

Email: Guidelines@astro.org

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The American Society for Radiation Oncology has reviewed the **2020 NCCN Breast Cancer guideline** for gaps relative to radiation therapy and offers **12 recommendations** supported by evidence-based rationales for your consideration.

We hope you find these recommendations useful to your panel as you review and update the guidelines.

Sincerely,

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Chief Executive Officer, American Society for Radiation Oncology

Recommendation 1: IBC-2 and BINV-I – Either in a footnote on IBC-2 or under “Chest Wall Radiation” section of BINV-I, a dose recommendation of 66 Gy should be added as a special consideration for inflammatory breast cancer.

Rationale: An RT dose to chest wall of 66 Gy for IBC significantly improved locoregional control, disease-free survival and overall survival for patients who experienced less than a partial response to chemotherapy, patients with positive, close or unknown margins, patients <45 years of age or patients treated with BID fractionation.

References:

- Bristol JJ, Woodward WA, Strom EA, et al. “Locoregional Treatment Outcomes After Multimodality Management of Inflammatory Breast Cancer” *IJROBP* 1 Oct 2008;72(2):474-484.
- Liao Z, Strom EA, Buzdar AU, et al. “Locoregional irradiation for inflammatory breast cancer: effectiveness of dose escalation in decreasing recurrence” *IJROBP* 15 July 2000;47(5):1191-1200.

Recommendation 2: BINV-I – Add a footnote saying “Emerging evidence suggests hypofractionation may be considered for patients who require regional nodal irradiation in the post-mastectomy setting.

Rationale: Meta-analysis data comparing survival and toxicity outcomes as well as randomized phase III data suggest that hypofractionation yields equivalent survival and toxicity outcomes compared to conventional radiation therapy in the postmastectomy setting.

References:

- Wang SL, Fang H, Song YW, et al. Hypofractionated Versus Conventional Fractionated Postmastectomy Radiotherapy for Patients With High-Risk Breast Cancer: A Randomised, Non-Inferiority, Open-Label, Phase 3 Trial. *Lancet Oncol.* 2019;20(3):352-360. PMID: 30711522

- Liu L, Yang Y, Guo Q, et al. Comparing Hypofractionated to Conventional Fractionated Radiotherapy in Postmastectomy Breast Cancer: A Meta-Analysis and Systematic Review. *Radiat Oncol.* 2020;15(1). PMID: 31952507

Recommendation 3: BINV-18 – For patients with locally recurrent disease and a history of adjuvant radiation therapy coupled with breast-conserving surgery, re-irradiation should be added as a possible management option with indications and techniques based off of RTOG 1014 addressed in the “Optimizing Delivery of Individual Therapy” section.

Rationale: Phase II data from RTOG 1014 and several smaller studies show acceptable acute and late toxicities associated with reirradiation in locally and/or regionally recurrent breast cancer.

References:

- Arthur DW, Winter KA, Kuerer HM, et al. NRG oncology–radiation therapy oncology group study 1014: 1-year toxicity report from a phase 2 study of repeat breast-preserving surgery and 3-dimensional conformal partial-breast re-irradiation for in-breast recurrence. *Int J Radiat Oncol Biol Phys.* 2017;98:1028–35.
- Arthur DW, Winter KA, Kuerer HM, et al. Effectiveness of Breast-Conserving Surgery and 3-Dimensional Conformal Partial Breast Reirradiation for Recurrence of Breast Cancer in the Ipsilateral Breast: The NRG Oncology/RTOG 1014 Phase 2 Clinical Trial. *JAMA Oncol.* 2019; PMID: 31750868.
- Marta GN, Hijal T, Carvalho HA. Reirradiation for locally recurrent breast cancer. *Breast.* 2017;33:159-165. PMID: 28395234
- Al-Hilli Z, Grobmyer, SR. Affiliations Management Strategies for Locally Recurrent Breast Cancer: Redo-Lumpectomy, Redo-Sentinel Node Biopsy, Redo-Radiation. *Ann Surg Oncol.* 2019; 26 (10): 3018-3024. PMID: 31342396

Recommendation 4: BINV-I – Proton therapy should be added as a possible radiation technique under “Optimizing Delivery of Individual Therapy” depending on patient anatomy, tumor anatomy, target volume definition, and/or treatment planning.

Rationale: Dosimetric comparison studies have shown an advantage of proton radiation therapy over photons relative to cardiopulmonary sparing +/- dose homogeneity while maintaining target coverage.

References:

- Jimenez RB, Hickey S, DePauw N, et al. Phase II Study of Proton Beam Radiation Therapy for Patients With Breast Cancer Requiring Regional Nodal Irradiation. *JCO.* 2019;37(30):2778-2785.
- Patel SA, Lu HM, Nyamwanda JA, et al. Postmastectomy Radiation Therapy Technique and Cardiopulmonary Sparing: A Dosimetric Comparative Analysis Between Photons and Protons With Free Breathing Versus Deep Inspiration Breath Hold. *Pract Radiat Oncol.* 2017;7(6):377-384. PMID 28734644
- Bradley JA, Ho MW, Li Z, et al. A Technical Guide for Passive Scattering Proton Radiation Therapy for Breast Cancer. *Int J Part Ther.* 2017;3(4):473-484. PMID: 31772997
- Kammerer E, Le Guevelou J, Chaikh A, et al. Proton Therapy for Locally Advanced Breast Cancer: A Systematic Review of the Literature. *Cancer Treat Rev.* 2018;63:19-27. PMID: 29197746
- Vyfhuys MA, Zhu M, Agyepong B, Nichols EM. Techniques for Treating Bilateral Breast Cancer Patients Using Pencil Beam Scanning Technology. *Int J Part Ther.* 2019;6(2):1-11. PMID: 31998816
- Bekelman JE, Lu H, Pugh S, et al. Pragmatic randomised clinical trial of proton versus photon therapy for patients with non-metastatic breast cancer: the Radiotherapy Comparative Effectiveness (RadComp) Consortium trial protocol. *BMJ Open.* 2019;9(10):e025556. PMID: 31619413

Recommendation 5: MS-11 – A discussion on the use of biomarkers/gene assays to predict local recurrence after breast conserving surgery should be considered.

Rationale: The approved and validated multigene assay, Oncotype DX, generates a continuous DCIS Score that is statistically significantly associated with the risk of developing an ipsilateral breast recurrence with the use of surgery alone and can be used to better determine the benefit of adding adjuvant whole breast radiation therapy.

References:

- Solin LJ, Gray R, Bachner FL, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. *J Natl Cancer Inst.* 2013;105:701-710.
- Rakovitch E, Nofech-Mozes S, Hannah W, et al. A population-based validation study of the DCIS Score predicting recurrence risk in individuals treated by breast-conserving surgery alone. *Breast Cancer Res Treat.* 2015;152:389-398.

Recommendation 6: BINV-13 and BINV-14 – Add footnote about high-risk features that increase consideration of giving a boost to the tumor bed.

Rationale: While the use of high-risk features to determine need for a boost is mentioned in BINV-I, they are not actually specified until the discussion section.

Reference: Vrieling C, van Werkhoven E, Maingon P, et al. “Prognostic Factors for Local Control in Breast Cancer After Long-term Follow-up in the EORTC Boost vs No Boost Trial: A Randomized Clinical Trial” *Jama Oncol* 2017;3(1):42-48.

Recommendation 7: BINV-1 – Provide guidance on treatment for cT0N1 since mentioned at beginning of algorithm for work-up, but not mentioned in any subsequent treatment algorithms. MS-74 discussed work-up and mentions radiation may be more appropriate than mastectomy for treatment.

Rationale: Expert opinion needed on how to manage occult primary with clinically node positive disease. This can be placed in the “Special Considerations” section or simply as a footnote on BINV-1 with further explanation on MS-74.

References:

- Radiation bests mastectomy for occult breast cancer. ASBS 2017 – Lindsay Hessler, MD, University of Maryland, Baltimore
- Walker GV, Smith GL, Perkins GS, et al. “Population-based analysis of occult primary breast cancer with axillary lymph node metastasis.” *Cancer* 2010 Sep 1;116(17):4000-4006.

Recommendation 8: BINV-2 – 1-3 positive axillary nodes footnote s – add MA.20 and EORTC to Z-0011 for rational to treat with regional nodal irradiation.

Rationale: Z-11 compared sentinel node biopsy followed by axillary dissection to sentinel node biopsy followed by no directed therapy to the axilla. It did not address regional nodal irradiation in patient with 1-3 positive axillary nodes; MA-20 and EORTC addressed that.

References:

- Whelan TJ, Olivetto IA, Parulekar WR, et al. “Regional Nodal Irradiation in Early-Stage Breast Cancer.” *N Engl J Med* 2015;373:307-316.
- Poortmans P, Collette S, Kirkove C, et al. “Internal mammary and medial supraclavicular irradiation in breast cancer.” *N Engl J Med* 2015;373:317-327.

Recommendation 9: PHYLL-1 – Consider including “+/- RT” within the algorithm under the “TREATMENT” column instead of just the explanation under footnote. This could include the category level of recommendation (e.g. category 2B), as appropriate.

Rationale: Many other NCCN Guidelines disease sites will include additional therapies, such as RT, within the algorithm, also having a footnote for a robust explanation/reference. Inclusion of RT within the algorithm itself allows for visual confirmation of the possibility of its use. This would also be consistent with page PHYLL-2, where the consideration of postoperative radiation is listed in the algorithm.

References: N/A

Recommendation 10: BINV-F 1 OF 2, BINV-F 2 OF 2 – Create a brief table to be included on the bottom half of page “BINV-F 2 OF 2” summarizing all of the margin recommendations from the text included in this section.

Rationale: To allow for a concise, brief reference facilitating extraction of pertinent information at a glance.

References: N/A

Recommendation 11: BINV-2 – Negative axillary nodes; add category level to recommendation to “consider regional nodal irradiation” in central /medial tumors and >2 cm with high-risk features.

Rationale: Authors in MA.20 specifically site “Since the number of node-negative patients in our trial was relatively small, the application of our results to node-negative patients is unclear. “ (page 315 of manuscript) EORTC did have larger numbers and similar results as MA.20, however.

Reference: Whelan TJ, Olivetto IA, Parulekar WR, et al. “Regional Nodal Irradiation in Early-Stage Breast Cancer.” *N Engl J Med* 2015;373:307-316.

Recommendation 12: BINV-3 – Negative axillary nodes and tumor ≤5 cm and negative margins but <1 mm; add category level to recommendation to “consider RT to chest wall +/- regional nodal irradiation”.

Rationale: This population was not represented in MA.20 and made up less than 25% of EORTC. Oxford meta-analysis of PMRT in node negative patients showed no benefit to RT in terms of locoregional recurrence, overall recurrence, or breast cancer mortality.

References:

- Poortmans P, Collette S, Kirkove C, et al. “Internal mammary and medial supraclavicular irradiation in breast cancer.” *N Engl J Med* 2015;373:317-327.
- EBCTCG. “Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 woman in 22 randomized trials.” *Lancet* 2014;383:2127-35.