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Postoperative Radiotherapy After Breast-Conserving Surgery for Early-Stage Breast Cancer
A Review

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IMPORTANCE Radiotherapy (RT) after breast-conserving surgery for early-stage disease has become an integral part of breast cancer treatment. This article reviews the rationale and indications for adjuvant radiotherapy to the breast and regional lymph nodes.

OBSERVATIONS Randomized trials have demonstrated a significant benefit in tumor control in the treated breast following whole-breast RT that, in aggregate, has resulted in an overall survival advantage compared with breast-conserving surgery alone. Recent studies have further assessed the impact of regional nodal irradiation in women with either high-risk node-negative or node-positive disease and suggest a significant benefit in regional control and breast cancer recurrence, but not in overall survival. Toxic effects, including lymphedema, were increased in the cohorts receiving comprehensive nodal RT. The benefits from regional RT should be weighed against potential radiation-associated toxic effects. Randomized trials have also demonstrated equal efficacy and toxic effects between hypofractionated and conventionally fractionated RT in appropriately selected patients. In addition, current efforts incorporating clinical, pathologic, and molecular features are under way to identify patients for whom RT to the breast can be safely omitted.

CONCLUSIONS AND RELEVANCE Adjuvant RT in early-stage breast cancer significantly reduces in-breast tumor recurrence and improves overall survival. Although risk reductions observed in randomized trials have been relatively consistent across series, the absolute benefit of RT is not equal for all women. Efforts are under way to identify which patients benefit the most from local or locoregional RT vs those at very low risk for recurrence in whom RT can be omitted. For patients who will benefit from RT and are appropriate candidates, hypofractionated RT should be strongly considered.

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The Benefit of Adjuvant Radiation Following Breast-Conserving Surgery

A remarkably consistent local control benefit has been demonstrated in multiple randomized phase 3 studies designed to assess the role of adjuvant radiotherapy (RT) in women treated with breast-conserving surgery. These trials[1-11] (**Table 1**), initiated over 2 decades (1976-1991), included a variety of surgical managements, systemic treatments, radiation doses and fields, and baseline recurrence risks. Despite these differences, all trials demonstrated a strikingly similar risk reduction in the rates of local recurrence with the addition of adjuvant RT. No single trial, however, was able to individually demonstrate an overall survival benefit. A survival benefit was not shown until the publication of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis[12] which, by aggregating the mature data, achieved sufficient power to demonstrate an overall survival advantage with adjuvant RT.

A potential reason that a survival advantage was not demonstrated in earlier randomized studies lies in the design of these trials, which individually were underpowered to detect an overall survival benefit. Furthermore, older RT techniques often used external-beam arrangements that delivered significant doses to the heart, particularly for left-sided cancers. Thus, competing risks of death from cardiac disease almost certainly overwhelmed any potential survival benefit that would have been derived from reducing locoregional recurrences with adjuvant RT.

The Role of RT Treatment in Women With Node-Positive Breast Cancer

The EBCTCG meta-analysis[12] demonstrated that women with either node-negative or node-positive disease derived a substantial benefit from RT for both local control and overall survival. In the node-negative group, local recurrence rates were 22.9% without RT and

Table 1. Randomized Clinical Trials of BCS With or Without RT

Source	Accrual Dates	No. of Patients	Inclusion Criteria	Treatment Arms	RT Dose	LN+, %	Treatment	Systemic Agents, %	Local Recurrence, %	OS
Fisher et al,[1] 1995 (NSABP B-06)	1976-1984	1851	Stage I/II, (<4 cm, negative margins)	Total mastectomy vs lumpectomy vs lumpectomy plus RT	50 Gy	38	Chemotherapy N+	Melphalan, fluorouracil	20 y: 14.3% with RT vs 39.2% without RT	No difference at 20 y
Liljegren et al,[3,4] 1994, 1999 (Uppsala-Orebro)	1981-1988	381	Stage I (<2 cm, N0)	Sector resection, ALND with or without RT	54 Gy; no boost	0	None	None	10 y: 8.5 with RT vs 24.5 without RT	No difference at 10 y
Renton et al,[9] 1996 (St George)	1981-1990	418	T1-T2, N0-N1	Wide local excision, level I ALND, chemotherapy with or without RT	Not stated	Unclear	ER+ received tamoxifen, ER− received chemotherapy	Cyclophosphamide, methotrexate, fluorouracil with or without tamoxifen	5 y: 13 with RT vs 35 without RT	No difference at 5 y
Clark et al,[5] 1996 (Ontario)	1984-1989	837	Stage I/II (<4 cm, LN−)	Lumpectomy and axillary dissection with or without RT	40 Gy/16 fractions with boost; 12.5 Gy/5 fractions	0	None	None	8 y: 11 with RT vs 35 without RT	No difference at 8 y
Forrest et al,[11] 1996 (Scottish)	1985-1991	585	Tumor <4 cm, age <70 y	Lumpectomy, ALND/SLN with or without RT	50 Gy with or without boost; if no ALND in axilla, received 45 Gy/20 fractions		ER+ received tamoxifen, ER− received chemotherapy	Cyclophosphamide, methotrexate, fluorouracil or tamoxifen	6 y: 6 with RT vs 24 without RT	No difference at 6 y
Semiglazov et al,[8] 1998 (St Petersburg)	1985-1996	360	T1-T2, N0, tumor <2.5 cm	Quadrantectomy with or without RT	Unclear	0	Chemotherapy	Unclear	5 y: 4 with RT vs 17 without RT	No difference at 5 y
Veronesi et al,[2] 1995 (Milan 3)	1987-1989	579	Size <2.5 cm	Quadrantectomy and ALND vs quadrantectomy, ALND with RT	50 Gy with 10-Gy boost	32	Low risk N+: tamoxifen; high risk N+: chemotherapy	Cyclophosphamide, methotrexate, fluorouracil	10 y: 6 with RT vs 23 without RT	N+: 34% without RT, 19% without RT (statistically significant)
Fisher et al,[7] 2002 (NSABP B-21)	1989-1998	1009	Stage I (tumors ≤1 cm)	Lumpectomy with ALND: randomized to RT, tamoxifen, or RT with tamoxifen	50 Gy; boost at discretion	0	Randomized to with or without tamoxifen	Tamoxifen	8 y: 2.8 with RT and tamoxifen vs 9.3 RT alone vs 16.5 tamoxifen alone	No difference at 8 y
Malmstrom et al,[6] 2003 (SweBCG)	1991-1997	1187	Stage I/II median tumor size 1.2 cm, all N0	Sector resection, ALND with or without RT	48-54 Gy, no boost	0	Chemotherapy at discretion of treating physician	9 Chemotherapy	5 y: 4 with RT vs 14 withoutRT	No difference at 5 y
Winzer et al,[10] 2010 (German GBSG)	1991-1998	347	pT1 N0, ER+, grade I-II, EIC−, LVI−, SM−, ALND with minimum 10 LNs	2 × 2 Factorial BCS with or without RT with or without tamoxifen	50 Gy with 10- to 12-Gy boost	0	Randomized to with or without tamoxifen	Tamoxifen	10 y: 5 for RT with tamoxifen vs 7 for tamoxifen alone vs 10 for RT alone vs 34 for BCS alone	No difference at 10 y

Abbreviations: ALND, axillary lymph node dissection; BCS, breast-conserving surgery; EIC, extensive intraductal component; ER, estrogen receptor; GBSG, German Breast Cancer Study Group; LN, lymph node; LR, local recurrence; LVI, lymphovascular space invasion; N, node; NSABP, National Surgical Adjuvant Breast and Bowel Project B-6; OS, overall survival; RT, radiotherapy; SLN, sentinel lymph node biopsy; SM, surgical margin; SweBCG, Swedish Breast Cancer Group; +, positive; −, negative.

6.7% with RT at 5 years, and 15-year breast cancer mortality risks were 31.2% and 26.1%, respectively. Corresponding estimates in patients with positive axillary nodes were 41.1% without RT and 11.0% with RT at 5 years, and 55.0% and 47.9% at 15 years, respectively. Given the competing risks for both local and distant failures, particularly among node-positive women, subsequent EBCTCG analyses focused primarily on the reporting of first recurrences. Use of RT in patients with pathologic node-positive cancer significantly decreased the risk of any first recurrence from 63.7% to 42.5% at 10 years (an absolute reduction of 21.2%) and the 15-year risk of breast cancer death from 51.3% to 42.8% (an absolute reduction of 8.5%).[13]

Since the EBCTCG reporting of the in-breast tumor recurrence (IBTR) results in patients with node-positive disease, additional series have shown even higher rates of tumor control in the treated breast using RT with contemporary systemic therapies. Wapnir et al[14] evaluated 2669 women with node-positive breast cancer enrolled in multiple National Surgical Adjuvant Breast and Bowel Project (NSABP) trials. In these studies, the 10-year rate of isolated IBTR was 8.7% and the other local or regional recurrence rate was 6.0% suggesting that, even in the node-positive patient population, the risk of locoregional recurrence was low with adjuvant RT therapy in the presence of contemporary systemic therapy.

Although these data clarified the benefit of adjuvant whole-breast RT in women who underwent breast-conserving surgery, the role of nodal-directed RT was less clear. Historically, cancer in the axilla has been managed surgically with axillary lymph node dissection (ALND), which is therapeutic and provides prognostic and staging information. Owing to the morbidity of ALND, particularly lymphedema, interest in using more conservative surgical approaches to manage disease in the axilla grew. Thus, sentinel lymph node (SLN) surgery was developed in an attempt to mitigate the morbidity of ALND in a patient population that, because of more aggressive screening, was at an ever-decreasing risk of having nodal metastasis. Multiple randomized trials (NSABP B-32,[15,16] Sentinella,[17] Axillary Lymphatic Mapping Against Nodal Axillary Clearance,[18] and Milan Sentinel Lymph Node[19]) have demonstrated that SLN surgery is an effective means of pathologically assessing the axilla in women who are clinically node negative and results in rates of axillary control and survival comparable to those with ALND in patients with pathologically node-negative disease.

In light of these results, investigators postulated that, even for women with positive SLN, ALND dissection was perhaps unnecessary. To that end, both the International Breast Cancer Study Group 23-01[20] and and American College of Surgeons Oncology Group [ACOSOG] Z0011[21] trials were designed to determine whether completion ALND was necessary for women with micrometastatic and macrometastatic nodal disease. These trials suggested that there are no significant differences in the rates of local, regional, distant recurrence, or disease-free survival at 5 years between groups. These results have been used to justify the omission of completion ALND, and therefore its associated morbidity, in patients with limited SLN involvement, particularly in those treated with whole-breast RT. However, a recent analysis[22] of the radiation fields from a subset of patients enrolled in ACOSOG Z0011 suggests that the undissected axilla was included in extended RT fields in some of the patients randomized to the no-ALND arm, suggesting that nodal RT could have contributed to the low axillary recurrence rate observed.

An additional question regarding axillary treatment was addressed by the European Organisation for Research and Treatment of Cancer (EORTC) 10981-22023 (AMAROS) trial,[23] which compared ALND and axillary RT efficacy and morbidity. In this trial, women with positive SLN were randomized to completion ALND vs axillary-directed RT (50 Gy in 25 fractions [to convert gray to rad, multiply by 100]). Although the median number of positive nodes was only 1 and the event rates for both arms of this noninferiority trial were lower than expected, the results showed comparable rates of tumor control with either completion ALND or axillary RT in patients with T1 to T2, cN0 breast cancer. The findings also demonstrated that there were significantly fewer toxic effects and less morbidity, especially related to lymphedema, with RT compared with surgery (5-year rates of 23% vs 11% for ALND vs RT, respectively) at the cost of slightly increased rates of shoulder morbidity with regional RT. The results from this trial suggest axillary RT as an alternative to ALND in patients with SLN involvement.

Regarding treatment of the internal mammary and supraclavicular nodes, several trials were designed to assess the effect of regional RT on these nodal regions in early-stage disease. A French randomized clinical trial[24] of internal mammary node (IMN) RT for node-positive or high-risk node-negative cancers treated with mastectomy demonstrated that, although the overall survival rate was not significantly improved at a median follow-up of 11.3 years (62.6% with vs 59.3% without RT) with IMN RT, certain subsets of patients benefited from IMN treatment, including those with node-positive disease. Further evidence of benefit was observed in a more recently published Danish population study[25] that looked at whether IMN treatment improved overall survival as a primary end point. In that study, patients who underwent operations for unilateral, early-stage, node-positive breast cancer were allocated to IMN treatment for right-sided disease, whereas those with left-sided disease were allocated to no IMN treatment because of the risk of radiation-induced heart disease. At a median follow-up of 8.9 years, the 8-year overall survival rate was significantly improved for those receiving IMN RT (75.9% vs 72.2%; $P = .005$). Other metrics, including disease-free survival and distant metastasis–free survival, were also improved with IMN RT.

Although these studies looked at the role of IMN RT specifically, a more recent Intergroup/National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) MA.20 trial[26] was developed to test whether comprehensive nodal irradiation (treatment of the supraclavicular and IMN regions) would benefit patients with high-risk, node-negative (pT3, pT2 with <10 nodes removed, and grade 3/estrogen receptor–/lymphovascular space invasion) and node-positive cancers. All women with node-positive disease underwent a complete level I or II ALND. Patients were randomized to undergo whole breast RT (50 Gy in 25 fractions with or without boost doses) vs whole-breast and comprehensive nodal (supraclavicular and internal mammary nodes with or without the axilla) RT (50 Gy in 25 fractions). With a median follow-up of 9.5 years, this trial showed a significant but modest improvement in locoregional disease–free survival with the addition of comprehensive nodal RT (95.2% vs 92.2%), which translated into a more robust improvement in distant disease–free survival (86.3% vs 82.4%) and disease-free survival (82% vs 77%). The absence of a more pronounced improvement in locoregional control may be explained by the delivery of whole-breast RT to both randomized groups and the difficulty in

documenting supraclavicular and internal mammary nodal recurrences. Overall survival was not significantly improved with (82.8%) vs without (81.8%) nodal RT. Thus, the investigators concluded that, although there was no improvement in overall survival, there was a significant decrease in breast cancer recurrences with the addition of adjuvant, comprehensive nodal RT in women predominantly with 1 to 3 lymph nodes involved after a completion ALND. Longer follow-up is needed to determine whether survival will be improved since benefits in survival often lag behind benefits in locoregional control as demonstrated in the EBCTCG meta-analyses.[12,13]

Results from the EORTC 22922 trial[27] that also tested the effects of comprehensive nodal RT were recently reported. In this randomized clinical trial of 4004 women with stage I to III disease, patients were randomized to undergo whole breast and/or chest wall RT or whole breast and/or chest wall RT plus IMN and supraclavicular lymph node irradiation (50 Gy in 25 fractions). With a median follow-up time of 10.9 years, the 10-year risk-adjusted overall survival (as a primary end point) was improved from 80.7% to 82.3% in the regional irradiation group ($P = .06$). Secondary end points, including disease-free survival (improved from 69.1% to 72.1%), distant disease–free survival (improved from 75.0% to 78.0%), and breast cancer mortality (improved from 14.4% to 12.5%) were also each significantly improved following regional RT.

However, the potential benefits of comprehensive nodal therapy must be weighed against the potential toxic effects of treatment. As shown in the NCIC-CTG MA.20 trial,[26] rates of pneumonitis were modestly increased with and without regional RT (1.2% vs 0.2%; $P = .01$); and lymphedema rates were almost doubled following RT (8.4% and 4.5%; $P = .001$). In addition, although increased cardiac toxic effects following RT have not been demonstrated thus far in the NCIC-CTG MA.20 study, multiple reports[28] have correlated cardiac injury with cardiac exposure to RT, implicating specific treatment techniques. The importance of individual treatment planning cannot be overemphasized to ensure that the heart is excluded from the radiation field.

Given the preponderance of recent data (Danish, French, EORTC 22922, and NCIC-CTG MA.20 trials) suggesting not only a locoregional benefit but also a systemic benefit from nodal RT, our practice is to generally recommend regional RT planned with conformal 3-dimensional techniques for women with macroscopic nodal metastasis if treatment can be delivered excluding the heart from the radiation field. However, the recommendation to treat is made only following a detailed risk-benefit assessment estimating the patient's baseline risk using factors such as patient age, extent of nodal involvement, tumor size and grade, receptor status, presence of lymphovascular invasion and comorbid conditions, the predicted locoregional and systemic benefit of treatment, and the potential for treatment-related complications.

Omission of RT in Women Treated With Breast-Conserving Surgery

Although adjuvant RT decreases the risk of local recurrence after breast-conserving surgery in patients with early-stage disease, data from the Oxford EBCTCG meta-analysis[12,13] demonstrated that most of these women are cured with surgery alone. With this realization, attempts have been made to define a sufficiently low-risk population for recurrence in whom adjuvant RT could be avoided. Although the factors previously noted have been associated with increased rates of local recurrence, other factors have been associated with reduced risk, and these selection factors have provided the platform from which randomized clinical trials looking at the feasibility of the omission of RT in patients with favorable risk have been generated. Factors such as older age, small tumor size, and estrogen receptor positivity have been most reproducibly linked to a lower risk of local recurrence. Based on these observations, several randomized clinical trials have looked at the omission of RT for these low-risk patients. One of the first of these trials was the NSABP B-21 study[7] (Table 1). The 8-year IBTR rate was 16.5% in the tamoxifen-alone arm, 9.3% in the RT-alone arm, and 2.8% in the combination arm. The relatively high rate of local recurrence in this low-risk patient population in the absence of RT demonstrated that adjuvant RT was still indicated as an important component of care.

In a similar study, investigators in Canada randomized 769 women 50 years or older with small (T1 to T2) tumors to receive tamoxifen with or without RT (40 Gy in 16 fractions followed by a boost of 12.5 Gy in 5 fractions).[29] Median patient age was 68 years and 81% of the cancers were estrogen receptor positive. The addition of RT significantly decreased the rates of local recurrence (from 7.7% to 0.6% at 5 years and 17.6% to 3.5% at 8 years). Thus, the importance of breast RT was again demonstrated despite the enrollment of a favorably selected patient cohort.

To further identify a low-risk patient population in whom RT could safely be omitted, investigators in the Cancer and Leukemia Group B (CALGB) and ECOG groups randomized 636 women 70 years or older with 2-cm or smaller estrogen receptor–positive, clinically node-negative breast cancers in CALGB 9343.[29,30] Patients received tamoxifen with or without RT (45 Gy in 1.8-Gy daily fractions with up to a 14-Gy in 7 fractions electron boost). Although there was a significant decrease in the rates of local recurrence at 5 and 10 years with RT (5% vs 1% and 9% vs 2%, respectively), the rates of IBTR in women receiving only tamoxifen was believed to be low enough that omission of RT in this patient population was clinically feasible.

More recently, investigators in the United Kingdom reported the first analysis of a multinational phase 3 trial that randomized women 65 years or older to receive 45 to 50 Gy in daily doses of either 2.0 or 2.66 Gy per fraction (boost permitted) or observation (Postoperative Radiotherapy in Minimum-Risk Elderly II).[31] This trial included 1326 women with small (≤3-cm), estrogen receptor–positive, node-negative tumors. At median follow-up of 5 years, the women who received RT had a significantly lower rate of IBTR (1.3%) compared with women who did not receive RT (4.1%). There was no difference in metastasis-free or overall survival noted after 5 years. The maturation of these data will be important in determining whether the rates remain acceptably low.

Although compelling, these trials make clear that not all patients at low risk for recurrence are identified using clinical criteria and additional biomarkers, including molecular biomarkers, could be useful in the identification of a true low-risk population. Indeed, the integration of clinicopathologic features and immunohistochemical markers to identify a surrogate luminal A subtype population in the previously described Canadian study[29] looking at the omission of RT showed that the luminal A subtype (as defined by immuno-

histochemical but not gene expression profiling) was prognostic but not indicative of response to RT.[32] The investigators[32] suggested that this population (defined as *very low-risk* by this group) may be spared breast RT subject to further validation. In addition, several other trials (Endocrine Therapy in Low Risk Luminal A Breast Cancer [Ontario, Canada], Profiling Early Breast Cancer for Radiotherapy Omission [Dana-Farber Cancer Institute], Individualized Decisions for Endocrine Therapy Alone [University of Michigan], and Examining Personalized Radiation Therapy Trial [Australia and New Zealand Breast Cancer Trials Group]) are currently evaluating the usefulness of gene expression signatures or OncotypeDx recurrence scores with clinicopathologic factors in the context of omission of RT.

The Evolution of Radiation Techniques and Fractionation

Radiotherapy techniques have evolved significantly over the past 4 decades. In the early era of breast-conserving surgery and RT, many radiation fields were planned using 2-dimensional techniques without the ability to clearly define the cardiac borders or limit the amount of lung in the treatment field. This technique led to the subsequent inclusion of portions of the heart and increased lung volumes in the primary RT field in some patients and markedly increased doses to the heart and lungs compared with more modern techniques. Reductions in cardiac and lung exposure are now achieved using 3-dimensional conformal RT planning systems, breath-holding techniques, normal tissue blocking, prone positioning, and other practices. More recently, with the development of intensity-modulated RT, which allows for the modulation not only of the radiation beam field size, but also the beam intensity, radiation doses to the heart and lung can be further reduced in some patients. This modulation allows for a more conformal and homogeneous dose distribution (compared with 2-dimensional planned, opposed tangential fields). In addition, studies with proton treatment are ongoing to test for additional heart and lung sparing over readily available photon treatment.[33] Even more recently,[34] partial breast irradiation techniques (using either balloon-based, interstitial brachytherapy treatment, or external-beam RT) seek to condense the duration needed to treat women with breast cancer after breast-conserving surgery from the traditional 5 to 6 weeks for conventionally fractionated radiation to a week or less using very conformal radiation doses immediately surrounding the lumpectomy cavity, a technique termed *accelerated partial breast irradiation* (APBI).

Discussion of the varying types of APBI and each trial comparing APBI with conventional whole-breast RT is not provided here; however, a meta-analysis[34] of APBI trials with 1140 patients demonstrated that, although there was no significant difference in overall survival, distant metastasis, or supraclavicular recurrences, there was an increased risk of local (odds ratio, 2.1) and axillary (odds ratio, 3.4) recurrences with APBI compared with whole-breast RT. These differences in outcome, in part, have been attributed to inclusion of patients unsuitable for APBI.[35,36] A significant portion of the lower axilla is treated with standard whole-breast RT, perhaps explaining the decreased rates of axillary recurrence in the whole-breast RT arm. Subsequent reports[37-39] suggest that, in appropriately selected patients, APBI may be an equally effective treatment option for women with breast cancer. With the maturation of multiple randomized clinical trials assessing the effectiveness of APBI, including the NSABP B-39/Radiation Therapy Oncology Group 0413, Randomized Trial of Accelerated Partial Breast Irradiation, UK Medical Research Council, Intensity Modulated and Partial Organ Radiotherapy Trial LOW, and the Intraoperative Radiotherapy trials, extensive data will be forthcoming.

Not surprisingly, the appropriate selection of patients for partial breast irradiation is critical since young age, multifocal or multicentric disease, positive margins, and the presence of an extensive intraductal component may lead to increases in local recurrence rates in women treated with APBI. Consensus statements from the American Society of Radiation Oncology,[40] the American Society of Breast Surgeons,[35] and the American Brachytherapy Society,[36] although slightly different from one another in their designation of suitable candidates, should be considered when determining whether APBI is appropriate treatment for a patient outside of a prospective study.

Recent data have emerged[41-44] regarding optimal dose and fractionation schemes to the whole breast in early-stage disease. Based on the radiobiology of normal and cancerous breast tissue and in an effort to limit late normal tissue toxic effects, fractions of 2 Gy/d or less were previously believed to be most effective and least toxic in the treatment of breast cancer. In recent decades, however, this dogma has been challenged and recent randomized clinical trials[41-44] have now proven the equivalence of whole-breast hypofractionated (fractions ≥2 Gy/d) RT with respect to tumor control and toxic effects compared with standard fractionation. At least 3 prospective randomized clinical trials of hypofractionated RT (**Table 2**)[41,42,44] have been reported in women with stage I or II disease, and all 3 have found no decrement in locoregional disease control and perhaps decreased toxic effects with hypofractionated radiation (39-42.5 Gy in 13-16 fractions).[41-44]

Based on this compelling evidence, the American Society for Radiation Oncology[45] has recommended that hypofractionation with a dose of 42.5 Gy in 16 fractions (as in the Canadian study[41]) be considered in appropriate patients older than 50 years with pT1-T2 pN0 disease in whom a relatively homogeneous dose distribution can be achieved.

Biomarkers and Future Directions

There has been much interest recently in developing better biomarkers to identify patients at sufficiently low risk of recurrence such that adjuvant RT can safely be omitted. As discussed above, clinicopathologic factors, including age, tumor size, and hormone receptor status, remain imperfect in their risk stratification, and it is clear that finding more reliable markers is an area of unmet clinical need. Furthermore, previous studies[46-49] have attempted to analyze rates of IBTR by subtype defined by immunohistochemical markers. These studies have consistently found that luminal A cancers are associated with extremely low rates of local recurrence compared with *ERBB2* (formerly *HER2*)-overexpressing or basal-like (including triple-negative breast cancer) tumors.[46-49] These data from *ERBB2*-associated cancers are confounded by the varying rates of anti-*ERBB2* therapy in these studies since *ERBB2* inhibition has been demonstrated[50,51] preclinically to be associated with radiosensitization. Conflicting data on the validity of these proposed biomarkers underscore the need for additional research regarding the role

Table 2. Randomized Clinical Trials of Hypofractionated RT After BCS

Source	Accrual Dates	No. of Patients	Inclusion Criteria	Treatment Arms	Boost, %	Systemic Agents, %	Local Recurrence, %	OS
Whelan et al,[41] 2010 (Ontario)	1993-1996	1234	T1-T2, N0 (by ALND), margins negative	42.5 Gy/16 fractions vs 50 Gy/25 fractions	No	Tamoxifen, 42; chemotherapy, 11	10 y: 7.4 (6.2 invasive) for hypofractionated vs 7.5 (6.5 invasive) for standard fractionated	No difference at 10 y
Bentzen et al,[44] 2008 (MRC START A)	1998-2002	2236	pT1-pT3a, N0-1, requiring RT after surgery; mostly BCS (mastectomy 15%)	50 Gy/25 fractions vs 41.6 Gy/13 fractions vs 39 Gy/13 fractions; all arms given over 5 wk	At discretion of provider (61); regional RT, 14	Tamoxifen, 54; chemotherapy, 11; both 25	10 y: 7.4 (50 Gy) vs 6.3 (41.6 Gy) vs 8.8 (39 Gy), not significant	No difference at 10 y
Bentzen et al,[42] 2008 (MRC START B)	1999-2001	2215	pT1-pT3a, N0-N1, requiring RT after surgery; mostly BCS (mastectomy 8%)	50 Gy/25 fractions (5 wk) vs 40 Gy/15 fractions (3 wk)	At discretion of provider (43); regional RT 14	Tamoxifen, 72; chemotherapy, 7; both, 15	10 y: 5.5 (50 Gy) vs 4.3 (40 Gy), not significant	No difference at 10 y

Abbreviations: ALND, axillary lymph node dissection; BCS, breast-conserving surgery; hypofractionated radiation; LR, local recurrence; LVI, lymphovascular space invasion; MRC START, UK Medical Research Council Systematic Techniques for Assisting Recruitment to Trials; OS, overall survival; RT, radiotherapy.

SI conversion factor: To convert gray to rad, multiply by 100.

of RT in cohorts of patients treated uniformly and for whom gene expression profiling is the determinant of intrinsic molecular subtype. Decisions regarding the usefulness and efficacy of adjuvant chemotherapy have been greatly improved with the development of tests such as OncotypeDx and Mammaprint, but no such test currently allows for similar risk stratification for adjuvant RT. Multiple groups are currently working on this issue, including Genomic Health (OncotypeDCIS), CyvergenX (a radiosensitivity index), and PFS Genomics (RadiotypeDx).[52-54] Furthermore, recent publications[55,56] have begun to inform this discussion, at least as it relates to the usefulness of RT in the postmastectomy setting, and further validation of these intriguing findings is eagerly awaited. The Danish group[55] recently published a 4-gene signature that, at least within the context of the Danish 82b/c trials, was predictive of benefit from postmastectomy RT and was able to identify a patient population at very low risk of local recurrence with the omission of RT. Similarly, researchers are investigating whether the OncotypeDx score may be predictive of the need for RT after mastectomy, even for node-positive participants in the NSABP trials.[56,57] Whether any of the developed biomarkers will be validated in phase 3 randomized clinical trials remains to be seen and, until such data are obtained, it is our opinion that these markers should not be adopted into clinical practice.

Conclusions

Radiotherapy is an important component of care in the management of early-stage breast cancer based not only on its ability to reduce tumor recurrence in the breast, but also on its ability to significantly improve breast cancer–specific survival. Recent randomized clinical trials have provided additional data regarding appropriate fields, radiation doses, and fractionation schemes based on clinical and pathologic features, and treatment outcomes and have helped to inform the next generation of trials that seek to identify patients and cancers with low-risk features in whom radiation can be safely omitted. Finally, as we look to the future, much work is ongoing to develop additional molecular markers that, in conjunction with readily available clinical markers, will further refine the selection of patients who benefit from breast RT.

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REFERENCES

1. Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med*. 1995;333(22):1456-1461.

2. Veronesi U, Salvadori B, Luini A, et al. Breast conservation is a safe method in patients with small cancer of the breast. Long-term results of three randomised trials on 1,973 patients. *Eur J Cancer*. 1995;31A(10):1574-1579.

3. Liljegren G, Holmberg L, Adami HO, Westman G, Graffman S, Bergh J; Uppsala-Orebro Breast Cancer Study Group. Sector resection with or without postoperative radiotherapy for stage I breast cancer: five-year results of a randomized trial. *J Natl Cancer Inst*. 1994;86(9):717-722.

4. Liljegren G, Holmberg L, Bergh J, et al. 10-Year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. *J Clin Oncol*. 1999;17(8):2326-2333.

5. Clark RM, Whelan T, Levine M, et al; Ontario Clinical Oncology Group. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. *J Natl Cancer Inst*. 1996;88(22):1659-1664.

6. Malmström P, Holmberg L, Anderson H, et al; Swedisj Breast Cancer Group. Breast conservation surgery, with and without radiotherapy, in women with lymph node-negative breast cancer: a randomised clinical trial in a population with access to public mammography screening. *Eur J Cancer*. 2003;39(12):1690-1697.

7. Fisher B, Bryant J, Dignam JJ, et al; National Surgical Adjuvant Breast and Bowel Project. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. *J Clin Oncol*. 2002;20(20):4141-4149.

8. Semiglazov VF, Kanaev SV, Bugrova IL. Preliminary results of the randomized trial the role of adjuvant radiotherapy in organ-preserving treatment of breast cancer [in Russian]. *Vopr Onkol*. 1998;44(4):414-421.

9. Renton SC, Gazet JC, Ford HT, Corbishley C, Sutcliffe R. The importance of the resection margin in conservative surgery for breast cancer. *Eur J Surg Oncol*. 1996;22(1):17-22.

10. Winzer KJ, Sauerbrei W, Braun M, et al; German Breast Cancer Study Group (GBSG). Radiation therapy and tamoxifen after breast-conserving surgery: updated results of a 2 x 2 randomised clinical trial in patients with low risk of recurrence. *Eur J Cancer*. 2010;46(1):95-101.

11. Forrest AP, Stewart HJ, Everington D, et al; Scottish Cancer Trials Breast Group. Randomised controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. *Lancet*. 1996;348(9029):708-713.

12. Clarke M, Collins R, Darby S, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;366(9503):2087-2106.

13. Darby S, McGale P, Correa C, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011;378(9804):1707-1716.

14. Wapnir IL, Anderson SJ, Mamounas EP, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. *J Clin Oncol*. 2006;24(13):2028-2037.

15. Ashikaga T, Krag DN, Land SR, et al; National Surgical Adjuvant Breast, Bowel Project. Morbidity results from the NSABP B-32 trial comparing sentinel lymph node dissection versus axillary dissection. *J Surg Oncol*. 2010;102(2):111-118.

16. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol*. 2010;11(10):927-933.

17. Zavagno G, De Salvo GL, Scalco G, et al; GIVOM Trialists. A Randomized clinical trial on sentinel lymph node biopsy versus axillary lymph node dissection in breast cancer: results of the Sentinella/GIVOM trial. *Ann Surg*. 2008;247(2):207-213.

18. Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. *J Natl Cancer Inst*. 2006;98(9):599-609.

19. Veronesi U, Paganelli G, Viale G, et al. Sentinel-lymph-node biopsy as a staging procedure in breast cancer: update of a randomised controlled study. *Lancet Oncol*. 2006;7(12):983-990.

20. Galimberti V, Cole BF, Zurrida S, et al; International Breast Cancer Study Group Trial 23-01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol*. 2013;14(4):297-305.

21. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA*. 2011;305(6):569-575.

22. Jagsi R, Chadha M, Moni J, et al. Radiation field design in the ACOSOG Z0011 (Alliance) Trial. *J Clin Oncol*. 2014;32(32):3600-3606.

23. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol*. 2014;15(12):1303-1310.

24. Hennequin C, Bossard N, Servagi-Vernat S, et al. Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy. *Int J Radiat Oncol Biol Phys*. 2013;86(5):860-866.

25. Thorsen LB, Offersen BV, Danø H, et al. DBCG-IMN: A Population-Based Cohort Study on the Effect of Internal Mammary Node Irradiation in Early Node-Positive Breast Cancer. *J Clin Oncol*. 2016;34(4):314-320.

26. Whelan TJ, Olivotto IA, Parulekar WR, et al; MA.20 Study Investigators. Regional Nodal Irradiation in Early-Stage Breast Cancer. *N Engl J Med*. 2015;373(4):307-316.

27. Poortmans PM, Collette S, Kirkove C, et al; EORTC Radiation Oncology and Breast Cancer Groups. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. *N Engl J Med*. 2015;373(4):317-327.

28. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*. 2013;368(11):987-998.

29. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol*. 2013;31(19):2382-2387.

30. Hughes KS, Schnaper LA, Berry D, et al; Cancer and Leukemia Group B; Radiation Therapy Oncology Group; Eastern Cooperative Oncology Group. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med*. 2004;351(10):971-977.

31. Kunkler IH, Williams LJ, Jack WJL, Cameron DA, Dixon JM; PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol*. 2015;16(3):266-273.

32. Liu FF, Shi W, Done SJ, et al. Identification of a Low-Risk Luminal A Breast Cancer Cohort That May Not Benefit From Breast Radiotherapy. *J Clin Oncol*. 2015;33(18):2035-2040.

33. MacDonald SM, Patel SA, Hickey S, et al. Proton therapy for breast cancer after mastectomy: early outcomes of a prospective clinical trial. *Int J Radiat Oncol Biol Phys*. 2013;86(3):484-490.

34. Valachis A, Mauri D, Polyzos NP, Mavroudis D, Georgoulias V, Casazza G. Partial breast irradiation or whole breast radiotherapy for early breast cancer: a meta-analysis of randomized controlled trials. *Breast J*. 2010;16(3):245-251.

35. American Society of Breast Surgeons. Consensus statement about partial breast irradiation. https://www.breastsurgeons.org/new_layout/about/statements/PDF_Statements/APBI.pdf. Revised August 15, 2011. Accessed April 14, 2016.

36. American Brachytherapy Society. Consensus statement for accelerated partial breast irradiation. https://www.americanbrachytherapy.org/guidelines/Guidelines_Accelerated_Partial_Breast_Irradiation.pdf. Published 2013. Accessed April 14, 2016.

37. Beitsch PD, Wilkinson JB, Vicini FA, et al. Tumor bed control with balloon-based accelerated partial breast irradiation: incidence of true recurrences versus elsewhere failures in the American Society of Breast Surgery MammoSite Registry Trial. *Ann Surg Oncol*. 2012;19(10):3165-3170.

38. Yashar CM, Scanderbeg D, Kuske R, et al. Initial clinical experience with the Strut-Adjusted Volume Implant (SAVI) breast brachytherapy device for accelerated partial-breast irradiation (APBI): first 100 patients with more than 1 year of follow-up. *Int J Radiat Oncol Biol Phys*. 2011;80(3):765-770.

39. Polgár C, Fodor J, Major T, et al. Breast-conserving treatment with partial or whole breast irradiation for low-risk invasive breast carcinoma—5-year results of a randomized trial. *Int J Radiat Oncol Biol Phys*. 2007;69(3):694-702.

40. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys*. 2009;74(4):987-1001.

41. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med*. 2010;362(6):513-520.

42. Bentzen SM, Agrawal RK, Aird EG, et al; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet*. 2008;371(9618):1098-1107.

43. Haviland JS, Owen JR, Dewar JA, et al; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two

randomised controlled trials. *Lancet Oncol*. 2013;14(11):1086-1094.

44. Bentzen SM, Agrawal RK, Aird EG, et al; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol*. 2008;9(4):331-341.

45. Smith BD, Bentzen SM, Correa CR, et al. Fractionation for whole breast irradiation: an American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Int J Radiat Oncol Biol Phys*. 2011;81(1):59-68.

46. Nguyen PL, Taghian AG, Katz MS, et al. Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. *J Clin Oncol*. 2008;26(14):2373-2378.

47. Kyndi M, Sørensen FB, Knudsen H, Overgaard M, Nielsen HM, Overgaard J; Danish Breast Cancer Cooperative Group. Estrogen receptor, progesterone receptor, HER-2, and response to postmastectomy radiotherapy in high-risk breast cancer: the Danish Breast Cancer Cooperative Group. *J Clin Oncol*. 2008;26(9):1419-1426.

48. Wang Y, Yin Q, Yu Q, et al. A retrospective study of breast cancer subtypes: the risk of relapse and the relations with treatments. *Breast Cancer Res Treat*. 2011;130(2):489-498.

49. Arvold ND, Taghian AG, Niemierko A, et al. Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy. *J Clin Oncol*. 2011;29(29):3885-3891.

50. Formenti SC, Spicer D, Skinner K, et al. Low HER2/neu gene expression is associated with pathological response to concurrent paclitaxel and radiation therapy in locally advanced breast cancer. *Int J Radiat Oncol Biol Phys*. 2002;52(2):397-405.

51. Pietras RJ, Poen JC, Gallardo D, Wongvipat PN, Lee HJ, Slamon DJ. Monoclonal antibody to HER-2/neureceptor modulates repair of radiation-induced DNA damage and enhances radiosensitivity of human breast cancer cells overexpressing this oncogene. *Cancer Res*. 1999;59(6):1347-1355.

52. Solin LJ, Gray R, Baehner 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(10):701-710.

53. Torres-Roca JF, Fulp WJ, Caudell JJ, et al. Integration of a radiosensitivity molecular signature into the assessment of local recurrence risk in breast cancer. *Int J Radiat Oncol Biol Phys*. 2015;93(3):631-638.

54. Speers C, Zhao S, Liu M, Bartelink H, Pierce LJ, Feng FY. Development and validation of a novel radiosensitivity signature in human breast cancer. *Clin Cancer Res*. 2015;21(16):3667-3677.

55. Tramm T, Mohammed H, Myhre S, et al. Development and validation of a gene profile predicting benefit of postmastectomy radiotherapy in patients with high-risk breast cancer: a study of gene expression in the DBCG82bc cohort. *Clin Cancer Res*. 2014;20(20):5272-5280.

56. Mamounas EP, Tang G, Paik S, et al. The 21 gene-recurrence score (RS) predicts risk of loco-regional recurrence (LRR) in node+, E+ breast cancer (BC) after adjuvant chemotherapy and tamoxifen: results from NSABP B28. *Ann Surg Oncol*. 2013;20(suppl 1):S6-S164.

57. Mamounas EP, Tang G, Fisher B, et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. *J Clin Oncol*. 2010;28(10):1677-1683.