

**American College of Radiology
ACR Appropriateness Criteria®**

CONSERVATIVE SURGERY AND RADIATION—STAGE I AND II BREAST CANCER

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Summary of Literature Review

Introduction/Background

Invasive breast cancer is the most common malignancy in women in the United States [1]. Breast-conserving therapy (BCT) has become firmly established as a standard therapeutic approach for eligible women with early-stage breast cancer over the past 2 decades, replacing mastectomy as the predominant treatment. BCT is defined as excision of the primary breast tumor with a rim of adjacent normal breast tissue sufficient to achieve negative resection margins, with or without axillary sentinel node (SN) biopsy or dissection, usually followed by irradiation. In the United States, the rates of BCT among early-stage breast cancer patients varies among single institutions, ranging from 45%–70% in selected large studies [2,3]. The goals of BCT are to 1) use moderate doses of radiation to eradicate microscopic foci of cancer that may remain in the breast after limited surgery to remove the primary tumor; 2) provide local control and equivalent survival rates comparable to those of mastectomy; and 3) maximize quality of life while minimizing complications and achieving an acceptable cosmetic result.

The following issues related to conservative surgery and radiation for stage I and II breast cancer are addressed below: the National Institutes of Health (NIH) Consensus Conference statement, results of prospective randomized clinical trials, patient selection and evaluation, radiation therapy (RT) following conservative surgery, treatment technique, the role of accelerated partial-breast irradiation (PBI), the integration of radiation and adjuvant systemic therapy, and follow-up care.

National Institutes of Health Consensus Conference

The Office of Medical Applications of Research of the NIH and the National Cancer Institute convened a consensus development conference on the treatment of early-stage breast cancer in June 1990. The panel concluded that “breast conservation treatment is an appropriate method of primary therapy for the majority of women with stage I and II breast cancer and is preferable to mastectomy because it provides survival rates equivalent to those of total mastectomy and axillary dissection while preserving the breast” [4]. The validity of this statement has been upheld by long-term data from prospective randomized trials. The rate of BCT for eligible breast cancer patients has risen steadily since the consensus conference statement.

Results of Prospective Randomized Clinical Trials

Six prospective randomized trials have compared mastectomy and BCT for stage I and II invasive breast cancer [5-10]. These data are very mature, with overall and disease-free survival rates reported for periods of 10 to over 20 years. They all have demonstrated no significant differences in distant metastases, cause-specific survival, or overall survival between the 2 treatment approaches. Three of these trials reported equivalent local regional control when BCT was compared to mastectomy. In all these trials, there was no difference between mastectomy

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and BCT in the incidence of subsequent contralateral breast cancer or second nonbreast malignancies. Of note, many of these older trials were unable to differentiate recurrence of the original cancer from new primary tumors, potentially confounding their results. Later studies have attempted to make this distinction [11].

Multiple prospective clinical trials have evaluated the benefit of radiation following conservative surgery [12-18]. In all these studies, RT resulted in a highly significant, approximately two-thirds reduction in local recurrence compared to lumpectomy alone. For most breast cancer patients undergoing lumpectomy, postoperative RT remains the standard of care.

Although individual trials did not demonstrate an overall survival benefit by the addition of RT following breast-conserving surgery, meta-analysis grouping the majority of trials have shown a small but significant increase in survival with the addition of RT [19]. The Early Breast Cancer Trialists' Group (EBCTG) meta-analysis of 17 randomized trials that evaluated breast-conserving surgery alone versus the same followed by RT demonstrated a statistically significant 3.8% absolute reduction in breast cancer-specific mortality and a 4.4% improvement in overall mortality at 15 years with the addition of radiation. The 1.3% absolute excess in non-breast cancer deaths were mostly from heart disease, emphasizing the importance of using careful radiation delivery methods to minimize exposure of normal tissues at risk [20]. RT did not increase the risk for development of contralateral breast cancer in any of the individual randomized trials comparing RT after lumpectomy to mastectomy [5,6,9,10], but it was found to contribute to the 1.8% absolute excess in second cancers associated with RT in the EBCTG meta-analysis [21]. In a large Surveillance, Epidemiology, and End Results (SEER) database analysis, the risk of contralateral breast cancer and second non-breast cancer malignancies was associated with higher dose, younger age (<40 years), and time since treatment (1970s versus 1980s) [22], although data from other cohorts have not confirmed this finding [23].

Complications from breast irradiation have been more thoroughly evaluated in retrospective series. The risk of symptomatic pneumonitis, rib fracture, pericarditis, brachial plexopathy, severe breast fibrosis, or soft-tissue necrosis is <1%–4% when the breast alone is irradiated [21,24]. Arm edema, which is primarily related to the extent of axillary node dissection, is more frequent after nodal irradiation [25]. Good to excellent cosmetic results are achieved in 85%–90% of patients and are influenced by surgical and RT techniques as well as the addition of adjuvant systemic therapy [26,27].

Although the rates vary regionally, according to SEER-based data, <50% of women with stage I and II breast carcinoma have BCT in spite of the aforementioned prospective randomized clinical trials [28]. A joint study of the American College of Radiology and the American College of Surgeons found that high mastectomy rates in the United States are the result of inappropriate use of medical selection factors (eg, tumor size, grade, node status) and a function of demographics (eg, age, geographical location) [3,29]. Contraindications to breast-conserving treatment are few and easily identified. These are discussed further in the clinical evaluation section.

Breast Imaging

Preoperative mammographic evaluation is necessary to determine a patient's eligibility for BCT. Mammography aids in defining the extent of a lesion and in determining whether the lesion is a unifocal or a multicentric process; it can also evaluate the contralateral breast. If the mass is associated with microcalcifications, the extent of microcalcifications, both within and outside of any tumor mass, should be noted. Magnification views and spot compressions should be performed to better delineate tumor extension and define the full extent of microcalcifications.

Postoperative mammograms can be obtained to assess the completeness of resection of tumors with microcalcifications when sufficient margins are in question or specimen radiography is discordant with either preoperative imaging or surgical results (see the Pathologic Factors section).

Ultrasound (US) can be important for further characterizing masses seen on mammography. It can better evaluate the size of the lesion in some cases and is helpful in determining the extent of a mass in breasts that are dense on mammography. In addition, it provides a convenient means to obtain a core biopsy of suspicious lesions.

Magnetic resonance imaging (MRI) is increasingly being used as an adjunct to mammography to help select patients for BCT by defining the extent of disease within the breast [30,31]. In particular, MRI can be beneficial in patients whose disease is not demarcated well on mammography, US, and/or clinical examination (eg, those with very dense breast tissue on mammography or lobular histology). Importantly, MRI can also lead to a change in a planned surgical procedure (particularly from breast conservation to mastectomy) [32-34]; however, it has not

been shown to improve local control or overall survival [35]. As such, although it is commonly used at many centers, it is not presently considered a part of the standard imaging for a newly diagnosed breast cancer patient.

Clinical Evaluation

Pregnancy

Pregnancy is an absolute contraindication to treatment with RT. Late in the third trimester, it may be possible to perform breast-conserving surgery and treat the patient with irradiation after delivery.

Prior Radiation Therapy

A history of prior RT (eg, for the treatment of Hodgkin lymphoma or lung cancer) that delivered significant doses to the chest and for which retreatment would result in an excessively high total radiation dose to the breast tissue is a relative contraindication for a breast-conserving approach. High radiation doses to the breast/chest may result in unacceptable long-term toxicity. Although radiation after breast-conserving surgery may potentially allow selected patients with newly diagnosed breast cancers to preserve the breast, data are limited and extreme caution is warranted in individual cases [36,37].

Collagen Vascular Disease

Collagen vascular diseases (CVD) in general represent a relative contraindication for breast RT. Larger retrospective studies have reported somewhat mixed results; however, one consistent finding is that a well-documented history of a preexisting scleroderma is associated with high risk for severe toxicities [38] and is therefore contraindicated. Data for patients with systemic lupus erythematosus remain somewhat controversial, although most studies indicate that patients with rheumatoid arthritis are not at high risk for late toxicity [39]. Breast cancer patients with CVD should be made aware of the potential for exaggerated acute and late toxicity related to RT.

Multiple Lesions

The presence of 2 nonadjacent primaries in the same breast is considered a relative contraindication for a breast-conserving approach. First, the cosmetic results after multiple wide local excisions may be poor, unless both primaries are very small relative to the breast size. Second, these patients may have a larger residual tumor burden after breast-conserving surgery, placing them at risk for higher rates of local failure. However, in some series, highly selected patients with early-stage multicentric disease may not have an inordinately high risk of local recurrence [40,41]. Given the limited data, these patients are most appropriately considered with caution on an individual basis. Diffuse malignant-appearing calcifications are associated with extensive intraductal components and have been classically considered a contraindication to breast conservation.

Breast Size

The treatment of women with very large breasts is technically more challenging and may require the use of higher-energy photons and specialized radiation techniques to minimize dose heterogeneity. Prone breast RT may be useful in this population [42], where a decrease in skin toxicity was noted for patients with high BMI.

Tumor Size

One major patient selection criterion is the ability to completely resect the primary tumor without causing unacceptable cosmetic deformity. There is no difference in recurrence rates based on the size of the tumor itself. Hence, tumor size is only a factor as it relates to the expected cosmetic result, although there are few published reports on tumors larger than 4 to 5 cm. Larger unifocal tumors that are considered borderline for breast conservation may be candidates for neoadjuvant chemotherapy to reduce the tumor size and improve the successful completion of BCT [43].

Retraction of skin or nipple is not a contraindication for BCT.

Subareolar Location

Subareolar tumors may require resection of the nipple areola complex for complete excision, but this is not a contraindication to a breast-conserving approach. Although the appearance of the breast may then be unacceptable to some patients, it is likely to be preferable to a reconstructed breast mound after mastectomy to many. Reconstruction of a nipple areola complex is feasible in this BCT setting.

Patient Age: Considerations for <40 and >65–70 Years

Many series have suggested that young patients (younger than 30–40 years) may have a higher risk of breast cancer recurrence than older patients. This risk can be explained at least in part by differences in the pathologic features of tumors, including tumor biology associated with a poorer prognosis in very young patients [44]. Overall, very young patients have an increased risk of local recurrence after BCT compared with older patients [45] and may also have poorer outcome following mastectomy [46]. Recent data comparing outcomes after BCT or mastectomy suggest that the risk of breast cancer–specific survival and overall survival are similar in patients <40 years of age having either approach [47,48].

The absolute benefit from radiation after lumpectomy may be relatively low for patients >65–70 years of age with node-negative, small, estrogen receptor (ER)–positive breast cancers who receive endocrine therapy for 5 years [18]. In the CALGB 9343 randomized trial conducted among patients >70 years of age, patients who underwent lumpectomy and received tamoxifen alone had a 10-year locoregional recurrence rate of 10%, versus 2% with tamoxifen plus breast irradiation. Time to local recurrence was also prolonged with radiation ($P<0.001$) [18]. The overall mastectomy-free survival rates have been equivalent between the 2 arms. Similarly, results from the PRIMEII trial reported comparable outcomes, 4.1% versus 1.3% local recurrence at 5 years ($P=0.0002$) without and with RT, respectively. This trial randomized women 65 years or older with node-negative, hormone receptor–positive cancers to whole-breast RT or no RT after lumpectomy and endocrine therapy [49]. Although there is a local-control advantage to radiation, the absolute benefits are relatively small in this selected patient population; consideration of treatment without RT following lumpectomy for older patients should be individualized based on clinical determination of competing medical risks from preexisting comorbidities and overall performance status. However, age alone should not be a criterion for omission of RT. Treatment is well tolerated among patients >70 years of age and logistical issues such as transportation problems can often be overcome. In sum, in older patients with low risk, favorable biology, and ER-positive tumors treated with hormonal therapy, omission of RT after lumpectomy may be a reasonable option [18,19].

Family History

Family history of breast cancer is not a contraindication to BCT or use of breast RT.

Hereditary Breast Cancer

The use of BCT in stage I and II breast cancer patients with germline mutations in breast cancer susceptibility genes 1 and 2 (BRCA1 and BRCA2) is a complex issue. There may be higher rates of late breast cancer events in mutation carriers compared to sporadic cases. All studies have reported significantly higher rates of contralateral breast cancer, ranging from 14%–42% at 10 years [50,51]. No decrement in overall survival has been reported, and there does not appear to be a higher risk of radiation-induced complications or any increase in local recurrence rates of the index cancer [52,53]. Local failure as first failure is significantly more likely in those treated with BCT compared to mastectomy, but most are considered new primary cancers [53]. Other more rare forms of hereditary breast cancer exist with varying penetrance, for which data on outcomes after RT are sparse [54]. Therefore, patients with known or suspected hereditary breast cancer require detailed discussions regarding risk-reduction strategies. Informed patients desiring BCT should receive counseling on subsequent risk reduction for contralateral breast cancer by using antiendocrine therapy if appropriate and undergoing prophylactic salpingo-oophorectomy. Bilateral mastectomy for treatment of the affected breast and for risk reduction on the contralateral side is an option that should be considered.

Prosthetically Augmented or Reconstructed Breasts

The development of significant capsular contracture may be increased after RT. The reported incidence varies widely, but capsular contracture has been reported to occur in 25%–60% of cases [55,56]. Patients should be advised that postlumpectomy RT may necessitate subsequent corrective surgery. However, the presence of a breast prosthesis is not a contraindication to RT (see [Variant 1](#) and [Variant 2](#)).

Pathologic Factors

Margins

The pathologic specimen must be appropriately sampled to document the presence or absence of gross or microscopic carcinoma in the margins of excision. Microscopic status of the resection margins is the most commonly used method for estimating the residual tumor burden in the breast remaining after conservative surgery. The goal of breast-conserving surgery is to achieve negative margins of excision. When margins are

microscopically involved, a re-excision should be performed. The precise width of the tumor-free distance remains under debate, and close margins <2 mm may not incur a higher risk of recurrence than widely negative margins in the era of modern systemic therapy [57,58].

Wider margins may be more important in younger patients, in those with ER-negative tumors, and in situations where there is an extensive intraductal component (EIC) [59-61]. A consensus conference by the Society of Surgical Oncology and the American Society for Radiology and Oncology (ASTRO) was based upon a meta-analysis of 33 studies in over 28,000 patients [62,63]. Conclusions were that positive margins (ink on invasive carcinoma or ductal carcinoma in situ [DCIS]) are associated with a 2-fold increase in the risk of ipsilateral breast tumor recurrence (IBTR) compared with negative margins. This increased risk is not mitigated by favorable biology, endocrine therapy, or a radiation boost. More widely clear margins than no ink on tumor do not significantly decrease the rate of IBTR compared with no ink on tumor [62,63].

Histology

Invasive ductal carcinoma (IDC) is the most common type of breast cancer, followed by invasive lobular carcinoma, which accounts for up to 15% of breast cancers. Large randomized trials of breast conservation therapy primarily represent IDCs, and early retrospective series gave conflicting reports on recurrence rates of lobular carcinomas after breast conservation therapy compared with ductal carcinomas. Lobular carcinomas often fail to form distinct masses, making clinical assessment of tumor extent more difficult, leading to increased re-excision rates [64]. In addition, lobular subtypes are associated with increased incidence of multifocality and contralateral disease [65]. Despite the difference in biology of lobular tumors, 3 modern retrospective series have shown equivalent long-term outcomes for lobular carcinomas compared to ductal carcinomas in patients undergoing breast conservation therapy, and therefore, lobular histology should not be considered a contraindication to this approach [65-67].

Molecular Subtype

Tumor biology has been traditionally characterized by pathologic features such as size and grade. In recent years, with the advent of array-based gene-expression profiling, molecular subtypes have been identified with prognostic value. In addition to standard patient and pathologic characteristics used to estimate local recurrence risk, molecular subtypes may provide further prognostic information [68,69]. Nguyen et al [59] found that the basal subtype, as approximated by ER-negative, progesterone receptor (PR)-negative, and human epidermal growth factor receptor 2 (HER2)-negative disease, predicted a higher risk of local recurrence in a retrospective study of 793 patients treated with breast-conserving surgery and radiation. Similarly, Millar et al [70], Voduc et al [71], and Demirci et al [57] have reported higher rates of local regional recurrence in patients with “triple negative” phenotypes than in those with ER-positive disease. This effect is seen both after BCT and after mastectomy.

Conversely, Luminal A tumors, approximated by ER-positive/HER2-negative, low-grade disease, consistently present with the lowest local recurrence rates in these series, ranging from 1%–5% with 10-year follow-up [57,70,71].

In addition, developments in molecular diagnostics have been applied to estimation of locoregional recurrence risk. Mamounas et al [72] stratified patients treated on 2 protocols of the National Surgical Adjuvant Breast and Bowel Project into risk groups based on their Oncotype DX score. Although preliminary and not yet validated, the results suggest that the Oncotype DX score may also help predict locoregional recurrence. Clearly, much additional work is necessary to help determine the optimal biologic determinant of locoregional recurrence, which may turn out to be very different than the markers of systemic recurrence. Hopefully, this will allow for further tailoring of treatment to the individual patient, where high-risk patients can have intensification of locoregional therapy, perhaps with a concurrent systemic agent, and lower-risk patients may be able to avoid treatment (see [Variant 3](#)). Currently, there is no molecular subtype that should be considered a contraindication for BCT.

Radiation Therapy Techniques

Simulation and Planning

Computed tomography (CT)-based treatment planning for megavoltage beam irradiation is strongly recommended by consensus of the panel for optimal RT following excision of the primary tumor and axillary SN biopsy or dissection. Appropriate beam modification should be used (eg, wedges, compensators, multileaf collimators [MLC]) to minimize dose heterogeneity throughout the treated breast, ideally to less than $\pm 7\%$ –10%. The use of dynamic wedges or MLC instead of physical wedges for beam modification is preferred as they will

reduce scatter—particularly to the opposite breast—from the medial tangent field(s). Adverse cosmetic results have been associated with the use of systemic therapy [73], a total dose to the breast of >50 Gy [74], and excess dose heterogeneity [75].

The use of multiple fields within fields, either using inverse or forward planning, has been studied as a means to improve dose homogeneity and outcomes. Three randomized trials have compared conventionally planned 2-D RT with forward planned field-in-field techniques. Pignol et al [76] found that field-in-field approaches improved the homogeneity of the radiation dose distribution and decreased acute toxicity. Similar randomized trials (Donovan et al [75] and Barnett et al [77]) reported that more homogeneous treatment planning translated into an improvement in cosmetic results.

Promising methods to reduce heart and lung dose include deep-inspiration breath hold, MLC, intensity-modulated radiation therapy (IMRT), and treatment in the prone position. In deep-inspiration breath hold, maximum inspiration is used to move the heart away from the chest wall, allowing standard tangents to largely avoid the heart. Multiple single-institution series have shown favorable dosimetry when compared to free breathing [78,79], and several commercial systems are available. However, it is unclear whether breath-holding techniques truly lead to a decrease in cardiac morbidity. Studies including 1 small randomized trial report increased cardiac perfusion defects with active breath hold [80].

Another study that reported higher cardiovascular morbidity in left- versus right-sided breast cancer patients showed no correlation between estimated cardiac dose and outcomes [81].

MLC can be used to conform dose to avoid the heart alone or in addition to other complementary techniques.

Prone positioning has been shown to reduce heart and lung dose when compared to treatment in the supine position [82,83]. A randomized trial of large-breasted women treated prone versus supine reported improved dose homogeneity and reduced acute skin toxicity and pain in the prone position compared to supine [83]. Prone positioning can also reduce intrafraction target motion related to breathing [84].

Dose and Fractionation

Whole-breast RT should be designed to treat the entire clinical breast to a total dose of 44–50.4 Gy in 1.8–2 Gy fractions for 4.5 to 5.5 weeks. The use of the more prolonged fractionation is not necessary if homogeneity parameters are met. Several clinical trials testing hypofractionated regimens have demonstrated equivalent survival and cosmetic outcomes in selected patient populations. In 1 randomized trial of 1234 patients with stage I breast cancer, a shorter course of breast radiation delivering 42.6 Gy in 16 fractions over 22 days proved to have 10-year local-recurrence-free survival rates and cosmetic results equivalent to those achieved with 50 Gy in 25 fractions [27]. A limitation of this study is that a boost, or additional radiation delivered to the lumpectomy site, was not permitted on either arm. In addition, patients with large breasts were not eligible. Two other randomized trials conducted in the United Kingdom evaluated multiple hypofractionated regimens: START A and START B. The START B trial reported similar tumor control and toxicity outcomes in women treated with 40 Gy in 15 fractions compared to women treated with 50 Gy in 25 fractions. A boost of 10 Gy in 5 fractions was allowed and was administered in approximately 40% of patients in that trial [85]. A task force from the American Society for Radiation Oncology stated that evidence supports the use of hypofractionated regimens in women 50 years or older at diagnosis with pT1-2N0 tumors who do not undergo systemic chemotherapy and who can be treated with dose homogeneity $\pm 7\%$ along the central axis [86].

Randomized clinical trials have supported the use of a boost to reduce in-breast recurrences [45] when standard fractionation is used. This benefit is most pronounced in younger women and in women with high-grade tumors. The boost dose is commonly 10–16 Gy to the lumpectomy cavity. For patients with negative resection margins, a range of 60–66 Gy cumulative dose to the boost volume is considered acceptable. Use of a boost is associated with higher rates of fibrosis. Multiple studies have demonstrated the inadequacy of clinically directed boost fields and have emphasized the importance of careful CT-based treatment planning to ensure the boost dose covers the targeted at-risk breast tissue [87]. In those cases where no boost is given, a breast dose of 50 Gy is most appropriate.

Regional Nodal Irradiation

Postmastectomy chest wall and regional nodal irradiation has been documented to improve survival in node-positive breast cancer patients in a meta-analysis of trials evaluating its efficacy after surgery, including in women with 1–3 positive axillary nodes [21]. The role of regional node irradiation (RNI) in patients with early-stage

breast cancer and positive nodes receiving BCT remains controversial in those with limited nodal disease. RNI is strongly recommended for women with 4 or more positive nodes but not routinely recommended for patients with histologically negative axillary nodes as determined by SN biopsy and/or axillary node dissection [21]. Among patients enrolled in the ACOSOG Z0011 trial randomized to axillary dissection after positive SN biopsy, patients were treated with external-beam RT using tangents, high tangents, or regional nodal fields [88]; therefore, it is unclear what the impact of the extent of regional nodal radiation was in these patients. When the SN is positive, it is appropriate to consider regional nodal irradiation after thorough discussion of the potential benefits and risks with the patient. Clinical factors that can influence the decision to irradiate the regional nodes in patients with 1 to 3 positive lymph nodes include the primary tumor size, nodal ratio (number of positive nodes/number of nodes removed) >20%, lymphovascular space invasion, extranodal extension, and the extent of axillary dissection.

Regional nodal irradiation volumes typically include the supraclavicular fossa and the undissected axillary lymph nodes. Radiation to the full axilla is indicated in some patients with invasive cancers in whom an SN or axillary dissection has been omitted or was inadequate as well as those with SN biopsy only showing positive nodes. Although clinical evidence of recurrence in internal mammary lymph nodes (IMN) is rare [89], consideration of treatment is reasonable, particularly in patients with medial, axillary node-positive tumors [90]. It is also reasonable to consider IMN radiation when the SN mapping shows IMN drainage. In a review of 6 modern studies of SN identification of IMNs, the rate of visualization of IMN nodes may be 20% and rate of positive IMN biopsy of these, 17%; this suggests the overall risk in modern early-stage breast cancer is much lower than extended radical mastectomy series and may be <5% [91]. In a study of selective IMN sampling during flap reconstruction, the rate of positive IMN was 2% overall and 14% of those biopsied [92]. Elective radiation of the IMN chain remains controversial as to the impact on survival. The risk of nodal recurrence is low in patients with 1 to 3 positive nodes after an appropriate level I/II axillary dissection [89]; however, a benefit in local recurrence and disease-free survival was reported (in abstract form as of this report) among patients who received comprehensive RNI in the NCIC-CTG MA.20 trial [90]. In a meta-analysis that included the unpublished results from the NCIC-CTG MA20 and EORTC 2292-10925 trials, the estimated survival benefit at 5 or 10 years from RNI was 1.6%–3.3% [93]. However, in the EORTC 22922-10925 [94] and NCIC CTG MA20 [88] studies, the survival benefit did not reach statistical significance, and the specific contribution of the IMN treatment to any trend is less certain due to the inclusion of supraclavicular radiation as well. Based upon the available data, consideration of treatment of the IMN is reasonable in high-risk patients, including patients with medial, axillary node-positive tumors, if the possible benefit is carefully weighed against the risk for added toxicity. When treating the IMNs, careful attention to the heart dose, even in right-sided patients, is required. Doses of 45–50.4 Gy delivered at 1.8–2 Gy per fraction should be used to treat regional nodes. In view of the added toxicity, careful 3-D CT-based planning with attention to maximizing homogeneity is necessary to minimize exposure to normal tissue while adequately covering the breast and regional nodes. The incidence of symptomatic pneumonitis [95] and lymphedema [96] is increased with the addition of nodal irradiation (see [Variant 4](#)).

Accelerated Partial-Breast Irradiation

Accelerated PBI delivers hypofractionated radiation to the 1–2 cm of breast tissue around the lumpectomy cavity, where the vast majority of in-breast recurrences occur. It is commonly delivered using balloon brachytherapy techniques in twice-daily treatments (minimal 6-hour interfraction time interval) over 5–8 days. The smaller target volume allows for accelerated and hypofractionated radiation. A growing body of data has demonstrated that PBI with multicatheter brachytherapy following lumpectomy in selected cases yields local control and cosmetic results similar to historical outcomes with whole-breast irradiation [97,98]. In these studies, radiation doses between 30–38 Gy of high-dose radiation were delivered in 7–10 fractions over 5–8 days or 45–50 Gy (0.4–0.05 Gy/hour) of low-dose radiation. With median follow-up times between 30–80 months, in-breast recurrence rates and good to excellent cosmetic outcome rates of 1%–6% and >80%, respectively, are seen. Other methods of PBI include balloon brachytherapy and 3-D conformal RT. Balloon brachytherapy devices were approved for breast cancer treatment by the FDA in May 2002 and prospective data are primarily from the initial 43 patients studied in a multi-institutional trial evaluating the safety of the device. At 5 years of follow-up, the recurrence rate across all risk stratifications was <5.5% [99].

Prospective trials of external-beam PBI have reported excellent control rates with early follow-up, with 5-year local recurrence rates of ≤5% [100,101]. However, studies such as the Canadian RAPID trial, a randomized study of whole-breast irradiation versus external-beam PBI, warrant caution with external-beam PBI techniques due to possible excessive toxicity [102]. Ongoing trials using intraoperative radiation PBI techniques with either

electrons or low-energy photons have reported low local recurrence rates and toxicity, with very early follow-up [103-106]. A phase III trial cosponsored by the National Surgical Bowel and Breast Program and the Radiation Therapy Oncology Group (RTOG®), randomizing patients with stage 0-II cancer who have undergone lumpectomy to either whole-breast irradiation or PBI, closed to accrual in June 2014. There are other randomized trials ongoing in Canada and Europe examining this question, but their results are several years away.

In the absence of an available clinical trial, the panel recommends following the consensus guidelines of ASTRO [107]. Suitable patients for treatment outside a clinical trial include those patients older than 60 years without BRCA mutations and with T1, lymphovascular invasion–negative, EIC-negative, node-negative, unicentric, ER-positive IDC excised with surgical margins >2 mm.

Integration of Radiation Therapy and Adjuvant Systemic Therapy

In most series, the addition of adjuvant chemotherapy to RT results in a decreased incidence of breast recurrence when compared with conservative surgery and RT alone. Early adjuvant systemic chemotherapy in patients at substantial risk of metastases is believed to be important. Concurrent regimens have the theoretical advantage of initiating both local and regional treatments with systemic therapy at the same time without delay in either modality, although there is concern about potential toxicity [108,109]. Given the lack of demonstrated benefit and higher toxicity rates from concurrent therapy, sequential therapy is considered standard. Some retrospective series had demonstrated that delaying the initiation of RT by at least 4 months results in an increased risk of breast recurrence. A randomized trial evaluating sequencing chemotherapy first versus RT first had initially demonstrated a trend toward increased local recurrence in the chemotherapy-first arm and increased distant metastases in the RT-first arm. However, at 10 years there was no difference in the rates of local or distant failure based on sequencing [110]. In practice, patients typically complete chemotherapy after breast-conserving surgery prior to beginning RT [111]. Tamoxifen can be given concomitantly or sequentially with RT, with no demonstrable differences in outcome [112-114]. Trastuzumab was continued during RT in those trials evaluating its efficacy [115,116]. No increased acute toxicity was seen when it was given concurrently with radiation on the North Central Cancer Treatment Group trial N9831, although late toxicity, particularly cardiac in women receiving left-sided radiation, remains to be seen [117].

Neoadjuvant Chemotherapy

Patients with large tumors relative to their breast size, in whom resection would result in a cosmetically unacceptable breast appearance, should be considered for neoadjuvant chemotherapy to reduce the tumor size. An approximately 20% relative increase in BCT is achieved with neoadjuvant chemotherapy, and overall breast cancer recurrence is equivalent to the results in the adjuvant setting [112]. There is equivalent overall survival from neoadjuvant compared to adjuvant chemotherapy. However, a small but not statistically significant increased rate of breast recurrence has been noted in downstaged patients who were initially ineligible for lumpectomy, compared to patients who were initially thought to be appropriate candidates for lumpectomy [43]. The area of the cancer should be clipped so lumpectomy can be appropriately localized in the case of complete clinical or complete pathologic response. Evaluation of the regional nodes with either thorough imaging, including axillary US, or prechemotherapy SN biopsy should be done to ensure that adequate information regarding indications for the addition of regional nodal irradiation are documented prior to neoadjuvant chemotherapy. Moreover, because of potential incongruent patterns of shrinkage within the primary tumors, it is prudent to obtain clearly negative margins in the post-preoperative chemotherapy setting. Thorough discussion with the patient and careful pathology review are needed prior to proceeding with BCT.

Follow-up

Women treated for breast cancer are recommended to have a history and physical examination including thorough breast and regional nodal examination performed every 3–6 months for the first 3 years after treatment, then every 6–12 months; the examination should be coordinated among specialties. A new baseline mammogram should be obtained approximately 6 months after completion of RT, after postsurgical and radiation changes have peaked. Annual mammograms should be obtained after mammographic stability. There are insufficient data to recommend the routine use of any other studies.

Management Guidelines

The vast majority of women with stage I or II breast cancer are good candidates for BCT. Whole-breast irradiation with or without boost is the standard of care following lumpectomy. Contraindications to BCT include patients with very extensive malignant-appearing calcifications on the mammogram. The presence of 2

nonadjacent primary tumors in the same breast is a relative contraindication to RT. Pregnancy is an absolute contraindication. A history of well-documented scleroderma and a history of prior RT to a high total dose, significant volume, or both are considered relative contraindications to a breast-conserving approach. Any other patient who desires a breast-conserving approach and in whom negative margins of excision around the primary tumor can be obtained with acceptable cosmesis (eg, in patients with EIC-positive tumors) is a good candidate for BCT.

RT to the entire breast to a total dose of 45–50.4 Gy in 1.8–2 Gy fractions for 4.5–5.5 weeks, often followed by a supplemental boost dose of radiation to the surgical tumor bed in those with high-risk features, is recommended. Regional nodal irradiation is not recommended for patients with negative axillary nodes. Regional nodal irradiation in patients with 1 to 3 positive nodes should be considered for select patients, including those with bulky nodes, a high nodal ratio, extracapsular extension, or those who do not undergo completion axillary dissection after a positive SN biopsy. Hypofractionated regimens should be considered as a standard alternative, particularly in postmenopausal patients with modest-sized breasts who do not undergo systemic chemotherapy. Accelerated PBI can be considered in selected low-risk patients who meet consensus statement criteria. Altered fractionated schemes incorporating a concomitant boost and/or regional nodal treatment are under investigation.

Summary of Recommendations

- Breast conservation is a safe and effective alternative to mastectomy for the majority of women with early-stage breast cancer.
- Adjuvant RT lowers the risk of recurrence within the breast and also confers a survival benefit.
- Acute side effects of RT are generally well tolerated; careful attention to treatment-planning parameters will minimize the long-term side effects of radiation, most prominently atherosclerotic heart disease.
- Efforts to define appropriate utilization in patients most likely to benefit from RT are underway. They include omitting treatment altogether in the elderly and using accelerated, hypofractionated whole-breast irradiation and accelerated PBI. Several randomized studies are underway to help determine the appropriate patients for these shorter treatments. Biology-based approaches are in development.

Summary of Evidence

Of the 117 references cited in the *ACR Appropriateness Criteria® Conservative Surgery and Radiation-Stage I and II Breast Cancer* document, 112 are categorized as therapeutic references including 36 well designed studies, 46 good quality studies, and 3 quality studies that may have design limitations. Additionally, 4 references are categorized as diagnostic references. There are 31 references that may not be useful as primary evidence. There is 1 reference that is a meta-analysis study.

The 117 references cited in the *ACR Appropriateness Criteria® Conservative Surgery and Radiation-Stage I and II Breast Cancer* document were published from 1989-2015.

While there are references that report on studies with design limitations, 82 well designed or good quality studies provide good evidence.

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

Clinical Condition: Conservative Surgery and Radiation—Stage I and II Breast Cancer

Variant 1: Healthy 70-year-old woman, 0.5-cm well-differentiated IDC, ER/PR (+), HER2 (–), left-sided primary excised with lumpectomy, margins (–) <2 mm; endocrine therapy planned.

Treatment	Rating	Comments
Principles of Treatment		
Mastectomy + sentinel lymph node biopsy	9	This procedure can be performed by patient choice with appropriate counseling.
Lumpectomy + sentinel lymph node biopsy + whole-breast RT	9	
Lumpectomy + sentinel lymph node biopsy + accelerated PBI	8	Long-term follow-up is limited.
Lumpectomy + sentinel node biopsy (no RT)	7	
Lumpectomy + sentinel lymph node biopsy (no RT, no endocrine therapy)	2	
RT Doses		
Whole breast: 40–42.5 Gy (15–16 fractions)	9	
Whole breast: 45–50 Gy (23–25 fractions)	9	
Total tumor bed dose: 50 Gy	8	
Whole breast + tumor bed boost: 60 Gy (30 fractions)	9	
Whole breast + tumor bed boost: 64–66 Gy (32–33 fractions)	7	
PBI: 34–38.5 Gy (8–10 fractions over 5 days)	7	Long-term follow-up is limited.
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: Conservative Surgery and Radiation—Stage I and II Breast Cancer

Variant 2: Premenopausal 41-year-old woman, 1.1-cm GII IDC, upper outer quadrant (UOQ), ER/PR (+), HER2 (–), primary excised with lumpectomy, margins (–), SN biopsy negative, BRCA1 mutation positive.

Treatment	Rating	Comments
Principles of Treatment		
Whole-breast irradiation	9	
Completion mastectomy	8	This procedure can be performed by patient choice with appropriate counseling.
Completion mastectomy + contralateral mastectomy	8	This procedure can be performed by patient choice with appropriate counseling.
Partial-breast irradiation	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 3: Postmenopausal 56-year-old woman, 2.5-cm UOQ moderately differentiated, EIC present, SN (–), ER/PR (+), HER2 (–), primary excised with lumpectomy, 1 focus of margin involvement; chemotherapy and antiendocrine therapy planned.

Treatment	Rating	Comments
Principles of Treatment		
Re-excision + whole breast RT if negative margins ± boost	9	
Completion mastectomy	8	This procedure can be performed by patient choice with appropriate counseling.
No further surgery + RT to 66 Gy (33 fractions)	5	This procedure can be performed if re-excision is not feasible or refused.
No further surgery + RT to 60 Gy (30 fractions)	3	Re-excision is highly desirable.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: Conservative Surgery and Radiation—Stage I and II Breast Cancer

Variant 4: Premenopausal 46-year-old woman, 2.6-cm UOQ IDC, primary excised with lumpectomy, margins (–), minimal DCIS, 2/10 LNs (+), level I-II axillary node dissection, ER/PR (–), HER2 (–), BRCA (–), chemotherapy planned, patient desires breast conservation.

Treatment	Rating	Comments
Principles of Treatment		
Whole-breast RT alone	7	
Whole-breast RT + nodal RT	8	Inclusion of the supraclavicular nodes in women with 1-3 positive axillary nodes remains controversial. Although the risk of an isolated supraclavicular recurrence in this setting is generally low, some clinicians recommend adding nodal radiation in select cases based on pathologic and patient-related risk factors.
Completion mastectomy	2	This procedure can be performed if the patient desires elective mastectomy (has no contraindications to breast conservation).
Nodal Radiation Volumes (assume breast RT given)		
Supraclavicular + apical (level III) axillary nodes	8	
Full axilla (level I-III)	2	
IMNs	4	
RT Doses, Negative Margins		
Whole breast: 40–42.6 Gy (15–16 fractions) + 10 Gy boost	4	Minimal data are available for hypofractionated RT in women receiving chemotherapy and in the younger patient population.
Whole breast: 40–42.6 Gy (15–16 fractions) (no boost)	2	There is limited published experience using boost with this fractionation.
Whole breast: 45–50 Gy (23–25 fractions) (no boost)	2	
Whole breast + tumor bed dose: 60–66 Gy (30–33 fractions)	9	
Supraclavicular ± axillary apex: 45–50 Gy (23–25 fractions)	9	
IMN: 45–50 Gy (23–25 fractions)	9	As above, treatment of the internal mammary nodes is controversial. However, if treated, there is uniform consensus that 45–50 Gy is an appropriate dose.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		