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Radiation Treatment Strategies in Patients Undergoing Breast-Conserving Surgery

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Abstract Breast-conserving therapy offers patients an oncologically sound opportunity to cure their cancer, preserve their breast, and maintain an excellent quality of life. Historically, radiation delivered as a component of breast-conserving therapy required up to 7 weeks of daily treatment after surgery, exacting a burden both on individual patients and the health-care system as a whole. In the past several years, new strategies have emerged which seek to retain the benefits of breast-conserving therapy but decrease the burden of protracted radiation courses. These strategies include omission of radiation in selected patients, hypofractionated whole-breast irradiation, and accelerated partial-breast irradiation, which can be delivered using multicatheter interstitial brachytherapy, single-entry catheter-based brachytherapy, external beam techniques, proton therapy, or intraoperative techniques. The promise and potential problems with these newer radiation strategies are discussed herein, with guidance provided as to the appropriate application of these techniques in clinical practice.

Keywords Breast-conserving therapy · Lumpectomy · Whole-breast irradiation · Partial-breast irradiation · Brachytherapy · Proton therapy

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Introduction

Breast-conserving therapy—defined as breast-conserving surgery (BCS) followed by ipsilateral breast radiotherapy (RT)—offers women a breast-preserving option with survival rates equivalent to that of mastectomy [1]. The benefit of adjuvant RT following BCS has been convincingly demonstrated in a series of meta-analyses conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [2, 3]. In aggregating 17 trials which randomized women to the application or omission of adjuvant whole-breast irradiation (WBI), significant reductions in recurrence (local plus distant) and breast cancer mortality were observed with the use of radiation (see Table 1). RT roughly halved the annual rate of recurrence (local plus distant recurrence combined, rate ratio (RR) 0.52, 95 % confidence interval (CI) 0.46–0.56), preventing one cancer-specific death at 15 years for every four recurrences prevented at 10 years.

Despite the proven safety and effectiveness of WBI as studied in the EBCTCG meta-analyses, WBI has certain limitations, principally the long duration of treatment, which in the USA has averaged about 6 to 7 weeks using conventional fractionation (CF). The burden of this long treatment course exacts significant cost on the health system and also significant personal costs, with respect to transportation, workplace productivity, and childcare. The burden of such protracted treatment may dissuade some women from pursuing a breast-conserving strategy or may lead certain patients not to complete radiation after their BCS, which may exert negative consequences on survival. This point was illustrated in recent work by our group which demonstrated that breast cancer patients with young children were less likely to receive radiation after BCS than breast cancer patients without young children [4].

Given these limitations of conventionally fractionated whole-breast irradiation (CF-WBI), much effort has been

Table 1 Oxford overview-reported outcomes for adjuvant radiotherapy

	Overall		Node negative		Node positive	
	Recurrence (%)	BCM (%)	Recurrence (%)	BCM (%)	Recurrence (%)	BCM (%)
+RT	19.3	21.4	15.6	17.2	42.5	42.8
−RT	35.0	25.2	31.0	20.5	63.7	51.3
Absolute risk reduction with RT	15.7	3.8	15.4	3.3	21.2	8.5
Absolute risk reduction with RT, 95 % CI	13.7–17.7	1.6–6.0	13.2–17.6	0.8–5.8	14.5–27.9	1.8–15.2
p value	<0.00001	0.00005	<0.00001	0.005	<0.00001	0.01

Recurrence reported at 10 years follow-up, BCM at 15 years. Data are abstracted from [2], but the formatting and presentation were developed by the authors of this submission

RT radiotherapy, *BCM* breast cancer mortality, *CI* confidence interval

devoted to developing alternative breast-conserving strategies that impose less burden on patients. This review will highlight the most salient advances in this arena, which broadly can be categorized as follows: omission of breast radiotherapy, hypofractionated whole-breast irradiation (HF-WBI), accelerated partial-breast irradiation (APBI), and intraoperative radiation therapy (IORT). Each of these strategies has particular appeal yet also certain limitations. The data associated with these emerging techniques will be the focus of the present review.

Omission of Radiotherapy

The EBCTCG study included 7 trials of low-risk women, defined by favorable features with regard to patient age, tumor grade, stage, and estrogen receptor (ER) status, as well as the lack of lymph node involvement. The Cancer and Leukemia Group B (CALGB) 9343 trial has been the most definitive in identifying a subgroup of women for whom RT may be reasonably omitted [5]. In this trial, 636 women aged 70 and older with T1 N0 ER-positive breast cancer were treated with BCS and endocrine therapy and were randomized to CF-WBI or no radiation. The whole-breast radiation dose was 45 Gy in 25 fractions with a subsequent tumor bed boost of 14 Gy in 7 fractions. The addition of RT was found to decrease the rate of local recurrence (LR) from 10 % to 2 % at 10 years with no significant differences in mastectomy-free, breast cancer-specific or overall survival. Authors concluded that this modest absolute reduction in LR may justify the routine omission of adjuvant RT for women in this very favorable subgroup.

Patients in the CALGB study were not stratified according to tumor grade or age. These factors were included in a retrospective analysis of 7403 patients from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, which encompasses a broad cross section of practices throughout the USA [6]. Patients with low- and intermediate-grade disease were found to have similar outcomes as those reported by the CALGB. However, patients aging 70–74 with high-grade tumors had a greater absolute reduction in subsequent mastectomy risk than anticipated from the CALGB trial results. Specifically, subsequent mastectomy risk at 10 years was 14.8 % among women who did not receive RT compared to 5 % among women who did receive RT. Given these population-based data, it remains our practice to favor radiation in CALGB 9343-eligible women with adverse risk factors for recurrence, such as high grade, close or positive margins, or extensive LVSI.

In an effort to make individualized risk estimates accessible to clinicians, a nomogram based on 16,092 women aging 66–79 from the SEER database was developed to predict the benefit of radiation with respect to the outcome of subsequent mastectomy [7]. Analyzed factors included age, race, tumor size, ER status, and nodal status. An illustrative example notes that a 75-year-old Caucasian woman with a 1.5-cm ER-positive tumor and no lymph node involvement carries a 3 % 10-year risk of subsequent mastectomy with radiation vs. 5 % without radiation. In contrast, a 70-year-old black woman with a 1.5-cm ER-positive tumor and node-positive disease carries a 7 % 10-year risk of subsequent mastectomy with radiation vs. 19 % without radiation. These absolute risk estimates can be helpful in determining which patients are most likely to benefit from the addition of radiation.

Randomized data have not identified a group of patients <70 years old for whom RT can be safely omitted. A subset analysis of the Canadian trial which included women aging 50 years and older with T1, ER-positive breast tumors found a reduction in LR from 15.2 % to 3.6 % with the application of RT [8]. National Comprehensive Cancer Network guidelines currently indicate that RT may be withheld in women aging 70 and older with ER-positive, stage 1 cancer who will receive endocrine therapy [9]. The values and perspective of the patient are critical in weighing these reductions in cancer control against the side effects of RT. The likelihood that the patient will take endocrine therapy must also be considered,

and the quality of life implications of radiation vs. endocrine therapy are paramount to these discussions. It should be noted that many women may prefer an abbreviated course of breast radiation to 5 years of endocrine therapy and its associated side effects such as joint pain, bone loss, and hot flashes.

Hypofractionated Whole-Breast Irradiation

HF-WBI refers to the use of fraction sizes greater than 2 Gy per day to treat the whole breast. The delivery of successive, incremental fractions allows normal tissues exposed to radiation to repair sublethal damage and abrogate the development of late-radiation side effects. Because tumor cells typically have a reduced repair capacity, incremental doses can reduce tissue toxicity while still delivering tumoricidal doses. Recently, increasingly precise technologic advances and radiobiologic insight into tissue-specific repair capacities have driven a trend towards larger fraction sizes, in search of a "sweet spot" which would give the greatest tumor control and least side effects, as well as shorter treatment times. Maturing randomized trials indeed indicate that larger fraction sizes are equivalent and perhaps even superior to conventionally fractionated whole-breast irradiation (CF-WBI) for most women.

An early major trial examining HF-WBI was carried out by the Ontario Clinical Oncology Group, randomizing 1234 women with T1–2 N0 breast cancer to HF-WBI (42.5 Gy in 16 fractions) or CF-WBI (50 Gy in 25 fractions) [10]. Local recurrence and disease-free and overall survival outcomes were equivalent between the two arms. Excellent/good cosmetic outcomes were reported in 71.3 and 69.8 % for the hypofractionated and control arms, respectively. In a pre-planned analysis, age <50 years old conferred no increased risk of adverse outcome for those treated with HF-WBI. While an earlier analysis suggested that high-grade tumors experienced inferior local control when treated with HF-WBI, this association became non-significant in a subsequent central pathology review of 989 tumor blocks which were examined using the more standard Nottingham scoring system (hazard ratio (HR) 1.61, 95 % CI 0.53–4.92, p=0.11) [11].

The START-A and START-B trials provide the largest set of mature randomized data with regard to hypofractionated breast RT. START-A compared CF-WBI (50 Gy in 25 fractions) to two HF-WBI regimens, either 41.5 Gy in 16 fractions or 39 Gy in 13 fractions, each delivered over 5 weeks [12]. The START-B trial compared the same standard to a regimen of 40 Gy in 15 fractions delivered over 3 weeks in 2215 women [13]. Recently published 10-year updates confirm the non-inferiority of hypofractionation [14•]. START-B included 13 % of women who did not receive tamoxifen, 21 % younger than 50 years old, 22 % who received adjuvant chemotherapy, 23 % with lymph node involvement, and 43 % who received a pre-planned tumor bed boost. At 10-year follow-up, locoregional recurrence was equivalent at 4.2 % and 5.5 % for the experimental and control arms, respectively (HR 0.74, 95 % CI 0.51–1.15, p=0.21). This equivalence was consistent across all pre-planned subset analyses, including age <50, breast size, tumor grade, and use of adjuvant chemotherapy or tumor bed boost. No increases in brachial plexopathy or heart disease in women with left-sided disease were found. Physician-assessed adverse cosmetic outcomes were significantly decreased in the HF-WBI arm, including breast shrinkage, telangiectasia, and breast edema. Surprisingly, the hypofractionated arm was also associated with fewer overall breast cancer events (18.3 vs. 22.2 %, HR 0.79, 95 % CI 0.65–0.97, p=0.02) and reduced overall mortality (15.9 vs. 19.2 %, HR 0.80, 95 % CI 0.65–0.99, p=0.04) at 10 years.

The Canadian trial excluded women with large breasts as defined by a maximal separation of 25 cm in the central plane in an attempt to avoid radiation hot spots. These dose inhomogeneities can occur peripherally when photons must traverse a larger distance of breast tissue and maintain sufficiently high dose in the center of the breast. Historically, there was concern that the effect of these hot spots may be amplified in the hypofractionated setting. START investigators did not exclude patients based on breast size but limited dose inhomogeneities to ±5 % in the central axis. Improvements beyond the techniques used in these trials currently allow for selective shielding of hot spots with additional fields. This approach, known as simple intensity-modulated radiation therapy (IMRT) or field-in-field dose modulation, has been compared with historical two-dimensional techniques [15–17]. Most recently, 815 women with inhomogeneous plans were randomized between the two techniques, with significant improvements in cosmesis and telangiectasia at 5 years [18].

Multifield planning also allows for differential dosing of higher-risk areas of the breast in a streamlined approach with the rest of the therapy. This is known as a concurrent or simultaneously integrated boost, in contrast to sequential tumor bed boost typically delivered following treatment of the whole breast. Several randomized trials are underway to investigate this concurrent boost technique (RTOG 10-05 [clinicaltrial.gov protocol NCT01349322] and IMPORT-HIGH [clinicaltrial.gov protocol NCT0081805]).

Preliminary and ongoing trials are underway to explore further abbreviation of the treatment course. The UK-FAST trial randomized 915 women to either CF-WBI (50 Gy in 25 fractions) or one of two five-fraction regimens, each delivered once per week for a total of 5 weeks (28.5 and 30 Gy total) [19]. Three-year cosmetic outcomes were worse in the 30-Gy group compared with the 50-and 28.5-Gy arms, with moderate/marked adverse effects in 17.3 %, 9.5 %, and 11.1 %, respectively. These data have informed the ongoing FAST-Forward trial, comparing hypofractionated therapy (45 Gy in 15 fractions) to 27- and 26-Gy fractionation schemes delivered in five fractions over 1 week (public.ukcrn.org.uk, number 10896).

Consensus guidelines published by the American Society of Therapeutic Radiation Oncology (ASTRO) support the off-trial use of HF-WBI for women >50 years old with T1–2 N0 disease not requiring chemotherapy [20]. Given the favorable 10-year results in the since-published updates of the START-B, we now advocate broader eligibility for HF-WBI and routinely treat women with DCIS, N1 disease not requiring the addition of a third field, and patients requiring high tangents to cover the undissected axilla. The appropriate age threshold for conventional vs. hypofractionation remains a matter of debate, given some concern that the alpha-beta ratio of breast cancer could theoretically vary as a function of age. In our practice, we tend to favor CF-WBI for women under the age of 40, but this remains a matter of active discussion.

Accelerated Partial-Breast Irradiation

Accelerated partial-breast irradiation (APBI) is a technique wherein only the operative bed and immediately surrounding breast tissue are targeted with RT. The rationale derives from the observation that most ipsilateral breast recurrences occur within several centimeters of the tumor bed. Reduced tissue exposure may decrease long-term toxicity and adverse cosmetic outcomes with the convenience of shorter treatment times. A variety of techniques are available to deliver APBI, the data for which will be described herein.

Brachytherapy

Brachytherapy (BT) involves the application of a sealed, radioactive source in close physical proximity to the treatment site and can be delivered via several means. In the multicatheter interstitial brachytherapy (MIB) approach, multiple catheters are inserted through the breast tissue such that the catheter planes traverse the operative bed and target tissue. Catheters may be placed with a freehand technique or using template guidance. The radioactive sources are placed into the catheters, with the delivered dose being a function of the source dwell time and the spatial arrangement of the catheters in relationship to each other. This technique is performed in a separate procedure after the surgical pathology results are finalized. High-dose rate (HDR) sources may be used—with dwell times on the order of minutes that allow for treatment within the HDR procedure suite—or with low-dose rate (LDR) sources which remain in place for several days while the patient stays in the hospital, a technique that is practiced much less commonly.

MIB has been performed for several decades at specialized centers and is one of the few APBI modalities with mature randomized data. Investigators from the National Institute of Oncology in Hungary randomized 258 women to WBI (50 Gy in 25 fractions) or partial-breast irradiation (PBI) delivered either through HDR MIB (36.4 Gy in 7 fractions, n=88) or electron beam RT (50 Gy in 25 fractions, n=40) [21]. Ten-year outcomes report LR in 5.9 % and 5.1 % of patients in the PBI and WBI arms, respectively (p=0.77). No differences were seen in the overall or disease-free survival rates. PBI was associated with better cosmetic outcomes, 81 % of whom scored excellent/good vs. 63 % in the WBI group (p<0.01).

Outcomes from a cohort treated with LDR MIB, however, reported less favorable control rates. In 50 patients with T1 N0 breast cancer treated on a phase I/II protocol, the 12-year actuarial LR rate was 14.6 %, with an additional 10 % of recurrences developing at >5 cm from the treatment site [22]. The Radiation Therapy Oncology Group (RTOG) conducted a phase II study of 100 patients treated with LDR or HDR MIB and found a low rate of LR of 4 % at 10 years [23]. Physician-assessed overall cosmesis at 5 years was excellent/good in 68 %, and 75 % of patients were satisfied with their treatment [24]. A prospective clinical study of 151 patients treated with HDR MIB reported very favorable cosmetic outcomes with 94 and 92 % excellent/good scores by physician and patient assessment, respectively, although follow-up was limited at 3 years [25].

MIB is not in widespread use given the technical challenges and expertise required for delivery. In contrast, the simpler and more reproducible intracavitary BT delivery approach has seen widespread adoption in recent years [26]. This modality involves a single-entry catheter which is placed within the lumpectomy cavity, an attached balloon which is inflated against the surrounding tissue, and an HDR source inserted into the catheter lumen. Single-lumen (MammoSite) or multilumen (Contura, SAVI) devices are available, with the latter allowing for more control in planning dose distributions. No randomized data are available regarding this technique, though the NSABP B-39/RTOG 0413 has completed accrual of 2053 patients, of whom approximately 500 would have been treated with a single-entry, catheter-based device. It should be recognized that the volume of tissue treated with a single-entry catheter is typically 1 cm beyond the edge of the device edge. This volume is smaller than the 1.5- to 2.0-cm volume of tissue beyond the cavity that is treated with MIB. As a result, it may not be appropriate to extrapolate the long-term experience with MIB to patients treated with single-entry catheters.

Multiple prospective cohort studies report acceptable tumor control and cosmetic outcomes for intracavitary BT. The American Brachytherapy Society prospective registry of 1440 women reported a 5-year LR rate of 3.8 % and excellent/good cosmetic outcomes in 90.6 % [27]. Recent analysis of national Medicare data, however, yields some reason for caution. We compared 85,783 women ages 67 and older treated with WBI and 6952 with BT between the years of 2003 and 2007 [28•]. The rate of subsequent mastectomy at 5 years was found to be nearly double in the BT group (4.0 vs. 2.2 % for WBI, p<0.001). BT also had a higher rate of complications including breast pain, fat necrosis, and rib fracture. A subsequent study found a 33.7 % rate of short-term

wound/skin complications for BT—double that reported for WBI ($p<0.01$) [29]. A third population-based study from SEER-Medicare data found that BT offered an intermediate breast preservation benefit. In comparison to no radiation, patients treated with BT experienced a 39 % reduction in subsequent mastectomy risk, where patients treated with WBI experienced a 78 % reduction in subsequent mastectomy risk [30]. Critics of these studies point to the wide variability in practice patterns captured by these national databases, as well as the improved patient selection criteria that have evolved in the intervening years. As a composite of outcomes for the application of BT across clinical practice, however, these data strike a cautionary note regarding routine use of BT prior to release of the RTOG 0413 randomized data, which is expected within the next few years.

External Beam Accelerated Partial-Breast Irradiation

External beam radiotherapy (EBRT) APBI is delivered using the same equipment and general setup as for WBI, but with a more limited treatment target. Applied modalities include photons (three-dimensional conformal radiotherapy [3DCRT] or intensity-modulated radiotherapy [IMRT]), electrons, or protons. Studied doses range from single-fraction treatments of 21 Gy [31] to the conventional 25 fractions used in WBI. The predominant fractionation scheme in use today involves 10 fractions of twice-daily RT. No mature data from randomized controlled trials are available regarding the risk of LR compared with WBI. A number of prospective single-arm cohorts have been reported with acceptable rates of local control and disease-free survival, but limited prospective data exist. A single phase III trial from investigators in Spain randomized 102 patients to 3DCRT APBI or WBI and reported no breast cancer events in either group at 5 years, with equivalent survival rates and cosmetic outcomes [32]. This study was designed with an 80 % power to detect a 10 % difference in local control. Patients in the WBI arm had a greater loss of elasticity in the high-dose areas of the breast tissue compared with APBI. The small numbers and short follow-up limit conclusive statements from this data.

Interim cosmetic and toxicity results from the multi-institutional RAPID trial were recently made available [33]. In this study, 2135 women >40 years old with T1–2 (≤3 cm) node-negative disease were randomized to 3DCRT APBI (28 Gy in twice-daily fractions) or WBI (42.6 Gy in 16 fractions or 50 Gy in 25 fractions with a 10-Gy boost in 4 or 5 fractions for high-risk features). At 3 years, the APBI group was associated with a higher rate of adverse cosmesis on patient (26 % vs. 18 %), nurse (29 % vs. 17 %), and physician (35 % vs. 17 %) assessments compared with the CF/HF-WBI arms ($p<0.002$). Grade 1/2 toxicities including telangiectasia, breast induration, pain, and fat necrosis were also more common in the APBI group. Data regarding disease control and survival outcomes are not yet mature and will be forthcoming. The authors recommend that the application of 3DCRT APBI be limited to the context of a controlled trial until further data are available.

Proton therapy is a relatively novel RT technique with expanding availability. The first published experience with proton APBI involved 20 patients treated to 32 Gy in 8 twice-daily fractions [34]. High rates of moderate to severe acute moist desquamation were seen, with an incidence of 22 %. At 7 years, physician-assessed excellent/good global breast cosmesis was 62 %, compared with 94 % for patients treated with photon-based APBI on the same prospective trial [35]. The incidence of late toxicities including telangiectasia (69 %) and pigmentation changes (54 %) was significantly higher in those treated with proton therapy. In contrast, the recently published Loma Linda experience reported excellent/good physician cosmetic rating in 90 % of the 100 patients at a median follow-up of 5 years treated to 40 Gy in 10 fractions delivered once daily, with no reported acute grade 3 skin toxicities and a 7 % incidence of telangiectasia [36•]. Differences that may account for these disparate results include the radiobiologic effects of once- vs. twice-daily fractionation, differing cosmetic and toxicity rating scales, as well as differences in planning and delivery techniques [37]. The Loma Linda group attributed their low incidence of skin toxicity to a rigid immobilization technique that allowed for multiple treatment fields and a skin-sparing planning approach [36]. The optimal dose and technique for this relatively novel application of proton therapy is an area of ongoing investigation.

Intraoperative Radiotherapy

Intraoperative radiotherapy (IORT) involves the insertion of a radiation guide into the tumor bed which directs electrons or superficially penetrating X-rays to the area. This may be performed either at the time of initial surgery or as a second procedure. Data from large randomized trials have recently been published which show an increased risk of LR when compared with WBI. The TARGIT-A trial from the UK randomized 3451 women with early-stage breast cancer to CF-WBI (40–56 Gy in 15–25 fractions with a tumor bed boost of 10–16 Gy in 5–8 fractions) or a single 20-Gy fraction delivered to the surface of the tumor bed using 50-kV X-rays delivered intraoperatively [38•]. Estimated radiation dose attenuated to 5–7 Gy at a 1-cm depth [39]. If unpredicted adverse pathology was found in the tumor specimen (15 % of patients), 45–50 Gy of WBI was subsequently delivered. At 5 years, LR in the conserved breast was 3.3 % in the experimental arm and 1.3 % in the control arm ($p=0.04$), which fell within the pre-specified absolute reduction non-inferiority margin of 2.5 %. Numerous statistical concerns regarding the analysis of the most recent TARGIT-A publication have been raised by individuals not involved in the trial [40–43], and given the relatively short follow-up, we continue to await

long-term data before fully embracing this treatment strategy in our practice.

The ELIOT trial from Italy randomized women aged 48–75 with early-stage breast cancer and tumors ≤2.5 cm to receive WBI (50 Gy in 25 fractions with a 10-Gy tumor bed boost) or intraoperative RT with electrons delivered in a single 21-Gy fraction [44•]. Electrons were generated from a dedicated linear accelerator with available energies ranging from 6 to 9 MeV with tumor coverage influenced by the applicator size applied [45]. No additional RT was delivered for adverse pathologic factors, including positive margins or lymph node involvement. At 5 years, LR was 4.4 % for IORT vs. 0.4 % in the EBRT group ($p<0.0001$). A higher rate of axillary recurrences was also observed in the IORT group, likely because level I axillary lymph node coverage is typically achieved with breast tangential fields but not with IORT. Characteristics associated with recurrence in the IORT group were tumors >2 cm, grade 3 disease, four or more positive lymph nodes, and triple-negative receptor status.

Conclusion

In the past decade, considerable progress has been achieved in designing breast-conserving strategies that reduce the time required to complete standard CF-WBI. Mature trial data now support the omission of RT in selected older women with favorable breast cancers, provided they plan to take endocrine therapy. It remains challenging, however, to determine whether the modest local control benefit of RT in this setting is worth the cost of treatment, and additional research is needed to fully understand the trade-offs between endocrine therapy alone vs. RT in this setting.

As breast cancer survival outcomes continue to improve with advances in multidisciplinary care, the significance of late cardiovascular effects and techniques to minimize these toxicities have increased in importance. This was highlighted in a recent study which retrospectively examined 2168 women treated in Scandinavia with RT for breast cancer between 1958 and 2001 [46]. The rate of major coronary events was found to increase at a rate of 7.4 % for each additional 1 Gy of mean heart radiation dose, with effects seen within the first 5 years of RT. Improvements in RT delivery have been significant over the last several decades and include CT-based planning and delivery techniques such as deep inspiration breath hold (DIBH). In DIBH, patients with left-sided disease receiving WBI hold their breath near end inspiration, often using biophysical feedback technology. This inflation of the lung causes maximal physical separation between the chest wall target and the heart. In our practice, DIBH is routinely used for left-sided breast cancers, and the total mean heart dose typically ranges from 40 to 80 cGy provided beams are carefully designed.

The available data now strongly support the use of HF-WBI for women who were well-represented in the available randomized trials, and we have now warmly embraced this treatment strategy. When a boost is planned, the START-B dose fractionation scheme of 40 Gy in 15 fractions followed by 10 Gy in a 5-fraction boost is particularly appealing and is likely to become the new standard for WBI dose fractionation. Additional research is needed to determine whether this new dose fractionation will be similarly safe and effective for women with more advanced disease who require regional nodal irradiation.

APBI is particularly appealing from a convenience perspective. Strong long-term data now support the safety and effectiveness of MIB, although these results are not uniform across studies, suggesting the importance of technique and operator experience. Multiple single-arm studies have demonstrated promising results with single-entry catheter-based brachytherapy, although population-based studies raise some concerns. Proton therapy is appealing with good early results, although availability limits the reach of this technique. IORT is the ultimate in patient convenience, yet the available data suggest modest increases in the risk of local recurrence with this approach. In the following years, multiple randomized trials should report important long-term data regarding various APBI modalities. These findings are likely to substantially shape our understanding of breast radiation for many years to come.

Compliance with Ethics Guidelines

Conflict of Interest Jonathan Grant declares no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with animal subjects performed by any of the authors. With regard to the authors' research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

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