Accelerated Partial Breast Irradiation: A New Standard of Care?

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Keywords

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Abstract

Background: Breast-conserving therapy including lumpectomy and adjuvant whole breast irradiation (WBI) has become the standard therapy for early-stage breast cancer (EBC). Without WBI, the recurrence rate is significantly increased. However, when selecting patients at a low a priori risk of local recurrence only a small breast-cancer-specific mortality benefit, but no overall survival improvement, was detected for WBI. As most recurrences occur close to the lumpectomy cavity, accelerated partial breast irradiation (APBI) delivered exclusively to a limited volume of tissue around the initial lumpectomy site, has gained increased attention and is now discussed as an alternative to WBI for selected EBC patients. **Summary:** Numerous techniques for APBI (interstitial brachytherapy, external beam-based APBI, intraoperative radiotherapy, MR-guided radiotherapy) allow treatment delivery in a shorter period of time, and radiation oncologists expect to further reduce side effects by using these new techniques, with improvements in cosmetics and quality of life. In this review, we aim to describe the existing

evidence for the feasibility and effectiveness of different APBI techniques used in modern radiotherapy. **Key Messages:** APBI has provided outcomes similar to WBI combined with potentially reduced toxicity. While appropriate patient selection persists to be crucial for acceptable recurrence rates, the precise definition of patients suitable for APBI remains a matter of discussion. As long-term data are often still lacking, special attention should be paid to late side effects and long-term outcomes. Decision-making on appropriate treatment techniques should take into account not only local control rates, but also the impact on the patient's quality of life.

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Introduction

Over the past 30 years, breast-conserving therapy (BCT) including lumpectomy and adjuvant whole breast irradiation (WBI) has become the standard therapy for early-stage breast cancer (EBC) [1–4]. Numerous phase III randomized studies demonstrated equivalent overall survival and local control rates after BCT when compared to radical mastectomy alone [3–8]. For WBI, conventional doses vary between 40 and 50 Gy, applied in 15–33 daily fractions for several weeks. Depending on patient

and tumor characteristics an additional boost dose of 10–16 Gy is delivered to the tumor bed [9]. Today, hypofractionated regimes with only 15–16 fractions are the preferred regime [10, 11]. For WBI, the entire ipsilateral breast is standardly irradiated by opposed beams oriented tangentially to the chest wall. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) demonstrated that in EBC patients adjuvant WBI reduces the 10-year risk of any first recurrence from 35.0% to 19.3% and reduces the 15-year risk of breast cancer death from 25.2 to 21.4% when compared to surgery alone [12]. In node-negative breast cancer patients, the impact of radiotherapy on breast cancer recurrence is demonstrated by a reduction of the 10-year recurrence rate from 31.0 to 15.6% and of the 15-year breast-cancer-related mortality from 20.5 to 17.2% [12].

Nevertheless, when selecting patients at a low a priori risk of local recurrence (age ≥ 70 years, small and estrogen-receptor-positive tumors, tamoxifen administration) only a small breast-cancer-specific mortality benefit but no overall survival improvement was reported by the EBCTCG [12]. Consequently, several trials tested the hypothesis that the addition of adjuvant WBI to endocrine therapy would not improve the outcome of patients with early-stage, low-risk breast cancer [13–18]. However, all of the individual trials identified a significant improvement for adjuvant WBI in terms of local control while no survival benefit was shown [13–18]: The BASO II study randomized patients with EBC in either breast-conserving surgery (BCS) followed by WBI plus tamoxifen versus only BCS plus tamoxifen versus BCS followed by WBI or BCS alone. Inclusion criteria were age ≤ 70 years, node-negative low-grade breast cancer with no lymphovascular invasion, and small tumor size ≤ 20 mm. After a median follow-up of 10.1 years, the ipsilateral recurrence rate was more than three times higher with 10.2% for patients without WBI (BCS or BCS + tamoxifen) versus 3.0% for patients who received WBI (BCS + WBI or BCS + WBI + tamoxifen), but no significant improvement of overall survival was detected [13]. For the NSABP-B21 trial, EBC patients were randomized to receive WBI and tamoxifen versus WBI alone versus tamoxifen alone following BCS and axillary dissection. Inclusion criteria were tumor size ≤ 1 cm, T1a–T1b, node-negative patients and estrogen-receptor-positive tumors. At an observation time of 8 years, local recurrence rates were 2.8 versus 9.3 versus 16.5% in the three treatment groups, respectively. Once again, without WBI there was an increase in the hazard rate of ipsilateral breast tumor recurrence (IBTR) by 81% compared to tamoxifen alone, but no difference in overall survival was observed [18]. In another randomized trial of Hughes et al. [15] including EBC patients aged ≥ 70 years with small estrogen-receptor-positive tumors, a remarkable improvement in local recurrence rate was de-

tected when WBI was added to tamoxifen (2% with tamoxifen + WBI vs. 10% with tamoxifen alone), while no significant difference was seen in overall survival, distant disease-free survival, or breast preservation after a median follow-up of 12.6 years. In a meta-analysis of Matuschek et al. [19], 5 randomized trials were evaluated, including in total 3,766 mostly elderly patients with EBC treated with either adjuvant endocrine therapy or endocrine therapy plus additional WBI after BCS. They demonstrated that adjuvant hormone therapy alone resulted in significantly shorter time to local relapse compared to radiation therapy combined with hormone therapy (hazard ratio, HR: 6.8, 95% CI: 4.23–10.93, $p < 0.0001$). Therefore, even for a low-risk subset of patients omitting radiation should be no alternative.

On the one hand, postoperative irradiation of the breast is crucial for reducing local recurrence, but on the other hand, in patients with EBC most local relapses occur in the proximity of the primary tumor bed, with less than 5% in-breast recurrences elsewhere. Consequently, the main benefit of adjuvant radiation is considered to arise from the treatment delivered around the surgical cavity [20–23]. For this reason, accelerated partial breast irradiation (APBI), applied exclusively to the breast tissue surrounding the initial lumpectomy site, has gained increased attention over the past years and is now considered as an alternative to WBI for selected EBC patients [4, 24, 25]. APBI offers a way to reduce the volume of the irradiated tissue and simultaneously shortens the treatment time by hypofractionation and acceleration of radiotherapy [26]. Furthermore, APBI is more convenient for patients and is expected to be associated with less toxicity. Following WBI, acute and long-term side effects, with acute toxicity grade 2 or greater including fatigue (18%), radiation dermatitis (40%), and pain (4%), are known [27]. The long course of radiotherapy during WBI is not only inconvenient for the patient, but also comes with significant social and economic impairments [27], as well as higher costs for the healthcare providers [28].

There are numerous techniques for APBI including interstitial brachytherapy, external beam-based APBI, intraoperative radiotherapy (IORT) during BCS, and new approaches using MR-guided radiotherapy (MRgRT). The commonly accepted fractionation schemes may include 34 Gy in 10 fractions for brachytherapy, 38 Gy in 10 fractions with external beam-based APBI, or 20–21 Gy in one single fraction with IORT [29, 30]. While early randomized studies of the 1980s demonstrated higher local relapse rates in patients treated with APBI compared to WBI [31, 32], more recent clinical trials using improved radiotherapy techniques published diverging outcomes concerning local recurrence rates with similar outcomes in overall survival for APBI and WBI [33–36]. The longest follow-up in the literature after APBI exists for

Table 1. Randomized trials for APBI

Study	Country	n	Technique	Treatment	FU, years	IBTR, %	Adverse cosmesis, %	Results (APBI)
Polgár et al. [43, 44, 47]	Hungary	258	IBT	WBI (50 Gy in 25 fr) APBI (36.4 Gy in 7 fr)	10	5.1 5.9	37 19	Noninferior regarding IBTR; improved cosmesis
GEC-ESTRO trial [34, 46]	International	1,184	IBT	WBI (50 Gy in 25 fr + 10-Gy boost) APBI (32 Gy in 8 fr or 30.1 Gy in 7 fr [HDR] or 50 Gy in 0.6–0.8 Gy per pulse [PDR])	5	0.92 1.44	9 8	No significant increase in IBTR; improved acute/late toxicity and equal cosmesis
Rodríguez et al. [53]	Spain	102	EBRT	WBI (48 Gy in 24 fr +/- 10-Gy boost) APBI (37.5 Gy in 10 fr)	5	0 0	25 25	No difference
IMPORT LOW trial [54]	UK	2,016	EBRT	WBI (40 Gy in 15 fr or 36 Gy in 15 fr and 40 Gy to the partial breast) PBI (40 Gy in 15 fr)	6	1.1 0.5	23 22	No increase in IBTR; improved cosmesis
Livi et al. [55–57]	Italy	520	EBRT	WBI (50 Gy in 25 fr + 10-Gy boost) APBI (30 Gy in 5 fr)	10	2.6 3.9	0.8 0	No increase in IBTR; improved acute/late toxicity and cosmesis
RAPID trial [58–60]	International	2,135	EBRT	WBI (50 Gy in 25 fr or 42.5 Gy in 16 fr) APBI (38.5 Gy in 10 fr)	8	2.8 3.0	18.4 26.2	No increase in IBTR; increased adverse cosmesis
IRMA trial [61]	Italy	983	EBRT	WBI (50 Gy in 25 fr +/- 10-Gy boost) APBI (38.5 Gy in 10 fr)	5	– –	19 20	No difference in toxicity
NSABP B-39/RTOG 0413 trial [62–64]	International	4,216	EBRT, IBT	WBI (50 Gy in 25 fr + 10-Gy boost) APBI (34–38.5 Gy in 10 fr)	10	3.9 4.6	– –	Decrease in recurrence-free interval rate; no difference in OS
ELIOT trial [33]	Italy	1,305	IORT	WBI (50 Gy in 25 fr + 10-Gy boost) APBI (21 Gy to the 90% isodose)	5	0.4 4.4 (1.7)	– –	Increase in IBTR, likely due to insufficient patient selection; improved acute/late toxicity
TARGIT-A trial [35, 68–71]	International	3,451	IORT	WBI (50 Gy in 25 fr +/- 10-Gy boost) APBI (20 Gy to the 90% isodose)	2.5	1.3 3.3	– –	Noninferior IBTR rate for the prepathology group; improved acute and equal late toxicity; equal cosmesis
APBI, accelerated partial breast irradiation; IBT, interstitial brachytherapy; fr, fractions; WBI, whole breast irradiation; PBI, partial breast irradiation; IBTR, ipsilateral breast tumor recurrence; FU, median follow-up; EBRT, external beam-based APBI; IORT, intraoperative radiation therapy; MRgRT, MR-guided radiotherapy; OS, overall survival; DFS, disease-free survival.								

brachytherapy techniques [29]. In the field of re-irradiation for early-stage ipsilateral breast cancer recurrence (T1 N0 M0, Her2 negative, positive hormone receptor status), partial breast irradiation (PBI) using different techniques has been known to demonstrate promising local control rates for patients refusing mastectomy in favor of a second BCT for a long time [37–41].

This review aims to describe the existing evidence for advantages of APBI as well as for the feasibility and effectiveness of different APBI techniques used in modern radiotherapy. An overview of the existing randomized trials evaluating different APBI techniques is shown in Table 1.

Interstitial Brachytherapy

The most reliable data for APBI exists for brachytherapy techniques, which can be used in an intraoperative or postoperative setting [42]. In any setting, interstitial brachytherapy is predominantly dependent on the experience and skills of the treating physician, and consequently is only available in experienced institutions. Nevertheless, several remarkable trials with interstitial brachytherapy have been published so far:

A Hungarian prospective trial of Polgár et al. [43, 44] randomized 258 patients with EBC (T1 N0–1mi, grade 1–2, nonlobular breast cancer) after BCS to receive either WBI ($n = 130$) with 50 Gy in 25 fractions without any boost to the tumor bed or APBI ($n = 128$) delivered twice per day with HDR brachytherapy (36.4 Gy in 7 fractions). After 5 years, the actuarial rate of local relapse was non-inferior with 3.4% for WBI and 4.7% for APBI as well as after 10 years with 5.1% for WBI and 5.9% for APBI ($p = 0.50$ and 0.77 , respectively). With respect to cosmetics, the results of Polgár et al. [43, 44] favored APBI with a rate of excellent to good cosmetic results of 81% for APBI versus 63% for WBI ($p < 0.01$). In a randomized trial by Lövey et al. [45], at 4 years, there was no significant difference in symptomatic fat necrosis between both treatment arms (8.5% for WBI vs. 11.4% for APBI).

The prospective GEC-ESTRO trial randomized 1,184 patients with EBC (stage 0–IA) after BCS to receive WBI ($n = 551$, 50 Gy in 25 fractions) followed by a 10-Gy boost to the lumpectomy cavity versus APBI ($n = 633$) delivered with HDR brachytherapy (32 Gy in 8 fractions or 30.1 Gy in 7 fractions) versus APBI applied with PDR brachytherapy (50 Gy in 0.6–0.8 Gy per pulse). The evaluation of early side effects again favored APBI for skin toxicity with grade 3 radiation dermatitis seen in 7% of cases for WBI and in only 0.2% for APBI ($p < 0.0001$). Grade 1–2 acute toxicity occurred in 86% of patients for WBI and in only 21% for APBI ($p < 0.0001$). While breast pain was the same in both of the radiation techniques, mild hematoma and mild breast infection rates were slightly increased in APBI

compared to WBI with 20 versus 2% and 5 versus 2%, respectively [46]. The 5-year local recurrence rate was 0.92% (95% CI: 0.12–1.73) for WBI and 1.44% (95% CI: 0.52–2.38) for APBI ($p = 0.42$) [34]. Concerning late toxicity after a median observation time of 6.6 years, 5-year cumulative incidence of late skin toxicity and 5-year cumulative risk for subcutaneous late effects $\geq$ grade 2 were 10.7% (95% CI: 8.0–13.4) for WBI versus 6.9% (95% CI: 4.8–9.0) for APBI ($p = 0.020$) and 9.7% (95% CI: 7.1–12.3) for WBI versus 12.0% (95% CI: 9.4–14.7) for APBI ($p = 0.28$), respectively. After a follow-up of 6.6 years, breast pain increased in WBI with 11.9% compared to 8.4% for APBI ($p = 0.074$), while fair to poor cosmetic outcome was more or less the same with 9% of cases in WBI and 8% in APBI (patient rated, 10 vs. 7% when physician rated) [47].

The results of the abovementioned randomized trials are similar to findings of previously published single-arm studies using interstitial brachytherapy. Throughout these studies, local recurrence rates are slightly higher and vary from 5.2 to 15% after a follow-up of more than 10 years with excellent cosmetic outcomes [48–52].

External Beam-Based APBI

While specialized radiation oncologists are crucial for the application of brachytherapy, external beam-based APBI is widely available. However, as higher skin doses have to be expected for external beam-based APBI, important concerns regarding skin toxicity and cosmetic outcome have been raised. Nevertheless, multiple randomized trials using this radiation technique have been published, demonstrating promising results:

In a prospective trial of Rodríguez et al. [53] from Barcelona, 102 patients with EBC were randomized after BCS to receive either WBI ($n = 51$, 48 Gy in 24 fractions with or without additional 10 Gy to the tumor bed) or APBI ($n = 51$, 37.5 Gy in 10 fractions delivered twice daily). After a median follow-up time of 5 years, no local recurrences were observed and no significant differences in survival rates were found. APBI reduced acute side effects and radiation doses to healthy tissues compared with WBI ($p < 0.01$). Late skin toxicity was no worse than grade 2 in either group, without significant differences between the two groups. Physician assessment showed that $>75\%$ of patients in the APBI arm, as well as in the WBI arm, had excellent or good cosmesis, and these outcomes appear to be stable over time.

The IMPORT LOW trial, a multicenter phase III non-inferiority study, randomized 2,016 patients with low-risk breast cancer (age ≥ 50 years, unifocal invasive ductal adenocarcinoma, grade 1–3, tumor size ≤ 3 cm, T1–2, N0–1) after BCS to receive one of the following: WBI ($n = 674$, 40 Gy in 15 fractions, control group), WBI with a reduced

dose of 36 Gy in 15 fractions and 40 Gy to the partial breast ($n = 673$, reduced-dose group), or partial breast irradiation ($n = 669$, PBI group) with 40 Gy in 15 fractions. The primary endpoint was ipsilateral local relapse, and the trial was powered to assess noninferiority of the cumulative incidence of local relapse for each of the experimental groups compared with the control group. For WBI a 2.5% incidence of local relapse at 5 years was assumed and the IMPORT LOW trial aimed to demonstrate that an increase of more than 2.5% in the cumulative incidence of local relapse would not occur in either experimental group. After a median follow-up of 72.2 months, the 5-year local recurrence rate was 1.1% (95% CI: 0.5–2.3) for WBI, 0.2% (95% CI: 0.02–1.2) for reduced-dose WBI, and 0.5% (95% CI: 0.2–1.4) for PBI only. Thus, noninferiority could be claimed for both reduced-dose and partial breast radiotherapy ($p = 0.003$ for the reduced-dose group and $p = 0.016$ for the partial breast group, compared with the whole breast radiotherapy group). Concerning late skin toxicity, the IMPORT LOW trial favored PBI for two criteria of cosmesis: breast appearance and breast firmness achieved significantly lower rates of adverse effects ($p = 0.007$ and $p < 0.0001$, respectively) [54].

In a randomized phase III trial of Livi et al. [55] from Florence, 520 patients with EBC (women aged >40 years, tumor size <25 mm) were randomly assigned to receive either conventional WBI ($n = 260$, 50 Gy in 25 fractions and a 10-Gy boost to the tumor bed in 5 fractions) or APBI ($n = 260$, 30 Gy in 5 fractions, intramuscular radiotherapy) after BCS. With 1.5%, the local recurrence rate was equal in both arms after a median observation time of 5 years ($p = 0.86$). Acute and late toxicity ($p = 0.0001$ and $p = 0.004$, respectively), as well as the cosmetic outcome ($p = 0.045$), were significantly superior for APBI compared with WBI [56]. All of the 260 patients in the APBI arm were reported to show good to excellent cosmesis at a median of 60 months of follow-up. Furthermore, the Florence study analyzed the health-related quality of life at the end of treatment as well as after 2 years of follow-up using the EORTC QLQ-C30 and BR-23 questionnaires. Already at the end of treatment, global health status ($p = 0.0001$) and most scores relative to the functional and symptoms scales of the QLQ-C30 questionnaire favored APBI. Functional and symptom scales of the BR-23 questionnaire were also superior for APBI, including body perception, future perspective, and breast and arm symptoms. Results were confirmed after 2 years of follow-up with QLQ-C30 global health status ($p = 0.0001$) as well as most functional and symptoms scales being still in favor of APBI. Body perception, future perspective, and breast and arm symptoms also remained superior in the APBI group, as assessed by the BR-23 questionnaire [55].

More recently, an update for the 10-year results has been presented at San Antonio Breast Cancer Symposium 2019. At 10 years, 3.9% of patients treated with APBI had experienced ipsilateral breast cancer recurrence compared with 2.6% in those who received WBI (HR: 1.57, 95% CI: 0.56–4.41, $p = 0.39$), which was not determined to be statistically significant. Furthermore, no significant differences were reported for locoregional recurrence rates with 3.9 versus 3.0% as well as for overall survival rates with 92.7 and 93.7% for the APBI and the WBI arms, respectively [57].

In a phase III trial, the Canadian RAPID study, 2,135 patients with EBC (age ≥ 40 years, invasive or noninvasive breast cancer, tumor size ≤ 3 cm) were randomized to receive either WBI ($n = 1065$, 50 Gy in 25 fractions or 42.5 Gy in 16 fractions) or APBI ($n = 1070$, 38.5 Gy in 10 fractions given twice daily) after BCS. The primary outcome was IBTR, analyzed by intention to treat. The RAPID trial was designed as a noninferiority trial on the basis of an expected 5-year IBTR rate of 1.5% in the WBI group. Noninferiority was assumed if a 1.5% increase in the IBTR rate could be excluded for the APBI group. After a median follow-up of 8.6 years, the 8-year cumulative rates of IBTR were 3.0% (95% CI: 1.9–4.0) in the APBI group and 2.8% (95% CI: 1.8–3.9) in the WBI group. Hence, APBI was demonstrated to be noninferior [58]. While acute toxicity (grade >2 , within 3 months) occurred less frequently in the APBI group (28% of patients) than in the WBI group (45% of patients, $p < 0.0001$), late toxicity (grade >2 , later than 3 months) was more common in patients treated with APBI (32 vs. 13%, $p < 0.0001$) [58]. Using a hypofractionated and highly accelerated form of APBI, the RAPID study demonstrated unexpected poor late cosmetic outcome for the APBI arm [59]. After 3, 5, and 7 years of follow-up, adverse cosmesis remained more frequent in the APBI group, with an absolute difference at 3 years of 11.3% (95% CI: 7.5–15.0), 5 years: 16.5% (95% CI: 12.5–20.4), and 7 years: 17.7% (95% CI: 12.9–22.3) [58]. The authors concluded that a 6-h interval between fractions may not suffice for normal tissue repair, resulting in increased grade 1–2 toxicities in the APBI arm [59]. Peterson et al. [60] reported the predictors of poor cosmesis of the RAPID study. While clinical and pathologic characteristics were similar in both treatment arms, tumor location (worse cosmesis associated with outer location), smoking, higher age (per 10 years), and larger seroma volume (per 10 cm²) were found to be significant predictors of adverse cosmetic outcome ($p < 0.05$).

For the IRMA trial, a prospective multicenter study from Italy, 983 patients with EBC (age ≥ 49 years, tumor size <3 cm, pN0–1) were randomly assigned to receive WBI (50 Gy in 25 daily fractions with or without a 10-Gy boost to the lumpectomy cavity) or APBI (38.5 Gy in 10 fractions delivered twice daily) after BCS. The results were

presented at the European Society of Radiation Oncology (ESTRO) meeting in 2017. Although similar fractionation schemes were applied as in the RAPID trial, no difference was observed in adverse cosmesis between both treatment arms after a median follow-up of 5 years (20% for APBI vs. 19% for WBI after 3 years when physician rated and 14% for APBI as well as WBI after 3 years when patient rated). Acute skin toxicity grade 3 was rare in both treatment schemes (0% in APBI vs. 1.4% in WBI) and no further acute toxicity grade ≥ 3 was observed. Late skin toxicity and late subcutaneous tissue toxicity grade 3–4 was 0.42 and 1.5% for APBI versus 0.79 and 1.2% for WBI ($p = 0.4$ and $p = 0.7$), respectively. The IRMA trial is still awaiting results for local control rates and overall survival [61].

Results of the NSABP B-39/RTOG 0413 trial, a prospective phase III equivalence study, have recently been presented at the San Antonio Breast Cancer Symposium 2019 [62] and have now been published in *Lancet* [63]. The NSABP B-39/RTOG 0413 trial randomized 4,216 patients with EBC (stage 0, I or II, 0–3 positive axillary nodes) to receive WBI ($n = 2109$, 50 Gy in 25 fractions with a sequential boost to the surgical cavity) or APBI ($n = 2107$, 34–38.5 Gy in 10 fractions given twice daily with either brachytherapy or external beam radiation) after BCS. The primary endpoint for analysis was IBTR (invasive and noninvasive) as first recurrence, analyzed in the intention-to-treat population, applying an equivalence test on the basis of a 50% margin increase in the HR (90% CI for the observed HR between 0.667 and 1.5 for equivalence). At a median follow-up of 10.2 years, 90 (4%) of 2,089 women eligible for the primary outcome in the APBI group and 71 (3%) of 2,036 women in the WBI group had an IBTR (HR: 1.22, 90% CI: 0.94–1.58), resulting in a 10-year cumulative IBTR incidence of 4.6% (95% CI: 3.7–5.7) in the APBI group versus 3.9% (95% CI: 3.1–5.0) in the WBI group [63]. To declare APBI and WBI equivalent in respect to the risk of IBTR, the 90% CI for the observed HR comparing APBI to WBI would have had to be entirely between 0.667 and 1.5. However, an HR of 1.22 with a 90% CI of 0.94–1.58 was observed, which did not meet the equivalence criteria and hence the trial favored WBI. No statistically significant differences existed between APBI and WBI in distant disease-free interval (time from randomization to first diagnosis of distant recurrence) ($p = 0.15$), overall survival ($p = 0.35$), or disease-free survival ($p = 0.11$) [63]. While grade 2 toxicity was slightly decreased in the APBI group (44 vs. 59% for WBI, not significant), grade 1 and 3 toxicity were slightly higher with 40% for APBI versus 31% for WBI and 9.6% for APBI versus 7.1% for WBI, respectively (not significant). Grade 4–5 toxicity was found to be 0.5 versus 0.3%, respectively [63]. Nevertheless, the absolute difference in the 10-year rate of IBTR was reassuringly low at <1% (4.8% APBI vs. 4.1% WBI) [62–64].

The SHARE trial, another large randomized phase III study closed to accrual in 2017. Results from this trial are still pending. The SHARE trial randomized 1,006 patients with EBC (age ≥ 50 years, tumor size <2 cm, all invasive) to receive either standard fractionated or hypofractionated WBI or APBI with external beam radiation (38.5 Gy delivered over 10 twice-daily fractions) [65, 66].

Intraoperative Radiotherapy

From a patient perspective, the most comfortable technique for APBI may be IORT delivered in a single fraction during BCS. IORT may not only improve patient compliance, but also decrease irradiation of healthy organs, reduce the dose to the skin, and induce lower treatment costs [67]. Several large clinical trials for IORT have been published so far:

In the ELIOT trial, a prospective randomized study, highly energized electrons were used to deliver radiotherapy to the lumpectomy cavity during surgery. A total of 1,305 patients with EBC (age ≥ 48 years, tumor size ≤ 2.5 cm) were randomly assigned to receive either a single dose of 21 Gy intraoperatively prescribed to the 90% isodose given to the tumor bed ($n = 651$), or WBI ($n = 654$, 50 Gy in 25 fractions with a 10-Gy boost to the lumpectomy cavity). The rate for IBTR was significantly increased in patients treated with IORT compared to WBI (4.4 vs. 0.4%, $p = 0.0001$) after 5 years. However, for a subgroup of low-risk patients (tumor size <2 cm, positive nodes <3, grade 1–2, estrogen receptor positive, not triple negative), the rate for IBTR was 1.7% at 5 years. With regard to skin toxicity, patients in the IORT arm presented with significantly lower rates of skin erythema, dryness, hyperpigmentation, and pruritus compared to patients in the WBI arm. Moreover, the pulmonary fibrosis rate was higher in the WBI group, while an increased rate of fat necrosis occurred in the IORT group (17 vs. 7% for WBI, $p = 0.04$) [33].

Another IORT study, the prospective TARGIT-A trial, randomized 3,451 patients with EBC (age ≥ 45 years, tumor size ≤ 3.5 cm, unifocal invasive ductal carcinoma) to receive a single shot IORT of 20 Gy to the resection cavity ($n = 1,721$, application of a 1.5- to 5.0-cm spherical applicator, 50 kV energy X-rays) versus standard WBI ($n = 1,730$, 50 Gy in 25 fractions with or without a 10-Gy boost to the tumor bed). IORT was either delivered during BCS (prepathology arm) or after BCS in a second surgical intervention (postpathology arm). However, due to risk factors seen during surgery or on final pathology (tumor-free margin <1 mm, extensive in situ component, or unexpected invasive lobular carcinoma), 21% of patients in the prepathology IORT arm received an additional WBI according to institutional standard ranging from 40 to 56 Gy. Additional WBI was scheduled as per protocol

(risk-adapted management). At a median follow-up of 2 years and 5 months, the risk for ipsilateral recurrence was 3.3% in the IORT arm compared to 1.3%, in the WBI arm ($p = 0.042$). The noninferiority margin of the trial (2.5%) was met by the prepathology group: 2.1% (1.1–4.2) for IORT versus 1.1% (0.5–2.5) for WBI ($p = 0.31$), but not by the postpathology group: 5.4% (3.0–9.7) for IORT versus 1.7% (0.6–4.9) for WBI ($p = 0.069$). For skin toxicities, a decreased rate of grade 3–4 adverse events was reported for IORT versus WBI (0.2 vs. 0.8%, $p = 0.029$). Interestingly, there were less non-breast-cancer-related deaths in the IORT arm (1.4 vs. 3.5% in the WBI arm, $p = 0.0086$). The authors ascribed these findings to supposed higher rates of cardiac events and second malignancies in the WBI group [35]. Except for telangiectasia, which occurred solely in WBI patients (17%), late side effects were more or less the same in both treatment arms, including fibrosis, breast edema, retraction, lymphedema, and pain. Breast and arm symptoms were decreased in the IORT arm [68]. After a median follow-up of 2 years and 5 months, results of cosmesis were equal between the treatment groups, while breast-related quality of life was increased for IORT compared with WBI [35, 69, 70].

Recently, results from the TARGIT-E trial were presented at ASTRO 2019. The TARGIT-E trial, a single-arm IORT study, enrolled 526 elderly patients with low-risk breast cancer (≥ 70 years, $cT1/2$ (< 3.5 cm), $cN0$, $cM0$, invasive carcinoma of no special type) to receive a single dose of 20 Gy (IORT, low-energy X-rays) during BCS. In the case of risk factors present in the final pathology (larger size, other histology, free margin < 1 cm, lymphatic vessel invasion, positive nodes, multifocal/central lesions, extensive intraductal component), patients were treated with WBI (46–50 Gy, 1.8–2.0 Gy per fraction). The primary outcome was the local recurrence rate measured at 2.5, 5, and 7.5 years. Of 526 patients, 474 were included in the analysis: 347 (73%) received IORT only, 99 (21%) IORT plus whole breast radiotherapy, 22 (5%) whole breast radiotherapy only, and 7 (1%) surgery only without subsequent adjuvant therapies. After a median follow-up of 3 years (range: 2–79 months), 4 ipsilateral in-breast recurrences after 11, 33, 42, and 43 months were reported, leading to estimated local recurrence rates of 0.2 and 1.5% at 2.5 and 5 years, respectively. Overall, 20 patients died (3 breast-cancer-related deaths, 17 non-breast-cancer-related deaths), resulting in estimated overall survival rates of 98.9 and 91.4% at 2.5 and 5 years, respectively [71].

Both the ELIOT and the TARGIT-A trial provide robust data supposing superiority of IORT with regard to toxicity and long-term cosmesis, which may have attributed to the reduced volume of irradiated breast tissue [30]. While in the ELIOT trial patient selection was not optimal to achieve acceptable local control rates, the results of the TARGIT-A trial were impaired due to the tim-

ing of IORT. In the postpathology arm, IORT was delivered during a second operation. Consequently, another prospective randomized phase II study, the COSMOPOLITAN trial, was designed at Heidelberg University, selecting patients on the basis of the ASTRO consensus statements for APBI. For the COSMOPOLITAN trial, a total of 202 patients with selected low-risk EBC (age > 50 years, tumor size < 2.5 cm, grade 1–2, estrogen-receptor-positive tumors, node negative) will be randomized to receive either single-dose IORT with electrons during BCS (21 Gy, prescribed to the 90% isodose) or postoperative hypofractionated WBI (40.05 Gy in 15 daily fractions, 5 weeks after surgery). In contrast to the ELIOT trial, patient selection criteria will be more restrictive and IORT will be compared to hypofractionated WBI, as hypofractionation has become the standard treatment following BCT for low-risk EBC patients. Recruitment of patients started in late 2019 and is expected to be completed in 2021. The primary endpoint will be patient-reported fatigue. Further endpoints evaluated are tumor control, overall survival, disease-free survival, acute and chronic toxicity, quality of life, and cosmesis. First results are expected in 2022 [72]. The flowchart of the COSMOPOLITAN trial is depicted in Figure 1.

MR-Guided Radiotherapy

One of the most recent approaches for APBI is MRgRT [73]. MRgRT enables direct visualization of the lumpectomy cavity as well as characterization and eventual tracking of anatomical motion by using real-time imaging. Especially in soft tissue, where targets need accurate definition, MR guidance may mark the beginning of a new era [73, 74]. In comparison to brachytherapy or IORT techniques, external beam-based APBI requires additional margins to account for chest wall movement, which may result in larger irradiation volumes. MRgRT may potentially overcome this disadvantage of external beam-based radiotherapy. On the one hand, MRgRT offers a superior soft-tissue contrast for precise detection of the cavity. On the other hand, MRgRT enables advanced motion management strategies like gating, providing “real-time” anatomical feedback. Respiratory gating is a process which allows for continuous monitoring of the cavity motion during normal breathing. Radiation is only delivered when the tumor cavity is tracked in exactly the right position in the real-time 4-D cine MRI, and the treatment beam automatically turns off if the tumor cavity moves out of the target field (Fig. 2). Therefore, required safety margins and hence treated volumes can be reduced.

However, availability of next-generation hybrid MR-LINAC systems is still limited, and MRgRT remains more time consuming [73]. Nevertheless, some experience in

Fig. 1. Flowchart of the COSMOPOLITAN trial.

the field of MRgRT used for APBI has already been gathered. In a prospective registry evaluating APBI using a 0.35-T MRgRT system, 30 patients with EBC (stage 0–1) were enrolled after BCS. Patients were treated with APBI (38.5 Gy in 10 fractions delivered twice daily). 4-D MR real-time imaging during treatment was applied for visualizing the surgical cavity. Compared to conventionally external beam-based APBI, the treated volume could therefore be reduced by 52% when using MRgRT. Results for efficacy and cosmesis of this MR-guided APBI approach are still pending [75].

Patient Selection

For patient selection, several societies have published recommendations to define whether patients are suitable or not for APBI, taking into account risk factors regardless of the selected APBI techniques [76–78]. The European Society for Radiotherapy and Oncology (GEC-ESTRO), as well as the American Society for Radiation Oncology (ASTRO) and the American Brachytherapy Society (ABS) recommend suitable patients to be 50 years

of age or older, to have a negative node status and absence of lympho-vascular space invasion. Tumor size must be ≤ 3 cm based on ABS and GEC-ESTRO recommendations and ≥ 2 cm according to the ASTRO. While the GEC-ESTRO and ASTRO consider only invasive ductal carcinoma with positive estrogen receptor status to be suitable for APBI, the ABS regards all invasive carcinomas and ductal carcinomas in situ as suitable for PBI, irrespective of the estrogen receptor status. The GEC-ESTRO recommendations furthermore exclude patients diagnosed with multifocal carcinoma and patients having received neoadjuvant chemotherapy. In contrast, the ASTRO and ABS do not take these criteria into consideration [76–79]. The different recommendations for APBI indicate the important criteria for appropriate patient selection. However, most data underlying these recommendations are weak and a universal consensus has not been found yet. Individual factors such as breast size, tumor bed location, and distance of the surgical cavity to the skin surface might also have to be taken into account. Consequently, current guidelines recommend the application of APBI preferably within clinical trials [10].

Final Remarks

In summary, several large randomized phase III trials showed that APBI has provided outcomes similar to WBI combined with potentially reduced toxicity [34, 43, 44, 46, 47, 54–56]. However, appropriate patient selection remains crucial to achieve ipsilateral tumor recurrence rates that are noninferior to those reported after WBI. This was underlined again by the recently published results of the NSABP B-39 trial [63]. Nevertheless, the precise definition of the subset of low-risk EBC patients that are suitable for APBI remains a matter of discussion. Special attention should be paid to late side effects and long-term outcomes. As the thorough assessment of late toxicities from high-dose focal radiotherapy requires at least 5 years of follow-up and long-term data are often still lacking, more robust information will be gathered in the future after a longer observation time [29, 80]. Nowadays, reported toxicity with APBI is generally mild; nevertheless, some authors showed higher incidences of fat necrosis and skin toxicity especially when using external beam-based APBI with hypofractionated and highly accelerated schedules [59]. These reports have fired concerns about cosmetic outcome following external beam-based APBI.

Many uncertainties remain concerning radiobiological aspects of APBI, as different techniques require a large heterogeneity of dose prescriptions, dose fractionation, and target volumes. Results from direct comparison of different APBI techniques (interstitial brachytherapy, external beam-based APBI, IORT, MRgRT) are still lacking.

Fig. 2. MR-guided APBI. **A, B** Treatment plan and dose-volume histogram of MR-guided APBI delivered at Heidelberg University with a total dose of 40.05 Gy in 15 fractions as second breast-conserving therapy due to local recurrence. The resection cavity is shown in orange, while the planning target volume is delineated in red. **C-F** MR real-time cine imaging with the target (resection cavity) within the specified gating margin (**C**) and the beam turned on (**D**) and >3% of the target located outside of the specified gating margin (**E**) and the beam turned off (**F**).

Furthermore, not all techniques are extensively available, as the required technical skills vary considerably depending on the selected APBI technique. In general, decision-making on appropriate treatment techniques (WBI or different APBI techniques) should take into account not only improvements in local control rates, but also treatment-associated toxicity and the impact on the patient's quality of life. The findings of ongoing trials will widen our understanding of the role of APBI in the therapy of EBC patients in the near future [72].

Conclusion

During the last years, increasingly profound data has been gathered to support APBI using various techniques as a treatment alternative to WBI for selected low-risk EBC patients. APBI is especially attractive, as it potentially offers fewer side effects combined with a reduction in treatment time, thus minimizing treatment burden for patients and healthcare systems. However, for ensuring acceptable recurrence rates, appropriate patient selection remains essential. Updated and new results from several

pending trials are eagerly awaited to complement current evidence and assist clinicians and patients with shared decision-making about the use of APBI.

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Author Contributions

T.F. carried out the literature search and analysis and drafted the manuscript. J.H.-R. helped with the literature search and to draft the manuscript. C.V.K.K. helped to draft the manuscript. All authors participated in manuscript revisions and approved the final manuscript.

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