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Long-term outcomes of three distinct once-daily schedules for accelerated partial breast irradiation

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A B S T R A C T

Background and purpose: To date, accelerated partial breast irradiation (APBI) regimens are highly heterogeneous. Twice-daily schedules show comparable local control to whole-breast radiotherapy but with worse toxicity and cosmesis profiles. Conversely, once-daily regimens are better tolerated, though dose and number of fractions are yet not standardized. Therefore, the aim of this study was to evaluate the efficacy and tolerability of three different once-daily APBI schedules.
Materials and methods: Three consecutive phase-2 trials were conducted at a single national cancer center to assess three once-daily APBI schedules (40Gy in 10 fractions, 35Gy in 7 fractions, and 28Gy in 4 fractions) delivered with 3D-conformal radiotherapy. All patients were at least 60 years old and had early-stage breast cancer (pT1-2,pN0-N1mic). Toxicity and cosmesis were evaluated by physicians using the CTCAE 4.0 scale and the Harvard score, respectively. Recurrence rates and survival outcomes at 5 and 10 years were estimated using the Kaplan-Meier method.
Results: A total of 189 patients were enrolled, with a median follow-up of 10.2 years. Patients treated with 40Gy in 10 fractions, 35Gy in 7 fractions and 28Gy in 4 fractions were 80 (42%), 73 (39%), and 36 (19%), respectively. Acute toxicity was low and comparable across schedules, whereas grade≥2 late toxicity and poor cosmesis were significantly worse with the shorter schedule. The 10-year estimated in-breast tumour recurrence rate was 5.5%, comparable to the limited literature reporting long-term outcomes.
Conclusions: Once-daily APBI delivered with 3D-conformal radiotherapy was effective; however, regimens with fewer than 5 fractions may be associated with increased toxicity and worse cosmesis.

1. Introduction

Radiation therapy is an essential part of loco-regional treatment following conservative surgery for breast cancer and reduces the risk of local relapse [1]. Despite its fundamental role, some patients opt for mastectomy over breast-conserving surgery due to concerns about toxicity associated with whole-breast irradiation (WBI) and the need for daily access to the hospital [2]. Moreover, many patients prefer the shorter courses of adjuvant radiation therapy [3], leading to the development of various hypofractionated radiotherapy regimens that reduce the volume of radiation therapy and/or the number of fractions.

Both moderate hypofractionation (15–16 daily fractions) and ultra-hypofractionation (5 daily fractions) [4,5], as well as accelerated partial breast irradiation (APBI), are valid modalities to shorten overall treatment time. APBI, in particular, targets a limited breast volume with a higher dose over a shorter course, providing an alternative to whole-breast radiotherapy for selected patients with early-stage breast cancer [6]. Clinical practice guidelines for APBI patient selection have

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been provided by the American Society for Radiation Oncology (ASTRO) and the Groupe Européen De Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) [7,8]. Two randomized phase 3 trials, RAPID and NSABP-B39 [9,10], with long-term follow-up data, have confirmed that APBI is effective for early-stage breast cancer, showing comparable rates of in-breast tumour recurrence (IBRT) to WBI.

In both studies, APBI was delivered to the tumour-bearing quadrant over five treatment days within an eight-day period, with a total dose of 38.5Gy administered in 10 fractions given twice-daily. However, this twice-daily schedule requires careful planning in radiotherapy departments since patients must travel twice daily to the facility. The RAPID trial found a higher rate of late adverse events in the APBI group compared to the WBI group (32.3% vs. 13.3%), which also negatively affected cosmetic outcomes [3,9]. Lastly, the Barcelona trial [11] that used a similar twice daily schedule reported a slightly higher toxicity in patients treated with APBI. For this reason ESTRO-ACROP and updated ASTRO recommendations discouraged the use of a twice daily regimen [7,12]. Consequently, several alternative APBI schedules with once-daily fractions have been studied, as a 24-h interval between fractions may promote the regeneration of healthy tissue and improve the convenience of hospital visits for patients. Two phase 3 studies, IMPORT LOW [13] and Danish trial [14] investigated moderated hypo-fractionated regimen (40Gy in 15 fractions) investigated, while ultra-hypofractionated schedules were used in Florence trial [15] and HYPAB trial [16] (30Gy in 5 fractions). All this trials used a once-daily schedule delivered with external beam radiotherapy, and obtained comparable local control and survival outcome, with a better cosmesis in comparison to standard whole breast irradiation. Currently, no standard once-daily regimen for external beam APBI has been established. For this reason, we conducted a study at a single national cancer center to investigate the most efficient and feasible once-daily APBI treatment schedule.

2. Materials and methods

This study reports long-term follow-up data from three consecutive phase-2 trials conducted at Centro di Riferimento Oncologico of Aviano (CRO) IRCCS between 2006 and 2016. The trial protocols were approved by the regional ethics committee and were registered in the national registry at number CRO-2008-042 (date of registration and informed consent permission: September 25th, 2008), CRO-2011-011 (date of registration and informed consent permission: February 24th, 2011), and CRO-2013-025 (date of registration and informed consent permission: December 17th, 2023). Informed written consent was obtained from all patients before APBI, and data were anonymized and recorded in a dedicated database. Date of CRO-2008-042 initiation was November 28th, 2008; date of CRO-2011-011 initiation was June 4th, 2011; date of CRO-2013-025 initiation was March 5th, 2014.

The inclusion criteria and statistical trial design were consistent across all three trials. Each trial evaluated a different once-daily APBI schedule: 40Gy in 10 fractions (4Gy/fraction, Group A), 35Gy in 7 fractions (5Gy/fraction, Group B), and 28Gy in 4 fractions (7Gy/fraction, Group C). The primary endpoint was high-grade toxicity, and the three tested schedules were designed to be iso-effective to a standard dose of 54Gy delivered in 2Gy fractions, calculated with an α/β ratio of 4Gy [17,18].

For sample size calculation, an incidence of high-grade toxicity greater than 2% was considered the null hypothesis. The minimum required number of patients for each treatment group was 67, based on $\alpha = 0.05$ and $\beta = 0.20$ (power$(1-\beta) = 80\%$). Each trial would have been prematurely closed if more than two cases of Grade 3–4 toxicity occurred. Patient inclusion criteria included early-stage breast cancer (pT1-T2; if pT2$\leq$3 cm), no evidence of macroscopic lymph node or distant metastasis (pN0-pN1mic; M0), age$\geq$60 years, breast conserving surgery with clear surgical margins, and unifocal disease. All histological grades, estrogen/progesterone/human epidermal receptor-2 (HER-2) status, and the presence of lymphovascular invasion were permitted. Patients with prior chest irradiation were not eligible.

2.1. Treatment

APBI was administered using a LINAC with the 3D-conformal radiation therapy (3DCRT) technique. Treatment volumes, organs-at-risk (OARs) constraints, and radiation therapy planning were based on the NSABP-B39/RTOG-0413 guidelines [19]. All patients underwent free-breathing computer tomography simulation in the supine position with the Quest Breastboard (Q-Fix System, Avondale, USA). The clinical target volume (CTV) included the lumpectomy cavity, identified by the post-surgery seroma and surgical clips, and was uniformly expanded by 15 mm, limited to 5 mm from the skin surface and 5 mm from the lung-chest wall interface. The planning target volume (PTV) was determined by adding a uniform 1 cm 3-dimensional (3D) expansion to the CTV. PTV_EVAL was the structure used for dose-volume histogram (DVH) constraints and analysis.

PTV_EVAL was defined as the PTV, excluding areas outside the ipsilateral breast, the first 5 mm of tissue beneath the skin, and tissues beyond the posterior extent of the breast. Uninvolved normal breast (UNB) was defined as the breast tissue excluding the PTV. To enhance dose homogeneity within the PTV, the planning process utilized multiple, coplanar or non-coplanar, 6-MV, 3D-conformal photon fields, applying the “field-in-field” technique. All treatments were planned using the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA), with dose-volume histograms (DVHs) generated for all relevant target volumes and OARs.

2.2. Follow up and statistics

Follow up was conducted periodically by radiation oncologists with expertise on breast cancer. Visits were scheduled at 1, 3, 6, and 12 months after completing radiotherapy, and annually thereafter.

Radiation-induced toxicity was assessed during follow-up visits and graded using the Common Toxicity Criteria for Adverse Events, version 4.0 (CTCAE v4.0). Cosmetic outcomes were periodically evaluated by physicians and categorized according to the Harvard scale [20]. In case of a score difference compared to the baseline value, to reduce the inter-observer variability two independent cosmesis evaluation were performed by different professionals.

Toxicity and cosmetic results were reported for each APBI schedule and compared using chi-square test or Fisher’s exact test, as appropriate. A dose/volume analysis across the three different schedules was conducted and compared with Wilcoxon test. A p-value of 0.05 or less was considered statistically significant.

Local, regional, and/or distant recurrence were identified through physical examination, blood tests, mammography, breast-axillary ultrasound, and whole-body computed tomography scans. IBTR was defined as the reappearance of a tumour in the same breast, regardless of histology. The risks of IBTR regional recurrence, and distant recurrence were estimated using the Kaplan-Meier method. The risk of IBTR was evaluated for the entire population and each treatment schedule, with comparisons made using the log-rank test.

Disease-free survival (DFS), overall survival (OS), and breast cancer-specific survival were estimated at 5 and 10 years with the Kaplan-Meier method.

A univariate analysis of potential risk factors for IBTR and DFS was also performed. In addition, the IBTR risk was estimated in two subgroups defined according to GEC-ESTRO and ASTRO criteria [7,8] to obtain data comparable with those in the literature.

Table 1
Patients and tumor characteristics.

	Group A 40Gy/10 fractions	Group B 35Gy/7 fractions	Group C 28Gy/4 fractions	All population
N°of patients	80	73	36	189
Age (years)				
Median	68	69	71	69
Range	60–83	61–85	61–88	60–88
Performance status				
ECOG 0	73 (91%)	66 (90%)	29 (81%)	168 (89%)
ECOG 1	7 (9%)	7 (10%)	7 (19%)	21 (11%)
T stage				
pT1a	10 (13%)	5 (7%)	4 (11%)	19 (10%)
pT1b	25 (31%)	28 (38%)	15 (42%)	68 (36%)
pT1c	37 (46%)	34 (47%)	12 (33%)	83 (44%)
pT2	8 (10%)	6 (8%)	5 (14%)	19 (10%)
N stage				
pN0	68 (85%)	63 (86%)	31 (86%)	162 (86%)
pN1mic	12 (15%)	10 (14%)	5 (14%)	27(14%)
Side				
Right breast	46 (58%)	41 (56%)	18 (50%)	105 (56%)
Left breast	34 (42%)	32 (44%)	18 (50%)	84 (44%)
Histology				
Invasive ductal carcinoma	75 (94%)	70 (96%)	35 (97%)	180 (95%)
Invasive lobular carcinoma	5 (6%)	3 (4%)	1 (3%)	9 (5%)
Lymphatic vessels invasion				
Present	18 (23%)	8 (11%)	4 (11%)	30 (16%)
Absent	62 (77%)	65 (89%)	32 (89%)	159 (84%)
In situ ductal carcinoma				
Present	42 (53%)	26 (36%)	14 (39%)	82 (43%)
Absent	38 (47%)	47 (64%)	22 (61%)	107 (57%)
Focality				
Unifocal	79 (99%)	73 (100%)	35 (97%)	187 (99%)
Multifocal	1 (1%)	0 (0%)	1 (3%)	2 (1%)
Histologic grade				
G1-G2	57 (71%)	62 (85%)	28 (78%)	147 (78%)
G3	23 (29%)	11 (15%)	8 (22%)	42 (22%)
Subgroups (immune-histochemistry)				
Luminal A-like	63 (79%)	69 (95%)	35 (97%)	167 (88%)
Luminal B-like	7 (9%)	2 (3%)	1 (3%)	10 (5%)
HER-2 positive	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Triple negative	9 (11%)	3 (4%)	0 (0%)	12 (6%)

3. Results

3.1. Population and follow up

A total of 189 patients were enrolled between 2006 and 2016. Group A included 80 (42%) patients treated with 40Gy in 10 fractions; Group B included 73 patients (39%) treated with 35Gy in 7 fractions; and Group C included 36 patients (19%) treated with 28Gy in 4 fractions. The number of patients in Group C was lower than in the other treatment schedules because more than two cases of Grade≥3 toxicity were observed during the first year of follow-up, leading the investigators to close the 28Gy/4 fractions arm before completing the planned accrual.

The median age at diagnosis was 69 years (range: 60–88 years). Patient and tumour characteristics are reported in Table 1. Tumour characteristics were well balanced across Group A, B, and C (p = NS). Twenty-six patients (14%) died within the first 10 years after APBI. The median follow-up duration for surviving patients was 10.2 years.

3.2. Safety results

The incidence of acute toxicity was very low, with only six cases of acute Grade-2 skin dermatitis and one case of acute Grade-3 pain reported. The acute Grade-3 pain resolved within one month after completing APBI. The incidence of acute Grade ≥2 toxicity was 5%, 2.7%, and 0%, in Groups A, B, C respectively (p = 0.22).

Table 2
Acute and late toxicity.

	Total	Group A 40Gy/10 fr	Group B 35Gy/7 fr	Group C 28Gy/4 fr	P-value
N° patients	189	80	73	36	\
Acute toxicity (skin)	G2: 6 (3.2%) G3: 0	G2: 4 (5%) G3: 0	G2: 2 (2.7%) G3: 0	G2: 0 G3: 0	\
Acute toxicity (pain)	G2: 0 G3: 1 (0.5%)	G2: 0 G3: 1 (1.3%)	G2: 0 G3:0	G2: 0 G3:0	\
Late toxicity (skin)	G2: 1 (0.5%) G3: 0	G2: 0 G3: 0	G2: 0 G3:0	G2: 1 (2.8%) G3:0	\
Late toxicity (pain)	G2: 2 (1.1%) G3: 0	G2: 0 G3: 0	G2: 0 G3:0	G2: 2 (5.6%) G3:0	\
Late toxicity (fibrosis)	G2: 13 (6.9%) G3: 3 (1.6%)	G2: 4 (5%) G3: 0	G2: 5 (6.8%) G3: 0	G2: 4 (11.1%) G3:3 (8.3%)	
Any acute toxicity Grade≥2		4 (5%)	2 (2.7%)	0	p = 0.22
Any late toxicity Grade≥2		4 (5%)	5 (6.8%)	8 (22%)	p = 0.008

Late adverse events included Grade-2 skin toxicity in one patient, Grade 2 chronic pain in two patients, and subcutaneous fibrosis in 16 patients (Grade-2 in 13 patients and Grade-3 in 3 patients). One case of radiation-induced breast angiosarcoma was recorded in Group B. In Group C, there were three cases of grade-3 fibrosis, two cases of chronic pain, and one case of late skin toxicity. The incidence of late Grade ≥2 fibrosis was 5%, 7%, and 19% in Groups A, B, and C, respectively (p = 0.03). The rates of late Grade ≥2 toxicity were 5%, 7%, and 22% in Groups A, B, and C, respectively (p = 0.008). Additional details on acute and late toxicities were summarized in Table 2.

The higher late toxicity observed in Group C had a significant adverse impact on cosmetic outcomes. The physician-rated cosmetic outcomes were “fair/poor” in 4%, 8%, and 22% of patients in Groups A, B, and C, respectively (p = 0.005). In Group C, two patients required lipofilling, and one patient required nipple reconstruction to improve cosmetic results.

A dose/volume analysis of the uninvolved normal breast (UNB = ipsilateral breast – PTV) was conducted across the three APBI schedules. The percentage of UNB volume receiving the 50% isodose was 41% in Group C compared to 43% in the other Groups (p = 0.1). The percentage of UNB volume receiving the 90% isodose was 22% across all groups (p = 0.45). Thus, the increased risk of late toxicity in Group C was not attributed to larger irradiation volumes of the UNB.

3.3. Efficacy results

A total of 10 in-breast recurrences occurred (0.5 recurrences per 100 person-years). Nine (90%) recurrences were localized, while 1 (10%) had local spread to the skin and chest wall. All localized recurrences were treated with mastectomy, whereas the diffuse local recurrence was not suitable for surgery and was managed with systemic therapy alone.

In-breast recurrences were located within the radiation field in 5 cases (50%) and outside the radiation field in the other 5 cases (50%). The 5-year and 10-year risks of IBTR were 2.8% (95% CI: 1.5%–4.1%) and 5.5% (95% CI: 3.5%–7.5%), respectively.

Only one regional recurrence occurred, 11 years post-treatment (the 5-year and 10-year risks were 0%). Distant recurrences were observed in 8 patients, with 5-year and 10-year risks of distant recurrence risk at 2.1% (95% CI: 1.0%–3.2%) and 4.2% (95% CI: 2.6%–5.8%), respectively.

Contralateral breast cancer occurred in 5 patients (2.6%) and was

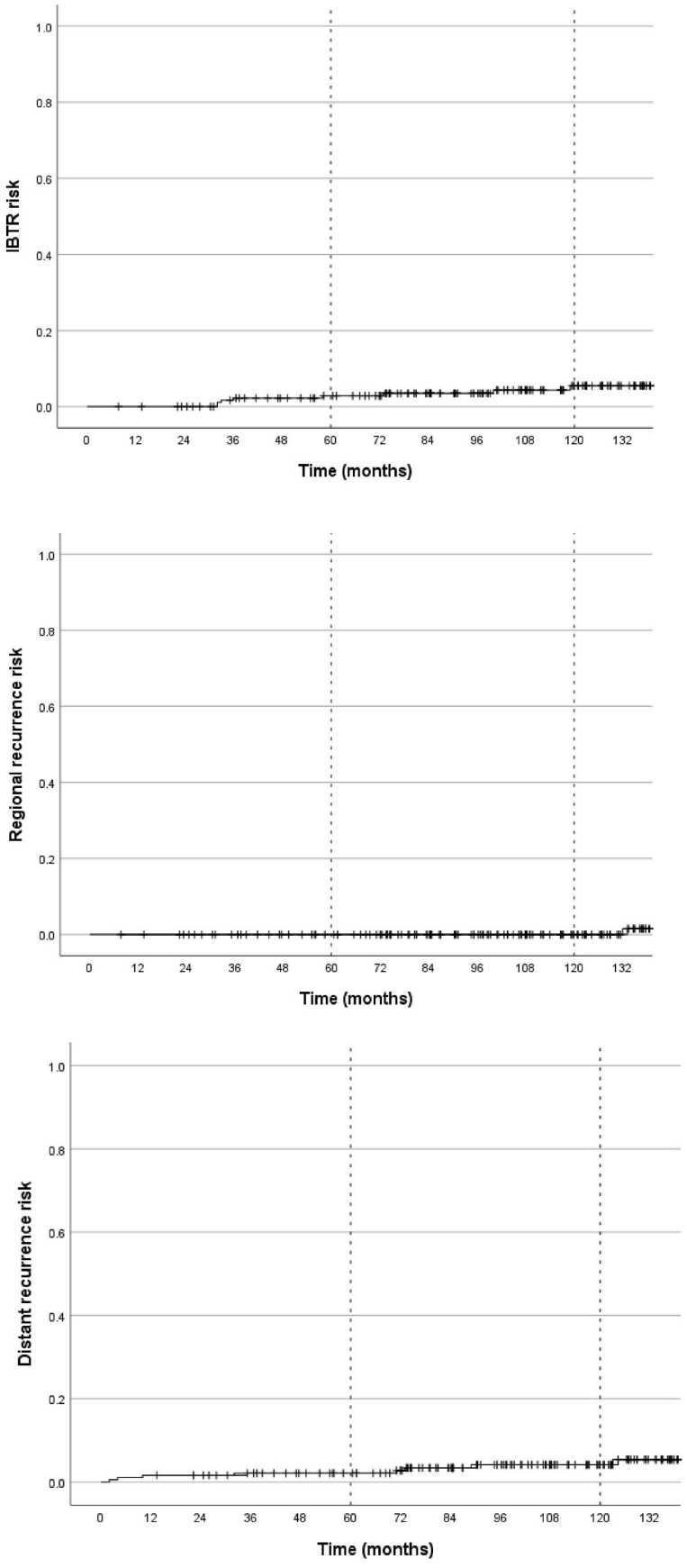

Fig. 1. Kaplan Meier plots of IBTR risk, regional recurrence disk, distant recurrence risk.

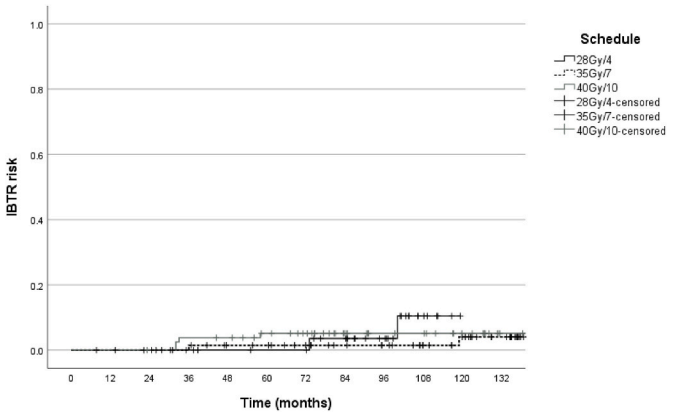

Fig. 2. Kaplan Meier plots of IBTR risk among different schedules.

Table 3
ASTRO and GEC-ESTRO criteria applied to present study population.

Parameter	GEC-ESTRO (2009)	ASTRO (2009)	Present study
Age (years)	≥50	≥60	≥60
Tumor diameter (cm)	≤3	<2	≤3
Tumor grading	Any	Any	Any
Tumor histology	IDC only	ICD only	ICD, mixed ICD + ILC
Ductal in situ carcinoma only	No	No	No
Node status	pN0	pN0	pN0 or pN1mic
Margins	≥2 mm	≥2 mm	Negative
Lymphovascular invasion	Absent	Absent	Any
Estrogen receptor	Any	Positive	Any
HER2 over-expression allowed	No	No	Yes
N° patients	83	67	189
5-years IBTR risk %(95%CI)	3.1 (1.3–4.9)	2.7 (1.2–4.2)	2.8 (1.5–4.1)
5-years IBTR risk % (95% CI)	5.8 (3.2–8.4)	5.1 (2.8–7.4)	5.5 (3.5–7.5)

ICD: invasive ductal carninoma; ILC: invasive lobular carcinoma; IBRT: in-breast tumor recurrence.

considered a primary tumour rather than a distant recurrence. Risk plots for local, regional, and distant recurrences are displayed in Fig. 1. A subgroup analysis of IBTR risk across the three APBI schedules showed no significant differences among Groups A, B and C ($p = 0.76$). A comparison of IBTR plots is shown in Fig. 2.

Factors such as lobular histology, tumour diameter ≥ 2 cm, nodal micrometastasis, absence of estrogen/progesterone receptors, grade 3, diffuse lymphovascular invasion, and diffuse ductal in situ component were evaluated as potential risk factors, but none were significantly associated with an increased risk of IBRT ($p = NS$). The inclusion criteria for this study were broader than standard partial breast irradiation criteria, with 67 out of 189 patients (35%) meeting ASTRO criteria and 83 of 189 patients (44%) meeting GEC-ESTRO criteria. No significant differences in outcomes were found between patients who did or did not meet the ASTRO ($p = 0.8$) or GEC-ESTRO ($p = 0.8$) criteria, as detailed in Table 3.

At the time of analysis, 150 patients (79%) were alive, and 39 patients (21%) had died. The majority of deaths (34 out of 39; 87%) occurred in patients without evidence of active breast cancer, while 5 deaths (13%) were related to breast cancer progression. The 5-year OS and breast cancer-specific survival rates were 94.5% (95% CI: 92.8%–96.2%) and 98.4% (95% CI: 97.5%–99.3%), respectively. The 10-year OS and breast cancer-specific survival rates were 82.4% (95% CI: 79.2%–85.6%) and 96.6% (95% CI: 95.1%–98.1%), respectively.

A total of 18 patients experienced breast cancer recurrence. The 5-year and 10-year DFS were 91.7% (95% CI: 89.7%–93.78%) and 77.6% (95% CI: 74.1%–81.1%), respectively. Survival plots are shown in Fig. 3. Tumour diameter ≥2 cm was associated with worse DFS (5-year DFS was 93.8% for T1 and 73.7% for T2, respectively; $p = 0.02$). No other risk factors were found to be statistically significant for DFS.

4. Discussion

In the present study, we report the long-term outcome of early-stage breast cancer patients treated with three different once-daily APBI schedules. Preliminary results for the first two regimens (40Gy in 10 fractions and 35Gy in 7 fractions) have already been published [21,22]. We observed a very low risk of acute toxicity (3.2% of the study population), but a significant higher risk of late side effects (Grade ≥2 late toxicity: 22%) in patients treated with the 28Gy in 4 fractions regimen ($p = 0.008$). Long-term follow-up (median = 10.2 years) enable us to estimate a 10-year IBTR rate of 5.5%, with no significant differences among the three schedules ($p = 0.76$).

The efficacy of PBI compared to WBI for early-stage breast cancer has been demonstrated by the long-term results of three phase 3 trials: the UK IMPORT LOW trial, the RAPID trial, and the NSABP B39/RTOG 0413 trials [9,10,13]. In the UK IMPORT LOW trial, patients were randomly assigned to receive standard WBI (40Gy in 15 fractions), reduced-dose WBI (36Gy in 15 fractions) plus a boost to the tumour bed (40Gy in 15 fractions), or PBI to the tumour bed (40Gy in 15 fractions). The 5-year local recurrence rates were 1.1%, 0.2%, and 0.5%, respectively, demonstrating the non-inferiority of PBI compared to WBI or reduced-dose WBI.

Lower side effects were observed in the APBI group. However, in the UK IMPORT LOW trial, the PBI schedule was not accelerated, providing no time-saving advantage. Both the RAPID and NSABP B-39/RTOG 0413 trials utilized an accelerated, twice-daily schedule (38.5Gy in 10 twice-daily fractions). The NSABP B-39/RTOG 0413 trial did not demonstrate equivalence between APBI and WBI; nevertheless, the 10-year cumulative incidence of in-breast recurrence was 4.6% in the APBI group versus 3.9% in the WBI group, with an absolute difference of 0.7% between treatment groups. The highest CTCAE-reported toxicity rates for PBI were 40% for Grade 1, 44% for Grade 2, and 10% for Grade 3 [10]. The RAPID trial demonstrated the non-inferiority of APBI compared to WBI, with 8-year in-breast recurrence rates of 3.0% for the APBI group versus 2.8% for the WBI group ($p = NS$). However, in the PBI cohort, authors reported a higher incidence of late Grade ≥2 toxicity (32% vs. 13%, $p < 0.0001$) and a poorer cosmetic outcome (absolute differences 17.7% at 7 years) [9].

Similar findings were recently observed in the IRMA trial [23], an ongoing phase 3 study comparing APBI (38.5 Gy in 10 twice-daily fractions) with WBI, which showed worse cosmetic outcomes and an increased risk of late soft tissue toxicity in the APBI arm. The authors attributed the higher toxicity rate to the twice-daily schedule, suggesting that the 6-h interval between radiotherapy fractions was likely insufficient for healthy tissue repair.

For this reason, it was suggested to investigate the once-daily schedule with a 24-h interval between radiotherapy fractions. In our population, the 10-year IBTR was 5.5%, similar to the 4.7% observed in the APBI arm of the NSABP B-39/RTOG 0413 trial. We observed a low risk of Grade ≥2 toxicity and good/excellent cosmetic outcomes with the 40Gy/10 fractions and in the 35Gy/7 fractions schedules. These results were consistent with those from the UK IMPORT LOW and NSABP B39/RTOG 0413 trials [10,13]. In contrast, we observed a higher risk of late fibrosis and fair/poor cosmetic outcomes with the shortest schedule (28Gy/4 fractions), similar to findings from the RAPID and IRMA trials [9,19]. Late toxicity could be influenced by the breast volume treated, the interval between fractions, and the dose per fraction. In this study, the treatment groups differed only in the dose per fraction, suggesting that the increase incidence of late side effects in Group C (28Gy/4 fractions) may be attributable to the higher dose per fraction

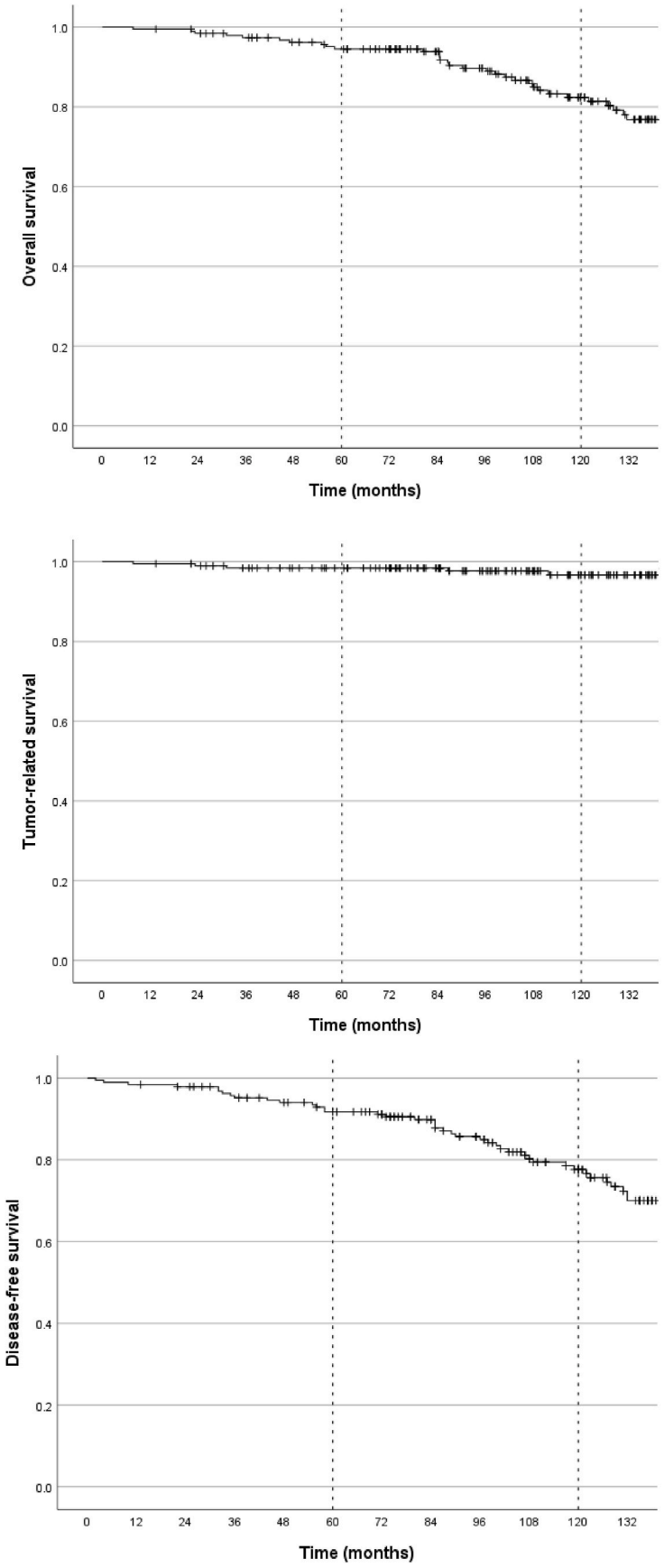

Fig. 3. Kaplan Meier plots of overall survival, tumour-related survival and disease-free survival.

(7Gy/fraction).

Several once-daily fractionation schedules have been investigated. Meattini et al. [15] conducted a Phase 3 study (the Florence trial) comparing APBI (30Gy delivered over 5 non-consecutive days) with standard WBI. The 10-year IBTR rate was 3.7% in the APBI arm, with a low incidence of toxicity and "excellent/good" cosmetic outcomes in more than 90% of patients, likely attributable to the 48-h interval between each 6Gy fraction. Another 5-fraction schedule (27Gy in 5 consecutive daily fractions) is currently being investigated in the ACCEL trial [24]. Although survival data from the ACCEL trial are not yet available, recent publications indicate favorable toxicity and cosmetic profiles.

Data on APBI schedules shorter than 5 fractions delivered via external beam radiotherapy remain limited, with brachytherapy techniques being more commonly employed. Preliminary results of the TRIUMPH-T study, a Phase 2 trial that enrolled 200 patients treated with multi-catheter brachytherapy to a total dose of 22.5Gy in 3 fractions, demonstrated excellent tolerance and cosmetic outcomes [25]. Another recent publication of a non-randomized controlled trial compared a 3-days PBI delivered with photons, protons or brachytherapy. Toxicity and cosmesis worsening were limited and similar in all arms, with a 5-years IBTR of 2% [26]. Extremely hypo-fractionated PBI in a single fraction delivered with high-dose rate brachytherapy was investigated in a phase 1-2 trial (SiFEBI trial) that enrolled a small cohort of elderly patients [27] and in a larger cohort of patients in the GEC ESTRO VAPBI study [28]. In this last publication patients treated with 1-fraction regimen (16Gy or 18Gy) appeared to be associated with lower rate of $G \geq 2$ late toxicity than the 3-fraction ($p = 0.004$). Current evidence of once-daily APBI schedule delivered with external beam radiotherapy in less than 5 fractions is limited and no phase 3 trials has been published.

4.1. Strengths and limitations

Our study provides long-term follow up data (10.2 years), and only a few published trials (e.g., NSABP B39/RTOG 0413 and the Florence trials) have estimated 10-year outcomes as we have done here. Additionally, we clarified the impact of dose per fraction on toxicity and cosmetic outcomes in a 24-h schedule. However, the study presents several limitations. Firstly, the study design did not include the collection of data regarding the patient quality of life and the patient-reported outcome, considering only the physician point of view. Secondly, the relative small sample size, especially in Group C (19% of the study population), may limit the generalizability of the findings. However, the sample size depended from the pre-planned safety limit, so for Group C the study was closed in advance due to the high rate of toxicity. Lastly, cosmetic outcomes were assessed by different physicians that might increase the scoring variability. To reduce variability, in case of a score difference compared to the baseline value two independent evaluations were performed by different professionals.

5. Conclusions

APBI regimens are highly heterogeneous, and the twice-daily APBI schedule (38.5Gy in 10 fractions) has generally shown a worse toxicity profile and poorer cosmetic outcomes compared to whole-breast radiotherapy. In our study, we tested three different once-daily APBI schedules: 40Gy in 10 fractions, 35Gy in 7 fractions, and 28Gy in 4 fractions.

The IBRT rates were low and comparable with those reported in the literature. Acute tolerance was excellent across all treatment groups; however, the rates of late toxicity and fair/poor cosmetic outcomes were significantly higher with the shortest schedule (28Gy in 4 fractions). The once-daily APBI approach appears promising, with comparable results in terms of local control and toxicity for regimens ranging from 10 to 5 fractions, as strongly recommended by the Royal College of Radiologists [29]. Similarly, in ESTRO-ACROP recommendations [12], moderate hypofractionation (40Gy in 15 fractions) and ultra-hypofractionation (26–30 Gy in five fractions) represent acceptable schedules for external beam PBI. However, schedules with fewer than 5 fractions delivered with external beam radiotherapy should likely be avoided.

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CRediT authorship contribution statement

Lorenzo Vinante: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Michele Avanzo:** Writing – review & editing, Writing – original draft, Formal analysis. **Angela Caroli:** Writing – review & editing, Writing – original draft. **Carlo Furlan:** Writing – review & editing, Data curation. **Andrea Sacilotto:** Data curation. **Lorena Baboci:** Writing – review & editing, Writing – original draft. **Tiziana Perin:** Writing – review & editing. **Martina Urbani:** Writing – review & editing. **Alessandro Favero:** Writing – review & editing. **Simon Spazzapan:** Writing – review & editing. **Fabio Puglisi:** Writing – review & editing. **Maurizio Mascarin:** Writing – review & editing. **Samuele Massarut:** Writing – review & editing. **Marco Trovò:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Data curation, Conceptualization.

Declaration of competing interest

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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