Breast Cancer

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Contents

1 **Introduction** 1

2 **Early-Stage Disease and Breast Conservation** 2
2.1 Radiation After Breast-Conserving Surgery 2
2.2 Omission of Radiation After Breast-Conserving Surgery in Patients with Favorable Features 2
2.3 Ductal Carcinoma In situ 7
2.4 Lobular Carcinoma In situ 10

3 **Techniques and Approaches to Treatment** 11
3.1 Hypofractionation 11
3.2 Hypofractionated Whole Breast Irradiation 11
3.3 Accelerated Partial Breast Irradiation 13
3.4 IMRT 18

4 **Locally Advanced Breast Cancer** 18
4.1 Postmastectomy Radiotherapy 18
4.2 Management of the Regional Lymph Nodes 23
4.3 Cardiac Toxicity Associated with Breast Radiotherapy 26

Conclusion 27

References 28

Abstract

Radiation therapy plays an integral role in the multidisciplinary management of breast cancer. In appropriately selected patients, radiotherapy not only prevents local recurrences by eliminating residual disease but also results in improved survival. However, not all patients have the same risk of harboring residual locoregional disease, resulting in considerable controversy regarding the role of radiotherapy in individual scenarios. Evidence from clinical trials and observational data analyses can help identify which patients with breast cancer are most likely to achieve a net benefit from adjuvant radiation therapy, both after lumpectomy and mastectomy. Additionally, evidence is emerging now about novel approaches in breast radiotherapy that may reduce burden or toxicity in ways that can optimize the therapeutic ratio, including hypofractionated whole breast radiation, accelerated partial breast irradiation (APBI), intensity-modulated radiation (IMRT), and cardiac avoidance techniques. The objective of this chapter is to review both established and emerging evidence regarding these important issues in an effort to clarify the rationale for increasingly complex and individualized decisions regarding breast radiotherapy.

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1 Introduction

Radiation therapy plays an integral role in the multidisciplinary management of breast cancer. In appropriately selected patients, radiotherapy substantially decreases the risk of recurrence and results in improved survival. Within the previous two decades, considerable progress has been made toward selecting patients most likely to benefit from radiation, along with technical improvements that minimize the burden and toxicity associated with treatment while maximizing clinical benefit.

In an effort to clarify the rationale for increasingly complex clinical decisions, this chapter reviews the rich literature from practice-changing clinical trials in recent years, with an emphasis on the indications for radiation in the context of evolving surgical and systemic treatments, optimal approaches that maximize the therapeutic ratio, and appropriate treatment targets, both after breast-conserving surgery and mastectomy.

2 Early-Stage Disease and Breast Conservation

2.1 Radiation After Breast-Conserving Surgery

Several randomized trials have demonstrated equivalent survival after mastectomy as compared to breast-conserving surgery with radiation in appropriately selected patients, allowing women to choose a more limited surgical procedure without compromising disease control (Fisher et al. 2002a; Arriagada et al. 1996; Veronesi et al. 2002; Poggi et al. 2003; van Dongen et al. 2000; Blichert-Toft et al. 1992). Radiation therapy has long been recognized as a key component of breast-conserving therapy, with results from numerous randomized trials demonstrating that postoperative radiation substantially reduces the risk of locoregional recurrence (Fisher et al. 2002a; Clark et al. 1996; Ford et al. 2006; Liljegren et al. 1999a; Veronesi et al. 2001a). For example, in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 randomized trial, the 20-year ipsilateral breast tumor recurrence rate was 14.3 % after lumpectomy and whole breast radiation versus 39.2 % after lumpectomy alone (Fisher et al. 2002a). Adjuvant radiotherapy after breast-conserving surgery has been recommended in consensus guidelines for over two decades (NCCN 2014) and is included as a measure of treatment quality (Surgeons ACo Commission on Cancer Quality of Care Measures; National Quality Measures for Breast Centers).

More recently, the improvement in locoregional control with radiotherapy has been associated with reduction in the overall risk of a recurrence and modest survival benefit as well. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of data from 10,801 individual patients in 17 studies demonstrated that radiation reduced the 10-year risk of any recurrence from 35 to 19.3 % and reduced the 15-year risk of death from breast cancer from 25.2 to 21.4 % (Clarke et al. 2005; Darby et al. 2011a). Similar findings were observed in a pooled analysis that demonstrated a three-fold increase in ipsilateral breast tumor recurrence and an 8.6 % increase in mortality with omission of radiation after breast-conserving therapy (Vinh-Hung and Verschraegen 2004).

However, while the relative benefits of radiation are similar for all patients, the absolute benefit obtained from radiotherapy varies considerably according to patients' baseline risk. The EBCTCG analyses have suggested that the survival benefit may be limited to those who obtain the largest absolute risk reduction from treatment, rather than those in whom the absolute benefit in recurrence risk reduction is less than 10 % (Darby et al. 2011a).

2.2 Omission of Radiation After Breast-Conserving Surgery in Patients with Favorable Features

The prevalence of early-stage breast cancer in a mammography-screened population raises concerns about potential harm associated with

overtreatment. With population-based screening, the incidence of in situ and early-stage invasive disease with favorable prognoses has nearly tripled, while the incidence of later-stage invasive disease has only slightly decreased (Glass et al. 2007; Jemal et al. 2007). Some have suggested that this increase in the incidence of early-stage breast cancer without a corresponding decrease in the incidence of advanced stage breast cancer is reflective of substantial overdiagnosis, accounting for approximately one-third of all newly diagnosed breast cancers (Bleyer and Welch 2012), and that screening is having only a modest effect on the rate of death from breast cancer (Welch and Frankel 2011). Furthermore, the risk of distant metastasis is lower for cancers detected by mammography than for tumors detected outside of screening (Joensuu et al. 2004). Given that approximately one-third of all new breast cancer diagnoses occur in women age 70 or older, and considering that the majority of these cases represent early-stage disease (Jemal et al. 2007), decisions surrounding use of adjuvant radiotherapy in this group affect tens of thousands of women.

In light of these epidemiologic trends, it is plausible that a substantial proportion of women in a mammography-screened population have been diagnosed with early-stage breast cancer that would be an unlikely cause of breast cancer-related mortality. In the EBCTCG meta-analysis, it is worth noting that although radiation significantly decreased the incidence of local recurrence, with lumpectomy alone, 69 % of node-negative patients would not have experienced any recurrence (Darby et al. 2011a). This suggests that a large proportion of women might not benefit from adjuvant radiotherapy. Taken together with concern for the burden, morbidity, and cost of adjuvant radiotherapy, researchers have sought to identify a subgroup of breast cancer patients in whom the risk of recurrence after lumpectomy is sufficiently small that consideration may reasonably be given to omission of radiotherapy.

An observational study from Nemoto et al. (Nemoto et al. 1991) published in 1990 noted that after median follow-up of 4 years, in women who underwent lumpectomy alone, no recurrences occurred in tumors <1 cm, and only 1 of 31 patients older than age 70 experienced a recurrence. Since that early observation, numerous prospective trials have unsuccessfully sought to identify a subgroup of patients who could undergo breast-conserving surgery without radiotherapy (Lim et al. 2006; Holli et al. 2009; Fisher et al. 2002b; Winzer et al. 2010; Forrest et al. 1996; Potter et al. 2007; Fyles et al. 2004).

A prospective single-arm study of lumpectomy alone from Harvard (Lim et al. 2006) observed an unacceptably high local recurrence rate of 23 % at 7 years in a highly selected group of patients with presumed low-risk clinical and pathologic features, such as tumor ≤2 cm, margins ≥1 cm, no involved nodes on axillary lymph node dissection, and no lymphovascular invasion or extensive intraductal component. Forty percent of tumors were positive for the estrogen receptor (ER); 49 % were unknown. Similar results were observed in a trial from Finland (Holli et al. 2009), which observed a recurrence rate of 27 % at 12 years with no adjuvant therapy in highly selected patients with the most favorable features suggestive of low aggressiveness, including progesterone receptor positive, well to moderately well differentiated, and low proliferation rate. Thus, even in women diagnosed with breast cancer with presumably low aggressiveness based on clinical and pathologic features, the rate of recurrence after lumpectomy with wide margins appears unacceptably high (16 to 34 %, see Table 1) without postoperative radiation, at least in the absence of systemic therapy.

Because use of tamoxifen is associated with significantly improved locoregional control (Fisher et al. 1989; Early Breast Cancer Trialists' Collaborative Group 1998), investigators hypothesized that in a favorable group of estrogen receptor-positive tumors treated with breast-conserving surgery, tamoxifen might be as effective as postoperative radiation in reducing the rate of ipsilateral breast tumor recurrence. With the objective of determining whether tamoxifen might be used in lieu of radiation, the NSABP conducted the B-21 randomized trial (Fisher et al. 2002b), in which 1009 women were randomized to tamoxifen, radiation, or both. Patients

Table 1 Prospective clinical trials evaluating omission of radiation after breast-conserving surgery in patients with favorable features

Study	*N*	Age	Tumor size	Estrogen receptor positive	Median follow-up	Other eligibility criteria	Adjuvant therapy after breast-conserving surgery	Locoregional recurrence	Statistical significance
Harvard Lim et al. (2006)	81	Median 66 years (range 27–84)	≤2 cm	40 % (49 % unknown)	7.2 years	Margin ≥1 cm, node negative on ALND	No adjuvant therapy	23 %	NA
Finland Holli et al. (2009)	264	>40	≤2 cm	100 % PR positive	12.1 years	Grade 1 or 2 tumors, low proliferation rate, margin ≥1 cm, node negative on ALND	No adjuvant therapy RT	27.2 % 11.6 %	$p = 0.0013$
NSABP B-21 Fisher et al. (2002b)	1009	20 % <50 years	<1 cm	56.7 %	8 years	Negative margins (no tumor on ink), node negative on ALND	Tamoxifen RT + placebo RT + tamoxifen	16.5 % 9.3 % 2.8 %	$p < 0.001$
Germany Winzer et al. (2010)	347	45–75	≤2 cm	93.7 %	9.9 years	Grade 1–2	No adjuvant therapy Tamoxifen RT RT + tamoxifen	34.2 % 9.7 % 13.2 % 6.8 %	$p < 0.001$
BASO II Blamey et al. (2013)	1135	<70	<2 cm	Not reported (estimated at 90 %)	10.1 years	Grade 1 or favorable histology (tubular, mucinous, papillary, or cribiform), negative margins, pathologically node negative	No adjuvant therapy Tamoxifen RT RT + tamoxifen	15.7 % 7.5 % 6.5 % 0 %	$p < 0.001$
Scottish Forrest et al. (1996)	585	<70	≤4 cm	58.6 %	5.7 years	Preferred negative margins, pathologic nodal assessment (23 % were node positive). Received systemic therapy based on receptor status: ER+ received tamoxifen; ER- received CMF	Systemic therapy alone RT + systemic therapy	24.5 % 5.8 %	SS

Italy Tinterri et al. (2014)	749	55–75	<2.5 cm	92.4 %	9 years	Unifocal, no EIC or LVSI, negative margins, 0–3 positive axillary lymph nodes (15 % were node positive)	Endocrine therapy RT + endocrine therapy	4.4 % 3.4 %	NS
Austria Potter et al. (2007)	869	≥50	<3 cm	99 %	4.5 years	Postmenopausal, grade 1 or 2, pathologically negative lymph nodes	Tamoxifen/anastrazole RT + tam/anastrazole	5.1 % 0.4 % ($p < 0.001$) (5 year)	$p < 0.001$
Canada Fyles et al. (2004)	769	≥50	≤5 cm	80.7 %	5.6 years	Negative margins (no tumor on ink), pathologically negative nodes (unless older than 65)	Tamoxifen RT + tamoxifen	17.6 % 3.5 %	$p < 0.001$
CALGB 9343 Hughes et al. (2004, 2013)	636	70	≤2 cm	97 %	12.6 years	Negative margins (no tumor on ink), clinically node negative	Tamoxifen RT + tamoxifen	10 % 2 %	$p < 0.001$

Abbreviations: BCS breast-conserving surgery, *ER* estrogen receptor, *NS* not statistically significant, *PR* progesterone receptor, *RT* radiotherapy, *SS* statistically significant

[a]In the studies presented in this table, there were no significant differences reported in distant metastasis, breast cancer-specific survival, or overall survival

underwent lumpectomy with negative margins (defined as no tumor on ink) and had invasive breast cancer <1 cm with pathologically negative lymph nodes upon axillary lymph node dissection. Estrogen receptor was positive in 57 % of cases, and 20 % of patients were younger than age 50. The incidence of ipsilateral breast tumor recurrence at 8 years was 17 % with tamoxifen, 9 % with radiation, and 3 % with both, leading the authors to conclude that tamoxifen is less effective than radiation in preventing an ipsilateral breast tumor recurrence and that adjuvant radiotherapy is necessary even when tamoxifen is used. An Austrian trial (Potter et al. 2007) of adjuvant endocrine therapy with or without radiation demonstrated a comparatively lower local recurrence rate of 0.4 % and 5.1 % at 5 years, respectively. In the absence of radiation, the local recurrence rate increased to 9 % after 6 years, leading the authors to conclude that further research and longer follow-up were needed to identify more favorable subgroups for whom radiotherapy was not beneficial.

In a German trial (Winzer et al. 2010), patients with estrogen receptor-positive tumors ≤2 cm were randomized to radiation or tamoxifen in a 2 × 2 factorial design. With breast-conserving surgery alone, there was a large excess of local recurrences, but similar event-free survival was observed with endocrine therapy, radiation, or both. However, the limited sample size and corresponding low power limited the impact of this finding. A Canadian multicenter study (Fyles et al. 2004) that included patients >50 years with tumors up to 5 cm found similarly high rates of local recurrence with tamoxifen alone, at 18 % after 8 years, in comparison to 4 % with both radiation and tamoxifen. These disappointing results were tempered by the finding that in tumors less than 1 cm, the 5-year recurrence rate was 2.6 %, and when further limited to patients who were older than age 60, there was no significant difference in local relapse with tamoxifen alone compared to radiation and tamoxifen (1.2 % vs 0 %, respectively, $p = 0.16$). While acknowledging the limitations of a small, unplanned subgroup analysis with limited follow-up, the authors suggest that further studies considering omission of breast irradiation may be best pursued in older patients with small tumors.

In the seminal CALGB 9343 study (Hughes et al. 2004, 2013), enrollment was limited to a favorable group of 636 elderly patients with early, estrogen receptor-positive tumors. Women ≥70 who were clinically node negative and had tumors ≤2 cm that had been resected with negative margins (no tumor on ink) were randomized to treatment with tamoxifen alone or tamoxifen plus radiation therapy. After 10 years, 90 % of patients receiving tamoxifen compared with 98 % of those receiving both radiation and tamoxifen were free from local and regional recurrence. Although the incidence of local recurrence was significantly higher with omission of radiation ($p < 0.001$), there were no significant differences in time to mastectomy, time to distant metastasis, breast cancer-specific survival, or overall survival between the two groups. The absence of a survival benefit in this cohort appears consistent with the observation from the EBCTCG that the survival benefit with adjuvant radiation is not apparent in patients with absolute recurrence risk reduction less than 10 % (Darby et al. 2011a). This study has been widely interpreted as establishing omission of radiotherapy as a reasonable option for similar women who intend to receive endocrine therapy, and the authors advocate that this cohort should have the option of breast-conserving therapy even without radiation.

Even more recently, mature results have emerged from studies in patients younger than those in CALGB 9343. These results include a British trial (Blamey et al. 2013) with a 2 × 2 factorial design that enrolled 1135 patients younger than age 70 with either grade 1 tumors or favorable histology (tubular, mucinous, papillary, or cribriform) measuring <2 cm. Consistent with results from the previous trials of favorable risk patients, the rate of recurrence without adjuvant treatment was unacceptably high at 16 % after 10 years. With either tamoxifen or radiation, the risk of local recurrence was reduced to 7.5 and 6.5 %. However, the greatest benefit was seen in those women who received both radiation and tamoxifen, as these 98 patients experienced no local recurrences. These results led the authors to

suggest that both radiation and tamoxifen may be a reasonable option for women wishing to minimize their risk of recurrence, but that the use of tamoxifen alone may be acceptable for select patients with low-risk tumors who wish to avoid radiation. Similar findings were reported in an Italian study that randomized 749 women age 55 to 75 to adjuvant radiation and endocrine therapy, or endocrine therapy alone. After 9 years, there was no appreciable difference in rates of ipsilateral breast recurrence (Tinterri et al. 2014).

Still, questions remain regarding whether these studies are generalizable to patients with other risk factors, such as close margins, lymphovascular invasion, or high-grade disease. There is also concern that patients in the general population may be less compliant with endocrine therapy than those enrolled on clinical trials. Some have expressed concern regarding omission of radiation in patients who have a longer life expectancy in the absence of longer-term and larger studies. In a population-based analysis of women between age 70 and 79, there was a significant increase in the risk of subsequent mastectomy with omission of radiation (3.2 % vs 6.3 %, $p < 0.001$), (Albert et al. 2012) in contrast to the non-significant difference observed in CALGB 9343. This was especially pronounced in healthy women between age 70 and 74, who had a number needed to treat of 21 to avoid one mastectomy or second ipsilateral breast cancer (Smith et al. 2006). In contrast, in the subgroup of women between age 75 and 79 who underwent pathologic nodal assessment and did not have high-grade tumors, there was no apparent benefit from radiation (Albert et al. 2012).

While the standard of care remains adjuvant radiation following breast-conserving surgery, there is now a consensus (NCCN 2014) that omission of radiation may be a reasonable alternative for highly selected women older than age 70 with small, estrogen receptor-positive tumors. For other patients, the limited and conflicting data on long-term control with endocrine therapy alone remains insufficient to convince most practitioners to consider omitting radiotherapy. The number of trials to date that have unsuccessfully sought to identify a subgroup of patients at low risk of recurrence with endocrine therapy alone after breast-conserving surgery indicates that clinical and pathologic features are inadequate discriminants for precisely indicating which patients are likely to experience treatment failure and, thus, to require therapy. Future efforts are focused on selecting patients at low risk of recurrence based on tumor biology, such as using the 21-gene recurrence score (Mamounas et al. 2010) or developing a new radiation sensitivity signature (Speers et al. 2013). Three prospective, single-arm clinical trials are investigating recurrence rates based on biologic identity, including luminal A disease (the LUMINA trial), a 21-gene recurrence score $\leq$18 (the IDEA trial), or based on the PAM50 gene expression signature (the PRECISION trial).

2.3 Ductal Carcinoma In situ

Ductal carcinoma in situ (DCIS) is a preinvasive process of the breast, in which the neoplastic lesion is confined to the ductal-lobular system though nonetheless possessing cytologic atypia with a predisposition toward malignant transformation (Lakhani et al. 2012). Owing to the recent increased utilization of mammography, DCIS has become a much more common diagnosis than in decades prior (Ernster et al. 1996). In the United States in 2014, there will be an estimated 62,570 new diagnoses of this disease compared to 232,670 new cases of invasive breast cancer (Siegel et al. 2014). Although not itself a cancerous lesion, several studies have examined the natural history of DCIS via clinical follow-up with women mistakenly diagnosed with benign disease on initial biopsy and without subsequent further treatment. These investigations found that breast cancer eventually develops in 39 to 53 % of such patients (Collins et al. 2005; Rosen et al. 1980; Sanders et al. 2005).

Given its substantial incidence as well as the possibility that DCIS might develop into frank malignancy, management of this disease has warranted careful deliberation on the part of the medical community. Historically, excellent rates of local control and overall survival were achieved with mastectomy. Although never examined in a prospective fashion, retrospective studies have demonstrated local recurrence rates of 3 % or less (Cutuli et al. 2001; Carlson et al. 2007; Kelley et al. 2011; Owen et al. 2013), and meta-analysis

has shown a recurrence rate of 1.4 % (Boyages et al. 1999). Similarly, rates of cause-specific survival have been excellent at 98 % or better (Kelley et al. 2011; Owen et al. 2013).

As mastectomy is an amputative procedure, it may represent too extensive a surgical approach for a disease that often does not progress to a cancerous condition. Concerns such as these have prompted investigation into whether lumpectomy – either alone or in combination with adjuvant radiotherapy – is adequate to address DCIS. Beginning in 1985, a total of four randomized trials have compared lumpectomy alone versus lumpectomy followed by radiotherapy in a broad range of patients (Wapnir et al. 2011; Bijker et al. 2001, 2006; Cuzick et al. 2011; Holmberg et al. 2008; Fisher et al. 1998, 1993; Julien et al. 2000; Houghton et al. 2003; Emdin et al. 2006; Pinder et al. 2010). Of note, these four trials – NSABP B-17, EORTC 10583, the UK/ANZ trial, and the SweDCIS trial – all included similar cohorts of patients: the majority in each trial were 50 years of age or older (67 to 93.5 % of patients) with mammographically detected small tumors (12.5–20 mm mean size) excised with negative margins (in 78–85 % of all cases). Areas of variability included the portion of women with high-grade lesions, ranging considerably from just 27 % of tumors in EORTC 10583 to 74.5 % in the UK/ANZ study (Bijker et al. 2001; Julien et al. 2000; Houghton et al. 2003; Pinder et al. 2010). Additionally, endocrine therapy was not routinely used in NSABP B-17, EORTC 10583, or the SweDCIS study, in contrast to the 2 × 2 factorial design of in the UK/ANZ study, in which tamoxifen was administered to 54 % of all patients (Houghton et al. 2003; Pinder et al. 2010). Unlike endocrine therapy, the approach to radiotherapy was rather uniform across trials: 50 gray (Gy) in 2 Gy daily fractions to the entire breast was the only regimen offered in NSABP B-17, EORTC 10853, and the UK/ANZ study, and this same approach was utilized in 80 % of radiotherapy patients in the SweDCIS study. Of note, boost techniques were infrequently employed, as these were not recommended in the UK/ANZ and SweDCIS studies and were performed in only 5–9 % of patients in the EORTC and NSABP trials, respectively (Wapnir et al. 2011; Bijker et al. 2001, 2006; Cuzick et al. 2011; Holmberg et al. 2008; Fisher et al. 1998, 1993; Julien et al. 2000; Houghton et al. 2003; Emdin et al. 2006; Pinder et al. 2010).

The results from these four trials were combined in an Early Breast Cancer Trialists' Collaborative Group individual patient-level meta-analysis (Correa et al. 2010). In all, outcomes from 3729 patients were analyzed. At a median follow-up of almost 9 years, radiotherapy roughly halved the rate of a woman developing an ipsilateral breast event (IBE), defined as either invasive disease or a recurrence of DCIS (rate ratio 0.46, $p < 0.00001$). The absolute risk reduction at 10 years was 28.1 % in the surgery-alone arm compared to 12.9 % in those that received radiotherapy. Radiotherapy was successful in reducing risk regardless of age, mode of detection (mammographic versus clinical), lumpectomy technique, margin status, focality, nuclear grade, histologic features, or subsequent tamoxifen use. Further, the proportional reduction was independent of all these factors except that it varied by age, as those women who were 50 years of age or older received a slightly larger benefit than those younger than 50 (rate ratios of 0.38 versus 0.69, respectively, $p = 0.0004$) (Correa et al. 2010).

Despite this profound reduction in disease recurrence, no survival benefit was detected: 10-year breast cancer mortality was 4.1 % in the radiotherapy arms versus 3.7 % in the surgery-alone arms. Likewise, 10-year overall survival was 8.4 and 8.2 %, respectively (Correa et al. 2010).

Finally, the authors of the meta-analysis examined a predefined subset of women thought to be at particularly low risk of local disease recurrence. This group of 291 patients included only those with negative margins as well as low-grade tumors, 20 mm or less in size. However, even for these women, radiotherapy conferred a highly significant benefit, reducing IBE rates at 10 years from 30.1 to 12.1 % (rate ratio 0.48, $p = 0.002$) (Correa et al. 2010).

Though this meta-analysis did not identify a subgroup of patients for whom radiation provided little or no benefit, the consistent finding

that such treatment does not confer a survival benefit – as well as its acute and long-term sequelae – has led to a continued efforts to identify low-risk women for whom omission of adjuvant radiotherapy might be appropriate.

One classification schema aimed at achieving this end was proposed by Silverstein et al. and is presently known as the University of Southern California/Van Nuys prognostic index (Silverstein et al. 1996; Silverstein 2003). In the creation of this index, outcomes from 706 DCIS patients were retrospectively analyzed. Of these patients, 426 were treated with surgery alone, while 280 were treated with excision as well as adjuvant radiation. On multivariate regression, four predictors of local recurrence were identified: tumor size, pathologic classification, margin width, and age. These categories were combined into a scoring system, in which each factor was assigned a value from 1 to 3, and the total prognostic score is the resultant sum (see Table 3). The authors recommend excision alone for women with a score of 4 to 6, excision followed by adjuvant radiotherapy for 7 to 9, and mastectomy for scores of 10 or greater. The recommendation that radiotherapy be omitted for those women in the lowest-risk category was a result of an observed 1 % IBE rate that was not impacted by radiotherapy (Silverstein 2003).

While promising, the broader applicability of a tool created from a modest sample of patients is limited by the extent to which it is externally validated in independent cohorts. Unfortunately, attempts at such validation have been inconsistent (Boland et al. 2003; MacAusland et al. 2007; Di Saverio et al. 2008; de Mascarel et al. 2000). Certain investigators have found that the Van Nuys prognostic index lacked meaningful discriminatory power (Boland et al. 2003; MacAusland et al. 2007), while others found a 12.7 % IBE rate in the low-risk population of women not treated with radiotherapy (de Mascarel et al. 2000).

Similarly, investigators from Memorial Sloan Kettering (MSK) have constructed a nomogram for recurrence risk based upon retrospective, single-institution data (Rudloff et al. 2010). However, the results of external and independent validation of this measure have been decidedly mixed (Collins et al. 2012; Sweldens et al. 2014; Yi et al. 2012). Given the lingering questions regarding validity, basing decisions regarding omission of treatment based upon either the University of Southern California/Van Nuys prognostic index or the MSK nomogram cannot be recommended at present.

Prospective attempts to identify a more suitable a low-risk population of DCIS patients have proceeded through three prospective trials (McCormick et al. 2012; Wong et al. 2014; Solin et al. 2013; Page et al. 1991; Hughes et al. 2009). The first of these investigations was a single-arm study at the Dana-Farber Cancer Institute that included only those women with low- or intermediate-grade DCIS, mammographic disease extent of 2.5 cm or less, and final surgical margins of at least 1 cm width (Wong et al. 2014, 2006). Endocrine therapy was not allowed. One hundred fifty-eight women enrolled, and after a median follow-up of 11 years for 158 patients, the 10-year IBE rate was 15.6 % (Wong et al. 2014). Nonetheless, it should be noted that the trial did allow enrollment of patients whose tumors exhibited a small number of DCIS cells with high-grade nuclei, and such high-grade lesions harbor a higher propensity for recurrence (Boyages et al. 1999; Solin et al. 1993).

ECOG 5194 was a multicenter, cooperative group single-arm study that also examined this issue, and it enrolled women with low- or intermediate-grade DCIS 2.5 cm or less in size or those with high-grade lesions that were 1 cm or less. Surgical margins of at least 3 mm were required as was a postoperative mammogram without residual calcifications. The study eventually enrolled 670 women. Slightly less than one-third of patients in each group received adjuvant tamoxifen. However, despite the rigorous entry criteria, the 10-year IBE rate was disappointingly high for both groups: 14.6 % in those with low- or intermediate-grade tumors and 19.0 % in those with high-grade tumors (Solin et al. 2013).

RTOG 98-04 was the most recently reported prospective study to attempt identification of a low-risk group of women. Unlike the Dana

Farber and ECOG 5194 studies, this was a randomized control trial (McCormick et al. 2012). Women were eligible for inclusion if they had low- or intermediate-grade tumors, 2.5 cm or less in size, and surgical margins of at least 3 mm. The randomization was between observation and adjuvant radiotherapy. A total of 636 patients enrolled, well short of the initial goal of 1790 patients, and the study was closed early due to poor accrual. Approximately two-thirds of women received adjuvant tamoxifen. After a median follow-up of 7.2 years, there was a large difference in local control between the two groups, with a 6.4 % IBE rate in the observation arm versus 0.9 % in the radiotherapy arm (McCormick et al. 2012).

These three studies have demonstrated the difficulty of utilizing histopathologic tumor characteristics and treatment factors to identify a low-risk population of women (McCormick et al. 2012; Wong et al. 2014; Solin et al. 2013; Hughes et al. 2009; Wong et al. 2006). This has prompted interest in developing genomic assays in order to better quantify recurrence risk. One such instrument is the Oncotype DX DCIS score, developed by Genomic Health Inc. through analysis of tumor samples obtained from almost half of the patients on ECOG 5194 (Solin et al. 2013). From these samples, the investigators constructed a 12-gene assay, consisting of a subset of those genes used in the better known 21-gene recurrence score that is commonly used to predict the recurrence risk for invasive breast cancers. This new assay was then able to stratify patients (from the same dataset used to construct the model) into low, intermediate, and high-risk categories, with corresponding 10-year risk of developing an IBE of 10.6, 26.7, and 25.9 %, respectively (Solin et al. 2013).

Nevertheless, concerns have been raised, including the fact that the test's low-risk group exhibited a high enough IBE rate that the assay might not identify a group with a meaningfully reduced risk of recurrence. On the other end of the risk spectrum, the test did not substantially differentiate between those with intermediate and high risk of any IBE, though it was able to distinguish these groups in terms of differing risks of developing an invasive recurrence (Solin et al. 2013).

Whether through genomic assays such as the Oncotype DX DCIS score or through the identification of clinicopathologic and treatment factors derived from retrospective and prospective investigations, efforts to define a subgroup of DCIS patients appropriate for omission of adjuvant treatment have fallen short of providing a single, simple answer. Rather, the evidence has consistently suggested benefit from adjuvant radiotherapy, and its use remains routine. If a woman desires to be treated with excision alone, the studies discussed herein should inform discussion and add to the clinician's repertoire of tools in the ongoing effort to properly individualize treatment.

2.4 Lobular Carcinoma In situ

Lobular carcinoma in situ (LCIS) is an uncommon lesion (Page et al. 1991; Akashi-Tanaka et al. 2000), which consists of a proliferation of noninvasive, non-cohesive, small epithelioid cells confined to the ductal-lobular system (Lakhani et al. 2012). Compared to women without such lesions, the presence of LCIS approximately doubles the relative risk of subsequently developing a histologically distinct invasive breast cancer in either breast (Page et al. 1991; Wheeler et al. 1974; Rosen et al. 1978; Chuba et al. 2005; Fisher et al. 2004). As such, this lesion is felt to be a marker of those at increased risk for invasive disease, rather than a direct precursor to breast cancer in and of itself. Given this, following excisional biopsy of LCIS to exclude the presence of concomitant malignancy, radiotherapy is not indicated.

In comparison to classic LCIS, pleomorphic lobular carcinoma in situ (PLCIS) is a less common lesion that exhibits clustered groupings of larger cells with abundant and granular cytoplasm (Eusebi et al. 1992; Middleton et al. 2000). In fact, it may also include areas of calcification and necrosis, similar in appearance to DCIS (Georgian-Smith and Lawton 2001). Given these similarities, PLCIS is most easily distinguishable from DCIS not on the basis of its histology but rather by its lack of E-cadherin expression on

immunohistochemical staining (Lakhani et al. 2012; Jacobs et al. 2001). Further, unlike LCIS, areas of PLCIS can contain components of morphologically similar though not frankly invasive disease (Bentz et al. 1998; Buchanan et al. 2008; Sneige et al. 2002), indicating that PLCIS might in fact be a true precursor of malignancy. This conclusion is bolstered by anecdotal evidence that women with excised PLCIS can experience recurrences, often of invasive cancer (Eusebi et al. 1992; Khoury et al. 2014). Given this, most believe that appropriate treatment for such patients is complete, margin-negative excision, followed by adjuvant radiotherapy. Still, prospective evidence in this arena is sorely lacking, and hence this recommendation awaits either confirmation or refutation by more thorough investigations.

3 Techniques and Approaches to Treatment

3.1 Hypofractionation

Radiotherapy delivered after breast-conserving surgery has conventionally involved dosages of 45–50 gray (Gy) to the entire breast – often followed by a boost to the lumpectomy cavity – given daily over a course of 5–6 weeks (Ceilley et al. 2005). Such an approach has yielded both excellent rates of disease control (Darby et al. 2011b), as well as satisfactory cosmetic results (Taylor et al. 1995; Vrieling et al. 1999). Nonetheless, preclinical studies have suggested that hypofractionated courses of radiation to a lower total dose – and hence over a shorter time course – might be just as effective (Cohen 1952; Douglas and Castro 1984). The motivation to shorten treatment delivery has stemmed from a desire to reduce imposed treatment burdens. In particular, it is difficult for many women to receive 5 or 6 weeks of traditional therapy: the inconvenience of numerous daily visits has been identified both as increasing the number of women who opt for mastectomy and as contributing to radiotherapy's lack of receipt after breast-conserving surgery (Morrow et al. 2001; Nattinger et al. 1992).

3.2 Hypofractionated Whole Breast Irradiation

One such approach to hypofractionation involves using a larger fraction size to treat the entire breast, rather than the 1.8 to 2.0 Gy most commonly employed in the past (Ceilley et al. 2005). While initial attempts to increase fraction size maintained the same total dosage as employed with conventional fractionation and hence resulted in significantly increased toxicity (Whelan et al. 2008), more modern trials have modified fractionation while using a lower total dose (Whelan et al. 2010; Haviland et al. 2013; Bentzen et al. 2008a, b; Owen et al. 2006).

Of these, the trial with the longest follow-up is a Canadian trial of accelerated whole breast irradiation (AWBI) reported by Whelan et al. (Whelan et al. 2010). This study enrolled women with small to moderate breast size, who, after lumpectomy as well as axillary lymph node dissection, were found to have pT1–2 pN0 disease. Negative margins were required and defined as no tumor on ink. Randomization was to 50 Gy in 25 fractions or 42.5 Gy in 16 daily fractions, and homogeneity of dose was allowed to vary by as much as 7 %. No boost was employed. In all, 1234 women were enrolled. Endocrine therapy was used in 41 % of women and chemotherapy in 11 %. At a median of a 12-year follow-up, there was no difference in overall survival (84.4 versus 84.6 %) or local recurrence rates (6.7 versus 6.2 %) between those who received conventional fractionation and hypofractionation, respectively (Whelan et al. 2010).

Importantly, rates of late toxicity were similar between the two arms, as were rates of good or excellent cosmesis, which were approximately 70 % in both arms. Even with this demonstration of equivalency between these two treatment approaches, adoption of hypofractionation has been limited (Ashworth et al. 2013; Bekelman et al. 2014; Jagsi et al. 2014a, b; Wang et al. 2014). There are several possible explanations for this, including a subset analysis reported in the initial publication, which showed that those with grade 3 disease were at an increased risk for local recurrence if they received hypofractionated treatment

(HR 3.08, $p = 0.01$) (Whelan et al. 2010). However, further exploration of this finding on subsequent central pathologic reevaluation of 989 of the total 1234 specimens demonstrated that high grade did not, in fact, significantly interact with treatment type (Bane et al. 2014). Similar findings that those with grade 3 disease are not adversely affected by hypofractionation have been seen in subsequent trials (Haviland et al. 2013). Other barriers to utilization might include concerns that rates of acceptable cosmesis in both arms were generally lower than that seen in American studies (Taylor et al. 1995), as well as the fact that this study did not utilize a boost, the benefit of which was confirmed after the trial was already completed (Bartelink et al. 2007). Finally, with rising rates of obesity impacting over a third of all women in the United States (Flegal et al. 2012), clinicians might be hesitant to adopt a technique that was investigated in those with limited body habitus and breast size (Whelan et al. 2010).

Confirmation of hypofractionation's utility has come from three trials performed in the United Kingdom (Haviland et al. 2013; Bentzen et al. 2008a, b; Owen et al. 2006). The first of these studies drew patients from the Royal Marsden Hospital and the Gloucestershire Oncology Center (Owen et al. 2006). It enrolled women who underwent lumpectomy and were found to have T1–3 N0–1 disease. Patients were randomized to 50 Gy in 25 fractions, 42.9 Gy in 13 fractions, or 39 Gy in 13 fractions. All regimens were delivered in a non-accelerated fashion over 5 weeks. The trial enrolled 1410 patients with a median follow-up of 9.7 years. The majority of women underwent endocrine therapy; chemotherapy was uncommon. Three-quarters of patients received a boost to the lumpectomy cavity in addition to their assigned whole breast regimen. Rates of local recurrence were not significantly different between the three arms: 12.1 % in the 50 Gy group, 9.6 % in the 42.9 Gy group, and 14.8 % in the 39 Gy group (Owen et al. 2006). In terms of cosmetic results, the 39 Gy arm fared best, with 72.3 % of patients free from long-term moderate to marked induration, compared to 63.7 % in the 50 Gy arm and 48.9 % in the 42.9 Gy arm (Yarnold et al. 2005).

The UK Standardization of Radiotherapy A (START A) trial randomized patients to 50 Gy in 25 fractions versus 41.6 Gy or 39 Gy, both in 13 fractions and delivered over a 5-week course (Haviland et al. 2013; Bentzen et al. 2008b). The trial enrolled 2236 women with a median follow-up of 9.3 years. Of note, over one-third of women in this trial received chemotherapy. Rates of local recurrences were not significantly different between arms: 7.4 % in the standard fractionation arm versus 6.3 and 8.8 % in the 41.6 and 39 Gy arms, respectively. Photographic evaluations of breast appearance showed superior cosmetic results in the 39 Gy arm compared to standard fractionation (HR 0.69, $p = 0.01$), though those who received a boost had worse outcomes in this regard (Haviland et al. 2013).

The START B trial randomized women to 50 Gy in 25 fractions versus 40 Gy in 15 fractions, delivered on an accelerated scheduled over 3 weeks (Haviland et al. 2013; Bentzen et al. 2008a). It enrolled 2215 patients and rates of local recurrence were not significantly different between the two groups (5.5 % in the standard fractionation arm and 4.3 % in the AWBI arm). Rates of moderate to marked breast shrinkage, telangiectasia, and breast edema were significantly lower in the 40 Gy arm (Haviland et al. 2013).

Given the available data, in 2011 ASTRO issued guidelines as to which women are particularly appropriate candidates for AWBI: those who are 50 years of age or older, with T1–2 N0 disease, not requiring chemotherapy, and whose radiotherapy plan achieves dose inhomogeneity of 7 % or less. The authors favored a regimen of 42.5 Gy in 16 fractions (Smith et al. 2011a).

Ongoing avenues of investigation include the FAST trial in the United Kingdom, which is comparing 30 Gy and 28.5 Gy – both delivered in 5 fractions over 5 weeks – to more conventionally fractionated treatment (Agrawal et al. 2011). Likewise, the FAST-Forward trial compares 26 and 27 Gy delivered over 1 week in 5 daily fractions versus 40.05 Gy in 15 fractions over 3 weeks. Finally, RTOG 1005 investigates reducing treatment time by incorporating a simultaneous integrated boost given via intensity-modulated radiotherapy (IMRT) based on favorable

outcomes from an earlier Phase II study (Freedman et al. 2007). Data from these trials require further maturation until the full promise of these regimens is known.

3.3 Accelerated Partial Breast Irradiation

Accelerated partial breast irradiation (APBI) is a developing alternative to whole breast irradiation (WBI). Theoretically, there are several potential advantages to APBI that have motivated research into refining its delivery. First, APBI has the potential to further reduce treatment times, making the receipt of radiotherapy more convenient, a possibility that is particularly important for those living in rural areas in which the distance to the nearest treatment facility can limit therapeutic options (Schroen et al. 2005). Further, by limiting the target volume to the lumpectomy cavity and immediately surrounding tissue, APBI may reduce the dose delivered to the nearby organs at risk, such as the heart, lung, and ribs (Moran et al. 2009; Rusthoven et al. 2008; Taghian et al. 2006a). Such an advantage might be of clinical importance in limiting late radiation-induced toxicities and is of particular note given the recent attention paid to radiotherapy-related cardiac disease (Darby et al. 2013a). Nonetheless, these dosimetric advantages may be offset by other concerns regarding toxicity and cosmesis (Olivotto et al. 2013; Liss et al. 2014; Jagsi et al. 2010; Hepel et al. 2009; Leonard et al. 2013).

In terms of disease control, irradiating only the area about the tumor bed may be reasonable in selected patients, given that this is the area most at risk for the development of a local recurrence (Clark et al. 1992; Liljegren et al. 1999b; Vicini et al. 2003a). Additionally, it may be possible to predict which patients are at low risk of harboring residual disease elsewhere in the breast, far from the surgical site (Vicini et al. 2004). Despite this, concerns remain as to whether APBI is truly adequate in this regard, as some researchers have found that microscopic disease may exist far from the initial lumpectomy cavity and that local recurrences can affect such distant portions of the breast (Veronesi et al. 2001b; Holland et al. 1985; Vaidya et al. 1996; Morimoto et al. 1993).

There are several techniques of APBI, the first of which is multicatheter interstitial brachytherapy. One of the earliest studies utilizing this approach is from Guy's Hospital in London. In this series of 27 patients implanted with iridium-192, 55 Gy was delivered over a course of 5 days (Fentiman et al. 1991, 1996). Unfortunately, ten patients experienced local failure, perhaps due to the inadequate patient selection and a lack of more sophisticated dosimetry in this early era. However, more recent investigations have yielded promising results. Prospective studies in the United States and Europe have enrolled older women (median age 60–65), with small tumors (median size 0.9–1.5 cm) and with estrogen receptor-positive disease (65–100 % of cases) (Kuske et al. 2006; Arthur et al. 2008; Rabinovitch et al. 2014; Ott et al. 2007; Garsa et al. 2013; Kaufman et al. 2007; Antonucci et al. 2009; King et al. 2000; Polgár et al. 2007, 2013; Aristei et al. 2013, 2009). Few women had evidence of nodal involvement, ranging from 0 to 19 % of participants. These studies have a follow-up of approximately 5 to 10 years and have shown excellent local control, as rates of ipsilateral breast events have ranged from 2 to 6 % (Kuske et al. 2006; Arthur et al. 2008; Rabinovitch et al. 2014; Ott et al. 2007; Garsa et al. 2013; Kaufman et al. 2007; Antonucci et al. 2009; King et al. 2000). The only outlier in terms of recurrence rate is a randomized Hungarian study that reported local failures in 9 % of patients, though this was no different than that observed in the WBI control arm (Polgár et al. 2007, 2013). Additionally, multicatheter brachytherapy has often shown good cosmetic outcomes, with acceptable results in 66 to 98 % of patients (Rabinovitch et al. 2014; Ott et al. 2007; Garsa et al. 2013; Kaufman et al. 2007; King et al. 2000; Polgár et al. 2013; Aristei et al. 2013, 2009). Nonetheless, conclusions regarding cosmesis are tempered by long-term results from other investigators, who have found moderate to severe fibrosis in over half of patients after 12 years of follow-up, raising significant concerns about this technique as applied in that era (Hattangadi et al. 2012).

From these studies, it is clear that multicatheter brachytherapy has demonstrated durable long-term results in selected patients, though its broader adoption may have been hampered by the invasiveness of the procedure, as well as its technical complication and clinician dependence. Further insight will come from a recently closed GEC-ESTRO randomized study that was open to women with early-stage invasive disease or DCIS. This trial enrolled 1195 women, who were randomized to standard WBI versus multicatheter APBI: either high-dose rate brachytherapy (32 Gy in 8 fractions or 30.3 in 7 fractions) or pulsed dose rate brachytherapy (50 Gy at 0.6 to 0.8 Gy per hour). Results have not yet been reported.

In contrast to the technical demands of the multicatheter approach, single entry, intracavitary brachytherapy is less dependent on clinician expertise and was initially developed as the single-lumen MammoSite device for use with iridium-192. The most extensive report on outcomes with this technique is from an analysis of the prospective American Society of Breast Surgeons MammoSite Registry Trial (Shah et al. 2012; Vicini et al. 2006). The trial enrolled 1961 patients, and the 5-year rate of local recurrence was 2.9 % (Shah et al. 2012). At 3 years, 90 % of women were judged to have good or excellent cosmetic outcomes (Vicini et al. 2006), which is comparable to findings from other studies (Benitez et al. 2007; Vargo et al. 2014).

Despite these results, a recent Medicare claims analysis has raised significant concerns about single-lumen, intracavitary brachytherapy (Smith et al. 2012). In this retrospective, population-based study of 92,735 women diagnosed with breast cancer between 2003 and 2008, 6952 women treated with brachytherapy were compared to 85,783 women treated with WBI. Those who received brachytherapy had approximately twice the risk of undergoing a subsequent mastectomy, with a 5-year rate of 3.95 % compared to 2.18 % of those who received external beam radiation (HR 2.19, $p < 0.001$). Further, the brachytherapy group experienced significantly greater rates of postoperative complications, rib fracture, and long-term breast pain (Smith et al. 2012). Of note, this study reflects the early experience with brachytherapy, prior to the development of more thorough criteria for patient selection (Smith et al. 2009), and thus it might not represent the technique as currently practiced (Cuttino et al. 2012). It remains to be seen whether refinement of the intracavitary technique through the use of recently developed multilumen catheters and better dosimetric planning will improve long-term toxicity rates (Arthur et al. 2013; Lu et al. 2012; Yashar et al. 2011; Manoharan et al. 2010), though early results from a registry trial are promising (Cuttino et al. 2014). Finally, concerns regarding toxicity may be clarified by results from RTOG 0413/ NSABP B-39, which is a randomized trial comparing WBI to a variety of APBI techniques, although only a minority received brachytherapy. Outcomes from this study are pending, and it is discussed in more detail later in the chapter.

Another option for the delivery of APBI is through the use of conformal external beam radiotherapy, an approach facilitated by the emergence of improved targeting and dosimetry. Two early randomized studies have compared external beam partial breast irradiation to more conventional, whole breast treatment (Ribeiro et al. 1990, 1993; Dodwell et al. 2005). The largest of these trials was undertaken at the Christie Hospital in Manchester, England (Ribeiro et al. 1990, 1993). Its enrollment criteria allowed for women less than 70 years old, with tumors less than 4 cm, and a clinically negative axilla. Margins following lumpectomy were required to be macroscopically uninvolved. The trial enrolled 708 women. APBI was given via an en face electron beam to 40 to 42.5 Gy in 8 fractions, compared to WBI, which consisted of 40 Gy in 15 fractions. After a median follow-up of 65 months, 14 % of those in the APBI arm experienced a local recurrence, compared to 6 % in the WBI arm. Cosmetic outcomes were also worse in the APBI group (Ribeiro et al. 1993). Likewise, a randomized study from Leeds Hospital in Yorkshire randomized 174 early-stage patients (Dodwell et al. 2005). The partial breast arm consisted of treatment with either photons or electrons, delivered to 50 Gy in 20 fractions, via an

en face or tangential technique. The WBI group received 40 Gy in 15 fractions with a corresponding nodal treatment. Similar to the study from Christie Hospital, after 8 years of follow-up, those in the APBI arm had a 24 % locoregional recurrence rate compared to 9 % in the WBI arm (Dodwell et al. 2005). No cosmetic outcomes were reported.

Subsequent investigators have refined patient selection and used more sophisticated planning and lower dosages to pursue external beam APBI. Physicians at New York University have reported on their experience with APBI, which utilized 30 Gy in five fractions over 10 days delivered to a prone patient via parallel-opposed minitangents (Formenti et al. 2012; Wernicke et al. 2006; Osa et al. 2014). Five-year results have been encouraging, with a less than 1 % local failure rate, as well as excellent or good cosmesis in 89 % of patients (Formenti et al. 2012). As opposed to this prone technique, radiation oncologists at Beaumont Hospital developed the use of external beam APBI with the patient in the supine position. This approach utilized four or five noncoplanar photon beams to deliver 34 to 38.5 Gy in ten fractions (Vicini et al. 2003b, 2007; Shah et al. 2013a). Results have been favorable, with no local recurrences and excellent cosmesis in 81 % of patients at 5 years (Shah et al. 2013a). Likewise, 38 Gy in in ten BID fractions was utilized in RTOG 0319, which was a Phase I/II feasibility trial that enrolled 58 patients (Vicini et al. 2010). Early results have shown a 6 % in-breast recurrence rate at 4.5 years of median follow-up, and only two patients developed grade 3 skin toxicity. Although this low rate of toxicity is promising, it did not correlate with cosmetic outcomes. When radiation oncologists participating in the study assessed cosmesis, the rate of fair or poor outcomes was substantial and increasing over time: 26 % of patients had unacceptable cosmesis at 1 year posttreatment, compared to 42 % at 3 years (Chafe et al. 2013).

In terms of efficacy, other prospective single institution studies have found excellent rates of local control (Pashtan et al. 2012; Rodríguez et al. 2013; Lei et al. 2013; Berrang et al. 2011). While these studies have shown acceptable cosmesis (Rodríguez et al. 2013; Lei et al. 2013; Berrang et al. 2011; Galland-Girodet et al. 2014), cautionary cosmetic outcomes have been reported not just from RTOG 0319 as discussed above (Chafe et al. 2013) but also from Tufts University and the University of Michigan (Liss et al. 2014; Jagsi et al. 2010; Hepel et al. 2009; Leonard et al. 2013).

These concerns regarding cosmesis have received renewed attention with the publication of interim results from the multicenter Randomized Trial of Accelerated Partial Breast Irradiation (RAPID) in Canada (Olivotto et al. 2013). This study randomized women to either WBI (either 42.5 Gy in 16 fractions or 50 Gy in 25 fractions, followed by a boost at the discretion of each participating center) or external beam APBI delivered to a total dose of 38.5 Gy in ten BID fractions over a course of 5 to 8 days. No boost was allowed in the APBI arm. Appraisal of cosmesis was extensive: evaluations were performed by patients, nurses, and physicians. Patients evaluated their own cosmetic outcomes using a validated breast cancer questionnaire (Whelan et al. 2000a; Levine et al. 1988). Nurses were trained using an EORTC module and rating system designed specifically for cosmetic evaluation of women who had undergone treatment for breast cancer (Aaronson et al. 1988). Finally, two different panels of physicians assessed cosmesis at 3 years by examining digital photographs of patients. Notably, these panels were blinded to each patient's treatment arm. Toxicity was captured using the Common Toxicity Criteria for Adverse Events (CTCAE) (Olivotto et al. 2013).

RAPID has closed to accrual after enrolling 2135 women with a median follow-up of 36 months. Rates of adverse cosmesis at 3 years were significantly worse in the APBI arm as compared to the WBI arm, whether judged by the patients themselves (26 versus 18 %, $p = 0.0022$), trained nurses (29 versus 17 %, $p < 0.001$), or a physician panel (35 versus 17 %, $p = 0.001$). Interestingly, poor cosmesis did not correlate strongly with CTCAE, as the rate of grade 3 or greater toxicity was only 1.4 % in the APBI group. The lack of correspondence between cosmetic outcomes and CTCAE has been prospectively documented by others (Liss et al. 2014; Jagsi

et al. 2010; Chafe et al. 2013) and calls into question the sensitivity of this scale in capturing cosmetically meaningful data. More so, this underscores the need to develop validated measures of acute toxicity (Shumway et al. 2014), as well as more thorough methods of evaluating cosmesis (Aaronson et al. 1988). Finally, cosmetic outcomes in the APBI arm have continued to worsen over the entire period of follow-up. For instance, at the 3-year mark, 33 % of APBI patients were rated by nurses as having adverse cosmesis, but this increased to 37 % at 5 years (Olivotto et al. 2013). A similar worsening of cosmesis over time was seen in both RTOG 0319 and the University of Michigan experience (Liss et al. 2014; Chafe et al. 2013).

There are several possible explanations for these poor outcomes, and the topic has been well discussed by the authors of the RAPID study and others (Olivotto et al. 2013; Liss et al. 2014; Jagsi and Haffty 2013). First, external beam APBI – as compared to other techniques – may result in a higher integral dose to the breast (Weed et al. 2005). Though RAPID is limited to less than 35 % the volume of breast that could receive 95 % of the prescription dose, this may still be too high. Likely, more sophisticated dose constraints will be required in order to avoid adverse outcomes, as evidenced by several investigations that have shown a dose-volume relationship with cosmesis (Liss et al. 2014; Hepel et al. 2009; Leonard et al. 2013). Further, both biological modeling and clinical findings have suggested that cosmetic outcomes of the breast may be disproportionately affected by large fraction sizes unless there is a corresponding reduction in total dose delivered (Bentzen et al. 2008a, b; Yarnold et al. 2005, 2011). This may be particularly true with twice-daily fractionation, as normal breast tissue might not have enough time to repair itself (Bentzen and Yarnold 2010).

As an aside, though these poor cosmetic results are concerning, outcomes derived from patients treated with external beam radiotherapy cannot be extrapolated to APBI delivered via brachytherapy, which has typically delivered radiation more conformally, to smaller volumes (Ott et al. 2007; Kaufman et al. 2007; Aristei et al. 2013; Vicini et al. 2006; Benitez et al. 2007; Vargo et al. 2014).

Ongoing questions regarding cosmesis outcomes with external beam approaches to APBI may be answered by RTOG 0413/ NSABP B-39, which is a randomized study of standard WBI versus APBI for women with DCIS or early-stage breast cancer. This trial closed to accrual in 2013, after enrolling 4311 patients. Those in the APBI arm could receive any of three various approaches to adjuvant treatment, either multicatheter interstitial brachytherapy, intracavitary brachytherapy, or external beam radiotherapy, but the vast majority of patients enrolled received external beam treatment. Though there have been reportedly low rates of CTCAE-graded toxicity (Wolmark et al. 2010), this correlates poorly with cosmetic outcomes, as discussed earlier (Olivotto et al. 2013; Liss et al. 2014; Jagsi et al. 2010). Therefore, no conclusion can be made regarding cosmesis in this trial until further data are released. Regarding the efficacy of APBI, this study will hopefully address whether it is truly comparable to WBI and for which subpopulations it might be appropriate, as it has enrolled substantial numbers of women younger than age 50, as well as patients with hormone receptor-negative disease or DCIS.

Two additional randomized trials of external beam partial breast irradiation versus WBI were recently closed. The first of these was opened at the University of Florence in 2005, and it randomized 520 women between APBI delivered with IMRT to 30 Gy in five fractions and WBI with 50 Gy in 25 fractions (Livi et al. 2010). Five-year outcomes have shown good to excellent cosmesis in over 90 % of patients in both arms, as well as equivalent disease control. However, longer follow-up is needed to see if these results are durable (Livi et al. 2014). The second study is the IMPORT-LOW study performed by the UK Medical Research Council. This included 2100 women, randomized to partial breast irradiation with IMRT to 40 Gy in 15 fractions versus WBI radiation to 36 Gy along with a simultaneous boost to the lumpectomy cavity of 40 Gy, delivered in 15 fractions. Results have not yet been reported.

One niche modality of external beam APBI that deserves mention is intraoperative radiotherapy (IORT), in which a woman is treated with radiation during her lumpectomy procedure,

thus maximizing her convenience and theoretically obviating the need for further, prolonged adjuvant radiotherapy. Unfortunately, outcomes with this technique have been less than promising (Vaidya et al. 2010, 2014; Kimple et al. 2011; Vanderwalde et al. 2013; Veronesi et al. 2013). The largest of these studies is the TARGIT-A trial, which randomized 2232 patients to APBI versus WBI. The experimental arm utilized 50 kilovolt photons to deliver a single dose of 20 Gy to the lumpectomy bed (with a rapid falloff of dose to 5 to 7 Gy at 1 cm) (Vaidya et al. 2002, 2001). Of note, even in those women randomized to APBI, 14 % subsequently required WBI due to unfavorable pathologic features. At 5 years, the rate of local recurrence was 3.3 % in the intraoperative group versus 1.3 % in those who received more standard treatment (Vaidya et al. 2014). Similarly, the ELIOT trial has also reported sobering outcomes (Veronesi et al. 2013). This study enrolled 1300 women, randomized to standard WBI versus IORT delivered via an electron beam to a dose of 21 Gy at the applicator surface. Five-year rates of local recurrence were 1 % in the WBI arm versus 5 % in those that received IORT (Veronesi et al. 2013). These two randomized studies are consistent with the results of a smaller investigation from the University of North Carolina, which employed intraoperative electron therapy to give a single 15 Gy fraction. Rates of ipsilateral breast events were 15 % at 6 years (Kimple et al. 2011; Vanderwalde et al. 2013).

Such high rates of local failure serve to highlight the need for careful patient selection when using emerging and novel techniques. To assist clinicians with this task as more mature randomized data accumulate, several consensus guidelines have been published that detail the patient and disease characteristics that define an appropriate group for receipt of APBI off protocol, as the evidence accumulates (Smith et al. 2009; Arthur et al. 2003; Shah et al. 2013b). Among these, the 2009 ASTRO guidelines are perhaps most widely used and are presented in Table 2 (Smith et al. 2009). In any case, given the evolving nature of evidence for APBI in comparison to the wealth of high-quality data for more standard approaches, patients who desire to receive partial breast irradiation should be informed of any available clinical trials and encouraged to participate when appropriate.

Table 2 ASTRO consensus criteria for selection of patients "suitable" for partial breast irradiation off protocol

Factor	Criterion
Patient factors	
Age	≥60 y
BRCA1/2 mutation	Not present
Pathologic factors	
Tumor size	≤2 cm[a]
T stage	T1
Margins	Negative by at least 2 mm
Grade	Any
LVSI	No[b]
ER status	Positive
Multicentricity	Unicentric only
Multifocality	Clinically unifocal with total size ≤2.0 cm[c]
Histology	Invasive ductal or other favorable subtypes[d]
Pure DCIS	Not allowed
EIC	Not allowed
Associated LCIS	Allowed
Nodal factors	
N stage	pN0 (i^-, i^+)
Nodal surgery	SN Bx or ALND[e]
Treatment factors	
Neoadjuvant therapy	Not allowed

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Criteria are derived from data (when available) and conservative panel judgment

Abbreviations: *APBI* accelerated partial breast irradiation, *LVSI* lymphovascular space invasion, *ER* estrogen receptor, *DCIS* ductal carcinoma in situ, *EIC* extensive intraductal component, *LCIS* lobular carcinoma in situ, *SN Bx* sentinel lymph node biopsy, *ALND* axillary lymph node dissection

[a]The size of the invasive tumor component as defined by the American Joint Committee on Cancer and referenced in Greene et al. (2002)

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

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

[d]Favorable subtypes include mucinous, tubular, and colloid

[e]Pathologic staging is not required for DCIS

Table 3 Scoring system for the University of Southern California/Van Nuys prognostic index

Score	Size (mm)	Margin width (mm)	Pathology	Age (years)
1	≤15	≥10	Grade 1 or 2 without necrosis	>60
2	16–40	1–9	Grade 1 or 2 with necrosis	40–60
3	≥41	<1	Grade 3	<40

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3.4 IMRT

Whole breast radiation has traditionally been delivered with tangent beams and use of simple wedges to improve homogeneity. However, due to the complex three-dimensional shape of the breast, conventional two-dimensional techniques are often unable to deliver a homogenous dose throughout the breast, resulting in substantial areas receiving excessive dose (known as "hot spots"). These hot spots may lead to acute and late toxicity.

With development of three-dimensional planning techniques, use of multileaf collimators and segmental blocking allow for differential attenuation of the radiation beam to significantly improve homogeneity throughout the breast. Rather than employing two opposed tangential fields, treatment is delivered using several segmented fields, often described as a step-and-shoot IMRT or "field-in-field" technique. This relatively simple "breast IMRT," which has the objective of improving homogeneity, should be distinguished from the more complex inverse-planned beamlet IMRT that is used to improve dose conformality.

Use of simple IMRT for whole breast radiation has been found to be dosimetrically superior to treatment techniques that employ only wedges and has been associated with reduced acute radiation dermatitis, edema, hyperpigmentation, and minimal late toxicity (Keller et al. 2012; Harsolia et al. 2007). Three randomized trials revealed improvement in acute and late effects of radiation with the use of breast IMRT. A Canadian study that randomized 358 patients to standard wedged technique versus breast IMRT observed a reduction in hot spots (5 % or higher hot spot decreased from 16.9 % of breast volume to 7.7 %), which corresponded with a significant decrease in moist desquamation from 47.8 % to 31.2 %, respectively (Pignol et al. 2008). Two prospective British trials reported improvements in long-term cosmesis with breast IMRT, assessed primarily using serial photographs (Donovan et al. 2007; Mukesh et al. 2013). Patients with large breast size were most likely to benefit from IMRT (Pignol et al. 2008; Mukesh et al. 2013). Thus, while there is strong evidence to suggest that breast IMRT decreases acute and late toxicity compared to conventional techniques, controversy remains regarding whether this treatment should be reimbursed at substantially higher IMRT levels or at levels closer to historical standards (Haffty et al. 2008; Smith et al. 2011b; Roberts et al. 2013) (Fig. 1).

4 Locally Advanced Breast Cancer

4.1 Postmastectomy Radiotherapy

Even after mastectomy and systemic therapy, occult disease may remain in the chest wall and regional lymph nodes, which if left untreated, could serve as a reservoir for distant tumor spread. By eliminating residual locoregional disease, postmastectomy radiation may therefore not only prevent morbid local recurrences but also has potential to reduce breast cancer-related mortality. However, not all patients have the same risk of harboring residual locoregional disease. Patients who are most likely to benefit from postmastectomy radiation are those with an isolated site of residual locoregional disease after mastectomy and systemic therapy or those with micrometastatic distant disease that is effectively eliminated with systemic therapy. Appropriate patient selection to identify which patients are likely to benefit from postmastectomy radiation has therefore been a key subject of controversy and research.

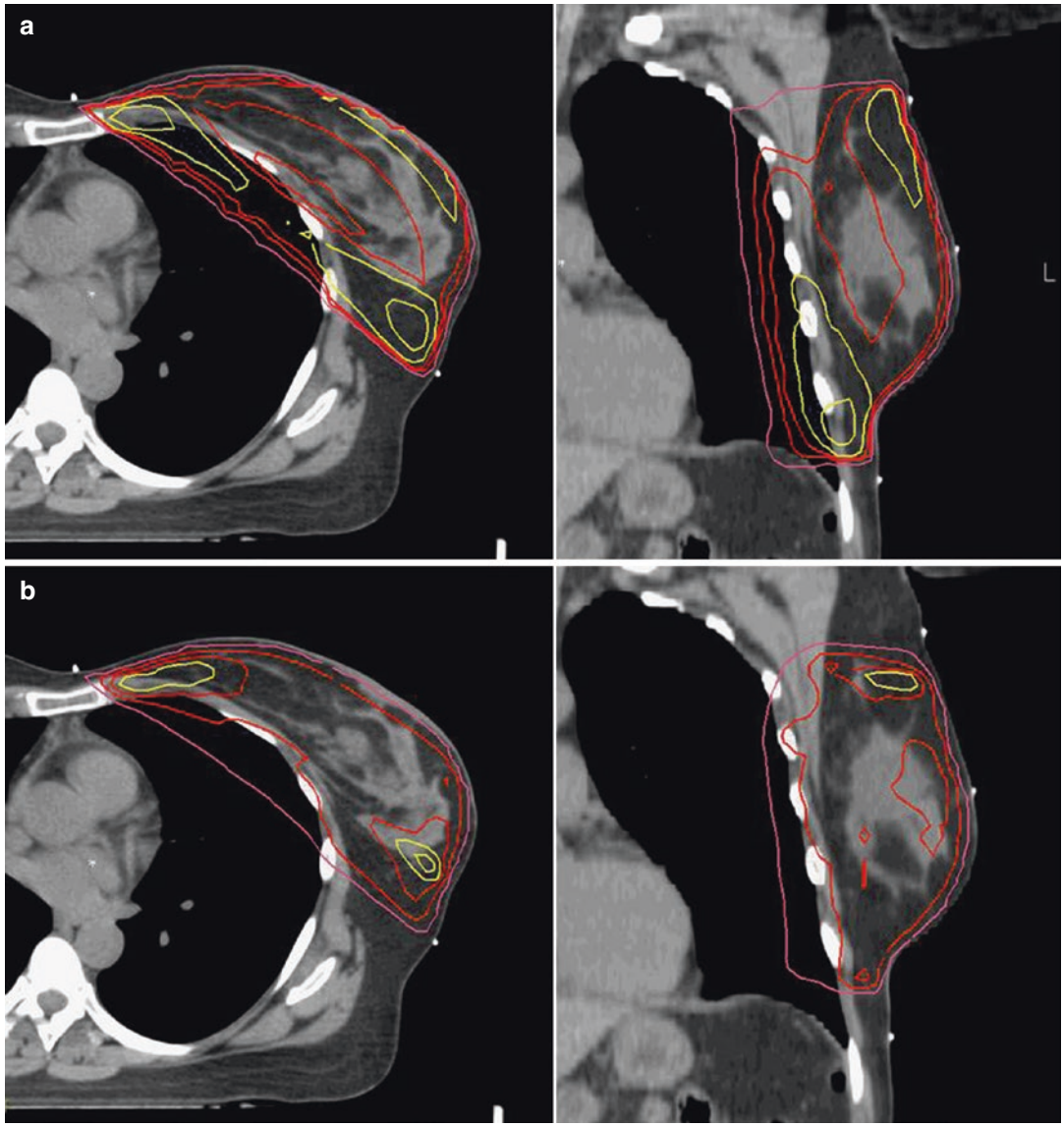

Fig. 1 (**a**) Simple tangential breast radiotherapy using a wedge. *Yellow* isodose lines depict areas receiving ≥107 % of the prescribed dose. (**b**) Segmented breast intensity modulated radiotherapy

Early trials of postmastectomy radiation consistently demonstrated a reduction in the rate of locoregional failure without improvement in overall survival (Early Breast Cancer Trialists' Collaborative Group 1995; Early Breast Cancer Trialists' Collaborative Group 2000; Pierce 2005). Prevention of locoregional recurrence after mastectomy is critical, as many patients subsequently develop distant disease and many locoregional recurrences cannot be successfully salvaged (Bedwinek 1994; Willner et al. 1997). Following mastectomy, systemic therapy reduces the rate of locoregional failure, though in many node-positive series, the risk of isolated locoregional failure remains 10 to 15 % or higher, even with the use of dose-dense anthracycline-based chemotherapy (Pierce 2005). Meta-analyses of several early trials investigating the role of postmastectomy radiation in conjunction with chemotherapy demonstrated that the benefit in disease control

was offset by treatment-related toxicity, likely related to exposure of large volumes of the heart and lungs to high doses of radiation (Early Breast Cancer Trialists' Collaborative Group 1995; Early Breast Cancer Trialists' Collaborative Group 2000; Cuzick et al. 1987; Cuzick et al. 1994). Only more recently, with development of more sophisticated radiation planning techniques and more effective systemic therapy, has the survival benefit become apparent (Clarke et al. 2005; Van de Steene et al. 2000; Whelan et al. 2000b). Trials of postmastectomy radiation from Denmark and British Columbia, which included largely lymph node-positive patients and a smaller number of individuals with locally advanced, lymph node-negative disease, revealed a substantial improvement in locoregional control, as well as a modest overall survival benefit, and serve as the foundation of existing clinical practice guidelines (NCCN 2014).

In a Danish trial of premenopausal patients with high-risk stage II or III breast cancer, 1708 patients were randomized to nine cycles of cyclophosphamide, methotrexate, and fluorouracil or eight cycles with postmastectomy radiation (Overgaard et al. 1997). After 9.5 years, postmastectomy radiation significantly reduced the frequency of locoregional recurrence from 32 to 9 % and improved overall survival from 45 to 54 % ($p < 0.001$). Multivariate analysis indicated that the benefit of postmastectomy radiation was applicable to all subgroups, regardless of tumor grade, size, or number of positive nodes. In the Danish 82c trial of postmenopausal patients, 1375 women who underwent modified radical mastectomy and received 1 year of adjuvant tamoxifen were randomized to postmastectomy radiation (Overgaard et al. 1999). After 10.3 years, locoregional recurrence decreased significantly from 35 to 8 %, and overall survival improved from 36 to 45 % ($p = 0.03$). Similarly, a 20-year follow-up of a Canadian study of 318 premenopausal patients with node-positive breast cancer who were treated with modified radical mastectomy and cyclophosphamide, methotrexate, and 5-fluorouracil revealed that postmastectomy radiation significantly reduced rates of both locoregional and systemic recurrence, resulting in substantially improved breast cancer-specific and overall survival (Ragaz et al. 2005).

Meta-analyses that included these more recent trials consistently demonstrated a two-thirds reduction in locoregional failure with the addition of postmastectomy radiation and confirmed the improvement in overall survival (Clarke et al. 2005; Whelan et al. 2000b). In a landmark publication from the EBCTCG in 2005 that included data from 8505 individual patients with positive lymph nodes, postmastectomy radiation decreased locoregional recurrence at 5 years from 22.8 to 5.8 %, resulting in a reduction of breast cancer mortality at 15 years from 60.1 to 54.7 % (absolute risk reduction 5.4 %) and all-cause mortality from 64.2 to 59.8 % (absolute risk reduction 4.4 %), all of which were statistically significant (Clarke et al. 2005). These findings led to the observation of a 4:1 ratio of absolute effects, such that for every four recurrences prevented after 5 years, one breast cancer death was avoided at year 15.

Although the Danish and British Columbia studies were influential in shifting opinion in favor of postmastectomy radiation, these studies met with criticism regarding their generalizability to the current era due to the use of older, low dose-intensity methotrexate-based chemotherapy (82b and Canadian studies) and use of tamoxifen for only 1 year (82c) and inadequate axillary surgery. In the Danish 82b and 82c trials, 62.6 % of patients had seven or fewer lymph nodes removed (Overgaard et al. 2007), likely resulting in underestimation of the true number of positive nodes and potential residual disease in the axilla due to inadequate resection (Iyer et al. 2000). Patients categorized as having one to three involved lymph nodes in the Danish trials might have been characterized as having four or more involved lymph nodes if a more complete axillary lymph node dissection had been performed. This inability to correctly identify patients with one to three involved lymph nodes may partially account for the observation of a higher rate of locoregional failure in the Danish and British Columbia studies (30–33 %) compared to other large cooperative groups (13–20 %) (Taghian et al. 2004a; Recht et al. 1999; Wallgren et al. 2003; Katz et al.

2000; Truong et al. 2005). Additionally, the rate of axillary failure without radiation in the Danish trials (13 %) (Overgaard 1999) was markedly higher compared to other cooperative groups (2.7–3.8 %) (Recht et al. 1999; Wallgren et al. 2003). Given these findings, it has been unclear to what extent the observed benefit of radiotherapy in these trials was a result of compensation for suboptimal surgery and/or suboptimal systemic therapy, particularly in patients with one to three positive lymph nodes. Consensus guidelines have uniformly recommended postmastectomy radiation for patients with ≥4 positive lymph nodes, but have tended to be more equivocal for patients with one to three involved lymph nodes (NCCN 2014; Harris et al. 1999; Recht et al. 2001; Taylor et al. 2000).

In response to these concerns, Danish investigators completed a pooled reanalysis of 1152 (37 %) patients from 82b and 82c with ≥8 lymph nodes removed (Overgaard et al. 2007). Though the absolute risk reduction in locoregional failure was smaller in patients with one to three positive lymph nodes compared to those with ≥4 involved nodes (41 % vs 23 %, respectively), both groups derived a similar absolute overall survival benefit from radiotherapy (9 %). The authors reason that patients with fewer involved lymph nodes, despite obtaining a relatively smaller absolute benefit in locoregional control, might be more likely to obtain a survival benefit from postmastectomy radiation due to a lower risk of distant metastasis. While patients with many involved lymph nodes may obtain a large reduction in locoregional failure, only a small proportion of these can obtain a survival benefit due to the high risk of distant metastasis. These observations, along with demonstration of a survival benefit in patients with one to three lymph nodes in the British Columbia trial (in which a median of 11 axillary lymph nodes were removed) (Ragaz et al. 2005), lend support for the role of postmastectomy radiation in patients with one to three involved lymph nodes. Most recently, an EBCTCG meta-analysis including 8135 individual patients from 22 prospective trials specifically investigated the role of postmastectomy radiation in patients with one to three positive lymph nodes. In the 1133 women with axillary lymph node dissection and one to three positive nodes who received systemic therapy, postmastectomy radiation reduced locoregional recurrence and significantly improved breast cancer-specific survival (McGale et al. 2014). In light of these data, guidelines from the National Comprehensive Cancer Network recommend that patients treated with mastectomy who are found to have one to three positive axillary lymph nodes should "strongly consider" postmastectomy radiation (NCCN 2014). The ongoing SUPREMO study, in which patients with T1–T2 tumors and one to three involved lymph nodes are randomized to postmastectomy radiation, may ultimately provide additional information in patients treated with contemporary systemic therapy (Russell et al. 2009).

Patients with negative axillary lymph nodes and certain high-risk features might also benefit from postmastectomy radiation. The Danish trials of postmastectomy radiation included patients with tumors >5 cm with negative axillary lymph nodes (Overgaard et al. 1997, 1999). Postmastectomy radiation significantly reduced locoregional recurrences in both pre- and postmenopausal patients at a 10-year follow-up and was associated with improved overall survival in premenopausal patients. However, the incidence of local failure in these node-negative patients without postmastectomy radiation was much higher in Danish trials (17 to 23 %) than in results from retrospective analyses of patients treated in NSABP trials (7.1 %) (Taghian et al. 2006b) and several other institutions (7.6–11 %) (Floyd et al. 2006; Mignano et al. 2007), leading to the conclusion that postmastectomy radiation may not be routinely indicated by tumor size alone.

The decision on whether to offer postmastectomy radiation to patients with T3 N0 disease can perhaps be further informed by retrospective studies of lymph node-negative patients with smaller primary tumors who were treated with mastectomy. These studies identified several risk factors associated with increased risk of locoregional recurrence, including lymphovascular invasion, higher grade, close or involved margins, larger tumor size, premenopausal status,

and omission of systemic therapy (Wallgren et al. 2003; Truong et al. 2005; Jagsi et al. 2005). Stage T1–T2 N0 triple negative breast cancer has also been associated with a higher risk of locoregional recurrence after modified radical mastectomy in some studies (Abdulkarim et al. 2011), and there are data from a Chinese randomized trial that suggest that triple negative patients may benefit from postmastectomy radiotherapy even if node negative (Wang et al. 2011). Further research in this area will be important to confirm these findings, as triple negative status is not currently considered an indication for postmastectomy radiotherapy in the absence of other adverse features such as nodal involvement. The 2014 analysis from the EBCTCG found that in patients who underwent axillary dissection and had no involved lymph nodes, only 1.4 % experienced a locoregional recurrence, and radiotherapy did not appear to provide an appreciable benefit. However, few patients with T3 N0 disease were included, and this analysis did not include primary tumor size as a covariate; therefore, these data cannot be taken as evidence against offering radiotherapy to patients with a large primary tumor (McGale et al. 2014). Thus, although some patients with large tumors who are treated with mastectomy might not require radiation, consultation with a radiation oncologist is warranted to individually assess the risk of local recurrence.

Given the morbidity of a chest wall recurrence and low likelihood of successful salvage, it is interesting to observe the heterogeneity of data regarding the role of radiation in the setting of a positive margin after mastectomy. The incidence of chest wall recurrence has been reported as high as 18 % after 8 years in patients with a positive or close margin <5 mm (Freedman et al. 1998). However, in a cohort from British Columbia with positive margins, there were no recurrences observed in patients with age >50 years, T1 tumors, grade 1/2 disease, and absence of lymphovascular invasion, suggesting that not all patients with node-negative breast cancer with positive margins after mastectomy routinely require radiotherapy (Truong et al. 2004). A retrospective study from Harvard observed a significantly higher rate of locoregional recurrence with positive margins (6.2 %) compared to close margins (1.5 %), which was similar to the rate observed in patients with negative margins (1.9 %) (Childs et al. 2012). Collectively, these results suggest that while many patients with close or positive margins may derive significant benefit from postmastectomy radiation, particularly young patients, other subgroups are likely to derive a much smaller absolute benefit.

Determining the indications for postmastectomy radiation following neoadjuvant chemotherapy is an area of ongoing research. Patient selection for postmastectomy radiation has been based on pathologic features observed prior to exposure to systemic therapy in all of the previously published trials, and less is known regarding the role of radiation when the observed pathology reflects the response to systemic therapy. Retrospective studies suggest that both the initial clinical stage and the final pathologic extent of disease provide important prognostic information. Data from MD Anderson Cancer Center found that patients with clinical stage III disease who achieved a complete response to neoadjuvant chemotherapy still experienced a high rate of locoregional failure, which was significantly reduced with radiation (33 to 3 % at 10 years) (Huang et al. 2004). A follow-up study evaluating only patients who achieved a pathologic complete response to neoadjuvant chemotherapy confirmed these findings with clinical stage III disease, though patients with stage I or II disease who experienced a pathologic complete response did not experience locoregional recurrence with or without radiation (McGuire et al. 2007). In two NSABP trials of neoadjuvant chemotherapy, B18 and B27, none of the patients received postmastectomy radiation, allowing for evaluation of features associated with a high risk of locoregional recurrence in the absence of radiation (Mamounas et al. 2012). On multivariate analysis, clinical tumor size >5 cm, clinically positive lymph nodes, and less than a complete response in the breast and/or axillary lymph nodes were independent predictors of locoregional relapse. The risk of locoregional relapse was consistently >10 % for all subgroups of

patients with one to three residual positive lymph nodes after chemotherapy. Taken together, these results are reflected in a statement from a multidisciplinary expert panel organized by the National Cancer Institute, which recommended that chest wall and regional nodal radiation should be considered after mastectomy for patients who present with clinical stage III disease or have positive lymph nodes after preoperative chemotherapy (Buchholz et al. 2008). The role of postmastectomy radiation in patients with stage II breast cancer who have negative lymph nodes after chemotherapy remains an area of controversy. The indications for postmastectomy radiation after neoadjuvant chemotherapy will become clearer with results from the ongoing NSABP B-51/RTOG 1304 trial, in which patients who receive mastectomy and have a pathologic complete response in the axillary lymph nodes are randomized to postmastectomy radiation or no radiation.

In summary, there is strong consensus regarding the role of postmastectomy radiation in patients with ≥4 involved lymph nodes. Decisions regarding radiation for patients with one to three involved lymph nodes have previously been an area of controversy, though consensus is growing that postmastectomy radiation affords important benefits to this subgroup as well (McGale et al. 2014; Marks et al. 2008). Data are less conclusive on the role of postmastectomy radiation with positive margins, large or high-risk node-negative tumors (such as triple negative breast cancer), and following neoadjuvant chemotherapy. Regardless, all patients with locally advanced breast cancer who undergo mastectomy merit referral to a radiation oncologist to discuss the available data to facilitate individualized decision-making.

4.2 Management of the Regional Lymph Nodes

The rationale for radiation therapy to the regional lymph nodes is similar to that articulated for postmastectomy radiation therapy. Some patients may harbor disease in the regional nodal basins, regardless of whether their primary surgery was a mastectomy or a lumpectomy. Recurrence in these nodal regions is a morbid event worthy of prevention in patients at sufficient risk. Moreover, in select patients with lymph node involvement, the regional lymph node basins may be the only reservoir of residual disease after local surgery and systemic therapy, and therefore eradicating this disease may have an impact on overall survival as well as locoregional control. The Danish and Canadian postmastectomy trials included treatment to the supraclavicular, axillary, and internal mammary lymph nodes; some have extrapolated from those trials that radiation therapy to those regions also should be considered for patients with node-positive disease who undergo breast-conserving surgery.

In the National Cancer Institute of Canada MA-20 trial, after undergoing breast-conserving surgery and axillary lymph node dissection, patients with node-positive and high-risk node-negative breast cancer were treated with whole breast irradiation and randomly assigned to the addition of regional nodal irradiation that included the supraclavicular, internal mammary, and level III axillary lymph nodes. Of the patients enrolled, 85 % had one to three involved nodes (identified on axillary lymph node dissection rather than sentinel lymph node biopsy); 25 % were ER negative and 42 % were grade 3. Preliminary results demonstrated that the addition of regional nodal irradiation improves disease-free survival with a trend toward improved overall survival, with a reduction in distant metastasis (absolute risk reduction 5.4 %) that was greater than the reduction in regional recurrence rates (absolute risk reduction 2.3 %). Regional nodal radiation was well-tolerated, but associated with a higher risk of pneumonitis (1.3 % vs 0.2 %) and lymphedema (7.3 % vs 4.1 %) compared to whole breast irradiation alone (Whelan et al. 2011).

Similar findings were observed in the EORTC 22922/10925 trial, in which patients with involved axillary lymph nodes or a medial tumor were randomized to the addition of medial supraclavicular and internal mammary nodal radiation. In contrast to previous trials that have sought to determine the benefit of internal mammary nodal

radiation (Hennequin et al. 2013), the EORTC trial was adequately powered to detect a small survival benefit and randomized over 4000 patients. Preliminary results demonstrated significantly improved disease-free survival, metastasis-free survival, and a trend toward improved overall survival, which was independent of the number of involved lymph nodes. There was no appreciable increase in non-breast cancer mortality related to treatment toxicity (Poortmans et al. 2013). These preliminary results, when taken together with reported findings from MA-20, are suggestive of a survival benefit with regional nodal radiation, even in patients with one to three involved nodes, similar to findings in the postmastectomy setting (McGale et al. 2014). Additionally, because 44 % of patients enrolled on EORTC 22922/10925 had negative lymph nodes and a medially located tumor, regional nodal radiation is an important consideration for this subgroup as well.

The decision to treat with a supraclavicular field in patients with node-positive disease has generally been less controversial, given that a non-trivial minority of failures occur in this region (Taghian et al. 2004a; Wallgren et al. 2003; Katz et al. 2000; Grills et al. 2003) and that treatment results in little increase in the risks of pneumonitis, brachial plexopathy, and lymphedema. In contrast, considerable controversy surrounds the decision to treat the internal mammary lymph nodes, resulting in widespread variation in practice patterns (Taghian et al. 2004b; Clavel et al. 2010).

In historical series, patients with advanced primary disease and positive axillary lymph nodes had rates of pathologically confirmed IMN involvement of 28–52 % and up to 65 % when the tumor was centrally or medially located (Chen et al. 2008; Freedman et al. 2000). More recent data from patients with early breast cancer demonstrated primary internal mammary lymph node drainage on lymphoscintigraphy in 13–37 % of cases (Chen et al. 2008; Paredes et al. 2005; Farrus et al. 2004), which has been associated with a higher incidence of distant metastasis and risk of mortality (Yao et al. 2007; Kong et al. 2012). Furthermore, patients with a centrally or medially located tumor also have a higher risk of metastasis and lower survival (Zucali et al. 1998; Brautigam et al. 2009). Taken together, these results suggest that internal mammary nodal involvement is neither infrequent nor trivial and may serve as an occult reservoir that seeds distant metastases and significantly influences prognosis.

Interest in treating the internal mammary lymph nodes increased with publication of favorable results from the Canadian and Danish trials of postmastectomy radiation (Overgaard et al. 1997; Overgaard et al. 1999; Ragaz et al. 2005), which included treatment of the internal mammary lymph nodes. However, several clinical trials have failed to demonstrate an improvement in survival with internal mammary nodal radiation (Hennequin et al. 2013; Freedman et al. 2000), and older meta-analyses suggested that any benefit of internal mammary nodal radiation may be effaced by increased non-breast cancer mortality, largely related to increased cardiac-related deaths (Early Breast Cancer Trialists' Collaborative Group 1995; Cuzick et al. 1994; Palmer and Ribeiro 1985). However, computed tomography planning and strict quality assurance have been lacking in these studies (Buchholz 2000), and the increased mortality has been attributed to antiquated radiotherapy techniques that delivered significant dose to the heart and coronary vasculature. A follow-up of the Danish 82b and 82c trials of postmastectomy radiation, which included treatment of the internal mammary nodal regions using an electron field, demonstrated no increase in rates of morbidity and death from ischemic heart disease in patients who received internal mammary radiation (Hojris et al. 1999). More recently, an elegant population-based cohort study of internal mammary nodal irradiation, the Danish Breast Cancer Cooperative Group IMN study (DBCG-IMN), included internal mammary nodal radiation only in patients with right-sided breast cancer but not for left-sided tumors. Preliminary results revealed 3 % improvement in overall survival in patients who received internal mammary nodal radiation (Thorsen et al. 2013), which was felt to outweigh the risk of ischemic heart death even for left-sided tumors (Thorsen et al. 2014). The value of radiotherapy to the internal mammary lymph

nodes is further confirmed by preliminary results from MA-20 and EORTC 22922/10925, which, although unable to isolate the impact of supraclavicular versus internal mammary nodal irradiation, have thus far demonstrated improved distant disease-free survival without an increase in non-breast cancer mortality (Whelan et al. 2011; Poortmans et al. 2013).

The greatest controversy surrounds internal mammary nodal irradiation for patients with T1–T2 tumors and one to three involved positive axillary lymph nodes (Buchholz 2000). It is our practice not to advocate for internal mammary nodal treatment in cases in which the risk of involvement is low (e.g., micrometastatic axillary involvement), but rather when axillary involvement is more substantial, particularly when the tumor is medially located and other high-risk features exist. With modern radiotherapy techniques and respiratory gating, we have been able to cover internal mammary lymph nodes when indicated, while exposing the heart and coronary vasculature to only low-dose scatter (Jagsi and Pierce 2013; Chung et al. 2013), as discussed in greater detail in the section on cardiac toxicity below.

Concerns about the risk of lymphedema associated with directed axillary radiotherapy after axillary dissection have generally dissuaded physicians from directed axillary radiotherapy unless exceptional circumstances exist, such as concerns about residual disease in the setting of extensive nodal disease, gross extranodal extension, or incomplete dissection. However, as a result of findings from two randomized trials – the American College of Surgeons Oncology Group Z0011 trial (Giuliano et al. 2010, 2011) and the International Breast Cancer Study Group 23-01 trial (Galimberti et al. 2013) – complete dissection of axillary levels I and II is no longer routine for patients with limited sentinel node involvement. The Z0011 trial randomized patients who had clinical T1–T2 invasive breast cancer, no palpable adenopathy, and one to two involved sentinel lymph nodes to axillary lymph node dissection versus no further axillary surgery. After 6.3 years of follow-up, local-regional recurrence rates and overall survival were equivalent between the two arms. Similar findings were observed in the IBCSG trial. Both trials demonstrated a rate of disease recurrence in the undissected axilla <1 %, suggesting that axillary dissection can be avoided in patients with early breast cancer and limited sentinel node involvement similar to those treated on these two trials.

The results of Z0011 and IBCSG 23-01 have quickly assimilated into routine clinical practice (Gainer et al. 2012; Massimino et al. 2012; Caudle et al. 2012), resulting in decreased use of axillary lymph node dissection. It is therefore not uncommon for a patient with positive sentinel lymph node to forego axillary lymph node dissection, even for patients who would not have been eligible for inclusion in Z0011 and IBCSG 23-01 or who have disease features that were uncommonly represented in the patients enrolled on those trials. For example, many breast surgeons are willing to consider omission of axillary lymph node dissection even in patients who will be treated with accelerated partial breast irradiation or who are not planning to receive radiation, despite the lack of data to support axillary lymph node dissection omission in this scenario (Gainer et al. 2012). Furthermore, some consider that the results of these two trials are applicable to all patients who would technically have been eligible for the studies, while others argue that the results are most applicable to patients who resemble the majority of patients who enrolled. For example, in both trials, 69–70 % had T1 tumors, 82–90 % had estrogen receptor-positive disease, and 71–96 % had only one positive sentinel lymph node. In Z0011, 41 % had micrometastatic nodal disease, in contrast to 98 % in IBCSG 23-01, which excluded patients with nodal macrometastatic disease. While premenopausal patients with a T2 tumor, hormone receptor-negative disease, and macrometastasis technically might have been eligible for one or both of these trials, the results of the trials may not be generalizable to patients lacking the favorable disease features that characterized the majority of patients who were actually enrolled.

Particularly challenging has been reconciling the results of NCIC MA20 and EORTC 22922, which seem to suggest a benefit with extensive nodal treatment including radiation of the

supraclavicular and internal mammary regions, with those of ACOSOG Z0011 and IBSCG 23-01, which suggest that perhaps even completion dissection is unnecessary, let alone regional irradiation. All of these trials primarily enrolled patients with N1 disease, though those in the former studies were likely higher-risk N1 patients than those in the latter. In any case, considerable controversy surrounds the optimal radiation field design in patients with limited disease detected on sentinel node biopsy, who have not received axillary lymph node dissection. Although the Z0011 study protocol required standard tangential radiotherapy, 51 % of evaluable patients were actually treated with high tangents and 19 % received directed regional nodal radiation using three or more fields (Jagsi et al. 2014c). While there was notably no difference between the arms in the use of protocol-prohibited nodal fields, the use of directed nodal irradiation in some patients has led to the conclusion that it is not unreasonable also to consider additional nodal treatment in selected patients who receive sentinel node biopsy alone for limited nodal disease.

Further insights have recently emerged from the AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery) trial, which randomized patients to completion axillary lymph node dissection or radiation to regional lymph nodes. The AMAROS protocol specified that the radiation field included the medial supraclavicular and level I–III axillary lymph nodes (with coverage of the internal mammary lymph nodes in 10 %, at the discretion of the treating physician). Disease characteristics on AMAROS were similar to Z0011: 80 % had T1 tumors, 77 % had one involved node, and 40 % had nodal micrometastasis or isolated tumor cells. Patients who received axillary radiotherapy had significantly less lymphadenopathy and postoperative complications in comparison to those who underwent axillary lymph node dissection, with comparable axillary control, suggesting that axillary radiotherapy may be preferred over axillary lymph node dissection in patients with a positive sentinel lymph node (Donker et al. 2014).

Thus, in patients with involved sentinel node(s) who forego axillary lymph node dissection, there is a spectrum of appropriate radiotherapy treatment fields ranging from conventional tangential fields to comprehensive breast and regional nodal irradiation. Intentionally targeting the axilla with high tangents can be accomplished with minimal adjustments to tangent field borders (Schlembach et al. 2001; Shahar et al. 2004). Nomograms may be helpful in determining the risk of having additional involved nodes in the undissected axilla and the need for a third field (Haffty et al. 2011; Center MSKC Breast Cancer Nomogram: Breast Additional Non SLN Metastases; Center MAC Breast Cancer Nomogram to Predict Additional Positive Non-SLN, without Neoadjuvant Chemotherapy).

Ultimately, all patients with macrometastatic involvement of the regional nodes, regardless of whether their primary tumor was treated with lumpectomy or mastectomy, are candidates for consideration of directed regional nodal radiotherapy. Decision-making must take into account multiple risk factors, including the extent of the nodal involvement, the axillary surgical procedure performed, the biology of the tumor, and systemic therapy receipt. It must also consider the patient's preferences with regard to prevention of recurrence versus avoidance of possible treatment-related toxicities, so that the treatment plan is appropriately individualized for each patient.

4.3 Cardiac Toxicity Associated with Breast Radiotherapy

Due to the proximity of the left ventricle and left anterior descending coronary artery to the chest wall and internal mammary lymph nodes, radiotherapy may result in significant dose to cardiac structures, causing increased cardiac toxicity. This likely accounts for the observation in the early EBCTCG meta-analyses (Early Breast Cancer Trialists' Collaborative Group 1995; Early Breast Cancer Trialists' Collaborative Group 2000) of improved breast cancer-specific survival with radiation, which was offset by increased risk of death from other causes, notably from vascular-related mortality. While several

individual studies did not find an increased risk of cardiac events or death from a cardiac cause associated with radiation (Hojris et al. 1999; Gustavsson et al. 1999; Rutqvist et al. 1998), larger population-based analyses (Paszat et al. 1998) and single institution series (Jagsi et al. 2007a; Harris et al. 2006) observed increased risk of cardiac events and cardiac mortality with left-sided breast cancer in comparison to patients with a right-sided tumor. A Swedish group described a positive correlation between death due to cardiovascular disease and irradiated cardiac dose and volume (Gyenes et al. 1998). A recent landmark population-based study from Denmark and Sweden found that there was a proportional increase in ischemic heart disease with increasing mean dose to the heart (7.4 % relative increase per 1 gray), with no apparent threshold below which no risk was incurred (Darby et al. 2013b). However, the radiation doses to the heart in this study were estimated by virtually reconstructing each patient's radiation plan "on the CT of a woman with typical anatomy" and may be least accurate in the low-dose region (<4 Gy), which is most relevant to current practice. Nonetheless, the study highlights the importance of minimizing the radiation dose to the heart.

The risk of death from ischemic heart disease after breast radiotherapy has decreased substantially over time (Giordano et al. 2005) with development of more sophisticated treatment planning techniques and increased awareness of minimizing radiation dose to the heart. In a population-based evaluation of 10,468 patients with ductal carcinoma in situ who were treated between 1989 and 2004, after median follow-up of 10 years, there was no evidence of increased risk for cardiovascular morbidity or mortality after radiotherapy when compared to surgery alone, nor when comparing radiotherapy for left-sided versus right-sided DCIS (Boekel et al. 2014; Feng and Pierce 2014).

However, it is concerning to note that radiation dose to the heart has been associated with cardiac perfusion defects. In a prospective study that evaluated pre- and posttreatment cardiac perfusion imaging, radiation caused volume-dependent perfusion defects in approximately 40 % of patients within 2 years of radiation, which were associated with corresponding wall motion abnormalities (Marks et al. 2005). However, although this study used CT-based treatment planning, it allowed inclusion of anterior portions of the heart within the tangential fields, and there was significantly increased incidence of perfusion defects with a greater volume of left ventricle within the radiation field. Furthermore, the clinical consequences of these abnormalities have not been defined, and there has been no associated change in ejection fraction. Reassuringly, in a similar prospective study in which no portion of the heart was allowed within the primary beam, there were no detectable perfusion defects 1 year after radiation (Chung et al. 2013).

Collectively, these studies clearly establish a relationship between radiation exposure to the heart and cardiac toxicity. However, it is important to note that the net overall survival benefit of radiation in the trials above and with longer follow-up of the EBCTCG meta-analyses (Clarke et al. 2005; Darby et al. 2011a; McGale et al. 2014) already account for any adverse effect from radiation-related cardiac toxicity. Therefore, patients who are likely to obtain significant benefit from radiation should not forego treatment due to concerns related to cardiac exposure. Current guidelines recommend that the heart should be excluded from the primary treatment fields (Smith et al. 2011c). This becomes feasible with CT-based treatment planning and respiratory motion management, such as deep inspiratory breath hold (Remouchamps et al. 2003; Jagsi et al. 2007b) or respiratory gating. With increased awareness regarding the importance of cardiac dose, the risks associated with breast radiotherapy will be further minimized with careful treatment planning and modern treatment techniques.

Conclusion

Considerable progress is being made toward appropriately selecting patients most likely to benefit from radiation, defining treatment targets, and reducing the burden and morbidity associated with treatment. At the present time, decisions regarding radiation are largely

informed by clinical and pathological features. Efforts to identify a subgroup of patients at sufficiently low risk of recurrence to forego radiotherapy suggest that clinical and pathologic features provide insufficient discriminatory power. There is an increasing appreciation of the influence of tumor biology on the risk of local and distant recurrence (Mamounas et al. 2010; Cheng et al. 2006; Nguyen et al. 2008; Millar et al. 2009; Voduc et al. 2010), as well as response to treatment (Abdulkarim et al. 2011; Paik et al. 2006; Kyndi et al. 2008). These findings highlight the central importance of obtaining a more comprehensive understanding of tumor biology and lend support to ongoing efforts to refine the accuracy of genomic assays with prognostic and predictive significance. Ultimately, a more thorough understanding of tumor biology will facilitate individualized treatment decisions, with sparing of those with low-risk disease from unnecessary treatment, targeting those most likely to benefit, and intensifying treatment for those likely to recur with currently available therapies.

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Center MAC Breast Cancer Nomogram to Predict Additional Positive Non-SLN, without Neoadjuvant Chemotherapy

Center MSKC Breast Cancer Nomogram: Breast Additional Non SLN Metastases

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Surgeons ACo Commission on Cancer Quality of Care Measures

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