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REVIEW ARTICLE

Use of Conventional Radiation Therapy As Part of Breast-Conserving Treatment

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INTRODUCTION

Whole breast irradiation following breast-conserving surgery is an integral part of breast-conserving therapy (BCT). Radiation therapy was introduced early in the development of breast-conserving surgery and techniques were based on the premise that limited surgery might leave microscopic residual disease in the breast. Early studies of mastectomy specimens demonstrated that microscopic disease could extend up to 2 to 4 cm beyond the primary site of the tumor within the breast tissue.[1] Trials comparing mastectomy to BCT (breast-conserving surgery plus radiation) demonstrated equivalent survival confirming the effectiveness of this combined approach.[2-5] Trials comparing breast-conserving surgery alone to breast-conserving surgery plus radiation confirmed a substantial decrease in the risk of local recurrence and the prevention of mastectomy with breast irradiation.[2,6,7]

Whole breast irradiation is normally delivered with two opposed tangential fields to encompass the breast, often including part of the underlying chest wall and the lower axilla. Beam modifying devices, usually lead wedges, are used to improve dose homogeneity. A dose of 45 to 50 Gy in 25 fractions (or daily doses) of 1.8 to 2 Gy, Monday to Friday for 5 weeks, is often used. Additional radiation limited to the site of the primary tumor, called boost irradiation, may be given using a variety of approaches to a dose of 10 to 16 Gy in five to eight fractions. This technique has been in existence since the early 1980s, with little changes until recently.[8] Increasingly, centers now use computed tomography (CT) to plan radiation therapy which permits clearer definition of underlying lung and heart and avoidance of these critical structures.[9,10] CT planning also permits for the correction of underlying lung density and optimization of compensation if necessary.

Patient selection criteria for whole breast irradiation are based on the eligibility criteria of the original trials[2,5,7] and include any patient with a primary tumor of less than 5 cm with clear margins of the excision following breast-conserving surgery. Absolute contraindications to breast irradiation include pregnancy and previous breast irradiation (including mantle irradiation for Hodgkin's disease).[11] Relative contraindications include scleroderma, systemic lupus erythematosis,[12] severe cardiopulmonary disease, or the inability to lie supine, which would limit the ability to deliver radiotherapy.

Breast irradiation is well tolerated. Common early toxicity includes fatigue, breast edema, and skin erythema and irritation, which can have a modest impact on quality of life.[13] Mild to moderate long-term effects are relatively uncommon: 5% to 10% of patients may experience limited breast pain attributed to radiation therapy or adverse cosmetic outcome associated with breast fibrosis, scar retraction, and telangiectasia.[14] Serious long-term adverse effects are relatively rare (less than 1%) and include radiation pneumonitis,

pericarditis, and rib fracture.[11] The risk of secondary malignancies, such as contralateral breast cancer, sarcoma,[15] or leukemia,[16] is extremely rare (less than one in 1,000).

Breast irradiation is normally delivered 3 to 6 weeks postsurgery in patients not receiving chemotherapy.[17] For patients treated with adjuvant chemotherapy, optimal sequencing of radiation and systemic therapy is unresolved. Early case series suggested that patients receiving radiation after chemotherapy were at increased risk of local recurrence.[18,19] However, a randomized trial that compared patients treated with radiation therapy before anthracycline-based chemotherapy versus radiation therapy after the same chemotherapy suggested an increased risk of distant recurrence for patients treated with radiation first.[20] As a result, breast irradiation is now usually given after anthracycline-based chemotherapy. The optimal sequencing of radiation therapy and hormonal therapy is also unclear.[21] Earlier trials evaluating the role of adjuvant tamoxifen often gave radiation concurrent with tamoxifen[22,23]; however, there remains theoretical concerns that tamoxifen, which causes arrest of breast cancer tumor cells in culture in the relatively radio resistant G0/G1 phases of the cell cycle, may limit the effectiveness of radiation therapy.[24] Studies have also suggested that tamoxifen given concurrently with radiation therapy may increase the risk of pulmonary and breast fibrosis.[25,26] Three retrospective studies[27-29] in patients treated with breast-conserving surgery have compared radiation given before the initiation of tamoxifen versus initiation of tamoxifen before or concurrently with radiation therapy. These studies, which are limited by their design, have failed to demonstrate any adverse effect of concurrent tamoxifen and radiation therapy. Further research is necessary to define the optimal sequencing of radiation and hormonal therapy.

Breast irradiation remains an important component of BCT. There have been seven published randomized trials demonstrating that breast irradiation substantially reduces the risk of local recurrence and prevents the need for subsequent mastectomy (Table 1).[30-36] These studies suggest that radiation remains effective in the absence or presence of systemic therapy.[30,34] A recent meta-analysis based on abstracted data from published trials also suggests that patients who receive breast irradiation have improved overall survival.[37]

In the original trials that demonstrated the effectiveness of breast irradiation, there was considerable variability in the radiation fractionation schedules used and the use of additional boost irradiation. Recent trials have evaluated the comparability of different radiation therapy approaches and the need for radiation in low-risk patients. Important areas of investigation have included accelerated hypofractionated radiation therapy the use of boost irradiation and regional nodal irradiation.

ACCELERATED HYPOFRACTIONATED RADIOTHERAPY

The concept behind accelerated hypofractionation is that radiation given in larger daily doses in a shorter overall period of time may be as effective as more standard approaches of smaller daily doses given over a longer period.[38] Accelerated hypofractionated radiation therapy (AHRT) could possibly be more effective, but the total dose is reduced to avoid an increase in late toxicity. The attraction of this approach is that reducing overall treatments and the time required results in improved patient convenience and potentially decreased treatment costs. AHRT has been evaluated in a number of randomized trials after breast-conserving surgery and mastectomy (Table 2).

The Ontario Clinical Oncology Group recently reported the results of a randomized trial in which AHRT (42.5 Gy in 16 fractions over 22 days) was compared to a more conventional course of radiation therapy to the whole breast (50 Gy in 25 fractions over 35 days) in women with node-negative breast cancer after breast-conserving

Table 1. Randomized Trials of Breast Irradiation Following Breast-Conserving Surgery

Study	Radiation Treatment	No. of Patients	Local Recurrence (%)	Overall Survival (%)	Median Follow-Up (years)
Fisher et al[30]	None	570	35	61	12
	50 Gy/25 fractions/5 weeks	567	10	64	
Liljegren et al[31]	None	197	24	78	9
	54 Gy/27 fractions/5.5 weeks	184	8	78	
Clark et al[32]	None	421	35	76	7.6
	40 Gy/16 fractions/3 weeks + boost of 12.5 Gy/5 fractions/1 week	416	11	79	
Veronesi et al[33]	None	273	24	77	9
	50 Gy/25 fractions/5 weeks + boost of 10 Gy/5 fractions/1 week	294	6	82	
Forrest et al[34]	None	294	25	83	5.7
	50 Gy/20-25 fractions/4-5 weeks + boost	291	6	83	
Holli et al[35]	None	72	18	99	6.7
	50 Gy/25 fractions/5 weeks	80	8	97	
Malstrom et al[36]	None	587	14	93	5
	48-54 Gy/20-25 fractions/5 weeks	591	4	94	

Table 2. Randomized Trials of Accelerated Hypofractionated Radiation Therapy

Study	Surgery	Radiation Treatment	No. of Patients	Local Recurrence (%)	Median Follow-Up (years)
Whelan et al[39]	Lumpectomy	50 Gy/25 fractions/5 weeks	612	3.2	5.8
		42.5 Gy/16 fractions/3 weeks	622	2.8	
Yarnold et al[40]	Lumpectomy	50 Gy/25 fractions/5 weeks	470	NA	~4.5
		43 Gy/13 fractions/5 weeks	466	NA	
		39 Gy/13 fractions/5 weeks	474	NA	
Baillet et al[41]	Lumpectomy or mastectomy	45 Gy/25 fractions/5 weeks	115	7	5.5
		23 Gy/4 fractions/2.5 weeks	115	5	

Abbreviation: NA, not available.

surgery.[39] Eligibility criteria required that women have clear resection margins after breast-conserving surgery. Women with large breast size, defined as more than 25 cm of tissue thickness at the midpoint of the radiation fields, were excluded. The study involved 1,234 women with a median follow-up of 5.8 years. The rates of local recurrence or cosmetic outcome (as a measure of late radiation morbidity) at 5 years were equivalent. In another large trial by the Institute of Cancer Research (United Kingdom), 1,410 women with early breast cancer were randomly assigned to three fractionation schedules for breast irradiation: 39 Gy in 13 fractions, 42.9 Gy in 13 fractions, or 50 Gy in 25 fractions, all delivered over a 5-week period. At a median follow-up of approximately 4.5 years, there was no observable difference in late radiation morbidity between 50 Gy in 25 fractions versus 42.9 Gy in 13 fractions. Patients receiving 39 Gy in 13 fractions had fewer normal tissue effects than those treated with the other two schedules. Local recurrence rates were not formerly reported but were uncommon with all three schedules. Two smaller trials in patients after breast-conserving surgery and mastectomy also have demonstrated comparable rates for both local recurrence and late radiation morbidity when comparing AHRT with more conventional treatment.[41,42] Two other large randomized trials by the United Kingdom Standardization of Radiotherapy Trial Group, which compare different approaches to hypofractionation, have recently completed accrual.[43]

Despite the positive results of published trials, some radiation oncologists remain concerned about the potential for long-term toxicity in patients treated with AHRT.[44,45] Concerns raised include potential progression of skin and soft tissue effects beyond 5 years and potential cardiac morbidity. While some effects may progress, this is likely not to be different then conventional fractionation schedules for whole breast irradiation.[14,30] AHRT has now been adopted in a number of countries including Canada, the United Kingdom, and parts of Europe. This is an important option for women who have difficulty traveling or attending daily sessions, such as older or infirmed patients. AHRT is likely to gain wider acceptance with supporting results from ongoing trials and longer follow-up of previous studies.

BOOST IRRADIATION

Additional radiation directed to the surgical site, after whole breast irradiation, has been commonly used in the United States and Europe. The concept supporting this approach is based on the observation that local recurrence in the breast occurs primarily at the surgical site[6,7] and a higher total dose in this area is likely to lead to improved local control.

Recently, there have been a number of randomized trials evaluating the role of boost irradiation (Table 3). The European Organisation for the Research and Treatment of Cancer (EORTC) reported a trial involving 5,318 early breast cancer patients with clear resection margins following breast-conserving surgery.[46] Patients were randomly assigned to whole breast radiation therapy of

Table 3. Randomized Trials of Boost Irradiation

Study	Radiation Treatment	No. of Patients	Local Recurrence (%)	Median Follow-Up (years)
Bartelink et al[46]	50 Gy/25 fractions/5 weeks	2657	7.3	5.1
	50 Gy/25 fractions/5 weeks + boost 16 Gy/8 fractions/1.5 weeks	2661	4.3	
Romestaing et al[47]	50 Gy /20 fractions/5 weeks	503	4.5	3.3
	50 Gy /20 fractions/5 weeks + boost 10 Gy /4 fractions/1 week	521	3.6	
Teissier et al[48]	50 Gy/25 fractions/5 weeks	337	6.8	6.1
	50 Gy/25 fractions/5 weeks + boost 10 Gy/5 fractions/1 week	327	4.3	
Polgar et al[49]	50 Gy/25 fractions/5 weeks	103	15.5	5.3
	50 Gy/25 fractions/5 weeks + boost 12-16 Gy/3-8 fractions/1.5 weeks	104	6.7	

50 Gy in 25 fractions over 5 weeks plus a boost to the primary site of 16 Gy in eight fractions over 1.5 weeks or whole breast radiotherapy alone. Boost radiation was delivered using a variety of techniques including a single direct electron field, two parallel photon fields, or brachytherapy. Approximately 80% of patients had node-negative disease and 28% received adjuvant systemic therapy. Median follow-up was 5.1 years. The rate of local recurrence at 5 years was 4.3% among patients who received boost radiation and 7.3% among patients who did not ($P < .001$). There was no difference detected in survival between the groups. Radiation morbidity was increased in patients who received boost irradiation; the percentage of patients with an excellent or good cosmetic outcome was reduced from 86% in patients who did not receive a boost to 71% of patients who did ($P < .001$).[50] Although boost irradiation was effective overall, patients deemed to receive the greatest absolute benefit were those patients younger than 50 years who were at high risk of local recurrence. There was limited benefit observed in patients older than 50 years.

In another trial from Lyon, France, 1,024 women with tumors ≤ 3 cm and clear margins after breast-conserving surgery were randomly assigned to receive whole breast irradiation therapy of 50 Gy in 20 fractions over 4 weeks plus a boost to the surgical site of 10 Gy in 4 fractions over 1 week or whole breast radiation therapy alone.[47] Boost irradiation was delivered by a single direct field to the surgical site using electrons. Approximately 50% of the patients in this study received adjuvant chemotherapy or tamoxifen. Median follow-up was 3.3 years. The rate of local recurrence at 5 years was 3.6% among patients who received the boost and 4.5% among patients who did not ($P = .04$). More patients in the boost group than in the control group experienced radiation morbidity, notably skin telangiectasia (12.4% *v* 5.9%; $P = .003$). Two other smaller trials have shown similar relative benefits for boost irradiation, which border on statistical significance.[48,49] In the latter trial, the incidence of late radiation morbidity (skin telangiectasia and soft tissue fibrosis) was increased in patients who received boost irradiation ($P = .03$).

Results of these trials support the effectiveness of boost irradiation in reducing local recurrence but at the expense of increased radiation morbidity. The EORTC study supports the use of boost irradiation for women at moderate to high risk of local recurrence after whole breast irradiation (eg, those who are ≤ 50 years of age, large tumor size, or positive or close resection margins). For women who are at low risk of local recurrence after whole breast irradiation (eg, those who are older than 50 years and have clear resection margins), the absolute benefit of boost irradiation is small and it may not be necessary. When boost irradiation is considered, it should be delivered with the techniques used in the definitive trials (eg, 10 to 16 Gy in four to eight fractions given by a linear accelerator or brachytherapy). Patients receiving boost irradiation should be informed about the absolute benefits and risks.

REGIONAL NODAL IRRADIATION

Randomized trials have demonstrated improved survival when locoregional irradiation is given to women after mastectomy who are treated with systemic therapy.[51-53] As a result, the American Society of Clinical Oncology recommends that patients at high risk of locoregional recurrence after mastectomy (> 5 cm primary tumor, or more than three positive axillary nodes) be treated with locoregional irradiation.[54] In patients treated with breast-conserving surgery and whole breast irradiation, the role of additional nodal irradiation is less clear given that breast irradiation may treat a substantial portion of the lower axilla and part of the internal mammary nodal chain.[55] This is an important question because regional irradiation may be associated with increased toxicity and cost. Previous studies have demonstrated an increased risk of lymphedema, pulmonary pneumonitis, cardiac disease, and secondary malignancies.[56] Two trials are currently evaluating the role of regional nodal irradiation.

The EORTC 10925 trial, which recently completed accrual, randomly assigns patients with node-positive or medially or centrally located primary tumors to irradiation of the upper internal mammary and medial supraclavicular nodes or to no nodal irradiation.[57] The National Cancer Institute of Canada Clinical Trials Group MA.20 trial is ongoing and randomly assigns patients with node-positive or high-risk, node-negative disease following breast-conserving surgery and adjuvant systemic therapy to breast irradiation plus regional nodal irradiation (supraclavicular, high axilla, and upper internal mammary nodes) or to breast irradiation alone.[58] Together, these trials should address questions regarding efficacy of additional nodal irradiation after breast-conserving surgery and the need to include the internal mammary nodes.

OMISSION OF BREAST IRRADIATION IN LOW-RISK PATIENTS

Several trials have recently evaluated the need for breast irradiation in women at low risk of recurrence who are also treated with or without tamoxifen (Table 4). National Surgical Adjuvant Breast and Bowel Project B-21 randomly assigned 1,009 women with < 1 cm node-negative breast cancer to tamoxifen plus breast irradiation, tamoxifen alone, or breast irradiation alone.[59] Median follow-up was 7.3 years. At 8 years, the rate of local recurrence was 2.8% in patients treated with tamoxifen plus radiation, 9.3% in patients treated with radiation alone, and 16.5% in patients treated with tamoxifen alone ($P < .01$

Table 4. Randomized Trials of Omission of Breast Irradiation in Low-Risk Women

Study	Radiation Treatment	No. of Patients	Local Recurrence (%)	Overall Survival (%)	Median Follow-Up (years)
Fisher et al[59]	50 Gy/25 fractions/5 weeks (+/− boost) and tamoxifen	334	2.8	93	8
	breast irradiation alone	332	9.3	94	
	tamoxifen alone	334	16.5	93	
Fyles et al[60]	40 Gy/16 fractions/3 weeks + boost and tamoxifen	386	0.6	92	5
	tamoxifen only	383	7.7	92	
Hughes et al[61]	45 Gy/25 fractions/3 weeks + boost and tamoxifen	317	1.0	87	5
	tamoxifen alone	319	4.0	86	
Winzer et al[62]	BCS only	79	27.8	90	6
	BCS and 50 Gy/25 fractions/5 weeks + boost	94	3.2	96	
	BCS and tamoxifen	80	2.8	96	
	BCS and breast irradiation and tamoxifen	94	3.8	94	

Abbreviation: BCS, breast-conserving surgery.

for all comparisons). Survival for the three groups was 93%, 94%, and 93% respectively ($P = .03$). Investigators were unable to identify a subgroup of patients who did not benefit from breast irradiation. In patients with estrogen receptor (ER) -positive tumors, the rate of local recurrence at 8 years was 1.7% with tamoxifen plus radiation, 5.4% with radiation alone, and 12.6% with tamoxifen alone. In the Canadian trial, 761 women who were 50 years of age or older with T1 to T2 node-negative breast cancer were randomly assigned to tamoxifen plus breast irradiation or tamoxifen alone.[60] Median follow-up was 5.6 years. At 5 years, the rate of local breast recurrence was 0.6% in the tamoxifen plus radiation group and 7.7% in the tamoxifen only group ($P < .001$). However, there appeared to be an increase in the risk of late relapse when tamoxifen was discontinued; at 8 years the rate of local relapse was 3.5% and 17.6%, respectively. In the subgroup of women with T1 ER-positive tumors, the rate of relapse at 8 years for patients treated with tamoxifen only was 15.2%. There was a suggestion that the rate of local recurrence was lower for patients with tumors < 1 cm and women > 60 years of age but the numbers in the subgroups were quite small. In the Cancer and Leukemia Group B trial,[61] 636 women who were 70 years of age or older with clinical T1 and N0 ER-positive cancers were randomly assigned to breast irradiation plus tamoxifen or tamoxifen only. At the median follow-up of 5 years, the rate of local failure was 1% in the tamoxifen plus radiation group and only 4% in the tamoxifen only group ($P < .001$). No difference was observed in the rate of mastectomy or overall survival between the two groups. A smaller German trial studied women at low risk of local recurrence, defined as age > 45 years and < 75 years, primary tumors ≤ 2 cm, ER-positive, grade I or II with no extensive intraductal component or lymphovascular invasion, and clear margins of excision following breast-conserving surgery.[62] In this study, 347 women were randomly assigned to breast-conserving surgery alone, breast-conserving surgery plus radiation, breast-conserving surgery plus tamoxifen, or breast-conserving surgery plus irradiation plus tamoxifen. Median follow-up was 5.9 years. The interpretation of this study is limited by the small sample size, incomplete follow-up, and the fact that not all patients were randomly assigned to receive tamoxifen or not. The British Association of Surgical Oncology has completed a similar trial with 1,172 randomly assigned patients.[63] The mature results of this study have not yet been published. Together, the results of these trials suggest that there may be a group of women who are at sufficiently low risk for local recurrence so as not to require breast irradiation. Further follow-up is necessary to confirm these promising early findings. At the present time, breast irradiation following breast-conserving surgery remains part of standard treatment.

FUTURE DIRECTIONS

Radiation therapy following breast-conserving surgery continues to be an active area of research. More recent work has been directed at evaluating the role of breast-conserving therapy in women with a genetic predisposition to breast cancer, and the development of new technologic approaches to radiation therapy.

There is increasing interest in evaluating the role of breast-conserving therapy in women with invasive breast cancer who have *BRCA1/BRCA2* mutations. There is concern that such women may be at increased risk of subsequent breast cancers or of radiation-associated complications in view of the role of *BRCA1/BRCA2* in DNA repair.[64] As these genetic mutations are relatively rare, the frequency of this phenomenon is uncommon and as a result, studies have largely been retrospective and limited in terms of number of patients.[65,66] Recent work, however, suggests that patients with *BRCA1/BRCA2* mutations who have been treated with breast-conserving therapy may be at higher risk of both contralateral and late ipsilateral events compared to sporadic cases without mutations (42% *v* 9%; $P = .001$ and 49% *v* 21%; $P = .007$,

respectively[66]). An important study with the largest experience to date suggests that such women do not appear to be at increased risk of radiation complications and further contralateral and ipsilateral events may be decreased with oopherectomy and/or tamoxifen treatment.[67]

Technologic advances have focused on two important areas: accelerated partial breast irradiation (APBI)[68,69] and intensity modulated radiation therapy (IMRT).[10,70] APBI is discussed in more detail in the next section of this series. IMRT uses modern technology to vary the intensity of radiation beams, permitting a more homogeneous dose of radiotherapy to be delivered to the whole breast. Early studies have confirmed IMRT leads to improved homogeneity of dose to the breast and decreased radiation exposure to the heart, lung, and contralateral breast, which is likely to reduce acute and long-term adverse effects of breast irradiation.[10,70-72] Several randomized trials in the United Kingdom and Canada are currently evaluating the effectiveness of IMRT for whole breast irradiation.

Adjuvant radiation therapy remains a challenge as the majority of treatment is directed at patients who do not require it (ie, will not develop recurrent breast cancer) or who are unlikely to respond because their tumor is radioresistant. The incorporation of genetic correlative studies, eg, gene micro-arrays[73] and polymerase chain reaction techniques[74] in prospective trials may help to better identify patients who are likely to recur and respond to radiation with minimal toxicity.

SUMMARY

Over the last two decades, randomized trials have demonstrated the importance of breast irradiation for breast-conserving therapy. Recent trials have evaluated different approaches to the delivery of radiation therapy and support the use of AHRT and the avoidance of boost irradiation in selected patients. Wide adoption of such approaches will lead to improved patient convenience and quality of life and may increase access to radiation therapy following breast-conserving surgery. Novel techniques for breast irradiation, including APBI and IMRT, are designed to further improve the therapeutic index for women undergoing radiation therapy for early breast cancer.

Author's Disclosures of Potential Conflicts of Interest

The author indicated no potential conflicts of interest.

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