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REVIEW ARTICLE – BREAST ONCOLOGY

Adjuvant Radiotherapy in Early-Stage Breast Cancer: Evidence-Based Options

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ABSTRACT

Background. Patients with a diagnosis of early-stage breast cancer are offered the option of either mastectomy or breast-conserving therapy (BCT) secondary to multiple randomized trials demonstrating equivalent long-term outcomes. Traditionally, BCT has used standard whole-breast irradiation (SWBI) after breast-conserving surgery, although several alternatives have emerged during the past few decades.

Methods. This report reviews key studies supporting each radiation technique and its respective eligibility criteria to assist clinicians in deciding which adjuvant radiotherapy options are appropriate for their patients.

Results. In the past, completion of SWBI required 5–7 weeks of daily treatments. During the past two decades, alternatives to SWBI have emerged including hypofractionated whole-breast irradiation (3–4 weeks), accelerated partial-breast irradiation (1–3 weeks), and endocrine therapy alone. Multiple randomized trials have established the equivalence of these alternative strategies to SWBI for appropriately selected patients. Additionally, the current guidelines for patient selection demonstrate a large amount of overlap in the selection criteria for each technique.

Conclusion. Clinicians must evaluate patient and pathologic criteria and engage in informed discussions with patients when determining which adjuvant radiation techniques are appropriate. Future strategies being explored include using tumor genetics to identify low-risk patients and switching from paradigms that omit radiotherapy to those that omit endocrine therapy.

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Breast cancer represents the most common noncutaneous malignancy among women, with an incidence of more than 250,000 cases per year in the United States. At this time, early stage breast cancers and ductal carcinoma in situ (DCIS) represent more than 50 % of all new cases in the United States.[1–3] Multiple studies have confirmed that breast-conserving therapy (BCT), consisting of breast conserving-surgery (BCS) followed by adjuvant radiotherapy, is equivalent to mastectomy in terms of clinical outcomes with studies also finding improved quality of life and satisfaction with BCT.[4–7] The randomized studies used standard whole-breast irradiation (SWBI) with 5–7 weeks of daily treatment using doses of 1.8–2.0 Gy/fraction, which became the conventional radiotherapy approach.[4–6] However, during the past several years, alternatives to SWBI have emerged including hypofractionated accelerated whole-breast irradiation (AWBI), accelerated partial-breast irradiation (APBI), intraoperative radiation therapy (IORT), and the omission of radiation therapy altogether.

At this time, clinicians are faced with the challenge of guiding and educating patients regarding the numerous adjuvant treatment options. Therefore, this review aims to

summarize adjuvant radiotherapy options and the data supporting them to provide clinicians with a primer on what treatments may be best suited for their patients.

DISCUSSION

Standard Whole-Breast Irradiation

As noted earlier, SWBI represents the traditional adjuvant radiotherapy technique following BCS. Table 1 summarizes the outcomes for patients treated with SWBI from the initial BCT trials.[4–6,8–10]

A recent meta-analysis of more than 10,000 patients treated with BCT evaluated the long-term impact of radiation therapy (predominantly SWBI) and found a reduction in first recurrences at 10 years (35 vs. 19 %; $p < 0.00{,}001$) as well as a reduction in breast cancer mortality at 15 years (25 vs. 21 %; $p = 0.00005$) with the addition of adjuvant radiotherapy.[11] Although older data which utilized SWBI may appear to show less optimal results with respect to local control and toxicity as compared to modern series, much of this improvement can be attributed to optimized surgical techniques as well as new systemic therapies and radiation planning and delivery techniques (e.g., intensity-modulated radiation therapy [IMRT]).[12–18]

With respect to DCIS, SWBI was used in the four randomized studies evaluating BCS and was found to lower rates of local recurrence compared with BCS alone.[19–22] Figure 1 provides a summary of key studies investigating SWBI as well as other radiation therapy techniques and a summary of local control outcomes by technique.

Accelerated Whole-Breast Irradiation

Accelerated whole-breast irradiation allows for a reduction in treatment duration from 5–7 weeks to 3–4 weeks by increasing the dose per fraction while reducing the total number of fractions (hypofractionation); however, the target (the whole breast) remains unchanged, compared with SWBI. This has important implications for women undergoing BCT because many forgo radiation therapy due to the prolonged duration of SWBI.[23–25]

Multiple randomized studies evaluating AWBI with follow-up periods longer than 10 years have been published and are summarized in Table 1.[14–16,26,27] The Ontario Clinical Oncology Group trial randomized 1234 women to SWBI or AWBI (42.5 Gy/16 fractions). With 10 year follow up, no difference in local control or toxicity was noted with comparable cosmetic outcomes.[14] Similarly, 10-year outcomes from the START A trial (SWBI vs. 41.6 Gy/13 fractions vs. 39 Gy/13 fractions treated over 5 weeks) and the START B trial (SWBI vs. 40 Gy/15 fractions treated over 3 weeks) showed no difference in the rates of local recurrence, with reductions in breast toxicity noted using the 40-Gy regimen.[15,16] Recently, a randomized trial of 287 patients treated with either SWBI or AWBI was published and demonstrated a reduction in acute toxicity with AWBI.[27]

Based on these findings, guidelines have been developed that support the increased use of AWBI for appropriately selected patients.[28,29] Patients who may still require SWBI include those with positive lymph nodes, patients younger than 50 years old, and those with large breasts (difficulty meeting AWBI planning constraints). In addition, patients receiving neoadjuvant chemotherapy or concurrent trastuzumab were largely excluded from the randomized trials of hypofractionation. Patients with DCIS were not routinely included in initial studies evaluating the technique, but use of AWBI is supported by the outcomes of recent studies.[27,30]

Accelerated Partial-Breast Irradiation

Accelerated partial-breast irradiation (APBI) allows for a further reduction in treatment duration to 1–3 weeks by increasing the dose per fraction and limiting the target to the lumpectomy cavity with a margin. With seven contemporary randomized trials published, APBI represents a standard of care treatment option for appropriately selected women (Table 1).[17,18,31–34]

Delivery of APBI can be accomplished in several ways including interstitial brachytherapy, applicator-based brachytherapy, and external-beam techniques. Interstitial brachytherapy represents the technique with the longest follow-up period. The Hungarian National Institute of Oncology trial randomized 258 women (T1N 0-1mic, negative margins) to SWBI or APBI delivered with interstitial brachytherapy (36.4 Gy/7 fractions, 69 % of the cases) or electrons (50 Gy/25 fractions, 31 % of the cases). With 10 year follow-up, no difference in local recurrence (5.9 vs. 5.1 %) was noted, with improved cosmetic outcomes with partial-breast techniques.[31] Recently, 5-year results from the Groupe Europeen de Curiethrapie-European Society of Therapeutic Radiology and Oncology (GEC-ESTRO) phase 3 trial were published. This study randomized 1184 patients to SWBI or interstitial APBI. No difference in local recurrence was noted (1.4 % for APBI vs 0.9 % for WBI), with a trend for reduced late skin toxicity with APBI.[17] It should be noted that interstitial brachytherapy is technically complex, and its use is limited in the United States. Therefore, applicator-based brachytherapy has emerged as an alternative brachytherapy technique.[35–37]

Although not included in the initial randomized studies evaluating APBI, applicator-based APBI is comparable with interstitial brachytherapy in terms of dosimetry despite some differences.[38] Data from the MammoSite

TABLE 1 Outcomes by radiation technique

	Years of accrual	No of patients	F/U (years)	Inclusion criteria	Radiation dose	Local recurrence		Overall survival	
						Mastectomy (%)	Lumpectomy (%)	Mastectomy (%)	Lumpectomy (%)
Standard whole-breast irradiation									
Institut Gustave-Roussy	1972–1979	179	14.5	T1	45 Gy, 15 Gy boost	14	9	65	73
Milan	1973–1980	701	20	Age <70, T1	50 Gy, 10 Gy boost	2.3	8.8	59	58
NSABP B-06	1976–1984	1851	20.6–20.8	Stage 1/2, tumor <4 cm	50 Gy	10.2 (1st fail)	14.3	47	46
NCI	1979–1987	237	18.4	Stage 1/2	45.0–50.5 Gy, 15–20 Gy boost	0	22.3	58	54
EORTC 10801	1980–1986	868	22.1	Stage 1/2, T1–2	50 Gy, 25 Gy boost	12.2[a]	19.7[a]	45	39
Denmark	1983–1989	793	19.6	Age <70	50 Gy, 10–25 Gy boost	6.5	4.6	51	58

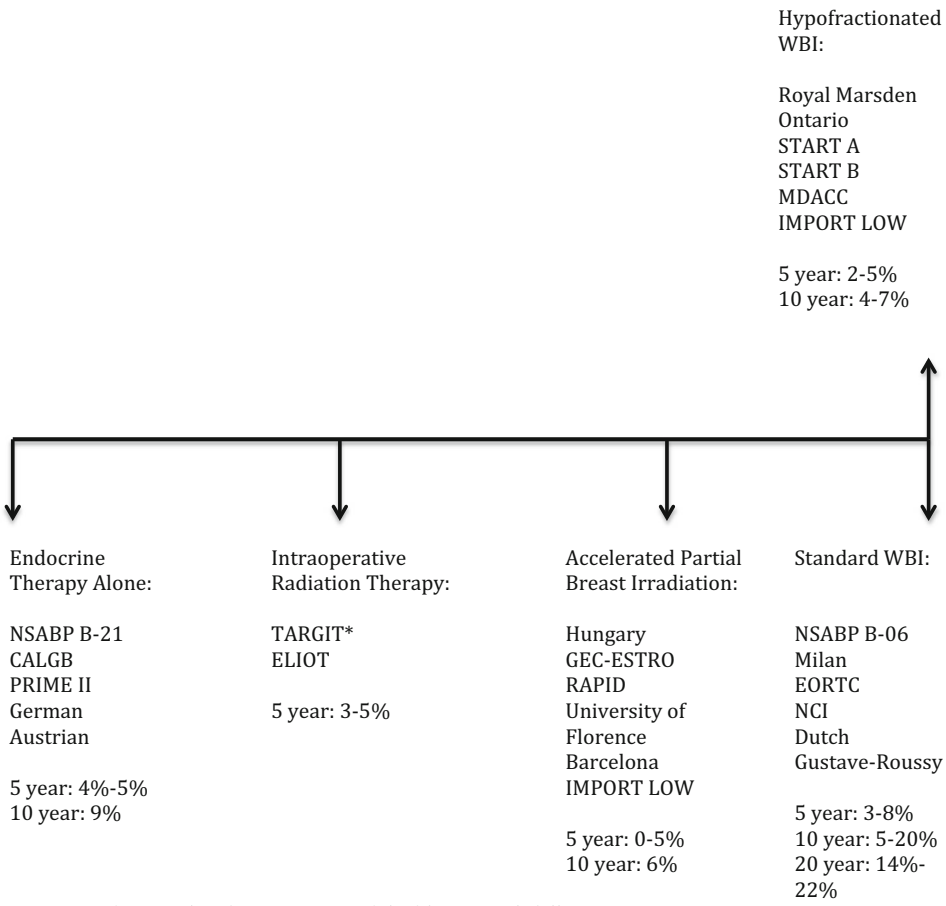
	Years of accrual	No of patients	F/U (years)	Inclusion criteria	Radiation dose	Local recurrence–SWBI (%)	Local recurrence–AWBI (%)	Toxicity	Boost (%)
Accelerated whole-breast irradiation									
RMH/GOC	1986–1998	1410	9.7	T1-3N1, age ≤75, complete macroscopic resection	50 Gy/25 fx 42.9 Gy/13 fx 39 Gy/13 fx (all over 5 weeks)	12.1	9.6 14.8	39.6 % 45.7 % 30.3 % Any change in breast appearance at 5 years	74 75 74
Ontario Oncology Group	1993–1996	1234	12	T1-2N0, negative margins, separation < 25 cm	42.56 Gy/16 fx 50 Gy/25 fx	6.7	6.2	No significant difference in excellent/good cosmetic outcomes (71.3 % SWBI vs. 69.8 % AWBI)	0 0
START-A	1999–2002	2236	9.3	T1-3aN0-1, complete excision	50 Gy/25 fx 41.6 Gy/13 fx 39 Gy/13 fx (all over 5 weeks)	6.7	5.6 8.1	No difference, 50 Gy, 41.6 Gy with moderate/marked normal tissue effects; reduced induration/telangiectasia/edema with 39 Gy versus 50 Gy	60.4 61.0 60.0
START-B	1999–2001	2215	10	T1-3aN0-1, complete excision	50 Gy/25 fx 40 Gy/15 fx	5.2	3.8	Breast shrinkage, telangiectasia and edema significantly lower with 40 Gy	41.4 43.8

TABLE 1 continued

	Years of accrual	No of patients	F/U (years)	Inclusion criteria	Radiation dose/technique	Local recurrence–SWBI/AWBI	Local recurrence–APBI	Toxicity
Accelerated partial breast irradiation								
National Institute of Oncology-Hungary	1998–2004	258	10.2	pT1, pN0-1 mi, grade ½, nonlobular, negative margins, age >40 (2001)	36.4 Gy/8 fx (interstitial) 50 Gy/25 fx (electrons)/ interstitial/electron	5.1 %	5.9 %	Improved cosmesis with APBI (81 vs. 63 %)
GEC-ESTRO	2004–2009	1184	6.6	pT1-2 (<3 cm), pN0-1 mi, margins >2 mm, no LVSI, IDC/ILC/DCIS, age >40	32 Gy/8 fx 30.2 Gy/7 fx (HDR)/50 Gy (PDR)/ interstitial	0.9 %	1.4 %	Trend for reduced late grade 2–3 skin toxicity with APBI
University of Florence	2005–2013	520	5.0	pT1-2 (<2.5 cm), negative margins, clips placed in tumor bed, age >40	30 Gy/5 fx/IMRT	1.5 %	1.5 %	Reduced acute/chronic toxicity with APBI, improved cosmesis with APBI
NSABP B39	2005–2013	4300 (1386 reported on)	3.5	pT1-2 (<3 cm), pN0-1 (no ECE, cN0), negative margins, adenocarcinoma or DCIS, age >18	38.5 Gy/10 fx (3D-CRT cohort)/3D-CRT (for subset analysis)	Not reported	Not reported	Grade 2 fibrosis 12 %, grade 3 3 %, no grade 4/5 toxicity
RAPID	2006–2011	2135	3.0	pT1-2 (<2 cm), pN0, negative margins, IDC/DCIS, age >40	38.5 Gy/10 fx/3D-CRT	Not reported	Not reported	Grade 1–2 toxicity, adverse cosmesis worse with APBI
Barcelona	–	102	5.0	pT1-2 (<3 cm), pN0, grade ½, negative margins, IDC, age >60	37.5 Gy/10 fx/3D-CRT	0 %	0 %	Lower rates of late toxicity with APBI, no difference in cosmesis
IMPORT LOW	2007–2010	2018	5.8	pT1-2 (≤3 cm), N0-1, margins ≥2 mm, age ≥50	40 Gy/15 fx 36/15 fx (40/15 partial) 40/15 partial/3D-CRT	1.1 % 0.2 %	0.5 %	Not reported

NSABP National Surgical Adjuvant Breast and Bowel Project, *NCI* National Cancer Institute, *EORTC* European Organisation for Research and Treatment of Cancer, *RMH/GOC* Royal Marsden Hospital/ Gloucestershire Oncology Centre, *START* Standardisation of Breast Radiotherapy, *GEC-ESTRO* Groupe Europeen de Curietherapie *RAPID* Randomized Trial of Accelerated Partial Breast Irradiation; FU, follow-up, *SWBI* standard whole-breast irradiation, *AWBI* accelerated whole-breast irradiation *APBI* accelerated partial-breast irradiation, *HDR* high dose rate; PDR, pulsed dose rate, *LVSI* lymphovascular space invasion, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *DCIS* ductal carcinoma in situ, *IMRT* intensity-modulated radiation therapy, *CRT* conformal radiotherapy, *ECE* extracapsular extension, *3D-CRT* 3-dimensional conformal radiotherapy

[a] 10-year outcomes



*5-year data from TARGIT trial with 29 month follow up

FIG. 1 Summary of adjuvant treatment options following breast conserving surgery and associated outcomes

Registry, which included more than 1400 patients demonstrated excellent outcomes with single-lumen applicator-based brachytherapy (5-year ipsilateral breast tumor recurrence, 3.8; 91 % excellent/good cosmetic outcomes), and the transition to newer, multi-lumen/strut applicators has allowed for a reduction in the dose to critical structures while improving target coverage.[36,37,39,40] Additional data with respect to applicator-based brachytherapy will be available as further studies are published in the years to come.

External-beam APBI represents a non-invasive alternative with multiple techniques available. Three-dimensional conformal radiotherapy (3D-CRT) represents the initial modern technique used, with promising early results.[41,42] However, concerns regarding cosmesis and toxicity have emerged in more recent trials.[43–45] For example, the RAPID trial enrolled 2135 women (age > 40 years, tumor < 3 cm) who had underwent 3D-CRT APBI or AWBI. Interim analysis (excluding efficacy data) demonstrated an increase in adverse cosmesis with APBI as well as an increase in grade 1 to 2 toxicities after 3 years, in contrast to an early report from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B39 trial and a small Spanish study.[32–34,46]

More recently, data have been published supporting the use of IMRT rather than 3D-CRT to deliver external-beam APBI.[47] The University of Florence trial included 520 patients (age > 40 years, tumor size ≤ 2.5 cm) who received APBI via IMRT (30 Gy/5 fractions every other day) or SWBI. With 5-year follow-up, IMRT APBI showed reduced toxicity and improved cosmetic outcomes, with no difference in local control as compared to SWBI.[18] Additionally, IMPORT LOW ($n = 2018$) evaluated once-daily external-beam APBI (40 Gy/15 fractions) administered over 3 weeks. The results have been published in abstract form, with no difference in local control at 5 years compared with AWBI.[33]

Multiple guidelines are available to assist clinicians in choosing appropriate candidates for APBI. The American Society for Radiation Oncology (ASTRO) guidelines initially published in 2009 have recently been submitted for update.[48,49] Similarly, the GEC-ESTRO working group published guidelines in 2009 that identified age older than 50 years, tumor smaller than 3 cm, negative nodes, negative margins (2 mm), no lymphovascular space invasion

TABLE 2 Comparison of guidelines by treatment technique

	Technique	Age (years)	Size	Nodal status	Histology	Margins	Estrogen receptor	LVSI	Chemotherapy	Endocrine therapy	Dose (%)	Grade
ASTRO	AWBI	≥50	pT1-2	pN0	–	–	–	–	No	–	±7	–
ASTRO	APBI	≥60	pT1	pN0	IDC/favorable	Negative	Positive	Negative	No neoadjuvant	–	–	Any
ABS	APBI	≥50	pT1-2 (≤3 cm)	pN0	IDC/ILC/DCIS	Negative	Any	Negative	–	–	–	–
GEC-ESTRO	APBI	≥50	pT1-2 (≤3 cm)	pN0	IDC/favorable, no EIC	Negative (≥ 2 mm)	Any	Negative	No neoadjuvant	–	–	Any
ASBS	APBI	≥45	pT1-2 (≤3 cm)	pN0	Invasive/DCIS	Negative	–	–	–	–	–	–

ASTRO American Society for Radiation Oncology, *ABS* American Brachytherapy Society, *GEC-ESTRO* Groupe Europeen de Curietherapie, *ASBS* American Society of Breast Surgeons, *LVSI* lymphovascular space invasion, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *DCIS* ductal carcinoma in situ, *EIC* extensive intraductal component

(LVSI), invasive ductal carcinoma, or favorable histology as characteristics appropriate for off-protocol APBI utilization.[50] More recently, the American Brachytherapy Society (ABS) has published guidelines based on the increasing clinical data available.[51] The recommendations for the off-protocol use of APBI include age 50 years or older, tumor 3 cm or smaller, negative nodes, negative margins, no LVSI, and DCIS/invasive histologies (Table 2).

Intraoperative Radiation Therapy

Intraoperative radiation therapy represents an intriguing opportunity for patients and clinicians, offering the ability to complete adjuvant radiation therapy at the time of surgery. Although IORT is a partial-breast technique, it differs notably from APBI. As a result, data from APBI trials should not be used directly to justify the use of IORT nor should APBI eligibility guidelines be used to select patients for IORT.

IORT differs from APBI in several key ways: (1) margins: APBI traditionally includes a margin of 1–3 cm, whereas the target for IORT typically is smaller, particularly with low-energy photons (50 kV prescribed to surface, approximately 25 % of prescription at 1 cm),[52] (2) an inability to visualize dose delivery through treatment planning, (3) a lack of consistent image guidance, and (4) a lack of pathologic information before treatment, which can translate into 15–20 % of patients requiring SWBI. At this time, the data available suggest that further study is needed before IORT becomes used outside a clinical trial.[49,52–55]

The TARGIT trial compared SWBI with IORT and with a median follow-up of 29 months demonstrated an increase in local recurrences with IORT (3.3 % vs. 1.3 %). In addition, the risk of recurrence exceeded the noninferiority cutoff of 2.5 % for the post-pathology cohort (5.4 % vs. 1.7 %), with up to 22 % of patients (22 % pre-pathology, 4 % post-pathology, 15 % overall) requiring supplemental WBI.[56]

The ELIOT trial randomized 1305 patients to SWBI or IORT (delivered with electrons, no supplemental WBI). At 5 years, the IORT arm had an increase in ipsilateral breast failures (4.4 vs. 0.4 %).[57] Notably, unlike IORT, increased rates of local recurrence have not been seen in the trials evaluating AWBI or APBI. In addition, limited data exist to suggest that IORT is more efficacious than endocrine therapy alone.[58] Nonrandomized studies also have demonstrated higher local recurrence rates than expected, as seen in TARGIT-R (a multi-institutional retrospective registry), with a 2.3 % IBF at 23 months, whereas a study of IORT for DCIS demonstrated a 5.7 % IBF rate at only 36 months.[59,60] Based on these findings, IORT has not been included in the evidence-based guidelines for the

TABLE 3 Rate of local recurrence with and without radiation therapy following breast-conserving surgery

	Years of accrual	No of Patients	F/U (years)	Randomization	Patient and tumor characteristics	Local recurrence	
						RT (%)	No RT (%)
NSABP B-06	1976–1984	1851	20.0	Lumpectomy ± RT	T ≤ 4 cm	14.3	39.2
Milan III	1987–1989	579	9.1	Quadrantectomy ± RT	T ≤ 2.5 cm, age ≤ 70 year	5.8	23.5
NSABP B-21	1989–1998	1009	7.2	Lumpectomy ± tamoxifen ± RT	T ≤ 1 cm, N0, margins negative	2.8 % (RT + Tam)/ 9.3 % (RT alone)	16.5
German	1991–1998	347	10.0	Lumpectomy ± tamoxifen ± RT	pT1N0, ER + , age 45–75 year, grade 1–2, margins negative	5 % (RT + Tam)/ 10 % (RT alone)	34 %/7 % (Tam alone)
Canadian	1992–2000	769	5.6	Tamoxifen ± RT	T ≤ 5 cm, age ≥ 50 year	0.6	7.7
CALGB 9343	1994–1999	636	12.6	Tamoxifen ± RT	T1N0, ER positive, age ≥ 70 year	2.0	9.0
Austrian ABCSG 8A	1996–2004	869	4.5	Tamoxifen/ anastrazole ± RT	pT1-2N0 (≤ 3 cm), Grade 1-2, ER+	0.4	5.1
PRIME II	2003–2009	1326	5.0	Endocrine therapy ± RT	T1-2 (≤ 3 cm), age ≥ 65 year, negative margins, grade 3 or LVSI	1.3	4.1

NSABP National Surgical Adjuvant Breast and Bowel Project, *CALGB* Cancer and Leukemia Group B, *FU* follow-up, *RT* radiation therapy, *Tam* tamoxifen, *PRIME* Postoperative Radiotherapy in Minimum-Risk Elderly, *LVSI* lymphovascular space invasion

application of APBI, with the recent ASTRO update submitted for review stating that IORT should not be recommended off protocol.[48,49]

Endocrine Therapy Alone

Omitting radiotherapy altogether after BCS has been evaluated since the inception of BCT (Table 3). In fact, one treatment arm of the NSABP B-06 trial included patients treated with lumpectomy alone and found an increase in the rate of local recurrence with the omission of radiotherapy (39 vs. 14 %).[4] Similarly, early prospective phase 3 trials evaluating the omission of radiotherapy found large increases in the rate of local recurrence.[61–63] These findings are consistent with the Early Breast Cancer Trialists' meta-analysis that demonstrated a reduction in local recurrence with the addition of radiotherapy, translating into a breast cancer mortality benefit.[10] However, these initial studies did not include adjuvant endocrine therapy, limiting their utility based on modern treatment paradigms. The NSABP B-21 trial evaluated the potential for omitting radiotherapy in patients receiving tamoxifen. However, long-term results demonstrated an increase in local recurrence without radiotherapy (16 vs. 3 %).[64]

More recently, a series of trials evaluated omitting radiation therapy for low-risk patients as defined by patient features (age) and clinical/pathologic features (tumor size, estrogen receptor status). A multi-institutional Canadian trial randomized 769 women, 50 years of age or older (median age, 68 years) with tumors smaller than 5 cm, to adjuvant tamoxifen with or without SWBI. At 5 years, the omission of radiotherapy not only increased rates of local recurrence (7.7 vs. 0.6 %) but also had led to a decrement in disease-free survival (84 vs. 91 %).[65]

The Cancer and Leukemia Group B (CALGB) 9343 trial examined a lower-risk cohort of patients (70 years or older, tumor < 2 cm, estrogen receptor positive) and randomized 636 women to tamoxifen with or without adjuvant radiotherapy. At 10 years, omitting radiotherapy led to an increase in rates of locoregional recurrence (10 vs. 2 %), with no difference in survival noted.[66]

Recently, the Postoperative Radiotherapy in Minimum-Risk Elderly (PRIME) II trial was published. This study randomized 1326 women (age 65 years or older with T1-2N0 (≤3 cm), negative margins, grade 3, or LVSI) to adjuvant endocrine treatment with or without radiotherapy. During the 5-year follow-up period, adjuvant radiotherapy reduced the risk of local recurrence (4.1 vs. 1.3 %), with no difference in survival, consistent with previous studies.[67–69]

However, taken together, the studies demonstrate that even the lowest-risk patients experience a reduction in the rate of local recurrence with the addition of radiotherapy although select elderly patients with competing risks of death may be spared from radiotherapy. Importantly, compliance with endocrine therapy is notably poor, and assessing a patient's ability to tolerate several years of endocrine therapy is an important consideration.

Future Directions

Previous studies have yet to identify a subset of patients who do not benefit from adjuvant radiotherapy in terms of local control. However, clinicians are increasingly turning to tumor genetics to better identify low-risk patients.

FIG. 2 Evidence-based treatment options in typical clinical scenarios

Clinical Scenario	SWBI	AWBI	APBI	ET
T1N0, IDC, ER+				
Age >70	+	+	+	+
Age 50-70	+	+	+*	+^
Age < 50	+	-	-	-
T1N0, IDC, ER-				
Age >70	+	+	+*	-
Age 50-70	+	+	+*	-
Age < 50	+	-	-	-
T2N0, IDC, ER+				
Age > 70	+	+	+(up to 3 cm)	+^(up to 3 cm)
Age 50-70	+	+	+*	+^
Age < 50	+	-	-	-
T2N0, IDC, ER-				
Age >70	+	+	+*(up to 3 cm)	-
Age 50-70	+	+	+*	-
Age < 50	+	-	-	-
DCIS, ER+				
Age >70	+	+	+&	-#
Age 50-70	+	+	+&	-#
Age < 50	+	-	-	-#

*- Per ABS, ASBS, GEC-ESTRO guidelines
^- May consider based on PRIME II (age $\geq$ 65 years old)
& Per ABS, ASBS guidelines
#- May consider based on RTOG 9804, ECOG E-5195, and Dana Farber trial

Several studies evaluating multigene assays have correlated risk scores with the rate of local recurrence for patients with DCIS.[70,71] However, the risk of local recurrence in these "low-risk" groups in the absence of radiotherapy still approaches 10 % at 10 years.[70] In addition, higher cost is associated with widespread use of such techniques, and the question emerges whether these additional costs are appropriate if a large percentage of patients will still receive adjuvant radiotherapy (e.g., the aforementioned DCIS studies found 30–40 % of cases to be intermediate or high risk). Furthermore, the lowest-risk group still had unacceptably high local recurrence rates.[70,71] However, updated data from the Canadian multi-institutional trial suggests that patients with luminal A tumors have a low risk of recurrence with adjuvant endocrine therapy alone, although further study is required.[72]

An alternative strategy currently being explored is to re-evaluate how conservative treatment after BCS is defined. Traditionally, as noted earlier, conservative treatment has consisted of BCS followed by endocrine therapy.[64–69] This paradigm makes the assumption that adjuvant endocrine therapy is the more conservative choice compared with radiotherapy. However, endocrine therapy is associated with toxicities including osteoporosis, hot flashes, arthralgias, and second malignancies and requires long-term daily administration, with well-documented low rates of compliance.[73–76] Additionally, the costs associated with endocrine therapy, particularly with nongeneric alternatives, are not insignificant.[77] Finally, the traditional paradigm, in the context of BCT, included SWBI.

With the advent of techniques such as AWBI, APBI, and IORT, patients currently can receive radiotherapy with reduced treatment duration, lower rates of toxicity, improved quality of life, and lower costs. The pendulum may be swinging from endocrine therapy alone to adjuvant radiotherapy as the preferred low-risk conservative approach in many cases. However, radiotherapy does not reduce the risk of contralateral breast cancers as with endocrine therapy, and further study is required.[78]

Summary and Conclusions

Multiple adjuvant treatment options following BCS have been developed ranging from radiation options including SWBI, AWBI, and APBI to endocrine therapy alone. It is important for clinicians to realize that multiple of these treatment options may be appropriate for a patient, with significant overlap in terms of eligibility criteria and anticipated outcomes (Table 2; Fig. 2), with recent data suggesting that 80 % of early stage breast cancers are eligible for AWBI, 41–90 % are eligible for APBI (depending on the selection criteria used), and 21–39 % are eligible for endocrine therapy alone.

DISCLOSURE None.

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