Opinion Viewpoint

Hypofractionated Whole Breast Radiotherapy
Adapting to the Evidence

Reshma Jagsi, MD, DPhil
Department of Radiation Oncology, University of Michigan, Ann Arbor; and Center for Bioethics and Social Science in Medicine, University of Michigan, Ann Arbor.

Increased consciousness about the costs of cancer care, which substantially impact both society and the finances of individual patients, motivates interest in opportunities to improve efficiency. In the field of radiation oncology, hypofractionation—reducing the number of daily radiation treatments by giving higher doses per fraction—is one of the most promising opportunities of this sort. Hypofractionation can improve convenience and lower costs, and growing evidence attests to its safety and efficacy in selected clinical settings. Therefore, it is unsurprising that hypofractionation is the subject of 2 of the first “top 5” opportunities in the Choosing Wisely campaign of the American Society of Radiation Oncology (ASTRO).

Given the sheer number of women who receive radiation therapy as part of breast-conserving therapy for breast cancer each year, hypofractionation has the potential for particularly dramatic impact in this setting. Numerous trials have demonstrated substantial improvements in locoregional control from the administration of radiotherapy after breast-conserving surgery, and meta-analyses have established a modest survival gain in patients with invasive disease. In light of the fractionation schedules administered in most of these trials, physicians have traditionally counseled patients to expect 5 or more weeks of daily radiation treatments after breast-conserving surgery if they wish to avoid mastectomy. Unfortunately, this could diminish access to breast conservation in populations that face geographic, financial, or other barriers to the receipt of protracted courses of radiotherapy.

Over the past decade, high-quality randomized trials2,3 have generated evidence supporting the efficacy and safety of hypofractionated whole-breast radiation therapy involving approximately 3 weeks of daily treatments in selected patients compared with traditional schedules spanning 5 weeks or longer. A large Canadian trial randomized women with invasive, node-negative breast cancer after lumpectomy to a hypofractionated course of 42.5 Gy in 16 fractions vs a standard course of 50 Gy in 25 fractions. Early results emerged over a decade ago, and a more recent report demonstrated continued equivalence in both efficacy and safety at 10 years.2 Similar results emerged from several British trials, including the UK Standardisation of Breast Radiotherapy (START) B trial,3 which randomized women to 40 Gy in 15 fractions vs 50 Gy in 25 fractions, finding that late adverse effects might actually be lower after hypofractionation.
ated treatment. In light of this accumulating evidence, ASTRO issued consensus guidelines in 2011 supporting the use of hypofractionation for patients 50 years or older with T1-T2, N0 breast cancer who do not receive chemotherapy and in whom dose homogeneity is within ±7% at central axis. Since these criteria identify about half of all women with invasive breast cancer who undergo breast-conserving surgery as ideal candidates for hypofractionation, the implications are manifest.

Nevertheless, many women who meet criteria for consideration of hypofractionation are not receiving this more convenient approach, even in studies of elderly women in whom the absolute benefit of radiotherapy overall is low and in whom omission of treatment altogether might be considered. Moreover, such studies document that most of the variation in use of hypofractionation occurs at the level of the practice and clinician rather than the patient, suggesting that this variation is not appropriate individualization of care (related to patient factors such as body habitus, chemotherapy receipt, age, histologic findings, or laterality—which some believe identify subgroups of patients in whom hypofractionation is less well established and potentially more risky), but rather evidence of undesirable inconsistency.

As a health services researcher who has documented some of these trends and as a breast radiation oncologist, I am often asked by my colleagues from other specialties how radiation oncologists can possibly justify treating patients with burdensome longer courses of radiation: for instance, “What is there to consider, really, if there are robust data to suggest equivalence, and one schedule is considerably more costly and burdensome?” At first glance, the practice seems the bust data to suggest equivalence, and one schedule is considerably more costly and burdensome? At first glance, the practice seems the

To understand the hesitation and relatively slow adoption of hypofractionation in the radiation oncology community, it is valuable to reflect on the underlying rationale for fractionated radiotherapy as well as the nature of radiation-related toxic effects. Although all medical interventions can have, in addition to acute adverse effects, unanticipated late toxic effects (think, for example, of adhesions from surgical interventions or secondary leukemias after chemotherapy), perhaps no intervention precipitates concern about late effects as dramatically as radiotherapy.

Numerous laboratory, animal, and clinical studies have demonstrated that fraction size has a larger impact on late effects than acute effects of radiotherapy. Radiation oncologists have been trained that cells from late-responding tissues have survival curves that are more curved in shape than those from early-responding tissues, and tumors tend to resemble early-responding tissues. In the recent trials of hypofractionated breast radiotherapy, the total dose was reduced to mitigate the risk of late toxic effects (as observed in older studies of hypofractionated whole-breast radiotherapy where total dose was maintained), prompting worry whether this approach would be ineffectiveness for tumor cells. Only very recently have mature results emerged from randomized trials to confirm preclinical data suggesting that breast cancer cells might actually have survival curves more similar to late-responding normal tissues, such that a lower total dose administered in larger treatment fractions can indeed be ineffectiveness.

Ultimately, the hesitation to embrace hypofractionation until the accumulation of robust, long-term data to support its safety and efficacy is less difficult to understand when one appreciates the conceptual leap it requires from physicians who have long been schooled to respect the risk of late toxic effects with larger fraction sizes (if administered to a total dose needed to control tumor) or inadequate disease control (if administered to a total dose that does not result in unacceptable late effects). When further contextualized by consideration of heuristics that drive many physician and patient decisions, including risk aversion and anticipatory regret, the slow adoption of hypofractionated whole-breast radiotherapy is far from surprising.

Nevertheless, now that long-term results are available from multiple clinical trials, it is incumbent on the radiation oncology community to embrace the promise of hypofractionated approaches to reduce the burden of cancer care for individual patients and for society more generally. Changes in reimbursement may help to accelerate adoption to the extent that it has been slowed by financial disincentives in the US health care system. However, widespread dissemination of this important idea will ultimately also require the radiation oncology community to refine how we apply the fundamental principles we were trained to respect. Only by adapting to an evolving evidentiary landscape can we hope to advance our field and benefit our patients.

ARTICLE INFORMATION
Published Online: February 19, 2015.
Conflict of Interest Disclosures: None reported.
REFERENCES