translated into significantly higher rates for disease-free survival (DFS): 94.5% group 1 vs 88.4% group 2, p = 0.0156. For distant metastases−free survival (DMFS) and overall survival (OS), respective 10-year rates amounted 96.7% and 86.6% for group 1 versus 96.4% and 87.6%, for group 2 (ns). WBI (hazard ratio [HR]: 0.27, p < 0.01) and tumour grading (HR: 3.76, p = 0.03) were found as significant predictors for IBR in multiple cox regression analysis.
Conclusions: After a median follow-up of 10 years, WBI resulted in a better local control and DFS compared with ET alone. The omission of WBI and tumour grading, respectively, were the only negative predictors for LRFS.

1. Introduction

For the treatment of invasive breast cancer, whole breast irradiation (WBI) after breast-conserving surgery (BCS) was repeatedly confirmed to be highly effective in terms of local control (LC), which translated into better overall survival (OS) after long-term observation [1]. However, partial breast irradiation either with postoperative hypofractionated external beam radiotherapy (RT) [2], intraoperative [3,4] or interstitial techniques [5,6] is now regarded as a valid alternative for patients presenting with 'very' low-risk subtypes [7–9]. Within the last 15 years, especially for this subgroup of postmenopausal 'elderly' women, a total of five randomized clinical trials investigated whether WBI can be replaced by systemic endocrine therapy (ET) [10–14]. Respective data were summarized in a recent meta-analysis, where WBI has been shown to be advantageous for the avoidance of in-breast relapses (for ET, HR: 6.8, p < 0.0001) but with no impact on OS (HR: 1.09, p = 0.57) [15]. In 2007, on behalf of the Austrian Breast and Colorectal Cancer Study Group (ABCSG), Pötter *et al.* [10] reported first results of 831 patients within the 8A trial, who were randomly assigned to receive either WBI plus ET (n = 414) or ET alone (n = 417). Local recurrence−free survival (LRFS), disease-free survival (DFS) and OS were defined as clinical end-points. After a median follow-up of 53.8 months, patients with WBI had a significantly lower 5-year in-breast local relapse rate (WBI plus ET: 0.4% vs ET alone: 5.1%, HR: 10.21, p = 0.0001), which contributed to a better DFS (5-year overall relapse rate after WBI plus ET: 2.1% vs ET alone: 6.1%, HR: 3.48, p = 0.0021). No difference between arms was seen for OS. The database of this study was now revisited after a 10-year observation period. In this investigational setting, long-term results are scarce, with only two publications from the US and UK study groups [12,13]. Therefore, the present study focuses on LC and survival outcome, both end-points requiring follow-up periods of at least 10 years for sufficient maturity [1,16].

2. Methods and Materials

2.1. Trial design and eligibility

The ABCSG 8-trial demonstrated a significant effect for the event-free survival of postmenopausal women if ET was switched from tamoxifen (Tam) to anastrozole [17,18]. Within this trial, a subgroup of 'low-risk' patients (n = 869) was assigned to a second randomization named 8A. Only postmenopausal women, who met the following criteria, were eligible: invasive ductal or lobular carcinoma; gradings G1, G2 and/or Gx; with tumour sizes not exceeding 3 cm corresponding to pathological tumour stages of T1 or T2 (early); negative lymph nodes and positivity for oestrogen and/or progesterone receptors, and no observed metastases. In this study, randomization separated two groups to receiving either standard WBI (+/− boost to the tumour bed) (n = 414) or not (n = 417). ET was prescribed in both groups. The results were first published in 2007 after a 5-year follow-up [10]. The present secondary analysis after 10 years provides additional information on tumour biological aspects for 519 patients (Fig. 1). Patients with Her2neu positive tumours and/or a KI67 level >20% were classified prognostically as 'high-risk', and those with a negative Her2neu status and a Ki67 of ≤20% as 'low-risk', respectively (Table 1).

2.2. Treatment

All patients provided written informed consent. The study was approved by the relevant ethic committees in Austria. Patients were recruited between 1996 and 2004 [10]. BCS consisted of a lumpectomy, wide-excision, or quadrantectomy (occasionally) which was accompanied by an axillary lymph node dissection of at least 10 nodes. Sentinel node biopsy was introduced in 2001 (Table 1). ET was given to all patients for a duration of 5 years, first as Tam (20 mg/day) and switched to anastrozole (1 mg/day) after two years or continued Tam alone. Thereafter, ET was either finished or continued for further two to five years (Fig. 1). The majority of patients was followed until December 2011 at the latest; only women with prolonged ET (28%) was observed until June 2016. For patients allocated to radiotherapy, WBI started within 6 weeks after surgery. WBI was applied with a mean dose of 51 Gy (+/− 4 Gy, standard fractionation) followed by a tumour bed boost (mean dose of 10 Gy (+/− 2 Gy) external electrons) in 269 patients.

2.3. Clinical end-points

In this exploratory analysis, which was originally unplanned, LRFS was defined as the primary end-point, accounting for all observed in-breast recurrences (IBRs) within the breast or chest wall. Further end-points were determined as follows: regional recurrence−free survival (RRFS) comprising all regional recurrences located in the ipsilateral axilla and/or supraclavicular or parasternal (mammaria interna) areas; DFS for IBR and distant metastases; recurrence-free survival (RFS) for IBR; regional recurrence and death from any cause; distant metastases−free survival (DMFS) for distant

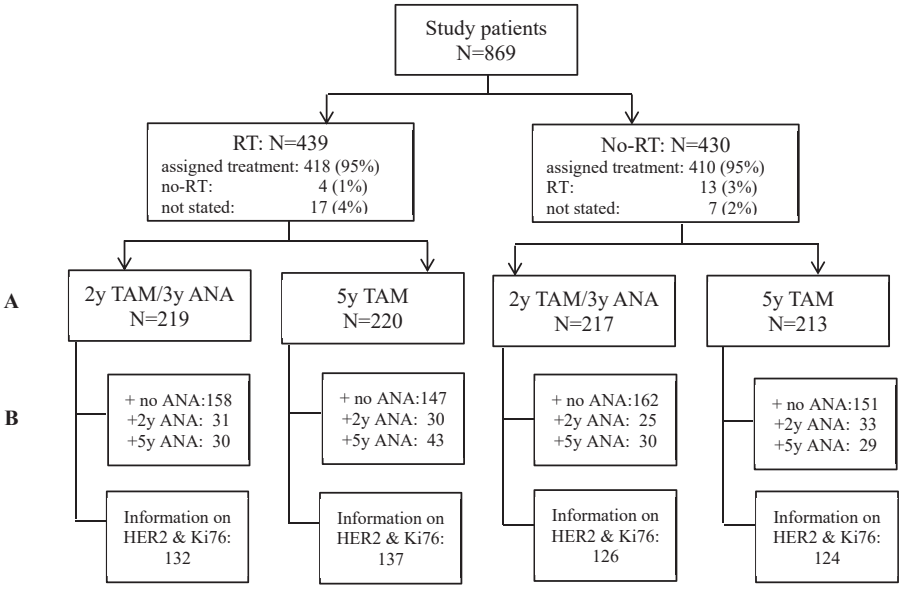

Fig. 1. Consolidated standards of reporting trials (CONSORT) diagram: study randomization into radiotherapy and endocrine treatment arms. RT = radiotherapy, 2y TAM/3y ANA = 2 years of tamoxifen followed by 3 years of anastrozole, 5y TAM = 5 years of tamoxifen.(A): 2y TAM/3y ANA and 5y TAM refers to the randomized treatment arms in ABCSG 8. (B): No ANA: no prolonged therapy, +2y ANA and +5y ANA = 2 or 5 years of prolonged therapy with anastrozole. ABCSG, Austrian Breast and Colorectal Cancer Study Group.

Table 1
Patient characteristics.

Characteristics	Radiotherapy N = 439 n %	No radiotherapy N = 430 n %	Total N = 869 n %
Age group			
<50	9 (2.1)	5 (1.2)	14 (1.6)
50–59	122 (27.8)	117 (27.2)	239 (27.5)
60–69	151 (34.4)	155 (36.0)	306 (35.2)
≥70	157 (35.8)	153 (35.6)	310 (35.7)
T-stage			
pT1b	143 (32.6)	135 (31.4)	278 (32.0)
pT1c	236 (53.8)	252 (58.)	488 (56.2)
pT2	45 (10.3)	37 (8.6)	82 (9.4)
not stated	15 (3.4)	6 (1.4)	21 (2.4)
Grading			
G1	138 (31.4)	142 (33.0)	280 (32.2)
G2	264 (60.1)	262 (60.9)	526 (60.5)
Gx	22 (5.0)	20 (4.7)	42 (4.8)
not stated	15 (3.4)	6 (1.4)	21 (2.4)
Oestrogen receptor			
+	43 (9.8)	29 (6.7)	72 (8.3)
++	115 (26.2)	108 (25.1)	223 (25.7)
+++	258 (58.8)	282 (65.6)	540 (62.1)
negative	6 (1.4)	5 (1.2)	11 (1.3)
not stated	17 (3.9)	6 (1.4)	23 (2.3)
Progesterone receptor			
+	78 (17.8)	77 (17.9)	155 (17.8)
++	135 (30.8)	134 (31.2)	269 (31.0)
+++	122 (27.8)	130 (30.2)	252 (29.0)
negative	87 (19.8)	81 (18.8)	168 (19.3)
not stated	17 (3.9)	8 (1.9)	25 (2.9)
Axillary surgery			
Axillary dissection	295 (67.2)	295 (68.6)	590 (67.9)
Sentinel node only	129 (29.4)	129 (30.0)	258 (29.7)
not stated	15 (3.4)	6 (1.4)	21 (2.4)
Biological risk stratification[a]			
High risk: KI 67 > 20 or Her2neu positive	20 (7.5)	23 (9.2)	43 (8.2)
Low risk: KI67 ≤ 20 and Her2neu negative	249 (92.5)	227 (90.8)	476 (91.8)

[a] Data exclusively available for 519 patients.

metastases only and OS for deaths from any cause. In contrast to the first publication in 2007, the following changes in end-point definitions were made: relapses only within the breast or thoracic wall were now counted as IBR (i.e relapses within the axilla were assigned to regional recurrences); and regional relapses detected in supraclavicular and mammaria interna lymph nodes were not further noted as distant metastases. These definitions of DFS and RFS are in line with the first publication and therefore differ from standardized definitions for efficacy end points (STEEP system) [19].

2.4. Statistical methods

Data analyses were performed on an intention to treat basis in 2018. For these, the last follow-up data were recorded in 2016. The median follow-up was calculated by using a reverse Kaplan-Meyer approach. Hypotheses were generated that for all defined clinical end-points, differences between patient groups with or without RT would be not statistically significant. Subjects were censored with the last available event-free date (competing events were not used for censoring). The 2-sided log-rank test was used to test for differences between RT and non-RT group. Results were presented as 10 years survival rates and their corresponding 95% confidence intervals. P values, when stated, belong to corresponding long-rank test. The multivariate Cox regression was performed using the primary end-point of LRFS with adjustment for ABCSG 8a and ABCSG 8 treatment, age group (<50,50–59,60–69), tumour grade, progesterone receptor status, and tumour stage. Cox regression was repeated on data including Ki67 and HER2 information. All analyses were calculated using SAS, version 9.3 (SAS Institute, Cary, NC).

3. Results

By November 2017, 869 randomized patients were identified for second statistical analysis. Of these, 439

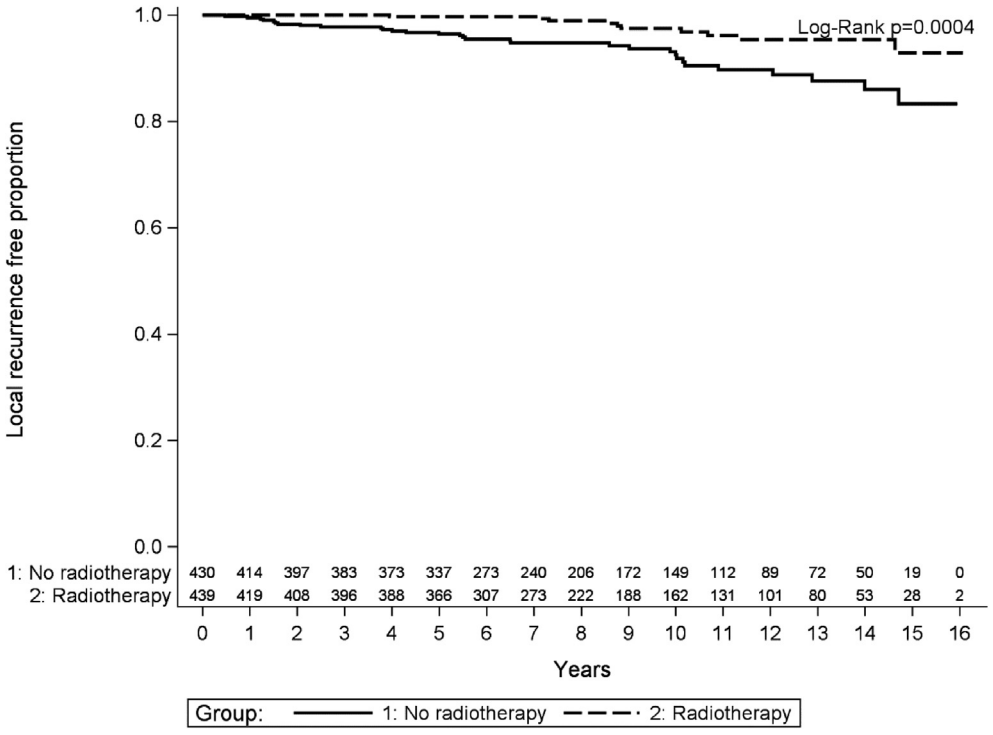

Fig. 2. Local recurrence–free survival.

were randomized to receive WBI plus ET (group 1) and 430 for ET alone (group 2). Patient and tumour characteristics are summarized in Table 1.

After a median follow-up of 9.89 years (range, 9.02–10.09), 10 IBR were detected in group 1 versus 31 in group 2, which translated into an actuarial 10-year LRFS of 97.5% (95% CI, 94.4%–98.9%) and 92.5% (95% CI, 88.6%–95.1%), respectively. As depicted in Fig. 2, differences between both groups were statistically significant ($p = 0.0004$). This was also true for DFS (Fig. 3, $p = 0.0156$), with an actuarial 10-year rate of 94.5% (95% CI, 91.1%–96.6%) for group 1 (27 events) versus 88.4% (95% CI, 83.9%–91.7%) for group 2 (45 events). In total, 112 patients died (57 in group 1 and 55

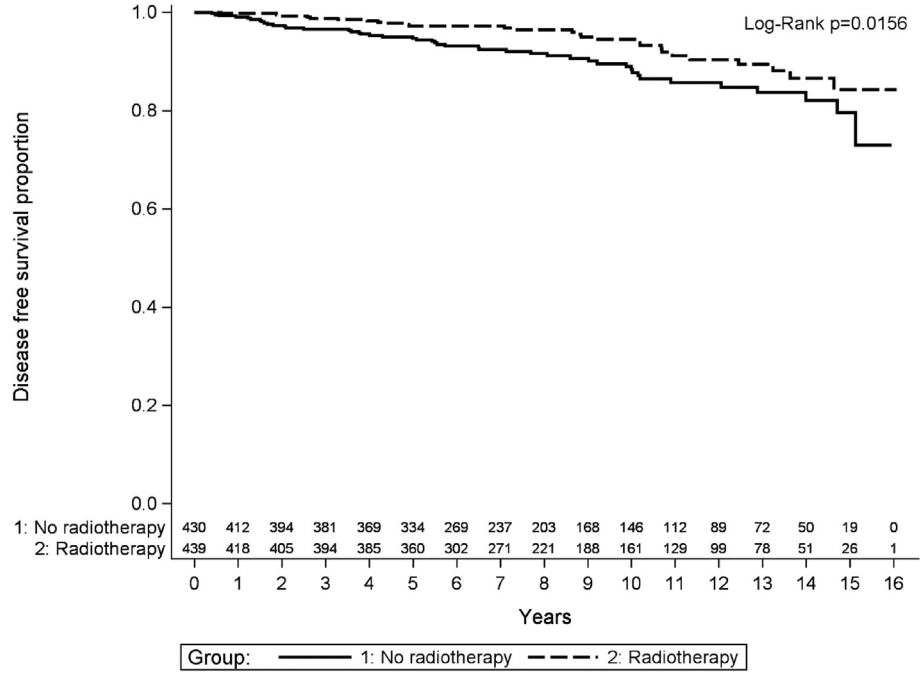

Fig. 3. Disease-free survival.

in group 2), 28 developed distant metastases (16 in group 1 and 12 in group 2), and eight patients experienced regional recurrences (four in both groups, respectively). Ten-year rates for RRFS, OS, DMFS, and RFS amounted 99.8 (95% CI, 98.2 to 100), 86.6% (95% CI, 82.3%–89.9%), 96.7% (95% CI, 94%–98.2%) and 82.5% (95% CI, 77.5%–86.4%) in group 1 and 98.7 (96.5–99.5), 87.6% (95% CI, 83.3%–90.8%), 96.4% (95% CI, 93.5%–98.1%) and 78.9% (95% CI, 73.8%–83.2%) for group 2 (ns).

3.1. Subgroup analysis of DFS in accordance with lymph node surgery

Among patients who had a sentinel node only of whom 129 were in group 1 and 129 in group 2, DFS was significantly better in group 1 98.3% (95% CI, 93.2%–99.6%) compared with group 2 (86.9% (95% CI, 78.1%–92.3%), p = 0.0074. Interestingly, this effect was not seen in patients after axillary lymph node dissection (group 1: 93% (95% CI, 88.4%–95.9%) versus group 2: 88.8% (95% CI, 83.2%–92.7%), p = 0.2459).

3.2. Risk factors for local recurrence–free survival

By Cox proportional hazards regression, tumour grading (Gx vs G1: HR = 3.76 (1.22–11.6), p = 0.028) and the omission of WBI (RT vs no RT: HR = 0.27 (0.13–0.57), p = 0.0006) were detected as the only significant risk factors for LRFS (Fig. 4) after multivariable analysis. According to a subgroup analysis for patients where biological features were available (n = 519) for a small number classified as high risk (group 1: n = 20 (7%) vs group 2: n = 23 (9%)), the corresponding HR was 2.12 (0.78–5.74, p = 0.1) compared with those defined as biologically low-risk subtype (group 1: n = 249 (93%) vs group 2: n = 227 (91%). However because absolute numbers for high-risk patients are low, these findings have to be interpreted with caution.

3.3. Occurrence of IBR overtime

In patients without WBI, IBRs were detected during the whole observation period, with two peaks in year two and eleven. In irradiated patients, the first IBR occurred in year four, all others between year eight and fifteen (Fig. 5).

4. Discussion

This 10-year secondary analysis corroborates the effectiveness of RT in addition to ET for postmenopausal women who are prognostically classified as 'low-risk'. Both end-points, LRFS and DFS, maintained significance after a follow-up of ten years, thus favouring WBI compared with ET alone. No further influence was seen on OS. These data are in line with those reported by Hughes [12] and Blamey *et al.* [13]. In the former, patients treated with Tam who received additional RT (TamRT) improved significantly in 10-year locoregional recurrence–free survival (Tam: 90% (95% CI, 85%–93%), TamRT: 98% (95% CI, 96%–99%), p=<0.001) [12]. Moreover, patients allocated to TamRT were observed with a higher LRFS than Tam alone (TamRT: 98% (95% CI, 87%–94%) vs Tam: 91% (95% CI, 87%–94%, no p-value stated). The study conducted by Blamey *et al* [13]. focused on IBR only resulting in a

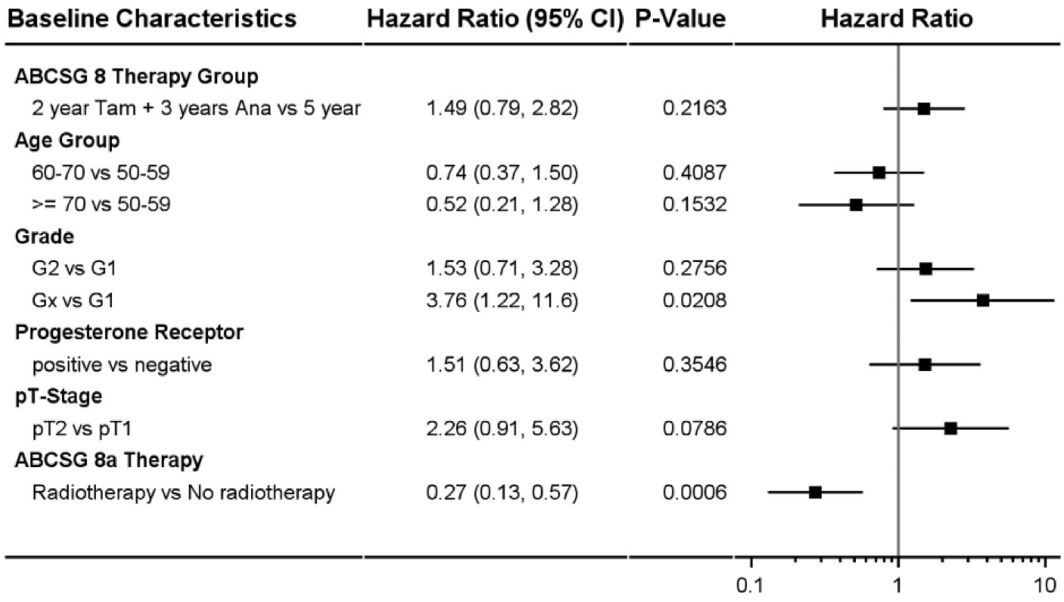

Fig. 4. Multivariate Cox regression analysis for local recurrence–free survival.

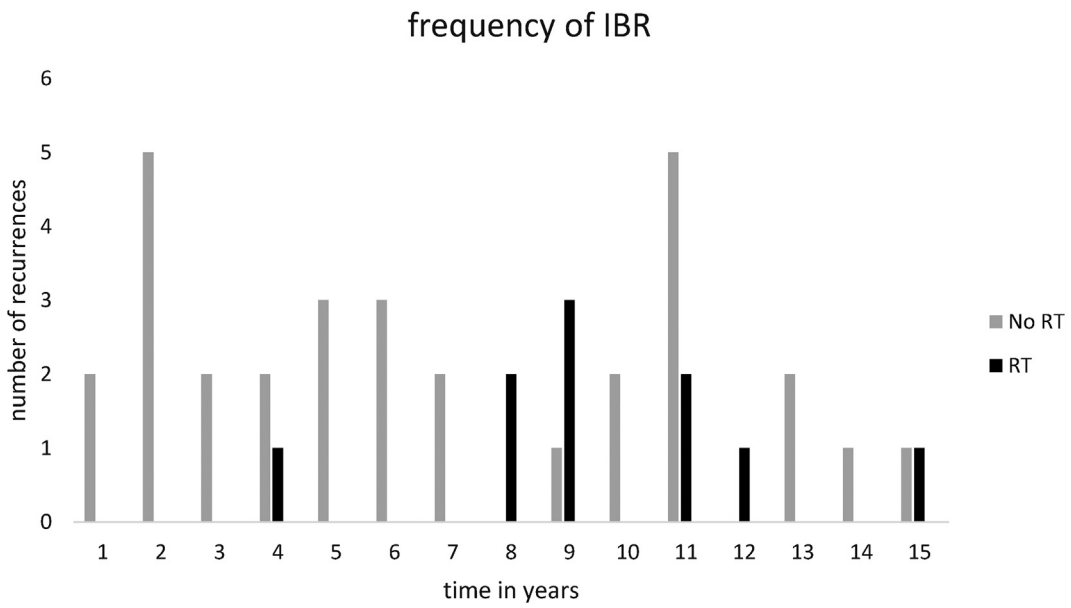

Fig. 5. IBR occurrence overtime. IBRs, in-breast recurrences.

significantly higher LRFS at 10 years: TamRT: 100% versus Tam: 93%, p = 0.006. However, in both trials [12,13], additional RT had no significant impact on survival, which was confirmed for OS in our own analysis. Furthermore, available prospective data investigating the randomization between ET with or without RT were pooled in two meta-analyses [15,20]. Van de Water *et al.* [20] examined five prospective randomized trials comprising 3190 patients. The 5-year rate for locoregional recurrence amounted 2.2% (95% CI, 1.6–3.1) for patients with ET plus RT versus 6.5% (95% CI, 5.3–7.9) for those with ET alone (odds ratio [OR] 0.36; 95% CI: 0.25–0.5). This difference of 4.3% (95% CI, 2.9–5.7) was translated into a number needed to treat 24 to avoid one locoregional recurrence in 5 years. No RT effect was shown for OS (OR, 0.92 (95% CI, 0.74–1.15), as well as for the development of distant metastases (OR, 0.96 (95% CI, 0.68–1.36). In a recent meta-analysis from randomized trials comprising 3766 patients, these findings were confirmed by Matuschek *et al.* [15].

Only one randomized trial, by Fyles *et al.* [11], reported a significant benefit in DFS for patients with TamRT. The respective 5-year rate for DFS was 91% for the group with RT versus 84% for those who were treated with Tam alone (p = 0.004). Whether this gain in DFS was influenced by the fact that RT avoided more regional relapses in axillary nodes than ET alone (5-year regional recurrence rate of 0.5% for TamRT versus Tam 2.5%, p = 0.049) is speculative. However, this fact did not translate into better OS. Of note, especially in the 476 patients without axillary lymph node dissection, those with WBI showed a by trend lower 5-year regional recurrence rate (TamRT: 0.6% versus Tam: 3.3%, p = 0.07) [11]. The question whether the omission of an axillary lymph node dissection may influence the occurrence of regional relapses and subsequently also survival of prognostically favourable patients with a positive sentinel node was investigated within the ACOSOG Z0011 trial published first in 2011 [21]. After 5 years, no difference in terms of OS and development of regional recurrences was demonstrated, which was confirmed in 2017 in the 10-year follow-up [22]. Unfortunately, in both publications, no technical details on RT were provided to reliably assess the contribution of radiation dose for the avoidance of regional node metastases. This lack of methodical information was, beside others, a major criticism [23,24]. Altogether, only in about 50% (n = 228) of patients (axillary lymph node dissection versus sentinel node only), technical RT-data were available for a retrospective secondary analysis. Of these, in the group without AD (n = 124), 21 patients were treated with additional supraclavicular fields, and furthermore 40 patients with 'high tangents' [25]. This left room for speculation as to whether inadvertent RT of axillary nodes had probably influenced the low rate of locoregional recurrence [26]. Several studies explored the proportion of regional axillary nodes covered by subclinical dosages applied by conventional tangential fields, also dependent on cranial field extensions [27–31]. This observation might also be relevant for patients with negative sentinel nodes who bear a risk of occult nodal metastases up to 15.9% [32]. A respective subanalysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-32 observed a small but significantly worse 5-year rate for OS and DFS in patients with negative sentinel nodes which converted into positive ones after pathological secondary analysis

compared with those whose lymph nodes remained negative (absolute differences for OS: 1.2%, p = 0.03 and for DFS: 2.8%, p = 0.02) [32]. A similiar effect may explain our own data: All of our patients were node negative and profited significantly from WBI in terms of DFS (absolute benefit: 6.1%, p = 0.01), putatively by sterilizing unrevealed lymph node metastases. This improvement in DFS was significant (p = 0.0023) for sentinel-only patients (absolute benefit: 12%) but not for those after axillary lymph node dissection.

Unlike earlier trials, the present study was able to provide information on more 'modern' biological features as possible risk factors for LRFS. In 519 patients, Her2neu receptor status and/or KI67 were assessed in tumour specimens and classified as 'high-risk' in 43 patients (8%) and as 'low-risk' in 476 patients (92%), respectively. In the present post-hoc subgroup analysis, we were not able to show a negative prognostic impact of biological high-risk features, which however might be attributable to the small number of patients. Nonetheless, especially in subgroups with these features, RT should maintain its essential role in any breast preserving approach. In times of de-escalation concepts by hypofractionation [33,34] or partial breast irradiation [2–6,35], the total omission of RT should be individually reserved for frail elderly patients with severe comorbidities and a low life expectancy [7,36].

4.1. Limitations to the article

In contrast to the first publication in 2007, 38 patients, who were primarily rated as ineligible, were now considered for statistical analysis by intention to treat. In addition, no data were available to further categorize local recurrences within the breast into 'true' local relapses (i.e. within the former index-quadrant) or elsewhere. No information is provided for pathological workup of local recurrences or the surgical salvage treatment (mastectomy or second BCS ± Re-RT). Thus, data generation for mastectomy-free survival rates was impossible. In addition, no data were available to quantify patients' satisfaction by standardized quality-of-life questionnaires.

5. Conclusion

In prognostically favourable patients with breast cancer, RT significantly improves LRFS and DFS in combination with ET also after ten-year follow-up, which does not translate into better OS. The omission of WBI and tumour grading were negative predictors for local recurrence. Dependent on axillary surgery, the benefit in DFS was detected after sentinel node excision only but not after axillary dissection. Additional biological risk classifications are warranted to better refine subgroups for RT de-escalation.

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Conflict of interest statement

F.S. reports a research collaboration with Elekta, during the conduct of the study.

R.G. has received honoraria, has been a consultant or has served an advisory role, has received research funding and has received travel and accommodations expenses from Celgene, Roche, Merck, Takeda, AstraZeneca, Novartis, Amgen, BMS, MSD, Sandoz, Abbvie, Gilead, Daiichi Sankyo, and Janssen.

G.M. has received institutional research support from AstraZeneca, Roche, Novartis, and Pfizer and has received lecture fees, honoraria for participation on advisory boards, and travel support from Amgen, AstraZeneca, Celgene, EliLilly, Invectys, Pfizer, Nanostring, Novartis, Roche, and Medison. He has served as a consultant for AstraZeneca and EliLilly and an immediate family member is employed by Sandoz.

The other authors report no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.11.024.

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