

## Practice Guideline

# 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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**Sources of support:** Guideline development was funded by ASTRO, and the systematic evidence review was funded by the Patient-Centered Outcomes Research Institute.

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Dr Coles is funded by the National Institute of Health and Care Research (NIHR) and supported by the NIHR Cambridge Biomedical Research Centre. The views expressed are those of the author and not necessarily those of the NIHR or the Department of Health and Social Care.

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Received 11 October 2023; accepted 7 November 2023

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

**Methods:** 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-dimensional conformal radiation therapy, intensity modulated radiation therapy, multicatheter brachytherapy, and single-entry brachytherapy results in similar IBR 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. Appropriate dose-fractionation regimens, target volume delineation, and treatment planning parameters for delivery of PBI are outlined. Intraoperative radiation therapy alone is associated with a higher IBR rate compared with WBI. A daily or every-other-day external beam PBI regimen is preferred over twice-daily regimens due to late toxicity 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.<sup>1,2</sup> The evidence identified from key questions (KQs) is assessed using the Population, Intervention, Comparator, Outcome, Timing, Setting (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  $\geq 75\%$  ( $\geq 90\%$  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

**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	<ul style="list-style-type: none"> <li>• Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits.</li> <li>• All or almost all informed people would make the recommended choice.</li> </ul>	Any (usually high, moderate, or expert opinion)	"Recommend/Should"
Conditional	<ul style="list-style-type: none"> <li>• Benefits are finely balanced with risks and burden or appreciable uncertainty exists about the magnitude of benefits and risks.</li> <li>• Most informed people would choose the recommended course of action, but a substantial number would not.</li> <li>• A shared decision-making approach regarding patient values and preferences is particularly important.</li> </ul>	Any (usually moderate, low, or expert opinion)	"Conditionally Recommend"
Overall QoE Grade	Type/Quality of Study	Evidence Interpretation	
High	<ul style="list-style-type: none"> <li>• 2 or more well-conducted and highly generalizable RCTs or meta-analyses of such trials.</li> </ul>	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.	
Moderate	<ul style="list-style-type: none"> <li>• 1 well-conducted and highly generalizable RCT or a meta-analysis of such trials <b>OR</b></li> <li>• 2 or more RCTs with some weaknesses of procedure or generalizability <b>OR</b></li> <li>• 2 or more strong observational studies with consistent findings.</li> </ul>	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	<ul style="list-style-type: none"> <li>• 1 RCT with some weaknesses of procedure or generalizability <b>OR</b></li> <li>• 1 or more RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes <b>OR</b></li> <li>• 2 or more observational studies with inconsistent findings, small sample sizes, or other problems that potentially confound interpretation of data.</li> </ul>	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*	<ul style="list-style-type: none"> <li>• Consensus of the panel based on clinical judgment and experience, due to absence of evidence or limitations in evidence.</li> </ul>	Strong consensus ( $\geq 90\%$ ) 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.	
<p><i>Abbreviations:</i> ASTRO = American Society for Radiation Oncology; QoE = quality of evidence; RCTs = randomized controlled trials.</p> <p>*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.</p> <p>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.</p>			

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.

## 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.<sup>3</sup> 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<sup>4,5</sup> to reflect recent developments in the management of patients with early-stage invasive breast cancer and ductal carcinoma in situ (DCIS). 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 alone to whole breast irradiation (WBI) with clinically comparable oncologic ipsilateral breast recurrence (IBR)<sup>6</sup> 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.<sup>7</sup> 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,<sup>8</sup> 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,<sup>9</sup> the Groupe Européen de Curiethérapie (GEC) and the European Society for Radiotherapy and Oncology (ESTRO) multicatheter interstitial brachytherapy (MIB) RCT trial at 10 years (n = 1184 patients),<sup>10</sup> and the Danish Breast Cancer Group RCT (n = 865 patients) with a median follow-up of 7.6 years.<sup>11</sup> Comparable IBR rates were also reported at 10 years on the Florence intensity modulated radiation therapy (IMRT) RCT (n = 520 patients),<sup>12</sup> at 20 years on the Budapest RCT (n = 258 patients),<sup>13</sup> at 3 years on the Hypofractionated Whole Breast Irradiation versus Accelerated Partial Breast Irradiation (HYPAB) RCT (n = 172 patients),<sup>14</sup> and at 10 years on a Spanish RCT (n = 102 patients).<sup>15</sup> A substantive volume of data on toxicities of PBI compared with WBI has also been published from these and other RCTs.<sup>16</sup>

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 the delivery of PBI without WBI.

## Methods

### Task force composition

The task force consisted of a multidisciplinary team of academic and community-based 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.

### 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 31 to July 2023. The final guideline was approved by the ASTRO Board of Directors and endorsed by the Canadian Association of Radiation Oncology, European Society for Radiotherapy and Oncology, Royal Australian and New Zealand College of Radiologists, and the Society of Surgical Oncology.

### 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.<sup>17</sup> This independent literature review and analysis prepared by the Mayo Clinic Evidence-Based Practice Center aimed to support a replacement of the prior ASTRO 2009 APBI consensus statement and 2016 focused update which included the use of intraoperative radiation therapy (IORT).<sup>4,5</sup> AHRQ performed a systematic search of the databases Embase<sup>®</sup> Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE<sup>®</sup> Daily, MEDLINE<sup>®</sup>, Cochrane Central Register of Controlled Trials, Ovid<sup>®</sup> Cochrane Database of Systematic Reviews, and Scopus<sup>®</sup> 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.<sup>17</sup>

For KQ1, the AHRQ review specified that only RCTs would be necessary to include because high-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 these factors. After reviewing the articles, the data were 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.<sup>10,11</sup> While not used to support recommendations, 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, acute and late toxicities, and cosmesis.

**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 invasive breast cancer +/- DCIS 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 [electron or photon]) as sole RT treatment

**Table 2 KQs in PICO format**

KQ	Population	Intervention	Comparator	Outcomes
1.	<b>In adult patients with early-stage invasive breast cancer or DCIS, what are the appropriate indications for PBI as an alternative to WBI?</b> Adult patients with early-stage invasive breast cancer or DCIS	• PBI	• WBI +/- boost	• IBR
2.	<b>In adult patients with early-stage invasive breast cancer or DCIS receiving PBI, what are the appropriate PBI techniques with respect to IBR outcomes?</b> Same as KQ1	<u>PBI techniques</u> • 3-D CRT • MIB • IMRT • IOERT • kV IORT • Single-entry catheter brachytherapy • Protons	• WBI +/- boost	• IBR
3.	<b>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?</b> Same as KQ1	<u>Timing</u> • Daily • Twice daily • Every other day <u>Dose-fractionation</u> • Moderate hypofractionation* • Ultrahypofractionation† <u>Target volumes</u> • Target definitions (Tumor bed/CTV/PTV) • OARs <u>Dose constraints</u>	<u>WBI</u> • Standard fractionation • Moderate hypofractionation	• IBR • Patient-reported and physician-assessed cosmesis • Adverse events

(Continued)

Table 2 (Continued)

KQ	Population	Intervention	Comparator	Outcomes
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	<u>PBI techniques</u> <ul style="list-style-type: none"> <li>• 3-D CRT</li> <li>• MIB</li> <li>• IMRT</li> <li>• IOERT</li> <li>• kV IORT</li> <li>• Single-entry catheter brachytherapy</li> <li>• Protons</li> </ul> <u>Timing</u> <ul style="list-style-type: none"> <li>• Daily</li> <li>• Twice daily</li> <li>• Every other day</li> </ul> <u>Dose-fractionation</u> <ul style="list-style-type: none"> <li>• Hypofractionation*</li> <li>• Ultrahypofractionation<sup>†</sup></li> </ul>	<u>WBI</u> <ul style="list-style-type: none"> <li>• Standard fractionation</li> <li>• Hypofractionation</li> </ul>	<ul style="list-style-type: none"> <li>• Patient-reported and physician-assessed cosmesis</li> <li>• Adverse events</li> </ul>
<p><i>Abbreviations:</i> 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.</p> <p>Moderate hypofractionation is defined as &gt;200 cGy up to 499 cGy per fraction.</p> <p>Ultrahypofractionation is defined as ≥500 cGy per fraction.</p>				

of their breast cancer. The AHRQ inclusion criteria required studies to involve adult women (age ≥18 years) with early-stage invasive breast cancer or ductal carcinoma in situ (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, the role of PBI followed by WBI, and oncoplastic surgery.

## Key Questions and Recommendations

### 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?**

Multiple RCTs evaluating the efficacy of PBI alone compared with WBI have demonstrated comparable IBR

and long-term overall survival.<sup>7-13,15,16,18</sup> Recommendations for the use of PBI require consideration of both patient and tumor characteristics as shown in Fig. 1. With increased prevalence of treatment de-escalation, ensuring comparable IBR rates compared with 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, grade 1 to 2, small tumor size, and no lymph node involvement).<sup>4,5,19-22</sup> 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, DCIS, invasive lobular carcinoma, larger tumor size, 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.<sup>5</sup> Evaluation of these subgroups was restricted to the patients enrolled in the RCTs using PBI techniques that are recommended in KQ2.<sup>7-9,12,13,15,18,23-26</sup> The KQ also highlights the importance of future investigation to develop more robust evidence to inform treatment recommendations.

**Table 3** Indications for PBI as an alternative to WBI

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
<b>Early-stage invasive breast cancer*</b>		
<p>1. PBI is recommended for patients with early-stage invasive breast cancer with all of the following factors:</p> <ul style="list-style-type: none"> <li>• Grade 1-2 disease</li> <li>• ER-positive histology</li> <li>• Age <math>\geq</math>40 years</li> <li>• Tumor size <math>\leq</math>2 cm</li> </ul>	Strong	<p>High (for grade, histology, &amp; age <math>\geq</math>50 years)</p> <p>Moderate (for age 40-49 years &amp; size) 7-9,12-15,18</p>
<p>2. PBI is conditionally recommended for patients with early-stage invasive breast cancer with the following factors:</p> <ul style="list-style-type: none"> <li>• Grade 3 disease or</li> <li>• ER-negative histology or</li> <li>• Size <math>&gt;2 - \leq</math>3 cm</li> </ul> <p><u>Implementation remark:</u> PBI may not be appropriate when multiple of these factors are present, given the possibility of a higher recurrence risk.</p>	Conditional	<p>Low 7-9,12-15,18</p>
<p>3. PBI is conditionally <b>not</b> recommended for patients with early-stage invasive breast cancer with any of the following factors:</p> <ul style="list-style-type: none"> <li>• HER2-positive tumors not receiving anti-HER2 therapy</li> <li>• Lymphovascular invasion</li> <li>• Lobular histology</li> </ul> <p><u>Implementation remark:</u> Given low patient numbers accrued to RCTs, higher risk of recurrence with PBI is possible.</p>	Conditional	Expert Opinion
<p>4. PBI is <b>not</b> recommended for patients with early-stage invasive breast cancer with any of the following factors:</p> <ul style="list-style-type: none"> <li>• Positive lymph nodes</li> <li>• Positive surgical margins</li> <li>• Known germline BRCA1/2 mutation</li> <li>• Age <math>&lt;</math>40 years</li> </ul>	Strong	Expert Opinion
<b>DCIS</b>		
<p>5. PBI is recommended for patients with DCIS with all of the following factors:</p> <ul style="list-style-type: none"> <li>• Low-to-intermediate grade</li> <li>• Age <math>\geq</math>40 years</li> <li>• Size <math>\leq</math>2 cm</li> </ul> <p><u>Implementation remark:</u> While represented in the RCTs, there was a lack of subgroup analyses for pathologic and clinical features of patients treated with DCIS.</p>	Strong	Expert Opinion
<p>6. PBI is conditionally recommended for patients with DCIS with the following factors:</p> <ul style="list-style-type: none"> <li>• High grade or</li> <li>• Size <math>&gt;2 - \leq</math>3 cm</li> </ul> <p><u>Implementation remark:</u> PBI may not be appropriate when both of these factors are present, given the possibility of a higher recurrence risk.</p>	Conditional	Expert Opinion
<p>7. PBI is <b>not</b> recommended for patients with DCIS with any of the following factors:</p> <ul style="list-style-type: none"> <li>• Positive surgical margins</li> <li>• Known germline BRCA1/2 mutation</li> <li>• Age <math>&lt;</math>40 years</li> </ul>	Strong	Expert Opinion
<p><i>Abbreviations:</i> 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.            Early-stage invasive breast cancer is defined as an invasive lesion <math>\leq</math>3 cm with 0-3 positive lymph nodes.</p>		

There has been reluctance to treat with PBI in patients age <50 years due to concern over increased IBR risks.<sup>5,27</sup> 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, although the forest plot in B39/R0413 neared significance favoring WBI.<sup>7,8,10</sup> Together, these trials included approximately 950 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.

Although the RCTs limited the size of the breast lesion for both invasive and noninvasive components to  $\leq 3$  cm, most patients enrolled in the RCTs had tumors  $\leq 2$  cm.<sup>7-10,12,13,15</sup> The RAPID<sup>8</sup> and B39/R0413<sup>7</sup> trials enrolled over 450 patients with larger tumors and reported outcomes based on tumor size, albeit using different cut points (1.5 cm and 2 cm, 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.<sup>8</sup> B39/R0413 performed an exploratory post-hoc analysis in the intention to treat population to determine if there were differences in treatment effects amongst the different patient subgroups. Review of the forest plot suggests that for patients with smaller lesions ( $\leq 1$  cm) and for patients with larger lesions (2.1-3 cm), there is no difference in recurrence rates between WBI and PBI, although the latter group were smaller in number and had a higher rate of recurrence in both arms of the study than patients with tumors  $\leq 1$  cm. Additionally, for patients with tumors >1 to 2 cm in size, there was a lower risk of recurrence with WBI compared with PBI. Overall, while increasing tumor size is an independent prognostic factor for higher risk of recurrence, the available data do not suggest a difference in recurrence risk when patients are treated with WBI versus PBI.<sup>7</sup>

Patients with grade 3 invasive disease were generally under-represented in the RCTs comparing PBI to WBI, comprising <10% of patients on these RCTs in total.<sup>7-10,12,13,15,18</sup> 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.<sup>8</sup> Grade was not studied in subset analysis in B39/R0413, but more than one-quarter of patients on the trial had grade 3 invasive disease.<sup>7</sup> 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.<sup>7-10,12,18</sup> 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.<sup>7-9,12-15,18</sup> 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<sup>28</sup> and there is uncertainty regarding whether WBI improves outcomes over PBI in patients with a single higher risk factor. Patients with ER-negative breast cancer represented a minority of patients treated on the RCTs, with B39/R0413 enrolling the largest percentage of patients with ER-negative breast cancer (approximately 20%).<sup>7</sup> For the remaining RCTs, ER-negative cancers represented <10% of patients enrolled, and in total 570 patients with ER-negative breast cancer received PBI on the RCTs examined.<sup>7-10,12-15,18</sup> Although there is no indication that patients receiving PBI had higher IBR compared with WBI, given the low representation of patients with this tumor characteristic, a conditional recommendation was deemed appropriate. HER2-positive receptor status further increases the complexity of PBI decision-making for patients with early-stage invasive 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.<sup>8,9,12,15</sup> 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 invasive breast cancer receiving modern anti-HER2-targeted therapy has shown excellent long-term results in terms of locoregional recurrence and overall survival.<sup>29,30</sup> 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.<sup>31</sup>

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.<sup>32</sup>

Most of the RCTs specifically excluded patients with lobular histology.<sup>8,9,13-15</sup> For the trials that did include patients with lobular histology, the population treated with PBI represented <5% of patients enrolled.<sup>7,12,18</sup> In



addition to the low representation on the RCTs, lobular histology is more likely to be multifocal or multicentric when compared with invasive ductal histology, making the appropriateness of PBI in this setting poorly defined.<sup>33,34</sup> Similarly, all but 2 of the aforementioned RCTs evaluated excluded patients with multifocal disease,<sup>7,8</sup> with no subset analysis presented, and all excluded multicentric cancers.

For patients with positive axillary lymph nodes, there are insufficient data to recommend PBI due to the limited sample size for this subgroup. Three RCTs<sup>7,9,12</sup> included patients with macroscopic lymph node involvement, and 3 RCTs<sup>8,13,18</sup> included patients with microscopic ( $\leq 2.0$  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.<sup>35,36</sup> Based on this, PBI is not recommended for patients with nodal disease.

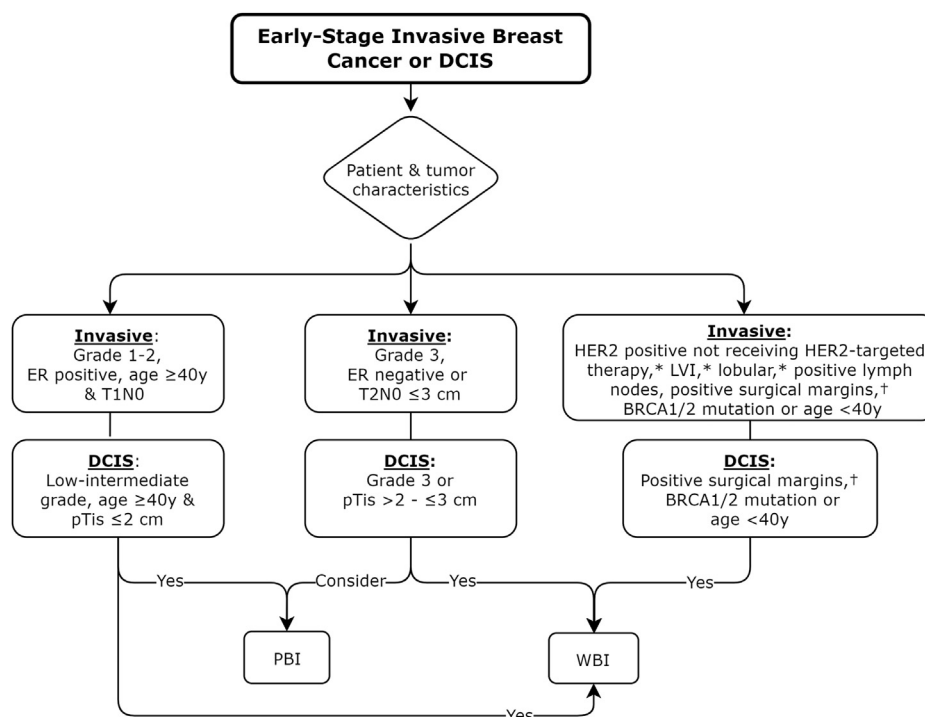
Surgical margin positivity represented an exclusion criterion for most of the RCTs examined, with the only exception being PBI trials of IORT.<sup>7-9,12,18</sup> Despite the allowance for positive margins,  $<1\%$  ( $n = 3$ ) of patients enrolled on the Intraoperative Irradiation for Early Breast Cancer (ELIOT) trial and 6% of patients enrolled on the Targeted Intraoperative Radiotherapy Versus Whole Breast Radiotherapy for Breast Cancer (TARGIT-A) trial (all of whom received WBI in addition to IORT) had positive margins.<sup>37,38</sup> The definition of negative margin also varied amongst the RCTs, with 2 trials defining this as no tumor on ink,<sup>7,8</sup> 1 as 2 mm microscopic margins,<sup>9</sup> 2 as 5 mm microscopic margins,<sup>12,14</sup> and 1 as 1 cm macroscopic margins.<sup>13</sup> 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.<sup>10,18</sup> Although there are an absence of RCT data specifically related to PBI and margin status, 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.<sup>39</sup> 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.<sup>40</sup>

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

Patients with 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 ( $n = 518$ ).<sup>7,8,10,12,18</sup> 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, leading to a summation of the quality of evidence as being based on expert opinion. 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,<sup>7,8</sup> although it should be noted that in B39/R0413 the IBR rates for DCIS were higher than for invasive disease for both PBI and WBI. 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.<sup>41,42</sup> Conversely, due to concern over the higher risk of IBR for high-grade and larger ( $>2$  cm) volume DCIS independent of RT approach, without RCT data on this subset, high-grade DCIS was evaluated as conditional based on expert opinion. The presence of an extensive intraductal component (EIC) had been included in the cautionary subgroup of previously published ASTRO guidelines.<sup>4,5</sup> Three of the RCTs<sup>12-14</sup> specifically excluded patients with EIC, while the other trials<sup>7-9,18</sup> 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 are insufficient data to make any statements regarding EIC.

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,<sup>7,8,10</sup> with only the Florence trial reporting a multivariable analysis for risk factors for IBR.<sup>12</sup> 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 locoregional and systemic recurrences and improving overall survival. A higher locoregional 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 adherence of completion of 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.



**Figure 1** Adjuvant radiation therapy treatment options for early-stage invasive breast cancer or DCIS.

*Abbreviations:* DCIS = ductal carcinoma in situ; ER = estrogen receptor; HER2 = Human epidermal growth factor receptor 2; LVI = lymphovascular invasion; PBI = partial breast irradiation; RCTs = randomized controlled trials; WBI = whole breast irradiation.

\*The characteristics HER2-positive not receiving HER2-targeted therapy, lobular, and LVI are *conditionally not* recommended, and the remaining characteristics in this box are *not* recommended, both due to low patient numbers accrued to RCTs. Higher risk of recurrence is possible with PBI, although this may be an option in limited situations.

†Re-excision to negative margins is preferred.<sup>43</sup>

## 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?**

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.<sup>7-9,11-14,18,37,38</sup> Notably, this prespecified KQ focuses on PBI techniques with regards to IBR outcomes alone and not on overall survival nor disease-free survival outcomes.

MIB was the first PBI technique to be compared with WBI in an RCT. Two such trials have been conducted, 1 with 20 years of follow-up<sup>13</sup> and the other with 10 years of follow-up,<sup>10,18</sup> 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.<sup>47</sup> None of these single-entry applicators have been exclusively compared with WBI in an RCT. Although 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.<sup>7</sup> 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%<sup>24</sup> and a smaller, multi-institutional registry study found a 4-year IBR rate of 3.6%.<sup>48</sup>

The majority of 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 twice daily) 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.<sup>7</sup> The RAPID trial treated PBI patients with 3-D CRT (3850 cGy in 10 fractions twice daily) and demonstrated a noninferior IBR rate of PBI versus WBI at 8 years of 3% versus 2.8%.<sup>8</sup> 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%.<sup>9,15</sup> Only 2 trials directly compared IMRT to 3-D

**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
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 7,23-26
5. For patients with early-stage invasive breast cancer receiving PBI, electron IORT is <b>not</b> recommended, unless part of a clinical trial or multi-institutional registry.  <u>Implementation remark:</u> For patients considered for electron IORT, the characteristics in KQ1 do not apply.	Strong	Moderate 37
6. For patients with early-stage invasive breast cancer receiving PBI, kV IORT alone (without WBI) is <b>not</b> recommended, unless part of a clinical trial or multi-institutional registry.  <u>Implementation remarks:</u> <ul style="list-style-type: none"> <li>• For patients considered for kV IORT, the characteristics in KQ1 do not apply.</li> <li>• WBI following kV IORT may be needed for patients with higher risk features.</li> </ul>	Strong	Low 38,44-46
<i>Abbreviations:</i> 3-D CRT = 3-dimensional conformal radiation therapy; DCIS = ductal carcinoma in situ; IBR = ipsilateral breast recurrence; IMRT = intensity modulated radiation therapy; IORT = intraoperative radiation therapy; KQ = key question; kV = kilovoltage; PBI = partial breast irradiation; WBI = whole breast irradiation.		

CRT PBI, both with primary endpoints of toxicities.<sup>49,50</sup> The Florence trial randomized patients to conventionally fractionated WBI + boost compared with 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 with 2.5% with WBI + boost.<sup>12</sup> 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, with some but not all WBI arms including a tumor bed boost.<sup>7-9,12,14,15,49</sup>

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 absolute 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. The 2 primary modalities of delivering IORT include electron IORT (IOERT) and photon (kV) IORT, which have distinct technical and physical properties. 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 + boost (5000 cGy in 25 fractions followed by a 1000 cGy in 5 fraction boost), IOERT

(2100 cGy in 1 fraction) as delivered in the ELIOT trial was found to have inferior IBR rates through 15 years of follow-up in 1305 patients (12.6% vs 2.4%), with comparable overall survival.<sup>37</sup> In an unplanned subset analysis, the authors defined a group of 141 women (75 in the ELIOT group and 66 in the WBI group) at a very low risk of IBR defined as <10%. This group consisted of patients with 4 concomitant characteristics (tumor size <1 cm, grade 1, luminal A molecular subtype and Ki-67 <14%). The 15-year IBR was 8.1% versus 3.1% in the ELIOT and WBI groups, respectively.<sup>37</sup>

Low-energy photon IORT (kV IORT) outcomes are more challenging to interpret, given that the trial design included a risk-adapted approach, which allowed adjuvant WBI following IORT for patients with features determined high risk at the time of pathologic assessment. The core protocol defined 3 such features, which included margin width <1 mm, EIC, and unintended lobular histology. Individual centers were allowed to prespecify additional factors allowing WBI following kV IORT.<sup>46</sup> The TARGIT-A trial randomized 2298 patients to receive WBI versus kV IORT, which could be given immediately following lumpectomy intraoperatively (“prepathology” cohort) or as a second procedure following pathology review (“postpathology” cohort).<sup>46</sup> The primary outcome of the TARGIT-A trial was absolute difference in local recurrence in all breast-conserved patients following kV IORT (2000 cGy in 1 fraction that attenuates to 500-700 cGy at 1 cm) versus WBI (termed “conventional radiation therapy”), with a noninferiority margin of 2.5%. As a part of an analysis of the primary endpoint, the 5-year IBR was

noninferior, 3.3% for TARGIT IORT versus 1.3% for WBI ( $P = .042$ ), with a median follow-up of 29 months. Interpretation of these data is challenging given that 15.2% of those patients who received TARGIT (21.6% of the “prepathology” cohort and 3.6% of the “postpathology” cohort) also received WBI. IBR outcomes appeared more favorable in the prepathology cohort (2.1% vs 1.1%) than the postpathology cohort (5.4% vs 1.7%).<sup>46</sup> Importantly, for patients receiving kV IORT at the time of initial lumpectomy, over 20% required the addition of WBI based on pathologic risk factors that varied by treatment center, making it difficult to determine which patients have optimal IBR outcomes with kV IORT intraoperatively alone. Similarly, the AHRQ analysis suggested “that caution is still warranted” for this technique.<sup>17</sup> The UK National Institute for Health and Care Excellence conducted a detailed analysis of the TARGIT-A trial, which re-analyzed its data using Kaplan-Meier statistics and concluded that the criterion for noninferiority was not met.<sup>51</sup> After the UK publication and an additional publication performing Kaplan-Meier analysis of the TARGIT-A trial also found that it did not meet noninferiority for IBR,<sup>52</sup> the TARGIT-A investigators then published a Kaplan-Meier analysis demonstrating comparable local recurrence-free survival for both treatment arms, although again this did not remove those patients who received WBI in addition to kV IORT.<sup>53</sup> It should be noted that the prespecified criteria for noninferiority was absolute difference in local recurrence for the entire cohort, not local recurrence-free survival, calling into question whether the predetermined endpoint was met. It is outside the purview of this guideline to provide a more in-depth statistical analysis of the TARGIT-A data given some of the aforementioned complexities. Given that the focus of this guideline is to inform about PBI techniques that can serve as an alternative to WBI and the accepted need to add WBI in addition to kV IORT, IORT alone is not recommended as treatment for early-stage invasive breast cancer or DCIS.

Given the increased patient convenience of receipt of IORT and the possibility of patient-informed preference

for IOERT or kV IORT even in the setting of a potential for higher risk of IBR, as well as a need for robust data, both forms of IORT may be reasonable to perform on a prospective clinical trial or multi-institutional registry. Notably, the patient selection criteria included in KQ1 did not include patients treated with either IOERT or kV IORT, with most individual subsets either having worse outcomes with IOERT or a lack of clarity on outcomes with kV IORT, and appropriate patient selection for these techniques remain to be further defined.<sup>37</sup>

### 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.

The recommended dose-fractionation regimens for delivering PBI via EBRT are based on the Florence, HYPAB, and IMPORT LOW studies.<sup>9,12,14</sup> The Florence and HYPAB RCTs demonstrated safety of PBI using 3000 cGy in 5 fractions on nonconsecutive days with multiple-field IMRT compared with WBI, with comparable local recurrence rates. For the WBI treatment arms, the Florence trial used conventional fractionation with a sequential boost (5000 cGy in 25 fractions followed by 1000 cGy in 5 fractions) 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).<sup>12,14</sup> IMPORT LOW tested 4005 cGy in 15 fractions over 3 weeks PBI using mini tangents compared

**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.	Strong	Moderate 7,18
<u>Implementation remark:</u> Single-entry PBI trials used 3400 cGy in 10 fractions delivered twice daily.		
<i>Abbreviations:</i> DCIS = ductal carcinoma in situ; HDR = high-dose-rate; KQ = key question; PBI = partial breast irradiation; PDR = pulsed-dose-rate.		

**Table 6 PBI target volumes and planning parameters\***

Dose-Fractionation Regimens	Target Volumes	Planning Parameters	Planning Parameters
<p><b>EBRT</b></p> <p>3000 cGy/5 fx in 2 weeks<sup>†,12,14</sup></p> <p>OR</p> <p>4005 cGy/15 fx over 3 weeks<sup>9</sup></p>	<p><b>Tumor bed:</b> volume is drawn around the clips<sup>‡</sup> and any change in the surrounding tissue architecture.<sup>§</sup></p> <p>Target volume expansions should take into consideration both margin status and imaging strategy.</p> <p><b>CTV:</b> 1-1.5 cm expansion from the tumor bed cropped 3-5 mm inside patient surface and limited posteriorly by the pectoralis muscle. For patients with closer margins, a 1.5 cm expansion should be considered.</p> <p><b>PTV:</b> 1 cm margin around CTV. For patients undergoing daily imaging, tighter margins may be considered depending on accuracy of patient set-up.</p> <p><b>PTV_EVAL:</b> PTV cropped 3-5 mm inside patient surface and limited posteriorly by the pectoralis muscle.</p> <p>Daily imaging is advised when using 5 fx to deliver PBI and when using PTV margins &lt;1 cm.</p>	<p><b>Ideal:</b></p> <p><b>PTV_Eval:</b></p> <p>V95% dose ≥95%</p> <p>V105% dose ≤5%</p> <p>Dmax ≤110% of prescribed dose</p> <p><b>Ipsilateral breast:</b><sup>  </sup></p> <p>V95% dose ≤25%</p> <p>V50% dose ≤50%</p> <p><b>Ipsilateral lung:</b></p> <p>V30% dose ≤10%</p> <p><b>Contralateral lung:</b></p> <p>V10% dose ≤5%</p> <p><b>Contralateral breast:</b></p> <p>Dmax ≤3%</p> <p><b>Heart:</b></p> <p><b>Right sided tumor</b></p> <p>V5% dose ≤5%</p> <p>Mean dose &lt;0.7 Gy</p> <p><b>Left sided tumor</b></p> <p>V15% dose ≤5%</p> <p>Mean dose &lt;1.5 Gy</p> <p><b>Thyroid:</b></p> <p>Dmax ≤3%</p> <p><b>Body outside PTV:</b></p> <p>V107% ≤2 cc</p> <p>Dmax ≤110% of prescribed dose</p>	<p><b>Variation acceptable:</b></p> <p><b>PTV_Eval:</b></p> <p>V95% dose ≥90%</p> <p>V105% dose ≤7%</p> <p><b>Ipsilateral breast:</b></p> <p>V95% dose ≤40%</p> <p>V50% dose ≤60%</p> <p><b>Ipsilateral lung:</b></p> <p>V30% dose ≤15%</p> <p><b>Contralateral lung:</b></p> <p>V5% dose ≤15%</p> <p><b>Contralateral breast:</b></p> <p>Dmax ≤5%</p> <p><b>Heart:</b></p> <p><b>Right sided tumor</b></p> <p>V5% dose ≤10%</p> <p>Mean dose &lt;1 Gy</p> <p><b>Left sided tumor</b></p> <p>V15% dose ≤10%</p> <p>Mean dose &lt;2 Gy</p> <p><b>Thyroid:</b></p> <p>Dmax ≤5%</p> <p><b>Body outside PTV:</b></p> <p>V110% ≤2 cc</p> <p>Dmax ≤112% of prescribed dose</p>
<p><b>HDR brachytherapy</b></p> <p><b>Multicatheter interstitial brachytherapy:</b></p> <p>3200 cGy in 8 fx or 3010 cGy in 7 fx,<sup>10</sup> or 3400 cGy in 10 fx; all twice daily<sup>7</sup></p> <p>Pulsed-dose-rate brachytherapy: total dose of 5000 cGy with pulses of 160-180 cGy/hour<sup>10</sup></p>	<p><b>Multicatheter interstitial brachytherapy volumes:</b></p> <p><b>Tumor bed:</b> volume is drawn around the clips and any change in the surrounding tissue architecture.</p> <p><b>Interstitial CTV:</b> if individual surgical margin data are 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 &lt;1 cm.</p> <p>All expansions from cavity to CTV limited to 5 mm from skin surface and by the posterior breast tissue extent (pectoralis muscle is excluded).</p> <p><b>CTV=PTV=PTV_Eval</b></p>	<p><b>Ideal:</b></p> <p><b>Interstitial:</b></p> <p>Optimize to keep the dose uniformity ratio (1-V150/V100) ≥0.75</p> <p><b>PTV_Eval:</b> V100% dose ≥90%</p> <p><b>Skin:</b></p> <p>Dmax &lt;70% of prescribed dose</p> <p><b>Ipsilateral breast:</b></p> <p>V150% dose &lt;70 cc</p> <p>V200% dose &lt;20 cc</p>	<p><b>Variation acceptable:</b></p> <p><b>Interstitial:</b> Optimize to keep the dose uniformity ratio (1-V150/V100) ≥0.65</p> <p><b>PTV_Eval:</b> V90% dose ≥90%</p> <p><b>Skin:</b></p> <p>Dmax &lt;100% of prescribed dose</p>

(Continued)

Table 6 (Continued)

Dose-Fractionation Regimens	Target Volumes	Planning Parameters	
<b>Single-entry intracavity brachytherapy:</b> 3400 cGy in 10 fx twice daily <sup>7</sup>	<b>Single-entry intracavity brachytherapy volumes:</b> <b>Single-entry CTV:</b> 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). <b>CTV=PTV=PTV_Eval</b>	<b>Single-entry intracavity:</b> <b>PTV_Eval:</b> V95% dose >95% <b>Skin:</b> Dmax <100% of prescribed dose <b>Ipsilateral breast:</b> V50% dose <60% V150% dose ≤50 cc V200% dose ≤10 cc	<b>Single-entry intracavity:</b> <b>PTV_Eval:</b> V90% dose >90% <b>Skin:</b> Dmax <125% of prescribed dose
<p><i>Abbreviations:</i> 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.</p> <p><sup>7</sup>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. These are restricted to techniques outlined as appropriate in KQ2.</p> <p><sup>†</sup>IMRT/VMAT was the technique used on these trials.<sup>9,12,14</sup></p> <p><sup>‡</sup>Placement of tumor bed clips at the time of surgery is helpful for tumor bed delineation.</p> <p><sup>§</sup>Feasibility of delivering PBI in the setting of oncoplastic surgery is dependent on the ability to confidently identify the tumor cavity.</p> <p><sup>  </sup>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).</p>			

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).<sup>9</sup> PBI demonstrated noninferior local control and similar or reduced late normal tissue toxicity. The Danish Breast Cancer Group<sup>11</sup> 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 other factors, including dose and fractionation, were constant between the WBI and PBI arms.<sup>9,11</sup> Although the task force acknowledges that the above cited PBI fractionation regimens (RAPID and B39/R0413) demonstrate comparable local control compared with WBI, concerns over toxicity with the twice-daily regimens as discussed in KQ4 and patient convenience were considered in forming these recommendations.

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.<sup>54</sup> 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.<sup>55</sup> 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%).<sup>56</sup> Few patients experienced grade >1 toxicity and approximately 90% had good to excellent cosmetic outcomes as reported by both patients and physicians.<sup>56</sup> 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.<sup>57</sup> Although preliminary data are 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).<sup>58</sup> 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.<sup>9,58</sup> As PBI can reduce late normal tissue toxicity for a constant dose-fractionation per IMPORT LOW and the Danish Breast Cancer Group Trials, 2600 cGy in 5 fractions is considered an appropriate dose-fractionation regimen for PBI in some countries and is part of the UK National Institute of Health and Care Excellence guidance.<sup>59</sup> The ESTRO-ACROP consensus recommendations

consensus states that 2600 cGy in 5 fractions may be used for WBI or PBI either as standard of care or within an RCT where there is equipoise or within a prospective cohort. It is currently being investigated in prospective trials (*NCT05417516* and *NCT03077841*).<sup>60,61</sup> Additional investigation is ongoing regarding very short courses of PBI delivered via multicatheter brachytherapy.<sup>62-64</sup>

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.<sup>7,18</sup> 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.<sup>18</sup> 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.<sup>7</sup> 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.<sup>10</sup> The B39/R0413 trial has not yet reported outcomes of the brachytherapy subgroup.<sup>7</sup>

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,<sup>7</sup> 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.<sup>65,66</sup> The GEC-ESTRO trial incorporated surgical margin information for target definition.<sup>18</sup> 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).<sup>18</sup> This compares with B39/R0413’s uniform margins of 1.5 cm for interstitial and 1.0 cm for single-entry brachytherapy.<sup>7</sup> As detailed margin information may not be universally available, the margins used in the B39/R0413 trial are included as an alternative.<sup>7</sup>

#### 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?**

Toxicity and cosmesis analysis were limited to PBI techniques as recommended in KQ2 only.

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.<sup>7-10,12-15,18</sup> In addition, the RCTs did not consistently measure the same toxicities, did not use the same scales to assess 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 <sup>9,12,14</sup>
2. For patients with early-stage invasive breast cancer or DCIS eligible for PBI, twice daily external beam PBI to a dose of 3850 cGy in 10 fractions is <b>not</b> recommended, based on poorer cosmetic outcomes.	Strong	Moderate <sup>8</sup>
3. For patients with early-stage invasive breast cancer or DCIS eligible for PBI, multicatheter brachytherapy is recommended, based on cosmetic outcomes.	Strong	Moderate <sup>67</sup>
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. ( <a href="#">Table 6</a> )	Strong	Moderate <sup>9</sup>

*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](#).

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.

External beam PBI delivered once daily on either nonconsecutive days compared with conventionally fractionated WBI + boost<sup>12,14</sup> or consecutive days compared with hypofractionated WBI alone<sup>9</sup> results in fewer acute toxicities,<sup>12,14</sup> late toxicities,<sup>9,12,14</sup> and improved cosmesis.<sup>9,12</sup> 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, which were reported as a part of secondary and primary analysis, respectively.<sup>12,14</sup> 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 with WBI. Of note, the technique used to deliver PBI was IMRT, whereas WBI was delivered with 3-D techniques on the Florence study.<sup>12</sup> Acute toxicities were not reported in the IMPORT LOW trial.<sup>9</sup> This trial demonstrated clinically meaningful and statistically significantly lower rates of patient-reported changes in breast appearance and breast texture at 5 years in the PBI cohort compared with WBI in a preplanned secondary analysis. Data from the Danish Breast Cancer Cooperative Group trial<sup>11</sup> of PBI versus WBI using 4005 cGy in 15 fractions, for which the primary endpoint was induration, are consistent with IMPORT LOW.

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 with WBI (28% vs 45%), with the majority of the difference due to less radiation dermatitis and breast swelling in the PBI group.<sup>8</sup> There were significantly higher rates of grade  $\geq 2$  late toxicities (32% vs 13%) and grade 3 toxicities (4.5% vs 1.0%) with PBI compared with WBI, largely attributable to more patients with breast induration and telangiectasias in the PBI group.<sup>8</sup> 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 postradiation. In contrast to RAPID, in the B39/R0413 trial, 10% of patients treated with PBI had a grade 3 toxicity compared with 7% of those 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.<sup>7</sup> 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.<sup>7</sup> In addition, the quality of life and cosmesis results from B39/R0413 have not been published to date. Nonetheless, the recently published IRMA trial,<sup>16</sup> 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.<sup>8</sup>

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 with WBI.<sup>18</sup> Acute toxicities were not reported in the Budapest study.<sup>13</sup> 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<sup>68</sup> in the GEC-ESTRO trial, although this was felt to be of little clinical relevance. However, MIB had comparable or higher rates of “good/excellent” cosmesis compared with WBI.<sup>10,13,67</sup> There are limited data available regarding toxicities and cosmetics of single-entry catheter PBI compared with 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 statistically significant reduced reports of change in breast appearance and/or breast hardening by patients compared with WBI.<sup>9</sup> 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%).<sup>11</sup>

Notably absent from Table 7 is a recommendation for IORT because (1) acute toxicities were only reported on the TARGIT-A study,<sup>44</sup> but not the ELIOT trial,<sup>37</sup> 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 are lacking regarding comparative late toxicities and cosmesis between IORT alone versus WBI and IORT + 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 when compared directly to photon toxicities,<sup>69</sup> although were reasonable in other published experiences.<sup>70-72</sup> 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.<sup>73,74</sup> Published longer term follow-up from prospective phase II trials will help guide decisions on the usage of proton PBI.

## 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 invasive breast cancer and DCIS. The inclusion criteria for these trials varied, as did the delivery and treatment planning parameters.

The treatment of early-stage invasive breast cancer and DCIS 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.<sup>75</sup> 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 or therapy is needed. With increasing data<sup>76,77</sup> 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 invasive breast cancer and DCIS.

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.

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.<sup>78,79</sup> 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.<sup>79</sup> 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.

It remains to be defined if more optimized patient selection criteria and treatment techniques will make IORT a recommended option. Given the increased patient convenience of completing RT at the time of surgery, investigation into a preferable IORT approach warrants further study. How best to weigh the potential higher local recurrence risk of IOERT and kV IORT with its increased efficiency and low toxicity when delivered without the addition of WBI remains to be defined. Publication of prospective data of patients treated with IORT (kV or IOERT) alone without WBI are encouraged and may inform a future update of this guideline. The UK National Institute for Health and Care Excellence has published a decision aid for patients with early-stage invasive breast cancer considering kV IORT.<sup>80</sup> The task force does acknowledge the increased patient convenience of a technique such as IOERT and kVIORT, which theoretically might enable all RT to be delivered at the time of surgery.

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* and *NCT04040569*).<sup>81</sup>

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. 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.<sup>7</sup> 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. There remain difficulties in offering PBI to patients who have undergone oncologic 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 with 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.

## 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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## Acknowledgments

We are grateful to the AHRQ Evidence-Based Practice Center Program who supported the development of the systematic review of the evidence and to the Patient-Centered Outcomes Research Institute for funding the systematic review. The task force thanks the peer reviewers for their comments and time spent reviewing the guideline. See [Appendix E1](#) for their names and disclosures.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.prro.2023.11.001](https://doi.org/10.1016/j.prro.2023.11.001).

## References

1. Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice. In: Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E, eds. *Clinical Practice Guidelines We Can Trust*. National Academies Press; 2011.
2. Institute of Medicine Committee on Standards for Systematic Reviews of Comparative Effectiveness. In: Eden J, Levit L, Berg A,

- Morton S, eds. *Finding What Works in Health Care: Standards for Systematic Reviews*. National Academies Press; 2011.
- Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN Estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209-249.
  - Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys*. 2009;74:987-1001.
  - Correa C, Harris EE, Leonardi MC, et al. Accelerated partial breast irradiation: Executive summary for the update of an ASTRO Evidence-Based Consensus Statement. *Pract Radiat Oncol*. 2017;7:73-79.
  - Tolaney SM, Garrett-Mayer E, White J, et al. Updated standardized definitions for efficacy end points (STEEP) in adjuvant breast cancer clinical trials: STEEP version 2.0. *J Clin Oncol*. 2021;39:2720-2731.
  - Vicini FA, Cecchini RS, White JR, et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: A randomised, phase 3, equivalence trial. *Lancet*. 2019;394:2155-2164.
  - Whelan TJ, Julian JA, Berrang TS, et al. 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): A randomised controlled trial. *Lancet*. 2019;394:2165-2172.
  - Coles CE, Griffin CL, Kirby AM, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet*. 2017;390:1048-1060.
  - Strnad V, Polgar C, Ott OJ, et al. Accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy compared with whole-breast irradiation with boost for early breast cancer: 10-year results of a GEC-ESTRO randomised, phase 3, non-inferiority trial. *The Lancet*. 2023;24:262-272.
  - Offersen BV, Alsner J, Nielsen HM, et al. Partial breast irradiation versus whole breast irradiation for early breast cancer patients in a randomized phase III trial: The Danish Breast Cancer Group Partial Breast Irradiation Trial. *J Clin Oncol*. 2022;40:4189-4197.
  - Meattini I, Marrazzo L, Saieva C, et al. Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: Long-term results of the randomized phase III APBI-IMRT-Florence trial. *J Clin Oncol*. 2020;38:4175-4183.
  - Polgar C, Major T, Takacs-Nagy Z, Fodor J. Breast-conserving surgery followed by partial or whole breast irradiation: Twenty-year results of a phase 3 clinical study. *Int J Radiat Oncol Biol Phys*. 2021;109:998-1006.
  - Franceschini D, Loi M, Chiola I, et al. Preliminary results of a randomized study on postmenopausal women with early stage breast cancer: Adjuvant hypofractionated whole breast irradiation versus accelerated partial breast irradiation (HYPAB trial). *Clin Breast Cancer*. 2021;21:231-238.
  - Li X, Sanz J, Foro P, et al. Long-term results of a randomized partial irradiation trial compared to whole breast irradiation in the early stage and low-risk breast cancer patients after conservative surgery. *Clin Transl Oncol*. 2021;23:2127-2132.
  - Meduri B, Baldissera A, Iotti C, et al. Cosmetic results and side effects of accelerated partial-breast irradiation versus whole-breast irradiation for low-risk invasive carcinoma of the breast: The randomized phase III IRMA trial. *J Clin Oncol*. 2023;41:2201-2210.
  - Shumway DA, Corbin KS, Farah MH, et al. Partial breast irradiation for breast cancer. Accessed February 2, 2023. <https://effectivehealthcare.ahrq.gov/products/partial-breast-irradiation/research>.
  - Strnad V, Ott OJ, Hildebrandt G, et al. 5-Year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: A randomised, phase 3, non-inferiority trial. *Lancet*. 2016;387:229-238.
  - Strnad V, Krug D, Sedlmayer F, et al. DEGRO practical guideline for partial-breast irradiation. *Strahlenther Onkol*. 2020;196:749-763.
  - Anderson B, Arthur D, Hannoun-Levi JM, et al. Partial breast irradiation: An updated consensus statement from the American Brachytherapy Society. *Brachytherapy*. 2022;21:726-747.
  - American Society of Breast Surgeons. Consensus guideline on accelerated partial breast irradiation. Accessed February 21, 23. <https://www.breastsurgeons.org/resources/statements>.
  - Goldberg M, Bridhikitti J, Khan AJ, McGale P, Whelan TJ. A meta-analysis of trials of partial breast irradiation. *Int J Radiat Oncol Biol Phys*. 2023;115:60-72.
  - Stecklein SR, Shaitelman SF, Babiera GV, et al. Prospective comparison of toxicity and cosmetic outcome after accelerated partial breast irradiation with conformal external beam radiotherapy or single-entry multilumen intracavitary brachytherapy. *Pract Radiat Oncol*. 2019;9:e4-e13.
  - Shah C, Badiyan S, Ben Wilkinson J, et al. Treatment efficacy with accelerated partial breast irradiation (APBI): Final analysis of the American Society of Breast Surgeons MammoSite breast brachytherapy registry trial. *Ann Surg Oncol*. 2013;20:3279-3285.
  - Yashar CM, Scanderbeg D, Kuske R, et al. Initial clinical experience with the strut-adjusted volume implant (SAVI) breast brachytherapy device for accelerated partial-breast irradiation (APBI): First 100 patients with more than 1 year of follow-up. *Int J Radiat Oncol Biol Phys*. 2011;80:765-770.
  - Cuttino LW, Arthur DW, Vicini F, Todor D, Julian T, Mukhopadhyay N. Long-term results from the Contura multilumen balloon breast brachytherapy catheter phase 4 registry trial. *Int J Radiat Oncol Biol Phys*. 2014;90:1025-1029.
  - Polgar C, Van Limbergen E, Potter R, et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: Recommendations of the Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) Breast Cancer Working Group based on clinical evidence (2009). *Radiother Oncol*. 2010;94:264-273.
  - Yersal O, Barutca S. Biological subtypes of breast cancer: Prognostic and therapeutic implications. *World J Clin Oncol*. 2014;5:412-424.
  - Tolaney SM, Guo H, Pernas S, et al. Seven-year follow-up analysis of adjuvant paclitaxel and trastuzumab trial for node-negative, human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*. 2019;37:1868-1875.
  - Bellon JR, Guo H, Barry WT, et al. Local-regional recurrence in women with small node-negative, HER2-positive breast cancer: Results from a prospective multi-institutional study (the APT trial). *Breast Cancer Res Treat*. 2019;176:303-310.
  - Arvold ND, Taghian AG, Niemierko A, et al. Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy. *J Clin Oncol*. 2011;29:3885-3891.
  - Jobsen J, van der Palen J, Riemersma S, Heijmans H, Ong F, Struikmans H. Pattern of ipsilateral breast tumor recurrence after breast-conserving therapy. *Int J Radiat Oncol Biol Phys*. 2014;89:1006-1014.
  - Dorn PL, Al-Hallaq HA, Haq F, et al. A prospective study of the utility of magnetic resonance imaging in determining candidacy for partial breast irradiation. *Int J Radiat Oncol Biol Phys*. 2013;85:615-622.
  - Pramod N, Nigam A, Basree M, et al. Comprehensive review of molecular mechanisms and clinical features of invasive lobular cancer. *Oncologist*. 2021;26:e943-e953.
  - Giuliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis:

- The ACOSOG Z0011 (Alliance) randomized clinical trial. *JAMA*. 2017;318:918-926.
36. Bartels SAL, Donker M, Poncet C, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer: 10-Year results of the randomized controlled EORTC 10981-22023 AMAROS trial. *J Clin Oncol*. 2023;41:2159-2165.
  37. Orecchia R, Veronesi U, Maisonneuve P, et al. Intraoperative irradiation for early breast cancer (ELIOT): Long-term recurrence and survival outcomes from a single-centre, randomised, phase 3 equivalence trial. *Lancet Oncol*. 2021;22:597-608.
  38. Vaidya JS, Bulsara M, Baum M, et al. Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial. *BMJ*. 2020;370:m2836.
  39. Meric F, Mirza NQ, Vlastos G, et al. Positive surgical margins and ipsilateral breast tumor recurrence predict disease-specific survival after breast-conserving therapy. *Cancer*. 2003;97:926-933.
  40. Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *Int J Radiat Oncol Biol Phys*. 2014;88:553-564.
  41. McCormick B, Winter KA, Woodward W, et al. Randomized phase III trial evaluating radiation following surgical excision for good-risk ductal carcinoma in situ: Long-term report from NRG Oncology/RTOG 9804. *J Clin Oncol*. 2021;39:3574-3582.
  42. Solin LJ, Gray R, Hughes LL, et al. Surgical excision without radiation for ductal carcinoma in situ of the breast: 12-year results from the ECOG-ACRIN E5194 study. *J Clin Oncol*. 2015;33:3938-3944.
  43. Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. *Pract Radiat Oncol*. 2016;6:287-295.
  44. Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): An international, prospective, randomised, non-inferiority phase 3 trial. *Lancet*. 2010;376:91-102.
  45. Vaidya JS, Bulsara M, Baum M, Tobias JS, TARGIT-A trial authors. Single-dose intraoperative radiotherapy during lumpectomy for breast cancer: An innovative patient-centred treatment. *Br J Cancer*. 2021;124:1469-1474.
  46. Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet*. 2014;383:603-613.
  47. Strnad V, Major T, Polgar C, et al. ESTRO-ACROP guideline: Interstitial multi-catheter breast brachytherapy as Accelerated Partial Breast Irradiation alone or as boost - GEC-ESTRO Breast Cancer Working Group practical recommendations. *Radiother Oncol*. 2018;128:411-420.
  48. Yashar C, Attai D, Butler E, et al. Strut-based accelerated partial breast irradiation: Report of treatment results for 250 consecutive patients at 5 years from a multicenter retrospective study. *Brachytherapy*. 2016;15:780-787.
  49. Leonard CE, Wang Y, Asmar L, et al. A prospective phase III trial evaluating patient self-reported pain and cosmesis in accelerated partial breast irradiation utilizing 3-D versus intensity-modulated radiotherapy. *Cancer Med*. 2021;10:7089-7100.
  50. Meszaros N, Major T, Stelczer G, et al. Accelerated partial breast irradiation with 3-dimensional conformal and image-guided intensity-modulated radiotherapy following breast conserving surgery - 7-year results of a phase II trial. *Breast*. 2020;54:222-228.
  51. National Institute for Health and Care Excellence (NICE). Intra-beam radiotherapy system for adjuvant treatment of early breast cancer technology appraisal guidance [TA501]. Accessed November 6, 2023. <https://www.nice.org.uk/guidance/ta501>
  52. Ward MC, Bentzen SM, Fasola CE, et al. An estimate of local failure in the TARGIT-A trial of pre-pathology intraoperative radiation therapy for early breast cancer. *Int J Radiat Oncol Biol Phys*. 2023;115:73-76.
  53. Vaidya JS, Bulsara M, Wenz F, et al. The TARGIT-a randomized trial: TARGIT-IORT versus whole breast radiation therapy: Long-term local control and survival. *Int J Radiat Oncol Biol Phys*. 2023;115:77-82.
  54. Livi L, Meattini I, Marrazzo L, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur J Cancer*. 2015;51:451-463.
  55. Marrazzo L, Meattini I, Simontacchi G, Livi L, Pallotta S. Updates on the APBI-IMRT-Florence trial (NCT02104895) technique: From the intensity modulated radiation therapy trial to the volumetric modulated arc therapy clinical practice. *Pract Radiat Oncol*. 2023;13:e28-e34.
  56. Shah BA, Xiao J, Oh C, et al. Five-fraction prone accelerated partial breast irradiation: Long-term oncologic, dosimetric, and cosmetic outcome. *Pract Radiat Oncol*. 2022;12:106-112.
  57. Kim DH, Theberge V, Provencher S, et al. OPAR: A multicenter phase II randomized trial of fractionation schedules for once-a-day accelerated partial breast irradiation (APBI). *Int J Radiat Oncol Biol Phys*. 2021;111(3 suppl):S6.
  58. Murray Brunt A, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *Lancet*. 2020;395:1613-1626.
  59. National Institute for Health and Care Excellence (NICE). Early and locally advanced breast cancer: Diagnosis and management (NG101). Accessed November 6, 2023. <https://www.nice.org.uk/guidance/ng101>
  60. Lewis P, Brunt AM, Coles C, et al. Moving forward fast with FAST-forward. *Clin Oncol (R Coll Radiol)*. 2021;33:427-429.
  61. Meattini I, Becherini C, Boersma L, et al. European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer. *Lancet Oncol*. 2022;23:e21-e31.
  62. Guinot JL, Gonzalez-Perez V, Meszaros N, et al. Very accelerated partial breast irradiation phase I-II multicenter trial (VAPBI): Feasibility and early results. *Brachytherapy*. 2021;20:332-338.
  63. Hannoun-Levi J-M, Montagne L, Sumodhee S, et al. APBI versus ultra-APBI in the elderly with low-risk breast cancer: A comparative analysis of oncological outcome and late toxicity. *Int J Radiat Oncol Biol Phys*. 2021;111:56-67.
  64. Yashar C, Khan AJ, Chen P, et al. Three-fraction accelerated partial breast irradiation (APBI) delivered with interstitial brachytherapy is safe: First results from the tri-fraction radiation therapy used to minimize patient hospital trips (TRIUMPH-T) Trial. *Pract Radiat Oncol*. 2023;13:314-320.
  65. Vicini FA, Keisch M, Shah C, et al. Factors associated with optimal long-term cosmetic results in patients treated with accelerated partial breast irradiation using balloon-based brachytherapy. *Int J Radiat Oncol Biol Phys*. 2012;83:512-518.
  66. Vargo JA, Verma V, Kim H, et al. Extended (5-year) outcomes of accelerated partial breast irradiation using MammoSite balloon brachytherapy: Patterns of failure, patient selection, and dosimetric correlates for late toxicity. *Int J Radiat Oncol Biol Phys*. 2014;88:285-291.
  67. Polgar C, Ott OJ, Hildebrandt G, et al. Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-

- conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2017;18:259-268.
68. Sprangers MA, Groenvold M, Arraras JJ, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: First results from a three-country field study. *J Clin Oncol*. 1996;14:2756-2768.
  69. Galland-Girodet S, Pashtan I, MacDonald SM, et al. Long-term cosmetic outcomes and toxicities of proton beam therapy compared with photon-based 3-dimensional conformal accelerated partial-breast irradiation: A phase 1 trial. *Int J Radiat Oncol Biol Phys*. 2014;90:493-500.
  70. Kozak KR, Smith BL, Adams J, et al. Accelerated partial-breast irradiation using proton beams: Initial clinical experience. *Int J Radiat Oncol Biol Phys*. 2006;66:691-698.
  71. Pasalic D, Strom EA, Allen PK, et al. Proton accelerated partial breast irradiation: Clinical outcomes at a planned interim analysis of a prospective phase 2 trial. *Int J Radiat Oncol Biol Phys*. 2021;109:441-448.
  72. Bush DA, Do S, Lum S, et al. Partial breast radiation therapy with proton beam: 5-year results with cosmetic outcomes. *Int J Radiat Oncol Biol Phys*. 2014;90:501-505.
  73. Mutter RW, Jethwa KR, Gonuguntla K, et al. 3 fraction pencil-beam scanning proton accelerated partial breast irradiation: Early provider and patient reported outcomes of a novel regimen. *Radiat*. 2019;14:211.
  74. Choi JI, Prabhu K, Hartsell WF, et al. Outcomes and toxicities after proton partial breast radiotherapy for early stage, hormone receptor positive breast cancer: 3-year results of a phase II multi-center trial. *Clin Transl Radiat Oncol*. 2022;37:71-77.
  75. Society of Surgical Oncology. Choosing wisely: Five things physicians and patients should question. Accessed February 21, 23. <https://www.choosingwisely.org/societies/society-of-surgical-oncology/>.
  76. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: Long-term follow-up of CALGB 9343. *J Clin Oncol*. 2013;31:2382-2387.
  77. Kunkler IH, Williams LJ, Jack WJL, Cameron DA, Dixon JM. Breast-conserving surgery with or without irradiation in early breast cancer. *N Engl J Med*. 2023;388:585-594.
  78. Lesniak DM, Millochou J, Wang K-C, et al. Breast-conserving therapy can be offered to women with prior breast augmentation. *Eur J Surg Oncol*. 2020;46:1456-1462.
  79. Serritzlev MS, Lorentzen AK, Matthiessen LW, Holmich LR. Capsular contracture in patients with prior breast augmentation undergoing breast conserving therapy and irradiation. *J Plast Surg Hand Surg*. 2020;54:225-232.
  80. National Institute for Health and Care Excellence (NICE). Intrabeam radiotherapy for treating early breast cancer decision aid for TA501. Accessed July 20, 2023. <https://www.nice.org.uk/guidance/ta501/resources/intrabeam-radiotherapy-for-treating-early-breast-cancer-patient-decision-aid-pdf-4908169693>.
  81. Horton JK, Blitzblau RC, Yoo S, et al. Preoperative single-fraction partial breast radiation therapy: A novel phase I, dose-escalation protocol with radiation response biomarkers. *Int J Radiat Oncol Biol Phys*. 2015;92:846-855.