Improving Radiotherapy After Breast-Conserving Surgery

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In assessing the value of innovations in breast cancer radiotherapy, it is important to consider not only the basis of their impact on mortality, local recurrence, and cosmesis; emphasis should also be placed on factors such as treatment tolerance, convenience, and delayed morbidities.

Drs. Mouw and Harris have reviewed data from randomized clinical trials (RCTs) and from selected institutional experiences with whole breast irradiation (WBI), usually delivered with tangent pair radiation therapy (RT) over 5 to 7 weeks, accelerated whole-breast irradiation (AWBI), usually delivered over 3 to 4 weeks, and accelerated partial-breast irradiation (APBI), usually delivered in a single treatment or via up to a week of twice-daily treatments.[1] The authors conclude that the RCTs demonstrate that AWBI is equivalent to “standard” WBI in terms of 5- and 10-year local control, cosmetic outcomes, and breast cancer–specific and overall survival. There is much less long-term data supporting the equivalence of APBI and WBI. The authors are correct to advise caution in selecting patients for APBI, and they emphasize that true rates of long-term morbidity will only be known as a result of ongoing follow-up of patients treated with various APBI techniques.

Mouw and Harris have been rather cautious in recommending the use of AWBI. They cite the American Society for Radiation Oncology (ASTRO) guideline[2] and ongoing trials but fall short of recommending AWBI despite level I evidence of equivalent efficacy and long-term tolerance.[3] For many decades, our institutions and others have been using and evaluating AWBI, and have found it to be acceptable for a much broader array of patients than those endorsed for treatment in the ASTRO guideline.[4-7] The use of shorter fractionation schedules has gained wider acceptance in the US since the publication of the Canadian trial,[8] but there is still reluctance to implement shorter, more convenient and less resource-intensive RT prescriptions. This may be fueled in part by unplanned subgroup analyses reported for the Canadian trial, one of which suggested that hypofractionated RT might be less effective in patients with grade III histology. That hypothesis was not substantiated when evaluated in patients participating in the RCTs of hypofractionation in the UK,[9] nor in a population-based study of patients with grade III breast cancer in British Columbia that included more than 1,000 patients treated with hypofractionation.[10] While not all patients are suitable candidates for hypofractionation, its use should not be based on pathologic factors of the primary tumor or on patient age. The concern about AWBI relates to the need for larger doses per fraction, and the potential for late fibrosis that may cause pain or cosmetic deterioration over time. Patients with large areas of dose inhomogeneity in the breast; with implants; and with significant post-operative breast problems such as hematoma, infection, or significant dependent edema are at greater risk of fibrosis with conventional or hypofractionated RT. For such patients there is no rationale to switch from, for instance, 42.5 Gy in 16 fractions to 50 Gy in 25 fractions, because there are 10-year RCT data demonstrating the radiobiological equivalence of these regimens.[8] Among patients with a relative contraindication for hypofractionation, a better strategy would be delivery of 45 Gy in 25 fractions to the whole breast, with a boost of 10 to 16 Gy in 5 to 8 fractions to compensate for the missing primary site dose.[11] Dual-energy photons, forward- or inverse-planned intensity-modeulated RT (IMRT), and prone-breast RT can be used to improve dose homogeneity and increase the use of hypofractionated RT for women with fuller breasts. In contrast to Mouw and Harris, we would put greater emphasis on the evidence that breast IMRT is an efficient way to reduce acute and delayed side effects of WBI. Three RCTs have shown consistent benefits using breast IMRT.[12-14] IMRT reduced acute dermatitis and moist desquamation, decreased patients’ pain, and improved quality of life. For women with large breasts, breast IMRT improved the cosmetic result and reduced delayed side effects such as telangiectasia. Whether using forward- or inverse-planned techniques, a core principle of modern breast RT is that the photon beam intensity should be modulated to improve dose homogeneity and create a more efficient way to deliver less toxic treatment.[15] We concur with Mouw and Harris’ conclusion that it is premature to wholeheartedly endorse the use of APBI, but we would put more emphasis on the risk/benefit balance inherent with APBI.[1] Use of...
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APBI has increased significantly over the past two decades, and accumulating local control data are encouraging. The 5-year ipsilateral breast tumor recurrence (IBTR) rate with APBI is about 3.6%.[16,17] As Mouw and Harris note, 5-year IBTR rates have been falling, and after WBI are now at about 2%.[1] This suggests the price of APBI may be an additional 1% to 2% risk of local recurrence. This increased IBTR risk is unlikely to have a significant impact on overall survival, but the real question is whether the short-term convenience and reduction in irradiated breast volume with APBI is worth a small increased risk of IBTR and mastectomy. To accept such a risk, the benefits as weighed against treatment tolerance and burden should be significant. Regarding treatment burden, single-fraction APBI treatments like intraoperative techniques or permanent breast seed implants[18] have an advantage over 3D-conformal RT (CRT) or high-dose-rate (HDR) brachytherapy that typically deliver 10 fractions over 5 days, meaning the patient needs to spend almost 5 full days at the RT center. Regarding tolerance, an early report from the MammoSite registry[16] and early data for external beam APBI from the National Surgical Adjuvant Breast and Bowel Project (NSABP)-B39/Radiation Therapy Oncology Group (RTOG) 0413 study[19] suggest APBI is well tolerated. However, APBI does not always minimize dose to adjacent normal structures. 3D-CRT is not all that conformal, which may lead to increased fibrosis and cosmetic deterioration over time. Longer follow-up of RCTs involving 3D-CRT are needed to evaluate these risks. HDR brachytherapy using iridium-192 can expose nearby normal structures to several thousand millisieverts of radiation,[20] which may increase long-term radiation-induced morbidities including secondary cancers. While brachytherapy is the APBI technique with the longest follow-up, its future should include the use (eg, 103Pd seeds) or development of low-energy sources (eg, electronic sources) that reduce radiation exposure.

In conclusion, there have been multiple innovations to improve breast radiotherapy over the past decade. In assessing the value of these innovations, it is important to consider not only the basis of their impact on mortality, local recurrence, and cosmesis; emphasis should also be placed on factors such as treatment tolerance, convenience, and delayed morbidities.

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