Public Comment Draft

Partial Breast Irradiation for Patients With Early-Stage Invasive Breast Cancer or Ductal Carcinoma In Situ: An ASTRO Clinical Practice Guideline

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Disclosures: All task force members' disclosure statements were reviewed before being invited and were shared with other task force members throughout the guideline's development. Those disclosures are published within this guideline. Where potential conflicts were detected, remedial measures to address them were taken.

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Abstract

Purpose: This guideline provides evidence-based recommendations on appropriate indications and techniques for partial breast irradiation (PBI) for patients with early-stage breast cancer.

Methods: The American Society for Radiation Oncology (ASTRO) convened a task force to address 4 key questions focused on the appropriate indications and techniques for PBI as an alternative to whole breast irradiation (WBI) to result in similar rates of ipsilateral breast recurrence (IBR) and toxicity outcomes. Also addressed were aspects related to the technical delivery of PBI including dose-fractionation regimens, target volumes, and treatment parameters for different PBI techniques. The guideline is based on a systematic review provided by the Agency for Healthcare Research and Quality. Recommendations were created using a predefined consensus-building methodology and system for grading evidence quality and recommendation strength.

Results: PBI delivered using 3-D conformal radiation therapy, intensity modulated radiation therapy, multicatheter brachytherapy and single-entry brachytherapy result in similar IBR and overall survival as WBI with long-term follow-up. Some patient characteristics and tumor features were underrepresented in the randomized controlled trials, making it difficult to fully define IBR risks for patients with these features. Intraoperative radiation therapy alone is associated with a higher IBR rate compared to WBI. A daily or every other day external beam PBI regimen is preferred over twice daily regimens due to cosmetic concerns.

Conclusions: Based on published data, the ASTRO task force has proposed recommendations to inform best clinical practices on the use of PBI.

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Preamble

As a leading organization in radiation oncology, the American Society for Radiation Oncology (ASTRO) is dedicated to improving quality of care and patient outcomes. A cornerstone of this goal is the development and dissemination of clinical practice guidelines based on systematic methods to evaluate and classify evidence, combined with a focus on patient-centric care and shared decision making. ASTRO develops and publishes guidelines without commercial support, and members volunteer their time.

Disclosure Policy—ASTRO has detailed policies and procedures related to disclosure and management of industry relationships to avoid actual, potential, or perceived conflicts of interest. All task force members are required to disclose industry relationships and personal interests from 12 months before initiation of the writing effort. Disclosures for the Chair and Vice-chair go through a review process with final approval by ASTRO's Conflict of Interest Review Committee. For the purposes of full transparency, task force members' comprehensive disclosure information is included in this publication. Peer reviewer disclosures are also reviewed and included (Supplementary Materials, Appendix E1). The complete disclosure policy for Formal Papers is online.

Selection of Task Force Members—ASTRO strives to avoid bias and is committed to creating a task force that includes a diverse and inclusive multidisciplinary group of experts considering race, ethnicity, gender, experience, practice setting, and geographic location. Representatives from organizations and professional societies with related interests and expertise are also invited to serve on the task force.

Methodology—ASTRO's task force uses evidence-based methodologies to develop guideline recommendations in accordance with the National Academy of Medicine standards.[1,2] The evidence identified from key questions (KQs) is assessed using the **P**opulation, **I**ntervention, **C**omparator, **O**utcome, **T**iming, **S**etting (PICOTS) framework. A systematic review of the KQs is completed, which includes creation of evidence tables that summarize the evidence base task force members use to formulate recommendations. Table 1 describes ASTRO's recommendation grading system. See Appendix E2 in Supplementary Materials for a list of abbreviations used in the guideline.

Consensus Development—Consensus is evaluated using a modified Delphi approach. Task force members confidentially indicate their level of agreement on each recommendation based on a 5-point Likert scale, from "strongly agree" to "strongly disagree". A prespecified threshold of ≥75% (≥90% for expert opinion recommendations) of raters who select "strongly agree" or "agree" indicates consensus is achieved. Recommendation(s) that do not meet this threshold are removed or revised. Recommendations edited in response to task force or reviewer comments are resurveyed before submission of the document for approval.

Annual Evaluation and Updates—Guidelines are evaluated annually beginning 2 years after publication for new, potentially practice-changing studies that could result in a guideline update. In addition, ASTRO's Guideline Subcommittee will commission a replacement or reaffirmation within 5 years of publication.

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Table 1 ASTRO recommendation grading classification system

ASTRO's recommendations are based on evaluation of multiple factors including the QoE and panel consensus, which, among other considerations, inform the strength of recommendation. QoE is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability of samples, settings, and treatments.

Strength of Recommendation	Definition	Overall QoE Grade	Recommendation Wording
Strong	• Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. • All or almost all informed people would make the recommended choice.	Any (usually high, moderate, or expert opinion)	"Recommend/ Should"
Conditional	• Benefits are finely balanced with risks and burden or appreciable uncertainty exists about the magnitude of benefits and risks. • Most informed people would choose the recommended course of action, but a substantial number would not. • A shared decision-making approach regarding patient values and preferences is particularly important.	Any (usually moderate, low, or expert opinion)	"Conditionally Recommend"

Overall QoE Grade	Type/Quality of Study	Evidence Interpretation
High	• 2 or more well-conducted and highly generalizable RCTs or meta-analyses of such trials.	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.
Moderate	• 1 well-conducted and highly generalizable RCT or a meta-analysis of such trials **OR** • 2 or more RCTs with some weaknesses of procedure or generalizability **OR** • 2 or more strong observational studies with consistent findings.	The true effect is likely to be close to the estimate of the effect based on the body of evidence, but it is possible that it is substantially different.
Low	• 1 RCT with some weaknesses of procedure or generalizability **OR** • 1 or more RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes **OR** • 2 or more observational studies with inconsistent findings, small sample sizes, or other problems that potentially confound interpretation of data.	The true effect may be substantially different from the estimate of the effect. There is a risk that future research may significantly alter the estimate of the effect size or the interpretation of the results.
Expert Opinion*	• Consensus of the panel based on clinical judgment and experience, due to absence of evidence or limitations in evidence.	Strong consensus (≥90%) of the panel guides the recommendation despite insufficient evidence to discern the true magnitude and direction of the net effect. Further research may better inform the topic.

Abbreviations: ASTRO = American Society for Radiation Oncology; QoE = quality of evidence; RCTs = randomized controlled trials.

*A lower quality of evidence, including expert opinion, does not imply that the recommendation is conditional. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials, but there still may be consensus that the benefits of a treatment or diagnostic test clearly outweigh its risks and burden.

ASTRO's methodology allows for use of implementation remarks meant to convey clinically practical information that may enhance the interpretation and application of the recommendation. Although each recommendation is graded according to recommendation strength and QoE, these grades should not be assumed to extend to the implementation remarks.

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1. Introduction

Breast cancer is the leading cause of global cancer incidence and remains a leading cause of cancer mortality worldwide, with an estimated 2.3 million new cases in 2020.[3] Partial breast irradiation (PBI) is a localized form of radiation typically delivered after lumpectomy to only the part of the breast where the tumor was removed. This evidence review and guideline updates previous ASTRO guidance,[4,5] to reflect recent developments in the management of patients with early-stage breast cancer. Accounting for multiple tumor- and patient-related factors requires a patient-centered decision-making process, particularly given the expanding number of therapeutic options available.

Over 10,000 patients have been enrolled in randomized controlled trials (RCTs) with published long-term results comparing PBI to whole breast irradiation (WBI) with clinically comparable oncologic ipsilateral breast recurrence (IBR)[6] outcomes. Multiple concepts have been addressed simultaneously in these clinical trials, including (1) evaluation of IBR when only the tumor bed (and not the whole breast) is targeted with radiation therapy (RT) and (2) the dose-fractionation regimen that provides optimal tumor control and minimizes toxicity. The NSABP B-39/RTOG 0413 Long-Term Primary Results of Accelerated Partial Breast Irradiation After Breast-Conserving Surgery for Early-Stage Breast Cancer (B39/R0413) RCT (n=4216 patients) did not meet the prespecified criteria for equivalence of PBI to WBI but did find an absolute difference of <1% in the 10-year cumulative incidence of IBR.[7] The External Beam Accelerated Partial Breast Irradiation Versus Whole Breast Irradiation After Breast Conserving Surgery in Women With Ductal Carcinoma In Situ and Node-Negative Breast Cancer (RAPID) RCT (n=2135 patients) demonstrated a noninferior IBR for PBI and WBI at 8 years,[8] as did the United Kingdom (UK) Partial-Breast Radiotherapy After Breast Conservation Surgery for Patients With Early Breast Cancer (IMPORT LOW) RCT (n=2018 patients), with 5-year reported outcomes,[9] the Groupe Européen de Curiethérapie (GEC) and the European Society for Radiotherapy & Oncology (ESTRO) multicatheter interstitial brachytherapy (MIB) RCT trial at 10 years (n=1184 patients),[10] and the Danish Breast Cancer Group RCT (n=865 patients) with a median follow-up of 7.6 years.[11] Comparable IBR rates were also reported at 10 years on the Florence intensity modulated radiation therapy (IMRT) RCT (n=520 patients),[12] at 20 years on the Budapest RCT (n=258 patients),[13] at 3 years on the Hypofractionated Whole Breast Irradiation versus Accelerated Partial Breast Irradiation (HYPAB) RCT (n=172 patients),[14] and at 10 years on a Spanish RCT(n=102 patients).[15] A substantive volume of data on toxicities of PBI compared to WBI has also been published from these and other RCTs.[16]

Because of the publication of a large quantity of high-quality trials evaluating PBI versus WBI outcomes, ASTRO sought to develop an updated PBI guideline to better inform clinical practice. In particular, the guideline was developed to clarify patient selection criteria and appropriate modalities for PBI delivery.

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2. Methods

2.1. Task force composition

The task force consisted of a multidisciplinary team of radiation, medical, and surgical oncologists; a medical physicist; and a patient representative. This guideline was developed in collaboration with the American Society of Clinical Oncology and the Society of Surgical Oncology, which provided representatives and peer reviewers.

2.2. Document review and approval

The guideline was reviewed by 17 official peer reviewers (Appendix E1) and revised accordingly. The modified guideline was posted on the ASTRO website for public comment from May 31st through June 2023. The final guideline was approved by the ASTRO Board of Directors and endorsed by the TBD.

2.3. Evidence review

In April 2021, ASTRO submitted a proposal for the Agency for Healthcare Research and Quality (AHRQ) to develop a comparative effectiveness evidence review on RT for PBI, which was accepted and funded by the Patient-Centered Outcomes Research Institute.[17] This review aimed to support a replacement of the prior ASTRO 2009 APBI guideline and 2016 focused update which included the use of intraoperative radiation therapy (IORT).[4,5] AHRQ performed a systematic search of the databases Embase® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE® Daily, MEDLINE®, Cochrane Central Register of Controlled Trials, Ovid® Cochrane Database of Systematic Reviews, and Scopus® from database inception to June 30, 2022. For comparisons of PBI as an alternative to WBI, only RCTs were included. For comparisons of different PBI techniques, eligible study designs included comparative observational studies as well as RCTs. In total, 23 studies representing 52 original articles were included for data abstraction. For details on the AHRQ methodology and systematic review explanation, including the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing the number of articles screened, excluded, and included in the evidence review, see Appendix A of the AHRQ systematic review report.[17]

For KQ1, the AHRQ review specified that only RCTs would be necessary to include since higher quality evidence was available. Because of concern that the RCTs did not have sufficient enrollment of patients with higher risk features, the task force performed an additional literature search of prospective, nonrandomized, and retrospective data using the following terms “partial breast radiation,” “PBI,” “APBI,” “grade 3,” “LVI,” “lobular,” “HER2,” and ”triple negative,” which identified 11 additional articles that reported on 1 or more of

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these factors. After reviewing the articles, the data was considered insufficient to support changing the recommendations based on the RCTs, so they are not cited in the guideline. In addition, newly published RCTs and long-term follow-up of previously reported RCTs were published during our evidence review. While not used to support recommendation, they are cited in the text as additional references.

References selected and published in this document are representative and not all-inclusive. Additional ancillary articles not in the AHRQ evidence tables or report are included in the text but were not used to support the recommendations. The outcomes of interest are IBR, overall survival, acute and late toxicities, and cosmesis.

2.4. Scope of the guideline

This guideline addresses only the subjects specified in the KQs (Table 2), which were studied in any setting. Studies included adult patients with early-stage breast cancer who received 1 of 6 PBI modalities (MIB, single-entry catheter brachytherapy [also known as intracavitary brachytherapy], 3-dimensional conformal radiation therapy [3-D CRT], IMRT, proton RT, or IORT). The AHRQ inclusion criteria required studies to involve adult women (age ≥18 years) with early-stage invasive breast cancer or DCIS defined as a small lesion ≤3 cm that has minimal (up to 3 positive) or no lymph node involvement treated with upfront breast conserving surgery, with reported outcomes of interest. The search did not include patients of male sex, as this was an exclusion factor in the RCTs. Outside the scope of this guideline are many other important questions that may be the subject of other guidelines on PBI, which include the role of PBI in the setting of neoadjuvant systemic therapy, more advanced cancers, recurrent or second primary breast cancers, breast augmentation, male breast cancers, and oncoplastic surgery.

Table 2 KQs in PICO format

KQ	Population	Intervention	Comparator	Outcomes
1	**In adult patients with early-stage invasive breast cancer or DCIS, what are the appropriate indications for PBI as an alternative to WBI?**			
	Adult patients with early-stage invasive breast cancer or DCIS	• PBI	• WBI +/- boost	• IBR • Overall survival
2	**In adult patients with early-stage invasive breast cancer or DCIS receiving PBI, what are the appropriate PBI techniques with respect to IBR outcomes?**			
	• Same as KQ1	<u>PBI techniques</u> • 3-D CRT • MIB • IMRT • IOERT • KV IORT	• WBI +/- boost	IBR

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		• Single-entry catheter brachytherapy • Protons		
3	**In adult patients with early-stage invasive breast cancer or DCIS, what are the appropriate dose-fractionation regimens, target volumes, and planning parameters for PBI?**			
	• Same as KQ1	Timing • Daily • Twice daily • Every other day Dose-fractionation • Hypofractionation* • Ultrahypofractionation† Target volumes • Target definitions (Tumor bed/CTV/PTV) • OARs Dose constraints	WBI • Standard fractionation • Moderate hypofractionation	• IBR • Patient-reported and physician-assessed cosmesis • Adverse events
4	**In adult patients with early-stage invasive breast cancer or DCIS receiving PBI, what are the appropriate PBI techniques with respect to toxicity and cosmesis?**			
	• Same as KQ1	PBI techniques • 3-D CRT • MIB • IMRT • Protons • IOERT • KV IORT • Single-entry catheter brachytherapy Timing • Daily • Twice daily • Every other day Dose-fractionation • Hypofractionation* • Ultrahypofractionation†	WBI • Standard fractionation • Hypofractionation	• Patient-reported and physician-assessed cosmesis • Adverse events

Abbreviations: 3-D CRT = 3-dimensional conformal radiation therapy; CTV = clinical target volume; DCIS = ductal carcinoma in situ; EBRT = external beam radiation therapy; IBR = ipsilateral breast recurrence; IMRT = intensity modulated radiation therapy; IOERT = intraoperative electron radiation therapy; IORT = intraoperative radiation therapy; KQs = key questions; KV = kilovoltage; MIB = multicatheter interstitial brachytherapy; OARs = organs at risk; PBI = partial breast irradiation; PICO = Population, Intervention, Comparator, Outcome; PTV = planning target volume; WBI = whole breast irradiation.

* Hypofractionation is defined as >200 cGy up to 499 cGy per fraction.

† Ultrahypofractionation is defined as ≥500 cGy per fraction.

3. Key Questions and Recommendations

3.1. KQ1: Indications for PBI as an alternative to WBI (Table 3)

In adult patients with early-stage invasive breast cancer or DCIS, what are the appropriate indications for PBI as an alternative to WBI?

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Table 3 Indications for PBI as an alternative to WBI

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with early-stage invasive breast cancer or DCIS with the following factors, PBI is recommended for: • grade 1-2 invasive disease • age ≥50 years • age 40-49 years • size ≤2 cm • low-to-intermediate grade DCIS	Strong	High (1st & 2nd bullets) 7-9,12-15,18 Moderate (3rd, 4th & 5th bullets) 7-9,12-15,18
2. For patients with early-stage invasive breast cancer or DCIS with the following factors, PBI is conditionally recommended for: • grade 3 invasive disease • ER-negative histology • size >2 - ≤3 cm • high-grade DCIS <u>Implementation remark:</u> PBI may not be appropriate when multiple of these factors are present.	Conditional	Low 7-9,12-15,18 (1st, 2nd, & 3rd bullets) Expert Opinion (4th bullet)
3. For patients with early-stage invasive breast cancer with the following factors, PBI is conditionally **not** recommended for: • HER2-positive tumors **not** receiving anti-HER2 therapy • lymphovascular invasion • lobular histology <u>Implementation remarks:</u> • Given low patient numbers accrued to RCTs; higher risk of recurrence is possible.	Conditional	Expert Opinion
4. For patients with early-stage invasive breast cancer or DCIS with the following factors, PBI is **not** recommended for: • positive lymph nodes • positive surgical margins • known germline BRCA1/2 mutation	Strong	Expert Opinion

Abbreviations: DCIS = ductal carcinoma in situ; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; KQ = key question; PBI = partial breast irradiation; RCTs = randomized controlled trials; WBI = whole breast irradiation.

Multiple RCTs evaluating the efficacy of PBI compared to WBI have demonstrated comparable IBR and long-term overall survival.[7-13,15,16,18] Recommendations for the use of PBI require consideration of both patient and tumor characteristics as shown in Figure 1. With increased prevalence of treatment de-escalation, ensuring comparable IBR rates compared to hypofractionated and conventionally fractionated WBI is essential. There is broad consensus that PBI is an acceptable treatment option for patients with favorable clinical features and tumor characteristics (ie, postmenopausal age range, estrogen receptor [ER]-positive status,

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grade 1-2, no lymph node involvement, and tumor size ≤2 cm).[4,5,19-22] Uncertainty remains regarding the magnitude of increased risk associated with features that are perceived as less favorable that were included within the eligibility criteria of RCTs but represented a minority of patients who participated (ie, age <50 years, invasive lobular carcinoma, tumor size 2.1-3 cm, grade 3, ER-negative status, human epidermal growth factor receptor 2 [HER2]-positive status, positive for lymphovascular invasion [LVI], and positive lymph nodes), as delineated in Appendix E3. This KQ addresses recommendations for the use of PBI in subgroups considered cautionary and unsuitable in a previous ASTRO PBI consensus statement.[5] It also highlights the importance of future investigation to develop more robust evidence to inform treatment recommendations.

There has been reluctance to treat with PBI in patients age <50 years due to concern over increased IBR risks.[5,23] Multiple subgroup analyses from RCTs did not show a difference in up to 10-year IBR rates according to age or menopausal status when comparing PBI to WBI.[7,8,10] Together, these trials included over 1000 patients age 40 to 49 years who were treated with PBI. Given the scarcity of patients under age 40 years treated on RCTs, there is not enough evidence to support the use of PBI in this age group.

Patients with ductal carcinoma in situ (DCIS) were included in 4 RCTs, comprising a total of 1527 patients, of whom 768 were treated with PBI, with the vast majority of patients treated with PBI on RAPID (n=191) and B39/R0413 (n=518).[7,8,10,12,18] Disease characteristics of included patients with DCIS were not universally reported, such as size of the lesion, the proportion with high-grade DCIS, or negative margin width. Subgroup analyses of patients with DCIS from RCTs found minimal numerical difference in up to 10-year IBR rates between those treated with PBI versus those treated with WBI.[7,8] Given low local recurrence risks with small, low-to-intermediate grade DCIS without RT, it is reasonable to conclude that those patients are appropriate candidates for PBI.[24,25] The presence of an extensive intraductal component (EIC) had been included in the cautionary subgroup of previously published ASTRO guidelines.[4,5] Three of the RCTs[12-14] specifically excluded patients with EIC, while the other trials[7-9,18] did not report any data regarding the number of patients included that had this feature or outcomes for patients with EIC. Additionally, EIC may be reflective of a range of features based on factors such as size, margin status, and grade. Overall, there is insufficient data to make any statements regarding EIC.

Although the RCTs limited the size of the breast lesion for both invasive and noninvasive components to ≤3 cm, most patients enrolled in the RCTs had tumors ≤2 cm.[7-10,12,13,15] The RAPID[8] and B39/R0413[7] trials enrolled over 450 patients with larger tumors and reported outcomes based on tumor size, albeit using different cut points (1.5 cm and 2cm, respectively). In a subset analysis of the RAPID trial, tumors larger than 1.5 cm were marginally more likely to experience a recurrence than patients with smaller tumors, but the interaction between size and treatment was not significant.[8] B39/R0413 performed an exploratory post-hoc analysis in the intention to treat population to determine if there were differences in treatment effects

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amongst the different patient subgroups. Review of the forest plot suggests that patients with smaller lesions may have better outcomes than patients with larger lesions.[7]

Patients with high-grade invasive disease were generally under-represented in the RCTs comparing PBI to WBI, comprising <10% of patients on these RCTs in total.[7-10,12,13,15,18] Grade 3 was studied only in a subset analysis in the RAPID trial and showed the 8-year IBR rate to be equivalent for those treated with PBI and WBI.[8] Grade was not studied in subset analysis in B39/R0413, but more than one-quarter of patients on the trial had high-grade invasive disease.[7] However, based on the overall low and comparable rates of recurrence to WBI, coupled with lack of data specifically showing a worse outcome for patients with high-grade disease, it is reasonable to consider PBI for patients with grade 3 invasive tumors.

Breast tumor subtype is an important factor that should be considered in RT treatment decisions. There is an abundance of data supporting the use of PBI for patients with ER-positive and HER2-negative breast cancer.[7-10,12,18] Conversely, caution is recommended for patients with potentially aggressive disease biology, such as HER2-positive and ER-negative disease as these patients represented a minority of patients enrolled in the RCTs.[7-9,12-15,18] However, in principle the presence of a single predictive higher risk factor for IBR should not represent an absolute contraindication for PBI, since tumor stage and biology rather than receptor status alone impacts patient prognosis.[26] HER2-positive receptor status further increases the complexity of PBI decision-making for patients with early-stage breast cancer. Although HER2-positive status was not considered an exclusion criterion in the RCTs, very few of the trials reported outcomes based on this factor.[8,9,12,15] For those trials that did report outcomes in this patient cohort, the data represented fewer than 100 patients in total, making it difficult to reach a strong recommendation in favor of PBI. Early-stage, HER2-positive breast cancer receiving modern anti-HER2-targeted therapy has shown excellent long-term results in terms of locoregional recurrence and overall survival.[27,28] Given the excellent outcomes for patients receiving anti-HER2-targeted therapy, PBI may represent a reasonable approach for select patients with HER2-positive tumors receiving an optimal anti-HER2 regimen or deemed low enough risk not to benefit from anti-HER2 therapy, although caution should be taken for HER2-positive tumors that are not treated with anti-HER2-targeted therapy.[29]

Patients with LVI were underrepresented and poorly reported in the RCTs studying PBI, making it difficult to know the implications of this factor on IBR for patients receiving PBI. Given concern over the potential for higher local recurrence risks and the lack of data supporting efficacy, caution should be employed when recommending PBI for patients with tumors demonstrating LVI.[30]

Most of the RCTs specifically excluded patients with lobular histology.[8,9,13-15] For the trials that did include patients with lobular histology, the population treated with PBI represented <5% of patients enrolled.[7,12,18] In addition to the low representation on the RCTs, lobular histology is more likely to be multifocal or multicentric when compared to invasive ductal histology, making the appropriateness of PBI in

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this setting poorly defined.[31,32] Similarly, most of the RCTs evaluated excluded patients with multifocal[7,9,10,12-15] or multicentric cancers.[7-10,12-15]

For patients with positive axillary lymph nodes, there is insufficient data to recommend PBI due to the limited sample size for this subgroup. Three RCTs[7,9,12] included patients with macroscopic lymph node involvement, and 3 RCTs[8,13,18] included patients with microscopic (≤2.0 mm) axillary involvement. Despite the inclusion of patients with low-volume nodal disease, most patients accrued to PBI RCTs had negative axillary lymph nodes. Additionally, in the modern era, most patients with 1 to 2 positive sentinel lymph nodes do not undergo completion axillary lymph node dissection. WBI may be an important part of local therapy of the undissected axilla.[33] Based on this, the recommendation regarding PBI is limited to patients without nodal disease.

Surgical margin positivity represented an exclusion criterion for most of the RCTs examined, with the only exception being PBI trials of IORT.[7-9,12,18] Despite the allowance for positive margins, <1% (n=3) of patients enrolled on the ELIOT trial and 6% of patients enrolled on the TARGIT-A trial (all received WBI in addition to IORT) had positive margins.[34,35] The definition of negative margin also varied amongst the RCTs, with 2 trials defining this as no tumor on ink,[7,8] 1 as 2 mm microscopic margins,[9] 2 as 5 mm microscopic margins,[12,14] and 1 as 1 cm macroscopic margins.[13] One trial had different margin status requirements based on histology, with 2 mm for invasive, non-lobular histology and 5 mm for DCIS and invasive lobular histology.[10,18] Although there is an absence of controlled data specifically related to PBI, inadequacy of final surgical margins is clearly recognized as one of the most important risk factors for local recurrence, potentially affecting disease-specific survival after breast conserving therapy;[36] PBI is not recommended for patients with positive surgical margins defined as tumor on ink, for whom re-excision is advised in the setting of WBI.[37]

Patients with a germline *BRCA1/2* mutation were specifically excluded from most PBI RCTs. Given this lack of data in a disproportionately younger patient cohort PBI is not recommended for this patient population.

It should be noted that the subgroup analyses pertaining to individual patient and tumor characteristics conducted in the RCTs largely looked at each feature in isolation,[7,8,10] with only the Florence trial reporting a multivariable analysis for risk factors for IBR.[12] It is possible that for patients with multiple higher-risk factors, recurrence risks may be higher and PBI may not be an appropriate treatment option. Appropriate systemic therapy tailored to individual patient and tumor characteristics is an important factor in reducing local and systemic recurrences and improving overall survival. A higher local recurrence risk is anticipated without use of optimal systemic therapy. Given that the duration of certain systemic therapies, such as endocrine therapy, can be up to 10 years, the intent to complete this therapy at the time of breast radiation decision-making cannot be determined. It is unclear if the use of systemic therapy has a differential effect in patients receiving PBI versus WBI.

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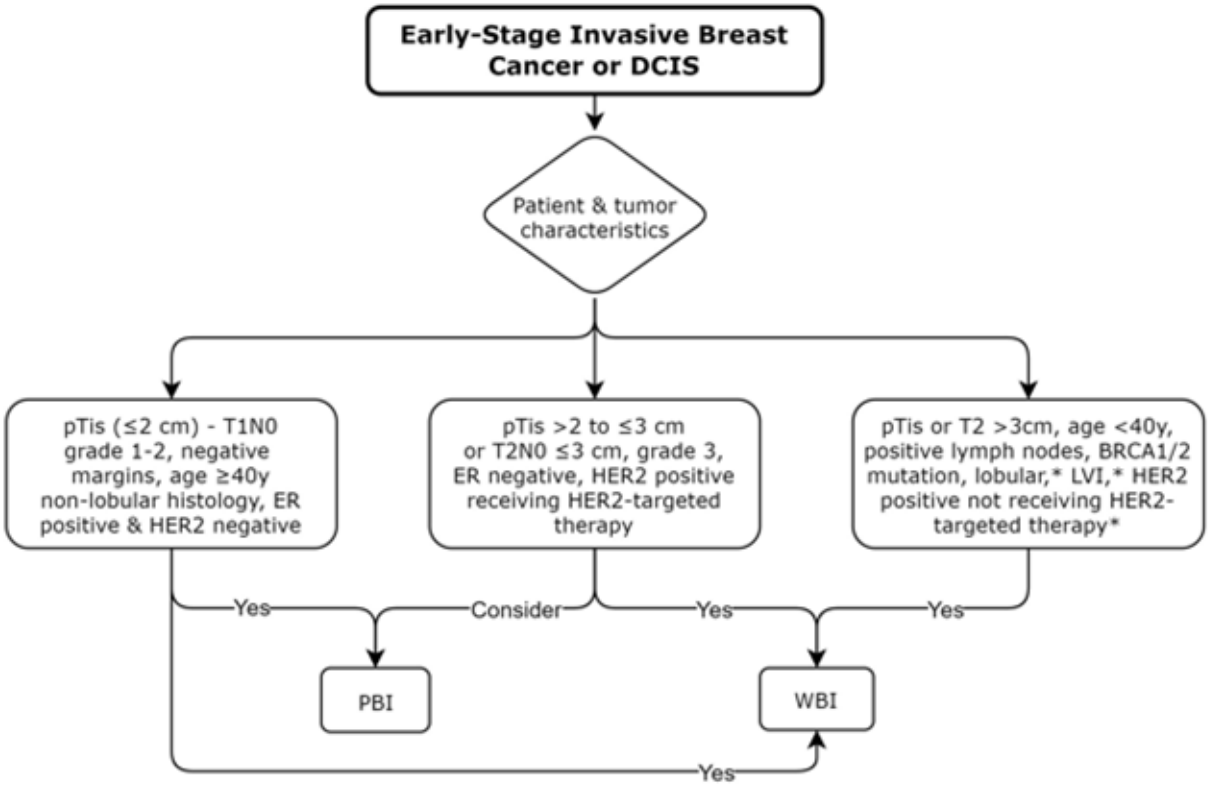
Figure 1 Adjuvant Radiation Therapy Treatment Options for Early-Stage Invasive Breast Cancer or DCIS



Abbreviations: BID = twice daily; DCIS = ductal carcinoma in situ; ER = estrogen receptor; ER + = estrogen receptor positive; fx = fractionation; HDR = high-dose-rate brachytherapy; HER2 = Human epidermal growth factor receptor 2; LVI = lymphovascular invasion; PBI = partial breast irradiation; PDR = pulsed-dose-rate; RCTs = randomized controlled trials; WBI = whole breast irradiation.

* Only the characteristics lobular, LVI, and HER2-positive not receiving HER2-targeted therapy are conditionally not recommended given low patient numbers accrued to RCTs. Higher risk of recurrence is possible although this may be an option in limited situations.

3.2. KQ2: Appropriate PBI techniques with respect to IBR (Table 4)

In adult patients with early-stage invasive breast cancer or DCIS receiving PBI, what are the appropriate PBI techniques with respect to IBR outcomes?

Table 4 Appropriate PBI techniques with respect to rates of IBR

KQ2 Recommendation	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with early-stage invasive breast cancer or DCIS receiving PBI, 3-D CRT is recommended.	Strong	High [7-9,15]
2. For patients with early-stage invasive breast cancer or DCIS receiving PBI, IMRT is recommended.	Strong	Moderate [12,14,38]

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3. For patients with early-stage invasive breast cancer or DCIS receiving PBI, multicatheter brachytherapy is recommended.	Strong	Moderate [13,18]
4. For patients with early-stage invasive breast cancer or DCIS receiving PBI, single-entry catheter brachytherapy is conditionally recommended.	Conditional	Moderate [7,39-42]
5. For patients with early-stage invasive breast cancer or DCIS receiving PBI, intraoperative radiation therapy alone is **not** recommended.	Strong	Moderate [34,35,43-45]

Abbreviations: 3-D CRT = 3-dimensional conformal radiation therapy; DCIS = ductal carcinoma in situ; IBR = ipsilateral breast recurrence; IMRT = intensity modulated radiation therapy; KQ = key question; PBI = partial breast irradiation.

Large phase III trials have not been conducted to directly compare the IBR rates of individual PBI techniques against one another, so there is insufficient evidence to estimate an effect on IBR outcomes from existing head-to-head comparisons. However, several large RCTs have been conducted comparing individual PBI techniques versus WBI which demonstrate the IBR outcomes achieved with distinct forms of PBI.[7-9,11-14,18,34,35]

MIB was the first PBI technique to be compared with WBI in an RCT. Two such trials have been conducted, one with 20 years of follow-up[13] and the other with 10 years of follow-up,[10,18] both showing no significant difference in IBR outcomes with MIB versus WBI. Given that breast brachytherapy is a highly specialized technique and the technical complexity of performing MIB implants, several single-entry brachytherapy applicators were developed to allow brachytherapy PBI to be adopted on a more widespread basis.[46] None of these single-entry applicators have been exclusively compared to WBI in an RCT. While B39/R0413 did allow both MIB and single-entry catheter brachytherapy, this included a minority of enrolled patients, and the trial was not designed to detect differences in IBR among individual PBI modalities.[7] The American Society of Breast Surgeons conducted a large prospective registry trial of single-entry catheter PBI that found a 5-year IBR rate of 3.8%[40] and a smaller, multi-institutional registry study found a 4-year IBR rate of 3.6%.[47]

Most patients enrolled on the RCTs comparing PBI to WBI were treated with external beam radiation therapy (EBRT), most of whom were treated with a 3-D CRT technique. B39/R0413 treated 73% of PBI patients with 3-D CRT (3850 cGy in 10 fractions bid) and demonstrated IBR rates for the overall cohort of PBI versus WBI at 10 years of 4.6% versus 3.9%, an absolute difference of 0.7% that did not meet the prespecified equivalence criteria.[7] The RAPID trial treated PBI patients with 3-D CRT (3850 cGy in 10 fractions bid) and demonstrated a noninferior IBR rate of PBI versus WBI at 8 years of 3% versus 2.8%.[8] The IMPORT LOW trial demonstrated a noninferior 5-year IBR rate of 3-D CRT with dose compensation (4005 cGy in 15 fractions) versus WBI of 0.5% versus 1.1%.[9,15] Only 2 trials directly compared IMRT to 3-D CRT PBI, both with primary endpoints of toxicities.[38,48] The Florence trial randomized patients to conventionally fractionated WBI

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compared to IMRT PBI using 5 once-daily 600 cGy fractions delivered every other day. At a median follow-up of 10 years, the IBR rate was 3.7%, comparable to 2.5% with WBI.[12] Of note, in addition to the RT technique varying on the EBRT RCTs, so did the dose-fractionation delivered to both the PBI and WBI arms of the trials.[7-9,12,14,15,38]

At the time of this assessment there are minimal data using modern techniques such as pencil beam scanning for proton beam PBI and as a result insufficient data to make a recommendation for its use. The dosimetric benefit of proton beam PBI over other external beam techniques may be limited except in unusual locations such as the parasternal area.

IORT is appealing from the perspective that it offers the possibility for RT to be completed at the same time as breast conserving surgery, which may improve access to care. However, inherent challenges to achieving optimal IBR exist with IORT modalities, including incomplete pathologic information at the time of treatment and lack of image-guided quality assurance of dose distribution. When compared with WBI, electron IORT (IOERT) as delivered in the ELIOT trial has been found to have inferior IBR rates through 15 years of follow-up in 1305 patients (12.6% vs 2.4%).[34] Low-energy photon IORT (KV IORT) outcomes are more challenging to interpret, given that the trial design included a risk-adapted approach which allowed WBI for patients with features determined high risk at the time of pathologic assessment. The TARGIT-A trial randomized 2298 patients to receive WBI versus KV IORT, which could be given immediately following lumpectomy ("prepathology" cohort) or as a second procedure ("postpathology" cohort). Outcomes of enrolled patients with a median follow-up of 29 months reported noninferior 5-year IBR outcomes with KV IORT (3.3% vs 1.3%), though IBR outcomes appeared more favorable in the prepathology group (2.1% vs 1.1%) than the postpathology group (5.4% vs 1.7%).[45] Importantly, for patients receiving KV IORT at the time of initial lumpectomy, over 20% required the addition of WBI based upon pathologic risk factors that varied by treatment center, making it difficult to determine which patients have optimal IBR outcomes with KV IORT alone. The UK National Institute for Health and Care Excellence conducted a detailed analysis of the TARGIT-A trial which notes that the published results of the TARGIT-A trial were not analyzed using Kaplan Meier statistics and when re-analyzed using Kaplan Meier statistics the criterion for noninferiority was not met.[49] Subsequent publications of the TARGIT-A trial have separated patients into prepathology and postpathology cohorts and have emphasized local recurrence-free survival rather than IBR outcomes.[35,50] With local recurrence-free survival, both local recurrence and death from any cause are counted as events, limiting the ability to assess IBR. Given the above uncertainties and the higher IBR seen on the ELIOT trial, IORT is not recommended.

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3.3. KQ3: Appropriate dose-fractionation regimens, target volumes, and planning parameters for PBI (Table 5)

In adult patients with early-stage invasive breast cancer or DCIS, what are the appropriate dose-fractionation regimens, target volumes, and planning parameters for PBI?

Appropriate PBI dose-fractionation regimens are enumerated in Table 5 and guidance regarding treatment planning is provided in Table 6. These were restricted to PBI regimens that were outlined as appropriate in KQ2.

Table 5 Appropriate PBI dose-fractionation regimens

KQ3 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with early-stage invasive breast cancer or DCIS receiving external beam PBI, 3000 cGy in 5 once daily fractions delivered on nonconsecutive days within 2 weeks is recommended.	Strong	Moderate [12,14]
2. For patients with early-stage invasive breast cancer or DCIS receiving external beam PBI, 4005 cGy in 15 once daily fractions over 3 weeks is recommended.	Strong	Moderate [9]
3. For patients with early-stage invasive breast cancer or DCIS receiving PBI with HDR brachytherapy, 3010 cGy in 7 fractions, 3200 cGy in 8 fractions, 3400 cGy in 10 fractions delivered twice daily or 5000 cGy with 160-180 cGy/hour PDR is recommended. Implementation remark: Single-entry PBI trials used 3400 cGy in 10 fractions delivered twice daily.	Strong	Moderate [7,18]

Abbreviations: DCIS = ductal carcinoma in situ; HDR = high-dose-rate; KQ = key question; PBI = partial breast irradiation; PDR = pulsed-dose-rate.

The recommended dose-fractionation regimens for delivering PBI via EBRT are based on the Florence, HYPAB, and IMPORT LOW studies.[9,12,14] The Florence and HYPAB RCTs demonstrated safety of PBI using 3000 cGy in 5 fractions on nonconsecutive days with multiple-field IMRT as compared to WBI, with comparable local recurrence rates. For the WBI treatment arms, the Florence trial used conventional fractionation with a sequential (5000 cGy in 25 fractions followed by 1000 cGy in 5 fractions) boost and HYPAB used hypofractionation with a simultaneous integrated boost (4005 cGy in 15 fractions to the whole breast and 4800 cGy in 15 fractions to the tumor bed).[12,14] IMPORT LOW tested 4005 cGy in 15 fractions over 3 weeks PBI using mini tangents compared with 4005 cGy in 15 fractions over 3 weeks WBI (control) and 3600 cGy WBI with 4005 cGy to the partial breast in 15 fractions over 3 weeks (reduced-dose).[9] PBI demonstrated noninferior local control and reduced late normal tissue toxicity. The Danish Breast Cancer Group[11] used a similar approach to IMPORT LOW and showed that the primary endpoint of grade 2 to 3 breast induration was noninferior with PBI compared with WBI. In both trials, the irradiated volume was the only variable and all

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other factors, including dose and fractionation, were constant between the WBI and PBI arms.[9,11] While the task force acknowledges that the above cited PBI fractionation regimens demonstrate comparable local control compared with WBI, concerns over toxicity with the BID regimens as discussed in KQ4 and patient convenience were considered in forming these recommendations.

Target volumes and planning parameters for EBRT PBI are listed in Table 6. Given differences in surgical margin width required, target volume expansions and image guided RT method in the RCTs, there is a range of tumor bed expansions needed for appropriate targeting when delivering PBI using EBRT. A range was given to allow for tailoring these volumes, with larger volumes suggested for patients with smaller surgical margins, or inability to perform daily imaging.

The recommended dose, fractionation, and planning parameters for delivering PBI with high-dose-rate (HDR) and pulsed-dose-rate brachytherapy are taken from the GEC-ESTRO and B39/R0413 trials.[7,18] The GEC-ESTRO trial used interstitial brachytherapy for PBI and allowed both pulsed-dose-rate (n=119) and HDR regimens of 7 (n=59) and 8 (n=451) twice daily fractions.[18] The 10-fraction twice daily regimen was used in the B39/R0413 trial for both interstitial (n=120) and single entry (n=451) HDR brachytherapy.[7] There was no significant difference seen in the updated 10-year results of the GEC-ESTRO trial, which demonstrated a local recurrence rate of 1.58% in the WBI group and 3.51% in the PBI group. There was a significantly lower rate of treatment-related grade 3 late adverse events in the PBI group.[10] The B39/R0413 trial has not yet reported outcomes of the brachytherapy subgroup.[7]

Where planning objectives differ between the GEC-ESTRO and B39/R0413 trials, the more stringent objective (generally GEC-ESTRO) is given as “Ideal” and the other, “Acceptable.” Planning objectives for single-entry catheters are taken from B39/R0413,[7] as GEC-ESTRO did not use this technique. The recommended maximum skin dose objective for single-entry catheters is more stringent than allowed by the B39/R0413 trial, reflecting both the lower doses achievable with modern, multilumen applicators and the correlation of skin toxicity to maximum skin dose.[51,52] The GEC-ESTRO trial incorporated surgical margin information for target definition.[18] The surgical-free margins reported by GEC-ESTRO were a median of 0.8 cm (range: 0.2-4 cm), corresponding to cavity-to-target expansions of 1.2 cm (range: 1.0-1.8 cm).[18] This compares with B39/R0413’s uniform margins of 1.5 cm for interstitial and 1.0 cm for single-entry brachytherapy.[7] As detailed margin information may not be universally available, the margins used in the B39/R0413 trial are included as an alternative.[7]

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489 **Table 6.** PBI target volumes and planning parameters*

Dose-fractionation regimens	Target volumes	Planning parameters	
EBRT **3000 cGy/5 fx in 2 weeks**†[12,14] OR **4005 cGy/15 fx over 3 weeks**[9]	**Tumor bed:** volume is drawn around the clips‡ and any change in the surrounding tissue architecture.§ Target volume expansions should take into consideration both margin status and imaging strategy. **CTV:** 1-1.5 cm expansion from the tumor bed. For patients with margin width ≥2 mm, a 1 cm expansion from the tumor bed is appropriate. For patients with closer margins, a 1.5 cm expansion should be considered. **PTV:** 1 cm margin around CTV. For patients undergoing daily imaging, tighter margins may be considered depending on accuracy of patient set-up. **PTV_EVAL**: PTV cropped 3-5 mm inside patient surface and limited posteriorly by the pectoralis muscle. Daily imaging is advised when using 5 fx to deliver PBI and when using PTV margins <1 cm.	**Ideal:** **PTV_Eval**: V95% dose ≥95% V105% dose ≤5% Dmax ≤110% of prescribed dose **Ipsilateral breast:**‖ V95% dose ≤25% V50% dose ≤50% **Ipsilateral lung:** V30% dose ≤10% **Contralateral lung:** V10% dose ≤5% **Contralateral breast:** Dmax ≤3% **Heart:** **Right sided tumor** V5% dose ≤5% Mean dose <0.7 Gy **Left sided tumor** V15% dose ≤5% Mean dose <1.5 Gy **Thyroid:** Dmax ≤3% **Body outside PTV:** V107% ≤2 cc Dmax ≤110% of prescribed dose	**Variation acceptable:** **PTV_Eval:** V95% dose ≥90% V105% dose ≤7% **Ipsilateral breast:** V95% dose ≤40% V50% dose ≤60% **Ipsilateral lung:** V30% dose ≤15% **Contralateral lung:** V5% dose ≤15% **Contralateral breast:** Dmax ≤5% **Heart:** **Right sided tumor** V5% dose ≤10% Mean dose <1 Gy **Left sided tumor** V15% dose ≤10% Mean dose <2 Gy **Thyroid:** Dmax ≤5% **Body outside PTV:** V110% ≤2 cc Dmax ≤112% of prescribed dose
HDR brachytherapy **Multicatheter interstitial brachytherapy:** 3200 cGy in 8 fx or 3010 cGy in 7 fx,[10] or 3400 cGy in 10 fx; all twice daily[7] Pulsed-dose-rate brachytherapy: total dose of 5000 cGy with pulses of 160-180 cGy/hour[10]	**Multicather interstitial brachytherapy volumes**: **Tumor bed**: volume is drawn around the clips and any change in the surrounding tissue architecture. **Interstitial CTV:** if individual surgical margin data is available: expand cavity by 2.0 cm minus each surgical margin to generate the target (ie, if medial surgical margin is 5 mm, then medial CTV margin should be 1.5 cm). Margin should not be <1 cm. All expansions from cavity to CTV limited to 5 mm from skin surface and	**Ideal:** **Interstitial:** Optimize to keep the dose uniformity ratio (1-V150/V100) ≥0.75 **PTV_Eval**: V100% dose ≥90% **Skin:** Dmax <70% of prescribed dose **Ipsilateral breast:** V150% dose <70 cc V200% dose <20 cc	**Variation acceptable:** **Interstitial:** Optimize to keep the dose uniformity ratio (1-V150/V100) ≥0.65 **PTV_Eval**: V90% dose ≥90% **Skin:** Dmax <100% of prescribed dose

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	by the posterior breast tissue extent (pectoralis muscle is excluded). **CTV=PTV=PTV_Eval**		
Single-entry intracavity brachytherapy: 3400 cGy in 10 fx twice daily[7]	**Single-entry intracavity brachytherapy volumes:** **Single-entry CTV:** 1 cm expansion beyond cavity edge after full deployment of device less the balloon/device surface volume, limited to 5 mm from skin surface and by the posterior breast tissue extent (pectoralis muscles excluded). **CTV=PTV=PTV_Eval**	**Single-entry intracavitary:** **PTV_Eval:** V95% dose >95% **Skin:** Dmax <100% of prescribed dose **Ipsilateral breast:** V50% dose <60% V150% dose £50 cc V200% dose £10 cc	**Single-entry intracavitary:** **PTV_Eval:** V90% dose >90% **Skin:** Dmax <125% of prescribed dose

Abbreviations: CTV = clinical target volume; Dmax = maximum point dose to an organ or tumor target; EBRT = external beam radiation therapy; fx = fraction; HDR = high-dose-rate; IMRT = intensity modulated radiation therapy; OARs = organs at risk; PBI = partial breast irradiation; PTV = planning target volume; VMAT = volumetric modulated arc therapy.

* This table is a combination of evidence-based target volumes, dose constraints, and expert opinion. It is meant as a starting point in achieving adequate coverage of the target volumes while minimizing dose to OARs and optimizing cosmetic outcomes.

† IMRT/VMAT was the technique used on these trials.[9,12,14]

‡ Placement of tumor bed clips at the time of surgery is helpful for tumor bed delineation.

§ Feasibility of delivering PBI in the setting of oncoplastic surgery is dependent on the ability to confidently identify the tumor cavity.

‖ In the Florence trial the constraint is respected both considering ipsilateral breast and uninvolved breast (ipsilateral breast minus PTV). Per personal communication with Livia Marrazzo, MsC January 2023 (University of Florence, Florence, Italy).

3.4. KQ4: Appropriate PBI techniques with respect to toxicity and cosmesis (Table 7)

In adult patients with early-stage invasive breast cancer or DCIS receiving PBI, what are the appropriate PBI techniques with respect to toxicity and cosmesis?

Table 7 Appropriate PBI techniques with respect to toxicity and cosmesis*

KQ4 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with early-stage invasive breast cancer or DCIS eligible for PBI, once daily external beam PBI is recommended, based on fewer late toxicities, and improved cosmesis.	Strong	Moderate [9,12,14]
2. For patients with early-stage invasive breast cancer or DCIS eligible for PBI, twice daily external beam PBI is **not** recommended, based on poorer cosmetic outcomes.	Strong	Moderate [8]

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3. For patients with early-stage invasive breast cancer or DCIS eligible for PBI, multicatheter brachytherapy is recommended, based on cosmetic outcomes.	Strong	Moderate [18]
4. For patients with early-stage invasive breast cancer eligible for PBI with an intended dose of 4005 cGy in 15 fractions, PBI is recommended over WBI, due to fewer late toxicities and improved cosmesis. (Table 6)	Strong	Moderate [9]

Abbreviations: DCIS = ductal carcinoma in situ; KQ = key question; PBI = partial breast irradiation; WBI = whole breast irradiation.

* Only techniques of PBI which received a strong strength of recommendation in favor of usage in Table 4 were evaluated in Table 7.

A central hypothesis of PBI is that the reduced target volume should result in a favorable toxicity profile (both acute and late) and improved long-term cosmesis relative to WBI. However, such a broad generalization is difficult to make, as data from the RCTs demonstrate a complex interplay between PBI technical factors (modality, treatment technique, fractionation regimen, dose per fraction, and total dose) and toxicities/cosmesis.[7-10,12-15,18] In addition, the RCTs did not consistently measure the same toxicities, did not use the same scales to assess cosmesis, and/or only collected toxicity/cosmesis data on subsets of patients, which further constrains the ability to make broad generalizations. Given the diversity in how intensity modulated treatment plans with forward or inverse planned techniques have been used on the trials, with variability in beam configuration allowed, as well as limited data on the long-term potential toxicities of the integral dose delivered with these, clinical judgement on how to best personalize PBI for a patient is still warranted. Finally, the fact that WBI regimens have changed substantially over the period of time during which these trials were conducted is another limitation that impairs our ability to easily apply these results to patients in our current clinical practice.

The data are clear that external beam PBI delivered once daily on either nonconsecutive[12,14] or consecutive days[9] results in fewer acute toxicities,[12,14] late toxicities,[9,12,14] and improved cosmesis compared to WBI.[9,12] The Florence and HYPAB studies reported acute and late skin toxicities, with significantly lower rates of grade 2 to 3 acute skin toxicity and grade 1 chronic skin toxicities seen in the PBI arms in both studies.[12,14] The Florence study also demonstrated substantially higher rates (98%-100%) of “Good” or “Excellent” patient-reported and physician-reported cosmesis by the 4-point Harvard scale compared to WBI. Of note, the technique used to deliver PBI was IMRT, whereas WBI was delivered with 3-D techniques on the Florence study.[12] Acute toxicities were not reported in the IMPORT LOW trial.[9] However, this trial demonstrated clinically meaningful and statistically significantly lower rates of patient-reported changes in breast texture at 5 years in the PBI cohort compared to WBI and significantly fewer patients with changes in breast appearance as scored by patients or physicians. Data from the Danish Breast Cancer Cooperative Group trial[11] of PBI versus WBI using 4005 cGy in 15 fractions are consistent with IMPORT LOW.

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In contrast, external beam PBI delivered with twice daily fractionation does not appear to have a favorable late toxicity and/or cosmetic outcome profile based on 1 of the 2 RCTs comparing this to WBI (5000 cGy in 25 fractions). The RAPID study demonstrated lower rates of all grade 2 acute toxicities (within 3 months of completing RT) with PBI compared to WBI (28% vs 45%), with the majority of the difference due to less radiation dermatitis and breast swelling in the PBI group.[8] There were significantly higher rates of grade ≥2 late toxicities (32% vs 13%) and grade 3 toxicities (4.5% vs 1.0%) with PBI compared to WBI, largely attributable to more patients with breast induration and telangiectasias in the PBI group.[8] Consistent with the objectively worse late toxicity rates, patient-reported and nurse-reported adverse cosmetic outcomes ("Fair" or "Poor") on the 4-point European Organisation for Research and Treatment of Cancer (EORTC) cosmetic rating system was seen in patients that received PBI at 3-, 5-, and 7-years post-radiation. In contrast to RAPID, in the B39/R0413 trial, 10% of patients treated with PBI had a grade 3 toxicity compared to 7% of whose treated with WBI (5000 cGy in 25 fractions with or without a boost), and in both treatment arms <1% of patients had a grade 4-5 toxicity.[7] The B39/R0413 trial included all PBI modalities as 1 group when reporting rates of acute and late toxicities, making it difficult to tease out from the current publication whether any differences in acute and late toxicities were noted between the patients receiving different methods of PBI and WBI delivery.[7] In addition, the quality of life and cosmesis results from B39/R0413 have not been published to date. Nonetheless, the recently published IRMA trial,[16] which randomized over 3300 patients to 3850 cGy in 10 fractions twice daily PBI versus 4000 to 5040 cGy in 15 to 28 fractions WBI +/- 1000 to 1600 cGy boost found low, but increased rates of late soft tissue toxicity (2.8% vs 1%) and bone toxicity (1.1% vs 0%) with PBI as well as higher rates of adverse cosmesis by the 4-point EORTC scale at 3 years (12.7% vs 9.2%) and 5 years (14% vs 9.8%), consistent with the RAPID study.[8]

The GEC-ESTRO trial demonstrated that MIB is associated with a lower incidence of mild (grade 1-2) and moderate (grade 3) acute (within 90 days of starting RT) dermatitis but with higher rates of grade 1 to 2 hematomas, breast infections, and breast injuries compared to WBI.[18] Acute toxicities were not reported in the Budapest study.[13] Overall, no significant differences in late toxicities were seen in either of the MIB RCT trials, with the exception of higher rates of late patient-reported breast or arm symptoms with WBI using the EORTC QLQ-BR23[53] in the GEC-ESTRO trial, though this was felt to be of little clinical relevance. However, MIB had comparable or higher rates of "Good/Excellent" cosmesis compared to WBI.[10,13] There is limited data available regarding toxicities and cosmetics of single-entry catheter PBI compared to WBI.

The results of the IMPORT LOW trial drive the inclusion of recommendation #4 in Table 7, as both PBI and WBI regimens used equivalent dose-fractionations and yet PBI resulted in fewer late toxicities and improved cosmesis compared to WBI.[9] Similarly, the Danish Breast Cancer Cooperative Group RCT, published after our literature search was conducted, found significantly lower breast induration rates with PBI (5.1% vs 9.7%).[11]

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Notably absent from Table 7 is a recommendation for IORT because (1) acute toxicities were only reported on the TARGIT-A study,[43] but not the ELIOT trial,[34] with some toxicities favoring IORT (acute dermatitis), but others favoring WBI (lower rates of fat necrosis and/or seromas requiring multiple aspirations); and (2) outcome data is lacking regarding comparative late toxicities and cosmesis between IORT versus WBI and IORT plus WBI versus WBI. Cosmesis was reported for <5% of the total patient population on the TARGIT-A trial, limiting our ability to draw any conclusions, and cosmesis was not reported on the ELIOT trial.

Early applications of protons to deliver PBI were associated with worsened acute and late skin toxicities compared to photon toxicities.[54-57] Preliminary phase II results using pencil beam techniques from the Proton Collaborative Group and the Mayo Clinic showed minimal toxicities, the latter with a 3-fraction regimen.[58,59]

4. Conclusions and Future Directions

Multiple RCTs, enrolling over 10,000 patients, have demonstrated oncologic equivalence between PBI and WBI for the treatment of early-stage breast cancer. The inclusion criteria for these trials varied, as did the delivery and treatment planning parameters.

The treatment of early-stage breast cancer continues to evolve, with efforts to further de-escalate local therapy, both from a surgical and radiation standpoint. The Society of Surgical Oncology's Choosing Wisely initiative encourages surgeons to not routinely perform sentinel lymph node biopsy in patients age >70 years, with clinically node negative, hormone receptor positive and HER2 negative breast cancer.[60] The patients with invasive breast cancer that were enrolled in the RCTs of PBI were required to have axillary lymph node sampling. As more patients are seen without axillary lymph node sampling, future studies will need to address the impact of de-escalation of the surgical management of the axilla on the role of PBI and whether additional axillary evaluation is needed. With increasing data[61,62] and ongoing efforts (*NCT04852887*) to robustly define increasing cohorts of patients with breast cancer able to safely omit adjuvant RT, patient-centered informed shared decision-making will play an increasing role in the nuanced clinical care discussions of the radiotherapeutic management of early-stage breast cancer.

Patients with known *BRCA* mutations were largely excluded from the previously conducted trials of PBI due to concern regarding the increased risk of developing new cancers in other parts of the breast. As our understandings of known genetic mutations evolve and new mutations are discovered with potential increased risks of developing additional breast cancers, it is important to understand the impact of these mutations on the appropriateness of PBI.

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In patients with implant-based breast augmentation, irradiation is associated with a high risk of capsular contracture, with associated adverse cosmetic results and a potential need for revision surgery.[63,64] RT to the breast is thought to cause fibrosis of the capsule surrounding the breast augmentation. Theoretically, if a smaller volume of breast tissue can be exposed to irradiation, such as with PBI, it may be possible to minimize the risk of capsular contracture.[64] Further studies are needed to determine the best fractionation schedule and technique to minimize this risk in this setting, as it is also possible PBI may lead to asymmetric contracture with irradiation of only part of the breast.

Additional trials using new dose-fractionation regimens continue to be published. The investigators from the Florence study have moved from multiple-field IMRT to a partial volumetric modulated arc technique and from nonconsecutive days to a consecutive day schedule.[65] A report of a small subgroup of 50 patients treated with this updated technique and schedule at a median of 4.5-year follow-up showed minimal acute and late toxicities with good cosmetic outcomes.[66] A retrospective single institution study of 331 patients used the same dose as the Florence trial with many patients receiving treatment on consecutive days (68%), and most treated in the prone position (94%). Few patients experienced grade >1 toxicity and approximately 90% had good-excellent cosmetic outcomes.[67] One phase II study presented in abstract form compared 3000 cGy in 5 fractions and 2750 cGy in 5 fractions and showed worse cosmesis with 3000 cGy, both delivered once daily.[68] Although preliminary data is encouraging, longer follow-up is needed to understand how differences in target volumes and techniques impact cosmesis and toxicity to determine the settings in which consecutive, daily short course PBI can be delivered safely. The FAST Forward trial compared 1-week of WBI (2600 cGy in 5 fractions over 1 week) with 3-week WBI as a control (4005 cGy in 15 fractions over 3 weeks).[69] This showed noninferiority for local control and similar late normal tissue toxicity for 1-week of WBI at 2600 cGy in 5 fractions, but worse late normal tissue toxicity when using 2700 cGy in 5 fractions, pointing to the potentially steep dose response curve relationship as dose and fractionation are modified. It was preplanned to assess the IMPORT LOW and FAST Forward trials together given that the control group used the same dose and fractionation regimen.[9,69] As PBI reduces late normal tissue toxicity for a constant dose-fractionation per IMPORT LOW and the Danish Breast Cancer Group Trials, 2600 cGy in 5 fractions may be an appropriate dose-fractionation regimen for PBI, as reflected in the current UK and ESTRO-ACROP consensus recommendations.[70,71]

Preoperative PBI offers an opportunity to better understand the biology of radiotherapeutic effects, like that seen with delivery of neoadjuvant systemic therapy. Clinical trials are evaluating the toxicities and tumor control in this setting, largely with ultrahypofractionation (*NCT02945579*).[72]

A number of subsets of patient and tumor characteristics were relatively underrepresented in the RCT outlined, limiting our ability to fully understand the differential impact of these features for WBI versus PBI.

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Additional study in prospective trials or from publication of real-world data would be beneficial to guide clinical practice and future revisions of this guideline. We anticipate that as genomic panels are increasingly incorporated into clinical decision making that these may offer new opportunities to stratify decision making in offering PBI to patients.

The RCTs of PBI included a paucity of data on race and ethnicity of enrolled patients. Only B39/R0413 reported such data, with 7% of enrolled participants African American and 4% Hispanic.[7] Future clinical investigations of PBI should purposefully seek to enroll a diverse patient population reflective of the general population and to report on the race and ethnicity of patients treated. Similarly, PBI should not be withheld from patients who are not largely reflected in the RCTs based on race and ethnicity but for whom clinicopathologic features otherwise meet the recommendations outlined in KQ1. The task force does acknowledge the increased patient convenience of a technique such as IOERT and KV IORT, which theoretically might enable all radiotherapy to be delivered at the time of surgery.

There remain difficulties in offering PBI to patients who have undergone oncoplastic procedures, and prospective, multidisciplinary input and study of the optimal means to potentially allow for both is warranted.

A robust assessment of the comparative toxicity of PBI compared to WBI remains challenging, in large part because of the variability of dose-fractionation regimens used for both in the RCTs. As both continue to evolve, as does the feasibility of omitting adjuvant RT, additional investigation and transparency for patients is warranted.

5. Acknowledgments

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Appendix E1. Peer Reviewers and Disclosures (Comprehensive)

Appendix E2. Abbreviations

3-D CRT = 3-dimensional conformal radiation therapy
AHRQ = Agency for Health Care Research and Quality
cGy = centigray
DCIS = ductal carcinoma in situ
EBRT = external beam radiation therapy
EIC = extensive intraductal component
ER = estrogen receptor
EORTC = European Organisation for Research and Treatment of Cancer
HDR = high-dose-rate
HER2 = Human epidermal growth factor receptor 2
IBR = ipsilateral breast recurrence
IMRT = intensity modulated radiation therapy
IORT = intraoperative radiation therapy
KQ = key question
LVI = lymphovascular invasion
MIB = multicatheter interstitial brachytherapy
PBI = partial breast irradiation
PICOTS = Population, Intervention, Comparator, Outcome, Timing, Setting framework
PTV = planning target volume
RT = radiation therapy
RCT = randomized controlled trial
WBI = whole breast irradiation

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Appendix E3. Patients Treated with PBI on RCTs: KQ1 Subgroups

Study	Total pt # receiving PBI	Age <50 y (pt # / %)	Node + (pt #/%)	LVI (pt # / %)	Size >2 cm (pt # / %)	ER neg (pt # / %)	G3 (inv) (pt # / %)	HER 2 + (pt # / %)	DCIS (pt # / %)	Lobular (pt # / %)
RAPID[8]	1070	None	5 (<1%)	60 (7%)	266 (30%) >1.5 cm-did not report 2 cm	76 (9%)	133 (15%)	56 (6%)	191 (18%)	None
B39/R0413[7]	2107	811 (38%)	210 (10%)	NR	186 (9%)	397 (19%)	558 (26%)	NR	518 (25%)	101 (5%)
Florence[12]	260	41 (15%)	19 (7.3%)	19 (7.3%)	14 (5.4%)	12 (4.6%)	26 (10%)	6 (2.8%)	23 (8.8%)	21 (8.1%)
IMPORT LOW[9]	669	None	16 (2%)	35 (7%)	NR	34 (5%)	63 (9%)	34 (6%)	None	None
GEC-ESTRO[10,18]	633	91 (14%)	5 (1%)	None	67 (11%)	39 (6%)	57 (9%)	NR	36 (6%)	85 (13%)
Budapest[13]	128	Only age <40 y reported	3 (2.3%) only microscopic	3 (2.3%)	None	10 (7.8%)	None	NR	None	None
HYPAB[14]	82	NR	NR	5 (6%)	None	None	2 (6%)	NR	None	NR
Li (Spain)[15]	51	All age >60 y	None	NR	4 (7.8%)	2 (2%)	None	1 (1%)	None	None

Abbreviations: DCIS = ductal carcinoma in situ; ER neg = estrogen receptor negative; G3 (inv) = grade 3 invasive ductal; HER2 = Human epidermal growth factor receptor 2; LVI = lymphovascular invasion; node + = node positive; NR = not reported; pt = patient; RCTs = randomized controlled trials.

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