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After reading the article "Progress and Controversies: Radiation Therapy for Invasive Breast Cancer," the learner should be able to:

1. Summarize the role of radiation therapy in breast-conserving therapy and after mastectomy.
2. Name and briefly describe new technologies for breast cancer radiation therapy.
3. Summarize current criteria for considering the use of accelerated partial breast irradiation.

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Progress and Controversies: Radiation Therapy for Invasive Breast Cancer

Reshma Jagsi, MD, DPhil[1]

Radiation therapy is a critical component of the multidisciplinary management of invasive breast cancer. In appropriately selected patients, radiation not only improves local control, sparing patients the morbidity and distress of local recurrence, but it also improves survival by preventing seeding and reseeding of distant metastases from persistent reservoirs of locoregional disease. In recent years, considerable progress has been made toward improving our ability to select patients most likely to benefit from radiotherapy and to administer treatment in ways that maximize clinical benefit while minimizing toxicity and burden. This article reviews the role of radiation therapy in invasive breast cancer management, both after breast-conserving surgery and after mastectomy. It focuses particularly on emerging evidence that helps to define the clinical situations in which radiotherapy is indicated, the appropriate targets of treatment, and optimal approaches for minimizing both the toxicity and the burden of treatment, all in the context of the evolving surgical and systemic management of this common disease. It includes a discussion of new approaches in breast cancer radiotherapy, including hypofractionation and intensity modulation, as well as a discussion of promising avenues for future research. **CA Cancer J Clin 2014;64:135-152.**

Keywords: breast cancer, radiation therapy, breast-conserving therapy, postmastectomy radiation, partial breast irradiation, hypofractionation, intensity-modulated radiotherapy

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Introduction

Radiation therapy is a critical component of the multidisciplinary management of invasive breast cancer. In appropriately selected patients, radiation therapy not only improves local control, sparing patients the morbidity and distress of local recurrence, but it also improves survival, presumably by preventing seeding and reseeding of distant metastases from persistent reservoirs of locoregional disease. In recent years, considerable progress has been made toward improving our ability to select patients most likely to benefit from radiotherapy and to administer treatment in ways that maximize clinical benefit while minimizing toxicity and burden.

This article reviews the role of radiation therapy in invasive breast cancer management, both after breast-conserving surgery and after mastectomy. It focuses particularly on emerging evidence that helps to define the clinical situations in which radiotherapy is indicated, the appropriate targets of treatment, and optimal approaches for minimizing both the toxicity and the burden of treatment, all in the context of the evolving surgical and systemic management of this common disease.

Radiation as Part of Breast-Conserving Therapy

Randomized trials comparing breast conservation with mastectomy have firmly established equivalent survival in appropriately selected patients, allowing most women with early stage disease to choose this more limited surgical procedure without compromising disease control. Radiation therapy has long been recognized as a key component of breast-conserving therapy and has been recommended in consensus guidelines for over 2 decades.[1,2]

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Initially, recommendations for radiation were grounded in results from individual randomized trials comparing breast-conserving surgery with and without adjuvant radiotherapy that suggested a substantial benefit from radiotherapy in reducing locoregional recurrence. For example, in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 randomized trial, the 20-year ipsilateral breast tumor recurrence rate was 14.3% after lumpectomy with whole breast radiation versus 39.2% after lumpectomy alone.[3] Only more recently has the impact of radiotherapy on overall survival in this setting been demonstrated.

The Early Breast Cancer Trialists' Collaborative Group meta-analysis first demonstrated in 2005 that the reduction in recurrence afforded by radiotherapy in this setting also provides a modest benefit in overall survival.[4] In the most recent update of the meta-analysis, which included 10,801 women in 17 trials of radiation or no radiation after lumpectomy, radiation reduced the 10-year risk of any recurrence in lymph node-negative women from 31% to 15.6% and reduced the 15-year risk of death from breast cancer from 20.5% to 17.2%.[5]

However, not all subgroups of patients attain the same absolute benefit from radiotherapy, and the survival benefit from treatment appears to be restricted to those patients who reap a large absolute reduction in recurrence risk from treatment rather than those in whom the absolute benefit in recurrence risk reduction is under 10% or even between 10% and 20%.

Seeking a Population With Favorable Features in Whom Omission of Radiation Is Safe After Breast-Conserving Surgery

Given the burden, morbidity, and cost of adjuvant radiotherapy, researchers have sought to identify a low-risk population of patients for whom the risk of recurrence in the absence of radiotherapy might be sufficiently small that omission of radiotherapy might reasonably be considered. Over 2 decades ago, in an early observational study, Nemoto et al remarked that, of 122 women who underwent lumpectomy alone, at a median of 4 years, none with a tumor size < 1 cm had recurred.[6]

Unfortunately, studies seeking to identify a subgroup of patients who could undergo breast-conserving surgery without radiotherapy, based upon clinicopathologic characteristics alone, have largely proved unsuccessful. For example, investigators at Harvard conducted a prospective study of lumpectomy alone in selected women with unicentric T1N0 invasive cancers of favorable histology (without extensive intraductal component or lymphovascular invasion) treated with a wide excision of pathologically negative margins measuring ≥ 1 cm.[7] No systemic therapy was given, and receptor testing was not required. The mean tumor size in that study was 0.9 cm, and the median age was 67 years. At 7 years of follow-up, the local recurrence rate was unacceptably high at 23%. Similarly, in a Finnish trial of patients with T1N0 disease who did not receive adjuvant endocrine therapy, the 12-year local recurrence rate was 27% among patients who did not receive radiotherapy after segmental resection.[8]

Because systemic therapy has an impact on locoregional control, the NSABP conducted the B-21 randomized trial in the hope of identifying whether tamoxifen might be used in lieu of adjuvant radiation in selected patients.[9] That study randomized 1009 women who had invasive breast cancers ≤ 1 cm in size after lumpectomy and negative margins (defined as no tumor on ink) to 1 of 3 treatments: tamoxifen alone, radiation alone, or tamoxifen and radiation. Estrogen receptor testing was not required, and 20% of patients were aged <50 years. Patients who received tamoxifen alone had an 8-year risk of ipsilateral breast tumor recurrence of 16.5% compared with 9.3% for patients who received radiation alone and 2.8% for patients who received both tamoxifen and radiation, leading the authors to conclude that adjuvant radiotherapy was necessary even in patients who had small tumors in the era of tamoxifen. Similarly, a Canadian multicenter trial randomized patients aged ≥ 50 years who had T1-T2, N0 tumors to receive either radiation plus tamoxifen or tamoxifen alone.[10] Again, the overall findings were disappointing, with unacceptably high rates of local recurrence (7.7% at 5 years and 18% at 8 years after tamoxifen alone). Even in the subgroup with T1N0, estrogen receptor-positive tumors, the 8-year rate of local recurrence was 15.2%. A German trial with a 2×2 factorial design demonstrated a large excess of local recurrences when both radiation and endocrine therapy were omitted but suggested that event-free survival might be similar in patients treated with endocrine therapy, radiation, or both.[11] However, the limited sample size and corresponding low statistical power to detect differences constrained the impact of this finding. An Austrian trial that randomized 869 women to undergo breast-conserving surgery and hormonal therapy with or without radiotherapy revealed a 5-year local relapse rate of 0.4% with radiotherapy versus 5.1% without radiotherapy, with no differences in distant metastases or overall survival; however, the group reported that, by 6 years, that difference had increased to 0.4% versus 9%.[12] Thus, they concluded that longer follow-up was necessary before reaching solid conclusions, and future research should seek to investigate whether an even more favorable subgroup can be prospectively defined.

To date, only 1 study has been interpreted by many as having successfully identified a limited subgroup of patients in whom the long-term risk of local recurrence

after breast-conserving surgery and endocrine therapy alone is low enough to consider the omission of radiotherapy: Cancer and Leukemia Group B (CALGB) 9343.[13] In that trial, 636 women aged ≥70 years with clinical stage T1N0M0, estrogen receptor-positive, invasive cancers received lumpectomy with negative margins (with or without axillary assessment) and tamoxifen for 5 years and were randomized to receive whole breast radiation versus observation. Radiation therapy decreased the risk of locoregional recurrence; and, at 10 years, 98% of patients who received radiotherapy were free from locoregional recurrence compared with 90% of those who did not receive radiotherapy. However, given the lack of difference in time to mastectomy, time to distant metastasis, breast cancer-specific survival, and overall survival,[14] many have concluded that the omission of radiation may be a reasonable option for elderly women with clinicopathologically favorable cancers who intend to receive endocrine therapy. Still, questions remain regarding whether the outcomes in CALGB 9343 are generalizable to patients who have risk factors like high-grade tumors, lymphovascular invasion, or close margins; to those who have a longer life expectancy; or to those who may be less compliant with endocrine therapy than the population that participated in the trial.

Hypofractionation

Because tens of thousands of women each year continue to require adjuvant radiotherapy after breast-conserving surgery, various alternative approaches to minimize the burden of treatment have been sought. Traditionally, radiation treatment after breast-conserving surgery has targeted the whole breast with total doses of 45 to 50 Gray (Gy) administered in 1.8- to 2-Gy daily fractions, followed in many centers by an additional 10- to 15-Gy boost dose to the tumor bed, for a total of 5 to 6 weeks of daily treatment.[15] Unfortunately, the cost and inconvenience of multiple weeks of radiation treatment may be a barrier to the use of breast-conserving therapy instead of mastectomy in some populations and may also partially explain the failure of some patients to receive the radiation therapy that is indicated after breast-conserving surgery.[16,17]

Hypofractionation of radiation treatment involves the use of larger daily doses of radiation and decreases the total number of fractions that must be administered. Radiobiologic studies have suggested that breast cancer cells have a relatively low "alpha-beta ratio,"[18,19] which indicates that it may well be possible to maintain equivalent tumor control with shorter hypofractionated schedules delivering lower total doses. Hypofractionation may involve treatment to the whole breast, or it may involve treatment to only part of the breast. The following sections discuss these 2 approaches in turn.

Hypofractionated Whole Breast Irradiation

Studies of hypofractionated whole breast radiation have a long history. Studies in the 1960s revealed substantial toxicity when the total dose was maintained and larger fractions were administered. Therefore, more recent attempts at hypofractionation have investigated the use of a larger dose per fraction along with a reduced total dose in an attempt to maintain normal tissue tolerance.[20]

Several trials have investigated the use of hypofractionated regimens of irradiation to the whole breast. For example, a large Canadian trial enrolled 1234 women with invasive, lymph node-negative breast cancer treated by lumpectomy with negative pathologic margins.[21] Patient accrual was limited to women of small to moderate breast size (breast separation ≤ 25 cm), and few patients received adjuvant systemic chemotherapy. The trial randomized women to receive hypofractionated whole breast irradiation of 42.5 Gy in 16 fractions over 22 days versus standard whole breast irradiation of 50 Gy in 25 fractions over 35 days. Acute toxicity was low and was similar between the arms, with grade 2 or 3 radiation skin toxicity observed in 3% of patients in each arm. Two cases of radiation pneumonitis developed in each arm, and 1 rib fracture developed in the standard arm.

More important, long-term outcomes also were similar between the arms. The 10-year risk of local recurrence was 6.2% in the hypofractionated arm and 6.7% in the standard arm, and the rate of good or excellent cosmesis was 69.8% in the hypofractionated arm and 71.3% in the standard arm.[22] Thus, hypofractionated whole breast irradiation has been shown to yield similar disease control and cosmetic outcomes, with considerably greater convenience, in patients with characteristics similar to those of patients entered on that study. However, the uptake of hypofractionation has not been uniform, even in Ontario. Although the importance of financial incentives to deliver greater numbers of radiation fractions may play some role in limiting the enthusiasm of US practitioners regarding this approach, the observation of a more limited impact of trial results than expected, even in Ontario, suggests that certain other barriers may have limited the diffusion of this approach into practice.[23,24] These barriers may include concerns about extrapolating the findings from that study to patients with larger body habitus or those receiving chemotherapy, as well as concerns about how to incorporate a radiation boost, which was discovered to be of benefit after the Canadian trial was already completed.[25] Moreover, some have noted that the overall rate of good to excellent cosmesis is somewhat lower than that observed in many US institutional series,[26] and long-term results regarding potential late effects in adjacent organs (such as the heart, which may take considerably longer to demonstrate late toxicity) have yet to mature.

Other data supporting hypofractionation come from the United Kingdom. In a randomized trial, 1410 patients were randomized to receive either standard fractionated whole breast irradiation or 1 of 2 nonaccelerated but hypofractionated schedules of 42.9 Gy or 39 Gy in 13 fractions over 5 weeks.[27] After 10 years, the proportion of patients who were free from moderate to marked breast induration was 63.7% in patients who received 50 Gy, 48.9% in those who received 42.9 Gy, and 72.3% in those who received 39 Gy. A subset of 723 patients were randomly assigned to receive either boost irradiation of 14 Gy delivered by electrons to the tumor bed or no boost; and an additional 687 patients received boost as part of their standard treatment. Patients who were randomized to boost irradiation had significantly higher rates of induration and telangiectasia.

The UK Standardization of Radiotherapy A (START A) trial built upon these findings by comparing 50 Gy in 25 fractions over 5 weeks with 41.6 Gy or 39 Gy in 13 fractions over 5 weeks in 2236 patients. Photographic assessments were similar between the 50-Gy and 41.6-Gy arms, but there were lower rates of change in breast appearance after 39 Gy than after 50 Gy, with a hazard ratio of 0.69 ($P = .01$). The START B trial compared 50 Gy in 25 fractions over 5 weeks versus 40 Gy in 15 fractions over 3 weeks in 2215 women. In that study, at a median follow-up of 6 years, photographic and patient assessments suggested lower rates of late adverse effects in the accelerated hypofractionated arm ($P = .06$ for photographic change in breast appearance).

Further studies are underway to build upon these findings. In the British FAST trial, women received even higher doses per fraction—50 Gy in 25 fractions, 30 Gy in 5 fractions, or 28.5 Gy in 5 fractions, all over 5 weeks—and maturation of the results will provide further interesting information on these issues.[28] In the United States, there is ongoing investigation of the incorporation of a concurrent boost with the use of intensity-modulated radiotherapy (IMRT).[29] These approaches hold significant promise for reducing the burden of adjuvant radiation treatment in patients undergoing breast-conserving surgery.

Accelerated Partial Breast Irradiation

Inspired by evidence that the majority of failures after breast-conserving therapy occur in the vicinity of the tumor bed[30-32] and the belief that it is possible to identify patients who have a low risk of residual disease remote from the lumpectomy cavity,[33] investigators have also begun to explore the possibility that an even more radically accelerated schedule of hypofractionated radiation might be tolerable if one treats only part of the breast. By further shortening treatment time, those developing these techniques of accelerated partial breast irradiation (APBI) hope that they may increase access to breast-conserving therapy for more women.[34] Moreover, it is possible that, by decreasing the volume of irradiated tissue, these techniques might lead to a decrease in treatment-related toxicity. In addition, because chemotherapy is still recommended in many patients with early stage disease, the potential for using APBI so that neither radiation nor chemotherapy is delayed by the other is appealing.[35] However, because other studies have shown that recurrences may develop outside even a generous volume beyond the primary tumor[36] and that microscopic disease may extend far from the original primary site,[37-39] both the toxicity and the effectiveness of APBI are the subjects of considerable ongoing investigation.

Various techniques are now available to deliver APBI. The earliest studies employed multicatheter brachytherapy techniques. A particularly early series from Guy's Hospital, London,[40,41] before the implementation of more rigorous patient selection and advances in dosimetric planning, reported a relatively high rate of ipsilateral breast recurrence of 37% among patients who received low-dose-rate brachytherapy alone after lumpectomy. However, more recent studies with proper patient selection and techniques have reported much lower rates of local recurrence after brachytherapy. For example, in the series of 199 strictly selected patients who received multicatheter brachytherapy at the William Beaumont Hospital,[32,42,43] the 5-year actuarial local recurrence rate was 1%, and the 12-year rate was 5%. This rate of local recurrence was not statistically different from the rate of local recurrence observed in a matched group of patients who received standard whole breast radiation. Infections were documented in 11% of patients, and fat necrosis—78% of which occurred in patients who had asymptomatic findings on mammography—was documented in 21%. Infection rates were higher with open (8.5%) versus closed (2.5%) cavity placement of the interstitial needles ($P = .005$). Promising results were also reported in other early, single-institution series in the United States[44-48] and in a multi-institutional Radiation Therapy Oncology Group (RTOG) phase 1/2 study that was initiated in 1995,[49] in which the actuarial 4-year rate of breast recurrence was 3% and the 4-year lymph node recurrence rate was also 3%. Long-term follow-up of certain specific series[50] has also illuminated that careful attention to technique, treatment planning, dose prescription, and total dose is important to avoid excess toxicity.[51] Modern interstitial brachytherapy tends to employ high-dose-rate treatment, like that used for the majority of patients who received partial breast irradiation on a small Hungarian randomized trial conducted from 1998 to 2004, in which no differences in local control were observed between those who received partial versus whole breast irradiation, and those treated with partial breast irradiation had significantly better cosmetic outcomes.[52]

Ultimately, the quality of a multicatheter implant depends on the skill of the radiation oncologist who places the catheters. Because experience with interstitial brachytherapy of the breast has decreased in recent years as electron-beam therapy has become the most common means by which to administer breast boost treatments, alternative, potentially more user-friendly devices for brachytherapy have been developed in recent years. Promising results with single-lumen balloon brachytherapy were reported approximately 1 decade ago by investigators associated with the manufacturer of the MammoSite device[53,54] and others.[55]

However, some have raised concerns regarding the outcomes of single-lumen brachytherapy, at least as it was performed in the early days of its development. In a highly publicized observational study of Medicare claims data, patients undergoing brachytherapy-based APBI had a higher mastectomy rate than those who received whole breast irradiation (3.95% vs 2.18%; $P < .001$).[56] However, it is important to note that this study considered the relatively early experience with brachytherapy, before criteria for appropriate patient selection and risk factors for complications had been articulated,[57] so its results may not reflect the toxicity or efficacy of brachytherapy as it is currently applied, now that experience with this approach is more mature.[58] For example, delayed catheter insertion may help to reduce what otherwise may be a substantial risk of persistent seroma formation.[59] Several institutions have reported favorable experiences with the approach, and a multi-institutional registry study by the American Society of Breast Surgeons recently reported a 90.6% rate of excellent or good cosmetic outcomes at 84 months, with rates of symptomatic seroma, fat necrosis, infection, and telangiectasia of 13.4%, 2.5%, 9.6%, and 13.0%, respectively.[60] However, given the potential for selection bias in these latter studies, debate continues in this area. More recently, interest has grown in the use of single-entry, multichannel applicators for the administration of high-dose-rate brachytherapy, given apparent dosimetric advantages from these approaches.[61-64]

Interest has also grown regarding the possibility of delivering partial breast irradiation with intraoperative treatment. Access is also increasing to technologies that allow for the delivery of a single fraction of radiation therapy while the patient is still on the operating table, before the surgical wound is closed. Initially, European investigators initiated studies of this approach. Using intraoperative electron therapy,[65,66] Veronesi and colleagues reported on a series of 237 patients who were treated with single-fraction doses of 17 to 21 Gy using electron energies of 3 to 9 megaelectron volts (MeV) administered with a portable linear accelerator.[67] After a median follow-up of 71 months, among 119 patients who were selected randomly from 1200 cases treated, grade 2 fibrosis was observed in 32%, and grade 3 fibrosis was observed in 6%.[68] Preliminary results from the intraoperative radiation therapy with electrons (ELIOT) randomized trial revealed a significant difference in local recurrence with this approach (5.3% after a single intraoperative fraction of 21 Gy vs 0.7% with standard, fractionated whole breast radiotherapy).[69] Researchers at the University of North Carolina have investigated intraoperative electron radiotherapy delivered before segmental mastectomy, delivering at least 15 Gy to the tumor plus a margin.[70,71] That group observed an alarmingly high 6-year rate of ipsilateral events (15%), and most of those events occurred in patients who had less favorable clinicopathologic features. In contrast, investigators at University College London have administered radiation using the Intrabeam, a miniature electron-beam–driven source of low-energy x-rays (50 kilovolts).[72,73] In the large targeted intraoperative radiotherapy (TARGIT-A) trial,[74] women with invasive ductal carcinoma were randomized to this approach versus whole breast external-beam radiotherapy. The 4-year rates of local recurrence were 1.20% in the intraoperative therapy group and 0.95% in the external-beam treatment group for the low-risk population that accrued to the study. Still, the shallow coverage offered with this technique has raised concerns regarding rates of in-breast tumor recurrence with longer follow-up.

Therefore, many investigators have turned their attention toward the possibility of accomplishing partial breast irradiation using fractionated conformal external-beam approaches, which are now possible given the improvements in target localization and dosimetric planning. External-beam treatment is noninvasive, allows treatment after full pathologic information is available without subjecting the patient to a second surgical procedure, and may be less operator-dependent compared with brachytherapy. Increased homogeneity of dose with external-beam therapy may reduce the complications from fat necrosis observed in brachytherapy series, but determining the appropriate dose for tumor control by extrapolating from doses used in the brachytherapy studies has been difficult precisely because of these large differences in dose homogeneity between techniques.

The most commonly used fractionation scheme for high-dose-rate brachytherapy has been 3.4 Gy delivered twice daily over 5 days, a schedule that was developed to be radiobiologically equivalent to a standard 5-week course of radiation and to minimize the time exposed to indwelling brachytherapy catheters, which increases the risk of infection. Those developing external-beam partial breast irradiation explored alternative schedules in order to address the differences in dose homogeneity with this approach.

In an early randomized trial, Christie Hospital's Holt Radium Institute treated 708 patients using either wide-field radiation therapy with 4-megavolt photons to a dose of 40 Gy in 15 fractions over 21 days or limited field radiation with 8- to 14-MeV electrons to a dose of 40 to

42.5 Gy in 8 fractions over 10 days.[75] After a median follow-up of 65 months,[76] a larger percentage of patients who received radiation to limited fields versus wide fields had marked telangiectasias (33% vs 12%) or marked fibrosis (14% vs 5%). Subsequent single-institutional studies generally used more cautious dosing schedules and more advanced planning techniques.

Investigators at New York University developed a technique of 3-dimensional (3D) conformal external-beam APBI in the prone position,[77,78] administering 30 Gy to the tumor bed plus a 1.5- to 2-cm margin in 5 fractions within 10 days, which produced promising results.[79] Investigators at the William Beaumont Hospital developed a technique of 3D conformal external-beam APBI performed in the supine position.[80] In contrast to the parallel-opposed minitangents generally used by the New York University group, the Beaumont group used 4 to 5 noncoplanar photon beams. The dose prescribed was 34 Gy to the tumor bed plus expansion in the first 6 patients and 38.5 Gy in the remainder, all in 10 fractions, again with promising outcomes.[81,82] The latter fractionation scheme was embraced by other institutions and was used for patients receiving conformal external radiation for partial breast irradiation on the large RTOG 0413/NSABP B-39 randomized trial seeking to explore both the efficacy and toxicity of partial breast irradiation further.[83]

As use of this approach spread, evidence emerged to suggest that the significantly higher integral dose to the normal breast[84] with this approach might cause detriment to cosmetic outcomes. Single-arm trials at Tufts[85,86] and the University of Michigan[87] suggested that rates of adverse cosmetic outcomes might be more substantial than usually observed with standard whole breast irradiation. However, an interim analysis of toxicity among patients enrolled on the large RTOG 0413/NSABP B-39 randomized trial revealed extremely low rates of severe toxicity in those receiving external-beam partial breast irradiation, as reported on physician case report forms using the Common Toxicity Criteria for Adverse Events.[88]

Recently, compelling evidence of a substantial negative impact of external-beam partial breast irradiation on cosmetic outcomes has been provided from the large, multicenter RAPID (Randomized Trial of Accelerated Partial Breast Irradiation) trial in Canada, which randomized patients to external-beam APBI, using a schedule of 38.5 Gy in 10 fractions, versus whole breast irradiation. Adverse cosmetic outcomes were more common in the patients who received APBI as assessed by trained nurse observers (29% vs 17%; $P < .001$), the patients themselves (26% vs 18%; $P = .002$), and blinded physician reviewers of photographs (35% vs 17%; $P < .001$). Therefore, additional research is necessary to identify which patients are most likely to experience adverse cosmetic outcomes after external-beam partial breast irradiation and to further refine dosimetric parameters and perhaps the dosing schedules themselves[89] for this approach.

In summary, in appropriately selected patients, and with appropriate techniques, APBI indeed may prove to be a safe and effective approach. Still, continued study is necessary, because only after mature data from randomized trials have been analyzed can the safety and efficacy of this treatment strategy be determined. Numerous ongoing and recently completed trials in the United States and abroad have been designed to evaluate both the efficacy and the safety of partial breast irradiation and will yield illuminating results along these lines in the coming years. Consensus guidelines do exist to guide patient selection while trial data mature.[57,90,91] Table 1 provides a summary of consensus guidelines developed by the American Society of Radiation Oncology. Nevertheless, given the rapidly evolving evidence regarding partial breast irradiation, patients should be fully informed of the nascent nature of our understanding in this area and encouraged to participate in clinical protocols whenever possible.

IMRT

Interest in reducing the burden of radiotherapy has also led in recent years to the investigation of techniques that may reduce treatment-related toxicity. Two-dimensional (2D) wedged techniques of radiotherapy delivery are limited by the fact that the breast contour varies considerably from the superior-most to the inferior-most aspect of the breast. Consequently, although a simple wedge may achieve excellent homogeneity along the central axis of the breast, substantial areas of dose higher than that prescribed (so-called "hot spots") may exist at other levels (see Fig. 1). These hot spots, in turn, may lead to both acute and late toxicity.

With the development of 3D treatment planning systems and the now widespread availability of linear accelerators with multileaf collimation capabilities, it has become possible to provide differential segmental blocking of the radiation beam through the treatment field to reduce hot spots in the dose distribution (see Fig. 2). This has led to an interest in administering radiation to the breast in several segmented fields, using either forward planning or inverse planning to determine beam weighting. This technique has commonly been called "breast IMRT." It is noteworthy that this relatively simple technique, which aims primarily to improve dose homogeneity, differs from the inverse-planned beamlet intensity modulation that is usually employed in other treatment sites with the aim of improving dose conformality.[92]

Investigators from William Beaumont Hospital observed decreased rates of dermatitis and edema in patients who were treated with a forward-planned IMRT technique

TABLE 1. "Suitable," "Cautionary," and "Unsuitable" Patient Groups for Accelerated Partial Breast Irradiation*

FACTORS	"SUITABLE" GROUP	"CAUTIONARY" GROUP	"UNSUITABLE" GROUP
Patient factors			
Age, y	≥60	50 to 59	<50
BRCA1/2 mutation	Not present	NA	Present
Pathologic factors			
Tumor size, cm	≤2[†]	2.1–3.0[†]	>3[†]
T stage	T1	T0 or T2	T3 or T4
Margins	Negative by at least 2 mm	Close (<2 mm)	Positive
Grade	Any	NA	NA
LVSI	No[‡]	Limited/focal	Extensive
ER status	Positive	Negative[§]	NA
Multicentricity	Unicentric only	NA	If present
Multifocality	Clinically unifocal with total size ≤2 cm[‖]	Clinically unifocal with total size 2.1 to 3.0 cm[‖]	If microscopically multifocal >3 cm in total size or if clinically multifocal
Histology	Invasive ductal or other favorable subtypes**	Invasive lobular	NA
Pure DCIS	Not allowed	≤3 cm in size	If >3 cm in size
EIC	Not allowed	≤3 cm in size	If >3 cm in size
Associated LCIS	Allowed	NA	NA
Nodal factors			
N stage	pN0 (i^-, i^+)	NA	pN1, pN2, pN3
Nodal surgery	SN Bx or ALND[††]	NA	None performed
Treatment factors			
Neoadjuvant therapy	Not allowed	NA	If used

*Patients are suitable for APBI if all criteria in "suitable" column are satisfied. Any of the criteria in the "cautionary" column should invoke caution and concern when considering APBI. Any of the criteria in the "unsuitable" column render patients unsuitable for APBI outside of a clinical trial. Criteria are derived from data (when available) and conservative panel judgment.

[†]The size of the invasive tumor component as defined by the American Joint Committee on Cancer.

[‡]The finding of possible or equivocal LVSI should be disregarded.

[§]Patients with ER-negative tumors are strongly encouraged to enroll in the National Surgical Adjuvant Breast and Bowel Project B-39/Radiation Therapy and Oncology Group 04–13 clinical trial.

[‖]Microscopic multifocality allowed, provided the lesion is clinically unifocal (a single discrete lesion by physical examination and ultrasonography/mammography) and the total lesion size (including foci of multifocality and intervening normal breast parenchyma) does not exceed 2 cm for the "suitable" group and 3 cm for the "cautionary" group.

**Favorable subtypes include mucinous, tubular, and colloid.

[††]Pathologic nodal staging is not required for ductal carcinoma in situ.

ALND, axillary lymph node dissection; APBI, accelerated partial breast irradiation; EIC, extensive intraductal component; ER, estrogen receptor; LCIS, lobular carcinoma in situ; LVSI, lymph-vascular space invasion; NA, the given criteria are not applicable; SN Bx, sentinel lymph node biopsy.

using multiple segments than among patients who were treated with 2D planning in an earlier era .[93–98] Researchers at Fox Chase Cancer Center also compared patients who were treated using IMRT with patients who were treated in an earlier era with 2D plans and observed a decrease in acute desquamation.[99]

A Canadian randomized trial in 358 patients compared breast IMRT versus 2D wedged treatment and reported a reduction in acute moist desquamation from 47.8% to 31.2% with the use of an IMRT technique that consisted of a mean of 4 to 6 segments.[100] Moreover, in another randomized trial, the British Breast Technology Group reported improvements in long-term cosmesis in patients randomized to IMRT compared with those randomized to standard 2D wedge-compensated treatment.[101] Still, although it is clear that intensity modulation leads to decreased toxicity

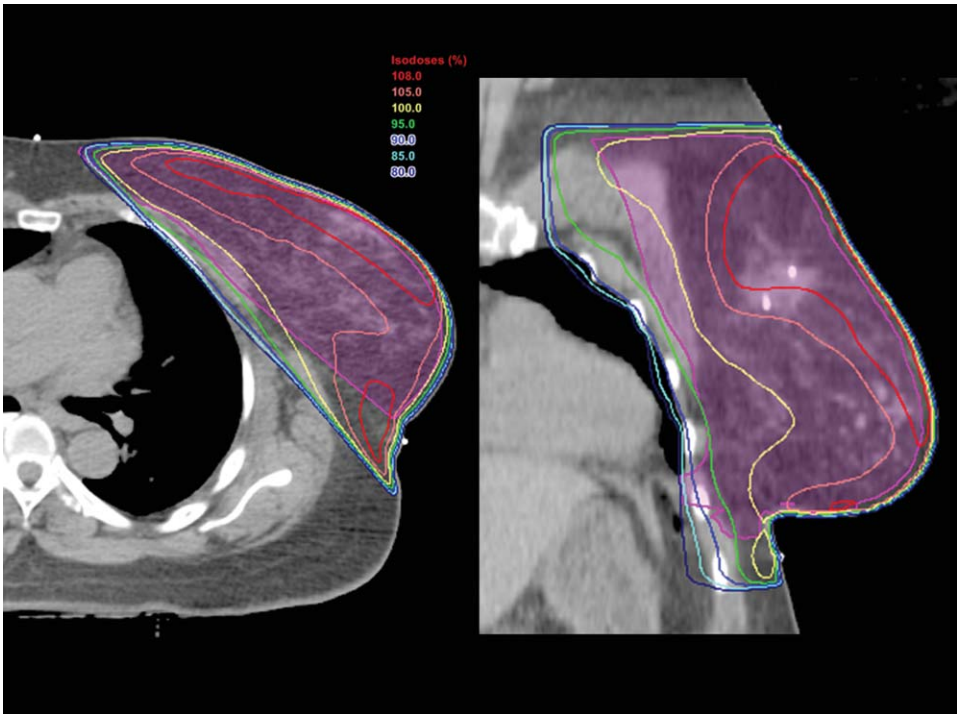

FIGURE 1. Dose Distribution With Simple Wedged Tangential Breast Radiotherapy. This figure demonstrates the inhomogeneity in dose that can occur when open, tangential, opposed photon beams with a single lateral wedge are applied to a typical breast. Like a topographic map, the peaks and valleys in dose are depicted here, including "hot spots" in which portions of tissue receive a higher dose than other regions. In this case, there are relatively large hot spots (as depicted in red). Figure courtesy of Robin Marsh, CMD.

compared with 2D planning, the question of how many segments are actually necessary to achieve the observed benefit and whether this treatment merits being billed at the substantially higher IMRT charge code remains the subject of ongoing discussion and investigation.[102]

Postmastectomy Radiotherapy

Appropriate selection of patients for postmastectomy radiation therapy continues to be another major subject of research and controversy. In patients at sufficient risk for harboring residual disease in the chest wall and regional lymph nodes after mastectomy and systemic therapy, radiation therapy not only may prevent morbid local recurrence but also may improve survival, presumably by eliminating an isolated microscopic reservoir of residual disease from which distant metastases may be seeded or reseeded after initial elimination by effective systemic therapy. However, not all patients have the same risk of harboring residual locoregional disease after mastectomy and systemic therapy or of that reservoir being an isolated one. Therefore, a key subject of research has been to identify which patients are likely to benefit from treatment.

Early randomized trials of postmastectomy radiation generally demonstrated a reduction in the risk of locoregional recurrence of breast cancer without improvement in overall survival, particularly before the advent of effective systemic therapies.[103-106] As experience with systemic therapy for breast cancer grew, it became increasingly apparent that certain subgroups of patients might harbor a burden of residual locoregional disease that systemic therapies could not eradicate and, thus, might benefit from the administration of postmastectomy radiation therapy. Therefore, several trials were initiated to explore the role of postmastectomy radiation in conjunction with chemotherapy.[107-112] Unfortunately, those early studies were designed before the late toxicity of radiation therapy was fully appreciated and sophisticated techniques of radiation field design were not yet available. Meta-analysis of those older studies revealed that the benefits in terms of disease control ultimately were offset by significant treatment-related toxicities, likely related to the exposure of large volumes of the heart and lungs to high doses of radiation.[113-116]

Subsequent trials ultimately did reveal a substantial benefit from postmastectomy radiation therapy in terms of both locoregional control and overall survival, and these trials have served as the foundation of existing clinical practice guidelines. These studies included mostly lymph node-positive patients along with a smaller number of individuals with locally advanced, lymph node-negative disease.

In a Danish trial of premenopausal patients, postmastectomy radiation therapy yielded both a substantial reduction in locoregional failure (from 32% to 9%) and a significant improvement in overall survival (the 10-year overall survival

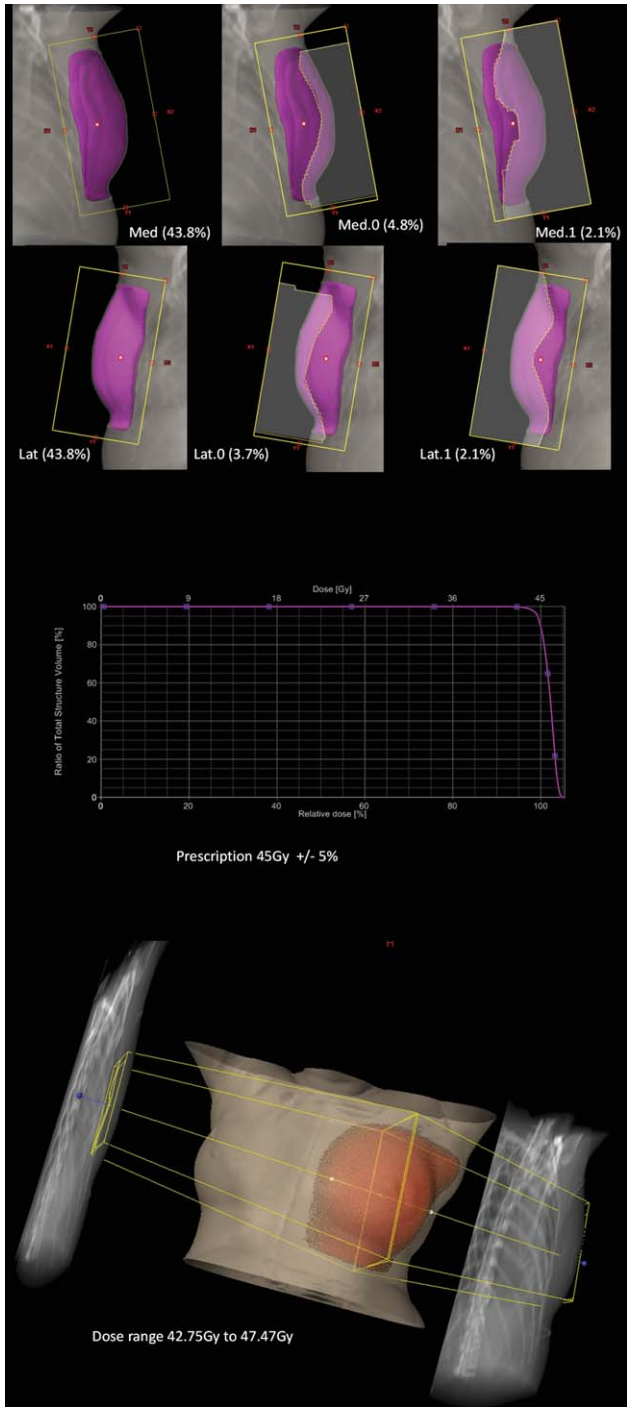

FIGURE 2. Segmented Breast Intensity-Modulated Radiotherapy. This figure demonstrates differential segmental blocking of the radiation beam through the treatment field to reduce hot spots in the dose distribution. (*Top*) Specifically, the first row shows an open medial tangent beam followed by 2 segmentally blocked beams, and the second row shows the open, lateral tangent beam followed by 2 segmentally blocked beams. These segmentally blocked beams deliver a small proportion of the total dose and improve the homogeneity of the total dose distribution. (*Middle*) This graph demonstrates that most of the treated volume receives the prescribed dose, and a very small amount receives slightly less or more (homogeneity, ± 5%). Gy indicates Gray. (*Bottom*) This schematic demonstrates the angles from which these treatments are administered. Figure courtesy of Robin Marsh, CMD.

rate improved from 45% to 54%; $P < .001$). On multivariate analysis, the study indicated that primary tumor size, the number of involved lymph nodes, grade, age, and use of radiotherapy were all significant independent predictors of outcome; no interactions were observed between radiotherapy and the other characteristics, so the results suggested that the benefit of radiotherapy existed for all subgroups. Moreover, no difference in survival was observed between patients with left-sided and right-sided disease in the initial report at 10 years, and a separate publication that considered ischemic heart disease morbidity and mortality revealed no excess risk of ischemic heart disease in irradiated patients versus unirradiated patients.[117]

Similar findings were reported in a Danish trial conducted in postmenopausal patients,[118] in whom postmastectomy radiation therapy also led to both a reduction in locoregional recurrence (from 35% to 8%) and improvement in overall survival (the 10-year overall survival rate improved from 36% to 45%; $P = .03$). In a smaller but similarly designed Canadian trial in premenopausal patients, the 20-year survival rate improved from 37% to 47% ($P = .03$) with postmastectomy radiation therapy.[119]

Meta-analyses that included the results from these more recent trials have suggested that radiation therapy after mastectomy does indeed improve both local control and overall mortality.[120,121] Perhaps the most influential of these has been the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis,[4] which reported in a landmark 2005 publication that, among 8340 women who underwent mastectomy and axillary clearance for lymph node-positive disease and enrolled in trials of radiation therapy (generally to the chest wall and regional lymph nodes) through 1995, the 5-year local recurrence risk was reduced from 22.8% to 5.8%, with a 15-year breast cancer mortality risk of 54.7% versus 60.1% (reduction, 5.4%; 2-sided $P = .0002$) and an overall mortality reduction of 4.4% (64.2% vs 59.8%; 2-sided $P = .0009$). This led the EBCTCG to conclude that there was a 4:1 ratio, such that, for every 4 local recurrences prevented at 5 years, 1 life was saved.

Nevertheless, concerns have been raised about the external validity or generalizability of the Danish and Canadian trials. These include concerns about the systemic therapies administered in the era during which the trials were conducted and concerns regarding the adequacy of surgery performed in these trials.[122] In the Danish 82b and 82c trials, the median number of lymph nodes removed was only 7, and 255 patients on the 82b trial had fewer than 4 lymph nodes removed. Because so few lymph nodes were examined, there may have been substantial underestimation of the true number of involved lymph nodes, such that patients characterized as having only 1 to 3 involved lymph nodes in the Danish trials might well have been categorized as having ≥ 4 involved lymph nodes if a more complete level I and II axillary lymph node dissection had been performed. Furthermore, residual disease in the axilla might have necessitated radiation therapy in a way that may not

TABLE 2. NCCN Guidelines for Patient Selection for Postmastectomy Radiation Therapy Among Patients With Operable Invasive Breast Cancer

FEATURES	RECOMMENDATION
≥4 Positive axillary lymph nodes	Radiation therapy to the chest wall, supraclavicular, and infraclavicular regions; strongly consider radiation to the internal mammary region
1–3 Positive axillary lymph nodes	Strongly consider radiation therapy to the chest wall, supraclavicular, and infraclavicular regions; if giving radiation, strongly consider radiation to the internal mammary region
Negative axillary lymph nodes and tumor >5 cm or positive margins	Consider radiation therapy to the chest wall with or without supraclavicular and infraclavicular lymph nodes; strongly consider radiation therapy to internal mammary lymph nodes
Negative axillary lymph nodes, and tumor ≤5 cm, and close margins (<1 mm)	Consider radiation therapy to chest wall
Negative axillary lymph nodes, and tumor ≤5 cm and margins ≥1 mm	No radiation therapy

be the case when a more extensive axillary lymph node dissection is performed. Indeed, this idea is supported by the finding that the axilla was a component of locoregional recurrence in 13% of unirradiated patients in the Danish trials,[123] contrasting sharply with the much lower rates generally expected from complete level I and II dissection.[124,125]

Indeed, retrospective analyses of patients who had 1 to 3 positive lymph nodes after mastectomy and did not receive radiation treatment have demonstrated considerably lower absolute rates of locoregional recurrence than the rates observed in the unirradiated patients on the Danish and British Columbian trials, ranging from 10-16%.[126-129] Given these findings, which diverge substantially from the rates of locoregional failure observed in unirradiated patients who had 1 to 3 involved lymph nodes in the Danish and British Columbia studies, it has been unclear whether radiation therapy is indicated for this subgroup of patients in the United States. Consensus guidelines have tended to clearly recommend postmastectomy radiation for patients who have ≥ 4 involved lymph nodes but are more equivocal regarding decisions for patients who have 1 to 3 involved lymph nodes.[130-133] For example, the guidelines of the National Comprehensive Cancer Network are provided in Table 2.[134]

Of note, in 2007, the Danish investigators published a pooled reanalysis of a subset of the patients treated on the 82b and 82c trials who had ≥ 8 lymph nodes removed.[135] Even within this subgroup, there was a survival benefit, and that benefit had the same absolute magnitude (9%) among patients who had 1 to 3 involved lymph nodes as among patients who had ≥ 4 involved lymph nodes, although the locoregional recurrence rates were lower in the former group. This led the authors to debate the EBCTCG's argument for a 4:1 ratio between locoregional recurrence prevention and survival, noting that the survival benefit of postmastectomy radiation therapy is likely related to the ability of systemic therapy to eliminate any existing metastatic deposits at the time of diagnosis. Therefore, they concluded that radiation therapy may be particularly important in the subgroup of patients who have less extensive lymph node involvement, in whom the burden of distant disease at diagnosis is likely to be less substantial (and potentially more amenable to elimination by systemic therapies) or absent. In light of these data, taken together with the evidence described above, the most recent set of consensus guidelines from the National Comprehensive Cancer Institute state that patients with 1 to 3 involved lymph nodes who undergo mastectomy should "strongly consider" radiation therapy.

Patients without lymph node involvement may also be considered for radiation therapy in select circumstances. One such group is those who present with large or otherwise locally advanced primary tumors.[136,137] The Danish trials suggested benefit in that population, with an improvement in both locoregional recurrence (from 17% to 3%) and survival (from 70% to 82%) in premenopausal patients and an improvement in locoregional recurrence in the postmenopausal group (from 23% to 6%). However, more recent retrospective studies have suggested that the risk of locoregional recurrence without radiotherapy in patients with lymph node-negative tumors measuring ≥ 5 cm in size may be 10% or less—more modest than originally expected.[138,139] However, few tumors of extremely large size were included in those retrospective studies, so patients with T3N0 tumors still warrant consultation with a radiation oncologist, who may discuss these data with the patient to facilitate individualized decision-making.

The decision regarding whether to pursue radiation therapy in patients with borderline T3N0 disease may be further illuminated by some insights gained from retrospective studies of lymph node-negative patients that included patients with smaller primary tumors.[140-142] These studies

have identified several risk factors for locoregional recurrence in lymph node-negative patients undergoing mastectomy. These risk factors include young patient age, larger tumor size, close or involved surgical margins, the presence of lymphovascular invasion, the omission of systemic therapy, and high nuclear grade. It may be useful to consider these factors when deciding whether a patient is likely to benefit from postmastectomy radiation therapy.

Particular attention has been given to the implications of close or positive surgical margins. Several retrospective studies have addressed this issue.[143] In a cohort from British Columbia, trends for a higher risk of locoregional recurrence were observed in early stage patients with positive surgical margins after mastectomy if they were aged <50 years versus ≥50 years (20% vs 0%), had T2 tumors versus T1 tumors (19.2% vs 6.9%), had high-grade disease versus low-grade or intermediate-grade disease (23.1% vs 6.7%), or had lymphovascular invasion present versus absent (16.7% vs 9.1%).[144] More recently, in a large series from Boston, patients who had positive margins had a 5-year locoregional recurrence rate of 6.2%, but patients who had close (≤ 2 mm) margins had a risk of only 1.5% (similar to the 1.9% risk observed in patients with negative margins).[145] Thus, margin status is an important consideration when determining whether to offer postmastectomy radiotherapy, but the level of evidence to guide practice in this area is less well established than in others.

Finally, a particularly active area of research concerns patients who have received systemic therapy in the neoadjuvant setting. Because the research regarding postmastectomy radiation therapy described above was conducted in patients who received the more traditional sequence of surgery followed by systemic therapy, much of our understanding of the role of radiation therapy after mastectomy relies on pathologic staging that was conducted before exposure to systemic therapies. Extrapolating from those data to the situation of patients who have received systemic therapy before definitive pathologic evaluation has been complicated.[146]

Retrospective studies from the MD Anderson Cancer Center have provided insights regarding the role of radiation therapy in patients undergoing mastectomy after neoadjuvant chemotherapy.[147] These studies have suggested that the extent of disease both at diagnosis and after neoadjuvant chemotherapy are relevant considerations. Even patients who experience a pathologic complete response to neoadjuvant chemotherapy appeared to have a substantial reduction in locoregional recurrence risk with radiation therapy if they had initially presented with clinical stage III disease (33% risk vs 3% risk). However, no locoregional recurrences were observed for those who achieved a pathologic complete response after diagnosis with earlier stage disease.[148]

Similarly, in a retrospective analysis of locoregional recurrence patterns in patients treated on the NSABP B18 and B27 randomized trials of preoperative systemic therapy,[149] in whom postmastectomy radiation was not allowed per protocol, only 1 recurrence was observed in 94 patients who had a pathologic complete response, regardless of tumor size and clinical lymph node status. These studies have inspired a national randomized trial to explore the role of postmastectomy radiation, as well as regional lymph node radiation, in patients who experience the eradication of lymph node disease by preoperative systemic therapy.

In sum, the oncology community continues to debate the potential value of postmastectomy radiation therapy for categories of "intermediate-risk" breast cancer, in which data have proven insufficient to warrant definitive recommendations by expert panels. However, there is strong consensus regarding the role of postmastectomy radiation in patients with truly locally advanced disease. Indeed, a survey of radiation oncologists indicated that the vast majority (>98%) reported that they would offer radiation to at least the chest wall in patients with ≥4 involved lymph nodes, although there was less consensus regarding patients with T3N0 disease (in which 88.3% would offer postmastectomy radiation therapy to the chest wall), and even less for patients who had 1 to 3 involved lymph nodes (with 85.2% offering postmastectomy radiation therapy to at least the chest wall if lymph node extracapsular extension was noted and 61.7% offering it if extracapsular extension were absent).[15] Thus, all patients with locally advanced breast cancer merit referral to radiation oncology, and postmastectomy radiation therapy is considered to be an integral component of their multimodal management.

Management of the Regional Lymph Nodes

The rationale for radiation therapy to the regional lymph nodes is the same as that articulated for postmastectomy radiation therapy. In select patients with lymph node involvement, the regional lymph node basins may be the only reservoir of residual disease after local surgery and systemic therapy. Eradication of that reservoir, if isolated, could improve survival. The Danish and Canadian postmastectomy trials included treatment to the supraclavicular, axillary, and internal mammary lymph nodes; and some have extrapolated from those trials that radiation therapy to those regions also should be considered for patients who undergo breast-conserving surgery.

In patients who have undergone complete level I/II axillary node dissections, there is generally consensus that directed radiotherapy to the axilla is unnecessary. However, axillary dissection is no longer routine in patients with positive lymph nodes. The American College of Surgeons Oncology Group Z0011 trial randomized patients who had clinical T1/T2 invasive breast cancer, no palpable adenopathy, and 1 to 2 sentinel lymph nodes containing metastases

to axillary lymph node dissection versus no further axillary surgery. In the patients who were treated on this trial, among whom a substantial proportion had micrometastatic disease and the vast majority of whom received adjuvant endocrine therapy, survival was equivalent between the 2 arms at 6.3 years. Although the study protocol recommended standard tangential radiotherapy, the radiation treatment was not audited, and it is possible that the radiation oncologists who treated patients on that trial did indeed use high tangent fields or other techniques for directed axillary treatment. Therefore, many practitioners in the United States have considered treatment to the axilla if undissected after a positive sentinel lymph node biopsy.[150]

Much debate surrounds the appropriate management of the supraclavicular and internal mammary lymph node regions in patients who have positive axillary lymph nodes but no clinical evidence of involvement in those regions. In the National Cancer Institute of Canada MA20 trial, 1832 patients who underwent breast-conserving surgery were randomly assigned to receive radiation therapy to the breast either alone or in conjunction with treatment to the regional lymph nodes. Preliminary results suggested a 5.4% absolute improvement in distant disease-free survival and a 2.3% benefit in locoregional disease-free survival from the addition of radiation therapy to the supraclavicular and internal mammary regions. Of course, the MA20 trial did not isolate the impact of supraclavicular versus internal mammary radiation, nor did the European Organization for Research and Treatment of Cancer 10925 trial, which still remains to be analyzed. Supraclavicular fields are generally less controversial, given that a nontrivial minority of failures occur in this region,[151] and it is believed that treatment results in little if any increase in the risks of pneumonitis, brachial plexopathy, and lymphedema. In contrast, concerns about the potential cardiac and pulmonary toxicity associated with treating the parasternal internal mammary lymph node region are significant. This has led to particular controversy surrounding treatment to the internal mammary region in particular[152-154] and widespread variation in practice patterns.[155] Considerable controversy remains regarding the need to treat this region,[156] and practice varies widely. The current National Comprehensive Cancer Network guidelines recommend strong consideration of treatment to the internal mammary lymph nodes.

Toxicity Concerns

In addition to the concerns about cosmetic outcomes of breast conservation discussed above, particular attention has been devoted in recent years to the potential cardiac toxicity of breast radiotherapy. As noted above, the cardiotoxic effects of older techniques, which exposed large volumes of the heart to high doses of radiation, have been clearly established.[157] More recent studies have raised concerns about even more conformal, modern techniques. The left anterior descending coronary artery may be incidentally irradiated to high doses by tangential fields, and treatment to the internal mammary lymph node region also can result in dose to the right coronary vessels.

Reassuringly, population-based studies have suggested that the magnitude of increased cardiac risk related to radiation therapy may have decreased in more recent years.[158] However, it is sobering that perfusion defects (for which the clinical consequences have yet to be defined) have been observed even in patients treated with relatively modern techniques.[159] Several single-institution studies have suggested that there may be an increase in the relative risk of ischemic cardiac events after radiation therapy for left-sided breast cancer, although the absolute magnitude of this increased risk appears to be low.[160] Recent studies have also suggested that radiation and other cardiac risk factors, such as hypertension or smoking, may be synergistic in their effects.[161,162] A recent population-based case-control study has highlighted the importance of minimizing the radiation dose to the heart.[163] However, it is important to note that the net survival benefit of radiation therapy that was documented in the trials discussed above and in the meta-analysis already accounted for any adverse impact of cardiac toxicity on survival. Therefore, although reducing the radiation dose to cardiac structures is a worthy and important endeavor, patients with a substantial likelihood of net benefit should not avoid treatment solely because of concerns related to cardiac exposure. Careful treatment planning, including consideration of sophisticated technology and respiratory gating in cases where cardiac anatomy is unfavorable, is essential to ensure that cardiac dose and the attendant risks are minimized.

Conclusions and Directions for Future Research

Considerable progress has occurred in our knowledge regarding appropriate patient selection and techniques for radiation in the treatment of breast cancer. Efforts continue to reduce the burden of radiotherapy in the setting of breast conservation, including the possibility of defining a subgroup that may safely avoid radiation altogether in an era of increasingly effective systemic therapy, as well as to ensure the appropriate targeting of treatment in the setting of mastectomy. Further research is necessary to define those patients at highest risk for radiation-related toxicity as well as to define the optimal management of that toxicity when it occurs.

In recent years, the field of oncology has begun to appreciate that breast cancer is a heterogeneous disease in which tumor biology can be at least as important as clinicopathologic stage in determining outcomes. Therefore, interest

has been growing in the evaluation of outcomes by biologic subtype as well as in defining genomic predictors of recurrence.[164,165] Already, retrospective studies have begun to evaluate the influence of subtype upon locoregional recurrence risk and response to radiotherapy.[166-169] Further research along these lines may be particularly valuable in the quest to better individualize locoregional therapy for breast cancer, ensuring that treatment is targeted toward those most likely to benefit and sparing those at lower risk from unnecessary toxicity and burden. ■

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