

Special Article

Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline

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Abstract

Introduction: The purpose of this guideline is to offer recommendations on fractionation for whole breast irradiation (WBI) with or without a tumor bed boost and guidance on treatment planning and delivery.

Methods and materials: The American Society for Radiation Oncology (ASTRO) convened a task force to address 5 key questions focused on dose-fractionation for WBI, indications and dose-fractionation for tumor bed boost, and treatment planning techniques for WBI and tumor bed boost. Guideline recommendations were based on a systematic literature review and created using a predefined consensus-building methodology supported by ASTRO-approved tools for grading evidence quality and recommendation strength.

Results: For women with invasive breast cancer receiving WBI with or without inclusion of the low axilla, the preferred dose-fractionation scheme is hypofractionated WBI to a dose of 4000 cGy in 15 fractions or 4250 cGy in 16 fractions. The guideline discusses factors that might or should affect fractionation decisions. Use of boost should be based on shared decision-making that considers patient, tumor, and treatment factors, and the task force delineates specific subgroups in which it recommends or suggests use or omission of boost, along with dose recommendations. When planning, the volume of breast tissue receiving >105% of the prescription dose should be minimized and the tumor bed contoured with a goal of coverage with at least 95% of the prescription dose. Dose to the heart, contralateral breast, lung, and other normal tissues should be minimized.

Conclusions: WBI represents a significant portion of radiation oncology practice, and these recommendations are intended to offer the groundwork for defining evidence-based practice for this common and important modality. This guideline also seeks to promote appropriately individualized, shared decision-making regarding WBI between physicians and patients.

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Introduction

Breast cancer is the most common malignancy treated with radiation therapy in the United States, and whole breast irradiation (WBI) is the most common radiotherapeutic approach for breast cancer.¹ Historically, the standard of care for WBI has been conventional fractionation (CF), defined as daily doses of 180 to 200 cGy to approximately 4500 to 5000 cGy, with or without a tumor bed boost. Recognizing the limitations of CF for convenience and cost, randomized trials in the 1990s and 2000s investigated if moderate hypofractionation (HF), defined as daily doses of 265 to 330 cGy, could yield oncologic and functional/cosmetic outcomes similar to CF-WBI. Initial trial reports supported the safety and effectiveness of HF-WBI and, in response, the American Society for Radiation Oncology (ASTRO) initially published an evidence-based guideline on dose-fractionation for WBI in 2011.²

Although the evidence supporting HF-WBI has subsequently grown substantially, adoption of HF-WBI among appropriate patients remains low,^{3–5} and research indicates nearly three-quarters of the variation is attributable to the treating radiation oncology practice and physician, rather than the patient.⁶ This new guideline replaces the

prior ASTRO document and aims to provide guidance regarding not only WBI dose-fractionation, but also treatment planning and delivery. It is hoped the physician contribution to variability in care will therefore be decreased and decisions more appropriately individualized based on tumor factors, anatomic considerations, and patient preferences.

This Executive Summary introduces the guideline and its recommendations. See the full-text guideline supplement for a discussion of the evidence underpinning the recommendations. This guideline is endorsed by the Royal Australian and New Zealand College of Radiologists and the Society of Surgical Oncology.

Methods and materials

Process

In June 2015, the ASTRO Guidelines Subcommittee convened a work group to evaluate new evidence published after the systematic review for the prior ASTRO WBI guideline and recommend whether the guideline should be withdrawn completely, updated,

replaced, or reaffirmed. The group comprised 1 colead of the original guideline, 2 subcommittee members, and 2 additional topic experts (1 not involved in the original guideline). The work group recommended development of a new guideline to replace the original. The work group also recommended regional nodal treatment not be included because this topic merited its own guideline. The ASTRO Board of Directors approved the proposal in October 2015. A task force of radiation oncologists specializing in breast cancer, plus a medical physicist and a patient representative, was recruited.

Through calls and e-mails, the task force formulated recommendation statements and narratives based on the literature review. The draft manuscript was reviewed by 6 expert reviewers (see Acknowledgments) and ASTRO legal counsel. The update was posted online for public comment in May and June 2017. The Board of Directors approved the final document in November 2017. The ASTRO Guidelines Subcommittee will monitor this guideline beginning at 2 years after publication and initiate updates according to ASTRO policies.

Literature review

The guideline was based on a systematic literature review. Literature searches were conducted for each key question (KQ) in MEDLINE PubMed to identify English-language studies between January 2009 and January 2016 for KQs 1 through 3 and January 2000 and May 2016 for KQs 4 and 5. This time window was selected for KQs 1 through 3 because content relevant to these KQs was included in the literature search conducted for the 2011 ASTRO guideline on dose-fractionation. Included trials evaluated adults with invasive breast cancer or ductal carcinoma in situ (DCIS) receiving breast-conserving surgery and WBI with or without a tumor bed boost. Both MeSH terms and text words were used. The electronic searches were supplemented by hand searches. In total, 528 abstracts were retrieved and screened by ASTRO staff and the task force. Subsequently, 428 articles were eliminated and 100 articles included and abstracted.

Grading of evidence, recommendations, and consensus methodology

Guideline recommendation statements were developed using the Grading of Recommendations, Assessment, Development, and Evaluations methodology^{7,8} and, when possible, based on high-quality data. When necessary, expert opinion supplemented the evidence. Recommendations were classified as “strong” or “conditional.” A strong recommendation indicated the task force was confident the benefits of the intervention clearly outweighed the harms, or vice versa, and “all or almost all informed people would make the recommended choice.” Conditional recommendations were

made when the risks and benefits were even or uncertain and “most informed people would choose the recommended course of action, but a substantial number would not,” suggesting a strong role for shared decision-making.⁷

The quality of evidence underlying each recommendation was categorized as high, moderate, or low, defined as:

- “High: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.”⁸

Task force consensus on the recommendation statements was evaluated through a modified Delphi approach adapted from the American Society of Clinical Oncology process.⁹ Task force members (except the patient representative) rated their agreement with each recommendation on a 5-point Likert scale, from strongly disagree to strongly agree. An asterisk (*) indicates that the medical physics representative abstained from rating clinically focused recommendations. A prespecified threshold of $\geq 75\%$ of raters selecting “agree” or “strongly agree” indicated consensus was achieved. If a recommendation statement did not meet this threshold, it was modified and resurveyed or deleted. Recommendations achieving consensus edited for other reasons were also resurveyed.

Results

KQ 1: For patients receiving WBI without additional fields to cover the regional lymph nodes, what is/are the preferred dose-fractionation scheme(s) and how should these vary as a function of:

- Grade
- Margins
- Estrogen receptor (ER)/progesterone receptor (PR)/human epidermal growth factor receptor 2 (HER2)-neu status and other assessments of tumor biology
- Normal tissue exposure
- Systemic therapy receipt (including prior chemotherapy, concurrent endocrine, or targeted therapies)
- Age
- Stage (including DCIS vs invasive disease)
- Histology
- Breast size and dose homogeneity
- Collagen vascular disease and other relative contraindications to radiation
- Intent to cover the low axilla?

Table 1 Patients for whom consensus supports use of HF-WBI: A comparison of the 2011 and 2018 ASTRO Guidelines *

Factor	2011 Guideline	2018 Guideline
Age	≥50 years	Any
Stage	T1-2 N0	Any stage provided intent is to treat the whole breast without an additional field to cover the regional lymph nodes
Chemotherapy	None	Any chemotherapy
Dose homogeneity	±7% in the central axis	Volume of breast tissue receiving >105% of the prescription dose should be minimized regardless of dose-fractionation

ASTRO, American Society for Radiation Oncology; HF-WBI, hypofractionated whole-breast irradiation.

* These guidelines are intended as a tool to promote appropriately individualized, shared decision-making between physicians and patients. None should be construed as strict or superseding the appropriately informed and considered judgments of individual physicians and patients; therefore, the task force recommends against any quality benchmarks requiring 100% utilization of HF-WBI, even in patients where recommendations for HF-WBI are strong because the distribution of reasonable patient values and preferences would be expected to yield a patient-centered choice for conventionally fractionated WBI in a certain proportion of individual patients.

See [Table 1](#) for a comparison of the recommendations from this guideline to those of the 2011 ASTRO Guideline.

Overall Statement

Statement KQ1A. For women with invasive breast cancer receiving WBI with or without inclusion of the low axilla, the preferred dose-fractionation scheme is HF-WBI to a dose of 4000 cGy in 15 fractions or 4250 cGy in 16 fractions.

Recommendation strength: Strong
Quality of evidence: High
Consensus: 100%

Grade, margins, and ER/PR/HER2 status and biology

Statement KQ1B. The decision to offer HF-WBI should be independent of tumor grade

Recommendation strength: Strong
Quality of evidence: High
Consensus: 100%

Statement KQ1C. The decision to offer HF-WBI may be independent of hormone receptor status, HER2 receptor status, and margin status.

Recommendation strength: Conditional
Quality of evidence: Moderate
Consensus: 100%*

Normal tissue exposure

Statement KQ1D. The decision to offer hypofractionation should be independent of breast cancer laterality.

Recommendation strength: Strong
Quality of evidence: Moderate
Consensus: 100%

Systemic therapy receipt

Statement KQ1E. The decision to offer HF-WBI should be independent of chemotherapy received prior to

radiation and trastuzumab or endocrine therapy received prior to or during radiation.

Recommendation strength: Strong
Quality of evidence: Moderate
Consensus: 92%*

Age

Statement KQ1F. There is no evidence indicating deleterious effects of HF-WBI compared with CF-WBI in either younger or older patients, and thus HF-WBI may be used regardless of age.

Recommendation strength: Conditional
Quality of evidence: Moderate
Consensus: 93%

Stage (including DCIS vs invasive disease)

Statement KQ1G. HF-WBI may be used as an alternative to CF-WBI in patients with DCIS.

Recommendation strength: Conditional
Quality of evidence: Moderate
Consensus: 86%

Histology

Statement KQ1H. CF-WBI may be preferred over HF-WBI when treating primary breast cancers with rare histologies that are most commonly treated with CF when arising in other parts of the body.

Recommendation strength: Conditional
Quality of evidence: Low
Consensus: 93%

Breast size and dose homogeneity

Statement KQ1I. The decision to offer HF-WBI should be independent of breast size (including central axis separation) provided that dose-homogeneity goals, as outlined in KQ4, can be achieved.

Recommendation strength: Strong
 Quality of evidence: Moderate
 Consensus: 100%

Collagen vascular disease and other relative contraindications to radiation

Statement KQ1J. In patients with breast augmentation, either HF-WBI or CF-WBI may be used.

Recommendation strength: Conditional
 Quality of evidence: Low
 Consensus: 85%*

Statement KQ1K. In patients with collagen vascular disease, if the patient and her physician opt for WBI, then either HF-WBI or CF-WBI may be used.

Recommendation strength: Conditional
 Quality of evidence: Low
 Consensus: 85%*

KQ 2: When should patients receive a tumor bed boost in conjunction with WBI and how should this vary as a function of:

- Stage/histology (including DCIS vs invasive disease)
- Age
- Grade
- Margins
- ER/PR/HER2-neu status and other assessments of tumor biology
- Dose-fractionation used for WBI
- Ability to limit dose to critical normal tissues, including heart and whole breast volume?

Age, grade, margins, and biology for invasive disease

Statement KQ2A. A tumor bed boost is recommended for patients with invasive breast cancer who meet any of the following criteria: age ≤ 50 years with any grade, age 51 to 70 years with high grade, or a positive margin.

Recommendation strength: Strong
 Quality of evidence: Moderate
 Consensus: 100%

Statement KQ2B. Omitting a tumor bed boost is suggested in patients with invasive breast cancer who meet the following criteria: age >70 years with hormone receptor-positive tumors of low or intermediate grade resected with widely negative (≥ 2 mm) margins.

Recommendation strength: Conditional
 Quality of evidence: Moderate
 Consensus: 100%*

Statement KQ2C. For patients with invasive breast cancer not meeting criteria articulated in KQ2A or

KQ2B, individualized decision-making is suggested because the decision in these cases is highly sensitive to patient preferences and values regarding the modest expected disease control benefit and the modest increase in treatment-related burden and toxicity associated with boost radiation therapy.

Recommendation strength: Conditional
 Quality of evidence: Moderate
 Consensus: 100%

Age, grade, and margins for DCIS

Statement KQ2D. A tumor bed boost may be used for patients with DCIS who meet any of the following criteria: age ≤ 50 years, high grade, or close (< 2 mm) or positive margins.

Recommendation strength: Conditional
 Quality of evidence: Moderate
 Consensus: 92%*

Statement KQ2E. A tumor bed boost may be omitted in patients with DCIS who, if age >50 years, meet the following criteria: screen detected, total size ≤ 2.5 cm, low to intermediate nuclear grade, and widely negative surgical margins (≥ 3 mm).

Recommendation strength: Conditional
 Quality of evidence: Moderate
 Consensus: 100%*

Statement KQ2F. For patients with DCIS not meeting criteria articulated in KQ2D or KQ2E, individualized decision-making is suggested as the decision in these cases is highly sensitive to patient preferences and values regarding the modest expected disease control benefit and the modest increase in treatment-related burden and toxicity.

Recommendation strength: Conditional
 Quality of evidence: Moderate
 Consensus: 100%

Dose-fractionation used for WBI

Statement KQ2G. The decision to use a tumor bed boost is recommended to be based on the clinical indications for a boost and be independent of the whole breast fractionation scheme.

Recommendation strength: Strong
 Quality of evidence: High
 Consensus: 100%

Ability to limit dose to critical normal tissues, including heart and whole breast volume

Statement KQ2H. Physicians may reduce the boost dose or omit the boost for patients believed to be at higher risk for normal tissue toxicity from a boost because of a large boost

volume relative to breast volume or inclusion of critical normal tissue in the boost radiated volume.

Recommendation strength: Conditional
Quality of evidence: Low
Consensus: 86%

KQ 3: What is/are preferred dose-fractionation scheme(s) for a tumor bed boost and how should this vary as a function of:

- Stage/histology (including DCIS vs invasive disease)
- Age
- Grade
- Margins
- ER/PR/HER2-neu status and other assessments of tumor biology
- Dose-fractionation used for WBI?

Statement KQ3A

In the absence of strong risk factors for local recurrence, such as those enumerated in KQ3B, 1000 cGy in 4 to 5 fractions is suggested as the standard tumor bed boost dose-fractionation, regardless of whole breast dose-fractionation, stage, or histology.

Recommendation strength: Conditional
Quality of evidence: Moderate
Consensus: 100%

Statement KQ3B

Particularly in the presence of strong risk factor(s) for local recurrence, such as the single risk factor of positive margins or a combination of risk factors such as young age and close margins, a higher radiation boost dose of 1400 to 1600 cGy in 7 to 8 fractions or 1250 cGy in 5 fractions may also be used.

Recommendation strength: Conditional
Quality of evidence: Low
Consensus: 85%*

KQ 4: What are preferred techniques for WBI treatment planning with respect to:

- Dose homogeneity (including planning approaches)
- Target delineation and coverage
- Cardiac delineation and avoidance
- Normal tissue doses
- Patient positioning and position verification/image guidance?

Dose homogeneity

Statement KQ4A. The volume of breast tissue receiving greater than 105% of the prescription dose should be minimized. To achieve this, 3-dimensional conformal

treatment planning with a “field-in-field” technique is recommended as the initial treatment planning approach.

Recommendation strength: Strong
Quality of evidence: Moderate
Consensus: 100%

Target delineation and coverage

Statement KQ4B. The tumor bed should be contoured with a goal of achieving coverage of the tumor bed with at least 95% of the prescription dose. The whole breast volume may be contoured or defined clinically, with a goal of covering at least 95% of the whole breast volume with 95% of the whole breast prescription dose. Treatment plans should be individualized after consideration of many factors, including tumor characteristics, patient anatomy, and comorbidities.

Recommendation strength: Strong
Quality of evidence: Moderate
Consensus: 100%

Cardiac delineation and avoidance

Statement KQ4C. The heart should be contoured on the treatment planning computed tomography scan in accordance with Radiation Therapy Oncology Group guidelines. Tangent beams should be delineated to minimize the dose to the heart. The mean heart dose should be as low as reasonably achievable. Deep inspiration breath hold, prone positioning, and/or heart blocks are recommended to minimize heart dose. Judicious tailoring of the whole breast dose coverage may be used to minimize the dose to the heart, provided that the tumor bed is remote from this region of the breast.

Recommendation strength: Strong
Quality of evidence: High
Consensus: 100%

Normal tissue doses

Statement KQ4D. Treatment techniques should also minimize dose to the contralateral breast, lung, and other normal tissues.

Recommendation strength: Strong
Quality of evidence: High
Consensus: 100%

Patient positioning and position verification/image guidance

Statement KQ4E. Patients should be positioned considering the reproducibility of the breast for treatment. Skin folds should be unfolded to the extent possible. For patients with a large breast size, prone positioning may be used to further minimize dose to normal tissues. Regardless of the positioning method, care should be taken to ensure that the contralateral breast is not in the treatment fields.

Recommendation strength: Strong
 Quality of evidence: High
 Consensus: 100%

Statement KQ4F. When designing the frequency and type of imaging, imaging of the treatment beam ports may be used to minimize dose to normal tissues such as the heart. For patients with significant daily positioning variations, daily imaging may be used. Doses are lowest with kilovoltage (kV) planar techniques but the appropriate imaging method depends on the localization needs for the patient.

Recommendation strength: Conditional
 Quality of evidence: Low
 Consensus: 93%

KQ 5: What are preferred techniques for tumor bed boost treatment planning with respect to:

- Technique/modality
- Dose homogeneity (and techniques to achieve this)
- Target delineation and coverage
- Cardiac avoidance
- Normal tissue doses
- Patient positioning and position verification/image guidance?

Technique/modality

Statement KQ5A. When a tumor bed boost is to be administered, external beam treatment is recommended with a radiation modality that will minimize high radiation dose to nontarget tissue.

Recommendation strength: Strong
 Quality of evidence: Moderate
 Consensus: 100%

Statement KQ5B. To facilitate immobilization and minimize normal tissue exposure, resimulation for boost planning may be used to allow for repositioning or in patients with large seromas at the time of whole breast treatment planning.

Recommendation strength: Conditional
 Quality of evidence: Low
 Consensus: 100%

Statement KQ5C. At this time, evidence is strongest in support of sequential administration of the boost after whole breast treatment; therefore, outside the context of trials, sequential boost is currently recommended.

Recommendation strength: Conditional
 Quality of evidence: Moderate
 Consensus: 100%

Target delineation and coverage

Statement KQ5D. 3-dimensional treatment planning should include delineation of the tumor bed, as noted in KQ4B. For boost treatment, conformal blocking with an adequate margin surrounding the tumor bed or boost PTV should be used, after consideration of factors such as risk of recurrence and the ability to spare normal tissues given the patient's anatomy.

Recommendation strength: Strong
 Quality of evidence: Moderate
 Consensus: 100%

Cardiac avoidance and normal tissue doses

Statement KQ5E. Caution should be taken to minimize dose to critical normal tissues, including the heart, and to minimize the volume of ipsilateral breast included in the boost field.

Recommendation strength: Strong
 Quality of evidence: Moderate
 Consensus: 100%

Patient positioning and position verification/image guidance

Statement KQ5F. With supine positioning for boost treatment, no additional immobilization is recommended. Daily imaging may be used in patients at risk for less reproducible setup.

Recommendation strength: Conditional
 Quality of evidence: Low
 Consensus: 100%

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