Indian J Surg Oncol (April–June 2011) 2(2):101–111
DOI 10.1007/s13193-011-0048-8

ORIGINAL ARTICLE

Radiation Therapy in Early-Stage Invasive Breast Cancer

Ray Lin · Prabhakar Tripuraneni

Received: 13 September 2009 / Accepted: 6 January 2010 / Published online: 6 May 2011

Abstract The treatment of breast cancer involves a multi-disciplinary approach with radiation therapy playing a key role. Breast-conserving surgery has been an option for women with early-stage breast cancer for over two decades now. Multiple randomized trials now have demonstrated the efficacy of breast-conserving surgery followed by radiation therapy. With the advancements in breast imaging and the successful campaign for early detection of breast cancer, more women today are found to have early-stage small breast cancers. Patient factors (breast size, tumor location, history of prior radiation therapy, preexisting conditions such as collagen vascular disease, age, having prosthetically augmented breasts), pathological factors (margin status, tumor size, presence of extensive intraductal component requiring multiple surgical excisions), as well as patient preference are all taken into consideration prior to surgical management of breast cancer. Whole-breast fractionated radiation therapy between 5 and 7 weeks is considered as the standard of care treatment following breast-conserving surgery. However, new radiation treatment strategies have been developed in recent years to provide alternatives to the conventional 5–7 week whole-breast radiation therapy for some patients. Accelerated partial breast radiation therapy (APBI) was introduced because the frequency of breast recurrences outside of the surgical cavity has been shown to be low. This technique allows treatments to be delivered quicker (usually 1 week, twice daily) to a limited volume. Often times, this treatment involves the use of a brachytherapy applicator to be placed into the surgical cavity following breast-conserving surgery. Accelerated hypofractionated whole-breast irradiation may be another faster way to deliver radiation therapy following breast-conserving surgery. This journal article reviews the role of radiation therapy in women with early-stage breast cancer addressing patient selection in breast-conserving therapy, a review of pertinent trials in breast-conserving therapy, as well as the different treatment techniques available to women following breast-conserving surgery.

Keywords Accelerated partial breast irradiation · Breast brachytherapy · Breast-conserving surgery and radiation · Hypofractionated whole-breast radiation · Breast irradiation in early-stage breast cancer

R. Lin · P. Tripuraneni (✉)
Department of Radiation Oncology,
Scripps Clinic and Scripps Green Hospital,
La Jolla, CA, USA
e-mail: prabhakar@tripuraneni.com

Introduction

Breast cancer remains the most commonly diagnosed cancer in women (excluding skin cancer) in the United States and the most developed European countries [1]. Although breast cancer has been known to be major cause of mortality in women living in affluent countries, this disease does not discriminate crossing racial, gender, geographic, and economic lines.

There have been recent reports that the breast cancer incidence and deaths has been increasing worldwide because of the "westernization" of women's risks in low and middle-income countries [54]. Nonetheless, there also have been some encouraging reports that there may be a trend toward decreasing breast cancer incidence in countries where there is a decline in hormone replacement therapy [39, 7]. Furthermore, it has been reported that

breast cancer mortality has fallen in industrialized countries in the last decade [9, 48, 7]. Reasons for declining mortality may include early detection and better treatment.

Treatment of breast cancer does require a multidisciplinary approach. The surgeon, medical oncologist, radiation oncologist, radiologist, and pathologist can all play a role in helping to develop treatment options for the patient. Radiation therapy has a significant part in the treatment of breast cancer, both for noninvasive and invasive cancers.

Breast-conserving surgery (partial mastectomy, lumpectomy, tylectomy, wide local excision, or quadrantectomy) followed by 5–7 weeks of radiation therapy has been known for more than two decades as breast conservation therapy or treatment in the management of early stage breast cancer. As a matter of fact, wide local excision of a breast tumor followed by breast irradiation has been performed as early as 1929 [38, 43]. Initially accepted as a form of breast cancer treatment in Europe, breast conservation therapy is now been accepted throughout the world and has gained popularity in the United States since the early 1980s.

Multiple international trials have clearly demonstrated the efficacy of breast-conserving surgery followed by radiation therapy for early invasive breast cancer [20, 69] [25, 28]. Patients, today, are presenting with even smaller and more favorable tumors than years ago [17]. Additionally, given the improvement in mammographic imaging and the emphasis on early detection and screening, the incidence of patients presenting with noninvasive breast cancer has increased tremendously in recent years, from about 5% to 30% [67]. Other advancements in breast imaging such as digital mammography, magnetic resonance imaging, and molecular imaging such as breast-specific gamma imaging and positron emission mammography will continue to change the landscape in breast cancer screening and detection.

With the advancements in computed tomography imaging (CT), simulation, treatment planning and deliver systems, more accurate and homogenous treatment can now be delivered. Today, radiation therapy options following breasts-conserving surgery may include whole breast radiation, accelerated partial breast radiation with external beam treatment or brachytherapy, and hypofractionated whole breast radiation treatment. Certainly, the role of radiation therapy in early breast cancer will continue to evolve.

Data Supporting Breast Conservation Treatment

Randomized trials worldwide comparing mastectomy to breast-conserving surgery followed by radiation therapy have clearly shown equivalent long-term survival in both groups [25, 28, 69, 51, 60, 11].

The Milan trial was one of the first landmark trials. From 1973 to 1980, 701 women with stage I breast cancer were randomized to radical mastectomy versus breast-conserving surgery (quadrantectomy) with adjuvant whole breast radiation therapy (50 Gy plus a 10 Gy boost). Patients with positive lymph node metastases also received adjuvant chemotherapy consisting of cyclophosphamide, methotrexate, and fluorouracil. There were no significant differences between the two groups in the development of contralateral breast cancers, distant metastases, or second primary cancers. At a median follow-up of 20 years, survival was shown to be equivalent between the two groups. Death rates from breast cancer was 26.1% in the breast conservation arm and 24.3% in the mastectomy arm (p=0.8) [69].

Other landmark European trials comparing mastectomy and breast-conserving treatment included the Institut Gustave-Roussy and the European Organisation for Research and Treatment of Cancer (EORTC) Breast Cancer Collaborative Group. The Institut Gustave-Roussy trial randomized women with 2 cm or smaller tumors to mastectomy or local excision followed by radiation therapy. The 15 year survival was 45% for the mastectomy arm and 55% for the breast-conserving treatment arm. Local recurrences were 14% in the mastectomy arm and 9% in the breast-conserving treatment arm [60]. In the EORTC trial, it was noted again that mastectomy and breast-conserving treatment had similar survival rates [68].

In the United States, the National Surgical Adjuvant Breast and Bowel Project (NSABP) initiated the B-04 study in 1971. A total of 2163 women with breast cancers (4 cm or less) were randomized to one of three treatment arms: total mastectomy, lumpectomy alone, and lumpectomy plus radiation therapy (50 Gy breast only, no boost). Patients with positive lymph nodes also received chemotherapy with melphalan and fluorouracil. Twenty-year follow-up analysis also showed no differences in overall survival in the three arms (p=0.57). However, patients who underwent lumpectomy alone had a 39.2% risk of local recurrence versus 14.3% risk of recurrence in the lumpectomy plus radiation therapy arm. This benefit was independent of the patient's nodal status. Radiation therapy also showed a marginally significant decrease in breast cancer-related deaths when compared to the lumpectomy alone arm [25, 28].

The U.S. National Cancer Institute conducted a prospective randomized trial involving 237 patients with clinical stages I-II breast cancers (T1/2 N0). From 1979 to 1987, patients received either a modified radical mastectomy or lumpectomy with axillary lymph node dissection followed by adjuvant radiation therapy 45–50 Gy breast plus 15–20 Gy boost). Again, after nearly 20 years, no significant differences noted between the two arms in overall survival,

disease-free survival, or the development of contralateral breast cancer [51]. In 1990, the National Cancer Institute made a consensus statement that breast conservation treatment as preferable to a mastectomy in selected patients. 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 because it preserves the breast." [45].

A pooled analysis of published randomized trials was performed comparing breast-conserving surgery with or without adjuvant radiation therapy [73]. Fifteen trials were found with a pooled data of 9,422 patients. The study looked at ipsilateral breast cancer recurrence and death from any cause. The findings were that the relative risk of ipsilateral breast cancer recurrence after breast- conserving surgery comparing patients treatment without and with radiation therapy was 3.00 (95% confidence interval, [CI]= 2.65–3.40. Mortality data from 13 available trials showed an estimated 8.6% (95% CI=0.3–17.5%) relative excess mortality if radiation therapy was not given. A large increase risk of recurrence and a small increase in mortality was noted if radiation therapy was not delivered.

The Early Breast Cancer Trialist's Collaborative Group (EBCTCG) evaluated information from 42,000 women in 78 randomized trials comparing radiotherapy versus no radiotherapy (23,500 subjects), more versus less surgery (9,300 subjects), and more surgery versus radiotherapy (9300 subjects). Radiation therapy was shown to reduce local recurrences in all women irrespective of age or tumor characteristics in all major trials randomizing patients to radiation therapy arm versus the no radiation therapy arm (including trials with and without systemic chemotherapy). Additionally, the older trials were noted to have an excess of non-breast cancer related mortality in women receiving radiotherapy, mainly from heart disease and lung cancer [20].

From the EBCTCG data, 5.4% decrease in breast-cancer mortality was seen in trials randomizing patients after breast-conserving surgery to radiation therapy versus those who did not receive adjuvant radiation therapy. This is a similar benefit seen in many multi-agent chemotherapy trials [20, 56]. There are some who believe that there is evidence that the analysis from the EBCTCG data provides "strong evidence of a causal link between the absolute magnitude of the reduction in local recurrence at 5 years and the absolute magnitude of the improvement in 15-year survival" [55]. Nevertheless, critics feel that such a claim of a causal relationship between reduction in local recurrence and improved survival cannot be made. There is also EBCTCG data showing decreased local-regional recurrence and distant disease with systemic agents [27, 15] in addition to the minimal risk of death attributed to receiving adjuvant radiation therapy [20, 18].

Fortunately, the outcome for patients treated with breast-conserving surgery continues to improve. There have been tremendous advancements in the last decade in surgical techniques, systemic treatment, diagnostic imaging, and radiation therapy delivery systems. Today, for patients with node negative disease, local recurrence for patients undergoing breast-conserving surgery with radiation therapy and systemic chemotherapy has now dropped to about 0.5% annually [14, 15, 16].

Patient Selection in Breast Conservation Treatment

There are clear guidelines in selecting patients who are candidates for breast-conserving therapy. These are readily available and found in American College of Radiology Practice Guidelines and the National Comprehensive Network Practice Guidelines. Most women diagnosed with localized breast cancer are candidates for breast-conserving surgery. However, there are contraindications to breast-conserving therapy including large tumor size to size of breast (although neoadjuvant chemotherapy can sometimes convert ineligible patients to eligible patients for breast-conserving therapy), multicentric breast cancer, diffuse malignant appearing or indeterminate microcalcifications, pregnancy, prior radiation therapy to chest, persistent positive margins after several re-excisions, pacemaker in radiation port that cannot be removed, and morbid obesity exceeding radiation therapy table limit. Having a collagen vascular disease (scleroderma, active lupus) is a relative contraindication to breast-conserving treatment. The American College of Radiology has also published an "appropriateness criteria" on breast conserving- surgery and radiation therapy [75]. Table 1 lists factors to consider when deciding on breast-conserving surgery, summarizing the American College of Radiology's Appropriateness Criteria® on Conservation Surgery and Radiation for Stages I and II Breast Carcinoma.

Breast- Conserving Surgery and Factors Affecting Local Recurrence

At least two-thirds of patients are eligible for breast-conserving surgery at diagnosis [7]. Several factors influence local regional recurrence. Obtaining gross negative margins at the time of surgery is no longer considered acceptable. Margins should be microscopically negative and as wide as feasibly possible. Most surgeons considered a 2–3 mm clear margin to be acceptable. The extensiveness

Table 1 American college of radiology appropriateness criteria® on conservative surgery and radiation: stages I and II breast carcinoma

	CLINICAL EVALUATION
Pregnancy	• Pregnancy, unless terminated, is an absolute contraindication to treatment with RT.
Previous Radiation Therapy	• A history of RT, for which retreatment would result in an excessively high total radiation dose to the breast tissue is a contraindication.
Collagen Vascular Disease	• A history of a preexisting collagen vascular disease is considered an absolute contraindication for BCT by some authors and a relative contraindication by most.
Multiple Lesions	• Multicentricity, such as seen by extensive malignant-appearing microcalcification on mammograms is a contraindication to BCT.
Breast Size	• Very large breasts may require the use of higher energy photons and specialized radiation techniques to minimize dose heterogeneity.
Tumor Size	• 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.
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.
Patient Age	• Young patients have an increased risk of local recurrence compared with older patients. It is not clear that the risk is greater in patients treated with a breast-conserving approach than with mastectomy
Family History	• Family history of breast cancer is not considered a contraindication to BCT
Hereditary Breast Cancer	• Patients require detailed discussions, and informed patients desiring BCT should received counseling on subsequent risk reduction for contralateral breast cancer.
Prosthetically Augmented or Reconstructed Breasts	• The development of significant capsular contracture may be increased after RT.
	PATHOLIGICAL FACTORS
Margins	• The goal of breast-conserving surgery is to achieve negative margins of excision. When margins are microscopically involved, a reexcision should be performed.
Presence of an Extensive Intraductal Component in Infiltrating Ductal Carcinoma	• Patients with EIC-positive tumors with positive or unknown resection margins who undergo BCT have unacceptably high rates of ipsilateral in breast cancer recurrence. These patients should undergo a reexcision to obtain negative margins. If negative margins of excision are obtained around the infiltrating and in situ tumor, the increased risk of recurrence is eliminated and these patients are excellent candidates for BCT.
	PATIENT PREFERANCE
Psychological Adaption	• Each patient must have a thorough discussion of options, addressing their fears and expectations. Patients who undergo BCT, however, have a more positive body image.

of surgical margins does impact local recurrence. The median rates of ipsilateral breast recurrence has been shown in one study to be 2%, 3%, and 6% when margins of clearance were determined clear, 1 mm clear and 2 mm clear [63]. Additionally, mastectomy may become necessary if margins remain positive following several surgical attempts [42].

The presence or absence of extensive intraductal component (EIC) has been traditionally felt to affect local regional recurrence. Holland et al. [34]showed that the presence of EIC is associated with breast cancer recurrence. In a series of 214 patients who underwent a mastectomy, 71% of patients with EIC had residual intraductal tumor, whereas only 28% of patients without EIC had residual disease. Other studies have not shown a significant impact of EIC on local tumor control [19, 24]. Nevertheless, the impact of EIC can be probably be minimized if clear surgical margins are achieved.

In certain studies, young age (usually 40, 35, or 30 years or less) has been associated with an increase risk of ipsilateral tumor recurrence following breast-conserving surgery [30] [72, 46]. However, many of these studies also show young age to correlate with other high risk features such as high grade and the presence of EIC [40, 21]. A boost dose delivered to the surgical cavity following whole breast radiation therapy is particularly significant for younger patients since higher doses tend to correlate with lower recurrences. In the landmark EORTC trial, the addition of 16 Gy boost to the tumor bed significantly reduced local recurrence for patients younger than 50 years at 5 years (19.5% to 10.2%, $p=0.002$) [5]. At ten-year follow-up, of 5318 patients (all ages) evaluated after a microscopically complete lumpectomy, the recurrences were 10.2% in the 0 Gy boost arm and 6.2% in the 16 Gy boost arm ($p<0.0001$). No statistically significant interaction per age group was noted at this time, but there was a trend toward

earlier recurrences in younger women. Nonetheless, the benefit of a boost decreased with increasing age [52]. The EORTC's evaluation of 251 patients on whether 26 Gy had a greater benefit than 10 Gy in patients with microscopically incomplete lumpectomy did not show a statistically significant benefit with the higher dose (10-year 17.5% relapse, lower dose versus 10.8% relapse, higher dose, $p>0.1$). More fibrosis was seen in the higher dose arm [53].

Outcomes of breast-conserving surgery and radiation therapy in patients who are BRCA 1/2 mutation carriers versus that of matched controls has been studied. In one publication, there was no significant differences in ipsilateral breast tumor recurrence between carriers and controls at 10 years [50]. Not surprisingly, the risk of developing contralateral breast cancers was higher in the carrier arm. The use of tamoxifen did reduce the incidence of developing contralateral breast cancers.

Systemic therapy has been shown in several studies to also decrease local tumor recurrence following breast-conserving surgery [26, 59, 25, 28]. Factors that may or may not influence local recurrence (with conflicting data) include tumor size, nodal status, hormone receptor status, BRCA1-2 status, and lobular histology.

External Beam Radiation Therapy

External beam radiation therapy typically begins 3 to 6 weeks following surgery unless systemic chemotherapy is given. Treatment planning starts with the simulation process. At this time, breast boards, wing boards, or customized cradles or molds are created or fitted to the individual patient. This allows the patient to be in reproducible position with each treatment. Patients are typically placed in the supine position with their torso angled 10–15°. The ipsilateral arm is abducted usually between 100 and 120° and the shoulder is externally rotated. At this time, radio opaque wires are placed and secured along the surgical scars. The radiation oncologist then defines the treatment field (borders of the breast/target/regional lymph nodes if needed). CT simulation is performed. The isocenter can be selected and the daily set-up marks are placed on the patient's skin. Three-dimensional treatment planning is done. The treatment volumes and critical structures are outlined. Optimal beam arrangements are chosen. The goal is to deliver the prescribed dose to the target with a homogenous dose distribution, minimizing cold and hot spots, to minimize doses delivered to critical structures (typically lungs and heart), and minimize the volumes of the critical structures in the treatment fields.

For early stage breast cancer, tangential fields that include the most anterior thorax are typically used. These fields can include level I and II lymph node chains (good CT planning can confirm this). Attention to tangent field borders especially cranial and posterior chest-wall interface is important if most of levels I and II axillary nodes are to be included [62]. Radiation therapy to the supraclavicular fossa plus or minus a posterior axillary boost is sometimes offered to certain patients (typically those with undissected nodes, four or more lymph node metastases or select patients with one to three positive nodes). There is no general consensus on when to radiate the lymph nodes or whether to include the internal mammary lymph nodes, but there are studies that show varying degrees of benefit when radiation is delivered to the regional lymph nodes [29, 41, 58]. For premenopausal women with any lymph node metastases, there is some suggestion that radiation to the regional lymph nodes may not only decrease local recurrence, but also give a survival benefit. This is inferred from the Danish and British Columbia postmastectomy phase III studies showing the benefits of radiation to the chest wall and lymphatics in premenopausal women [47, 57]. A typical supraclavicular field is a half-beam block field matched to the tangents with the beam angled 10–15° away from the cord. A table kick is utilized for the tangential fields to account for the divergence of the beam into the supraclavicular field. The posterior axillary beam supplements doses to the midaxillary plane. Pierce et al. discusses several techniques in treating the internal mammary nodes [49].

Four to six MV photon energy is most commonly selected for treating the breast and lymph nodes. Whole breast radiation treatments are administered Monday through Friday, delivering approximately 50 Gy in 25 to 28 fractions. For the boost treatment, electrons typically are used. The lumpectomy cavity is boosted for another 10–16 Gy at 1.8 to 2 Gy per fraction.

New advances in radiation treatment planning and delivery have led to the development of intensity modulated radiation therapy (IMRT) or forward planning IMRT to treat the breast. The dose to the contralateral breast is reduced with IMRT [12]. By conforming doses along the breast and blocking normal structures with multi-leaf collimators, the normal structures like the lungs or heart for left sided breast cancer treatment also receive reduced doses. The dose to the breast could be more homogenous with concave isodose curves, conforming to the target. Studies have shown that forward planning IMRT when compared to standard radiotherapy, can produce homogenous plans with fewer hot spots [4, 33] This could particularly benefit large-breasted women or those with large breast separation. Whether this translates to better cosmetic outcomes is unknown until these trials mature.

In some elderly patients particularly those over 70 years of age with early disease who receive adjuvant hormonal

therapy, breast-conserving surgery alone may be considered. There could be biological differences in the tumors in some elderly women. Additionally, some elderly patients tend to have more transportation, social, and other health-related issues that may affect their ability to receive daily radiation therapy. The Canadian trial [31] and the Cancer and Leukemia Group B (CALGB/Radiation Therapy Oncology Group (RTOG)/Eastern Cooperative Oncology Group (ECOG) trial [36, 65, 31] both randomized older women with estrogen-receptor-positive early breast cancer following breast-conserving surgery to tamoxifen with or without radiation therapy. Although both trials showed absolute benefits to women receiving radiation therapy, the benefits overall were small. Certainly, other more convenient treatment schedules and options for older women with breast cancer could be offered. These are discussed in the next section. A summary of the techniques and guidelines for breast radiation following breast-conserving surgery is also listed in Table 2.

Breast Brachytherapy and Partial Breast Radiation

The many trials supporting breast-conserving surgery followed by adjuvant radiation therapy have also shown that the risk of recurrence outside the tumor cavity is similar whether or not whole breast radiation was given. [25, 28, 69, 35]. This suggests that additional radiation given outside the tumor cavity may not be of additional benefit to patients.

Breast brachytherapy was historically used to treat the lumpectomy cavity as a "boost" following external whole breast radiation therapy. Many centers have now adapted the use of accelerated partial breast radiation therapy, either with interstitial needle implants, various applicators (i.e. Mammosite balloon, Contoura multilumen balloon, Savi, Xoft), or even through the use of 3D conformal external radiation therapy as the sole radiation treatment modality following breast-conserving surgery. By radiating less volume (the partial breast), higher radiation doses can be given per fraction to the tumor bed. This shortens treatment times significantly, decreasing the patient's travel time when compared to daily whole breast radiation therapy.

Patients are potential candidates for accelerated partial breast radiation therapy if they have Stage 0, I, or II tumors, with a single tumor less than 3 cm in maximum dimension. Minimal nodal involvement and clear surgical margins are also required. Typically, partial breast radiation is delivered twice a day, with each treatment separated at least 6 hours apart, for a total of ten fractions.

Interstitial breast brachytherapy alone has been successfully used at some US centers for over 10 years following

Table 2 Guidelines for breast radiation therapy following breast conservative surgery

Type of radiations		
Dose	Indication/other considerations	Comment
Whole Breast Conventional		
4,500–5,040 cGy at 180–200 cGy/fraction	Observation without radiation could be considered for elderly patients with stage 1 ER positive tumor	
Accelerated Partial Breast Radiation		
3,400–3,850 cGy at 340–380 cGy/fraction	External beam conformal, interstitial or catheter/balloon based brachytherapy; consider protocol	Usually twice daily, spaced greater than 6 h apart
Hypofractionated Whole Breast		
4,250 cGy at 266 cGy/fraction	Patient convenience, breast size	Omit nodal radiation
Boost		
1,000–1,600 cGy at 180–200 cGy/	Following whole breast radiation. Using En Face electrons typically	May consider omitting boost for elderly patients with widely clear margins
Nodal Irradiation		
4,500–5,040 cGy at 180–200 cGy/fraction	For those women with greater than 4 positive lymph nodes or 1–3 positive lymph nodes with high risk features, or for those with inadequate nodal sampling or without axillary sampling	Some may elect to treat internal mammary nodes (usually considered for medial tumors with positive axillary nodes or those with internal mammary nodal drainage based on imaging/lymphosintigraphy)

breast-conserving surgery. A trial was started by Vicini, et al. in 1993 using brachytherapy as the only radiation treatment modality for patients following breast-conserving surgery [70]. By 2001, 120 patients were enrolled in this trial. Four patients developed local recurrence at a median follow-up of 82 months. During 1997–2000, 100 patients were enrolled in a Radiation Therapy Oncology Group (RTOG), prospective Phase I/II study of breast brachytherapy. Patients were either high-dose or low-dose-rate brachytherapy. For the high-dose-rate group at a median follow-up of 6.14 years; 5-year estimates of ipsilateral breast, regional, and contralateral breast failures were 3%, 5%, and 2% respectively. For patients receiving low-dose-rate brachytherapy at a median follow-up of 6.22 years; 5-year estimates of ipsilateral breast, regional, and contralateral breast failures were 6%, 0%, and 6%, respectively. Both groups experienced good cosmesis and local control [3]. Several institutions have shown low recurrences with brachytherapy at 5 and 10 years [2, 6]

In 2002, the FDA approved Proxima Therapeutics MammoSite® balloon catheter for intra-cavitary high dose rate breast brachytherapy. Seventy patients were initially enrolled in a prospective multi-center trial evaluating the safety of the MammoSite® balloon catheter. Subsequent evaluation of 43 patients eligible for the therapy revealed only mild to moderate self-limited side effects [37]. Most recently, the American Society of Breast Surgeons reported results from their registry trial involving 1,440 women treated with the MammoSite® catheter following breast-conserving surgery. The 3-year actuarial rates of ipsilateral breast cancer and axillary recurrences were 2.15% and 0.36%, respectively. Cosmetic outcomes were reported to be acceptable and similar to patients treated with other forms of partial breast irradiation [44]. The advantages of the balloon catheter are that it is easier to place in the cavity, placement is more reproducible, and patient comfort is improved. Thus, it has become the most widely used device [66] and has the longest track record. The single catheter needs to be temporarily placed in the lumpectomy cavity, as opposed to 10–20 catheters with traditional interstitial implants. However, the balloon needs to "conform" properly to the tumor cavity and optimal dosimetry could be problematic if a large air pocket develops along the periphery of the cavity. The dose distribution is spherical or elliptical depending on the balloon chosen. Balloon-skin spacing should be at least 7 mm. Additionally, MammoSite® balloon catheters may not be appropriate for tumors near the skin surface. The American Society of Breast Surgeons showed that skin spacing in addition to the use of chemotherapy and breast wound infection were the most important factors of cosmesis at 36 months in their MammoSite® Breast Brachytherapy Registry Trial [32].

Many other applicator devices have come onto the market in recent years, with the advantages of having the potential for improved dosimetry in select patients when compared to the MammoSite applicator. The Contura™ Multi-Lumen Balloon catheter allows multiple offset lumens to provide dose shaping opportunities to reduce skin and rib doses [13]. This product may have the advantages of using a balloon type applicator, in which many surgeons and radiation oncologists are familiar and comfortable with. Additionally, air and blood around the cavity could be removed with the Contura™ catheter before treatment, potentially reducing air pockets and seroma formation. However, dosimetry is still limited to the confines of a "balloon catheter."

The ClearPath™ multicatheter device is one of the newest brachytherapy devices available. The catheter is placed through a single entry point but without the constraints of having a single radiation source. The use of a multicatheter hybrid can reduce doses to the skin and normal tissues in the breast when compared to a single catheter systems [22, 23, 10]. Both high-dose-rate as well as low-dose continuous release brachytherapy can be delivered. Facilities without high-rate-rate equipment can now offer brachytherapy. Additionally, patients can get continuous release treatments at home without having to make twice-daily trips to the treatment facility. Strands of I-125 seeds are inserted in the outer catheters. Patients must wear a fully shielded bra if low-dose continuous release treatment s given. Certainly, there are more safety concerns when continuous release delivery is given outside of the treatment facility.

Another recent addition to the radiation therapy armamentarium is the SAVI device, a single-entry multicatheter applicator which allows a radiation oncologist to selectively direct radiation through up to eleven catheter channels, allowing more tailored manipulation of the isodose lines. The device is a bundle of expandable catheters around a central lumen. This applicator tries to blend in the advantages of interstitial brachytherapy with a single-entry device. Dose feathering could be done along the skin and chest. Studies have shown the device to give good tumor bed conformance with minimal normal tissue exposure [61]. Patient positioning as well as maintaining a consistent inter-fraction position is important. A potential disadvantage is that removal of the device may be more difficult when compared to the smaller balloon type catheters.

The Xoft Axxent electronic breast brachytherapy device is also a new type of partial breast radiation device using an electronic source to produce X-rays. This treatment does not require a high-dose-rate afterloader nor does it require a shielded vault. It has been associated with delivering less dose to normal tissues and increased "hot spots" to the tumor bed when compared to MammoSite® applicator (A.

[22]). The treatment delivery system may be portable with the potential to bring one delivery system to multiple facilities, thus reducing cost.

Three-dimension (3D) conformal radiation technology has been developed and improved upon in recent years. This technique of accelerated partial breast radiation has the advantage of being noninvasive, eliminating an additional procedure, allowing many medical groups that do not perform brachytherapy to offer partial breast radiation therapy. No adverse side effects were seen in 28 patients treated with 3D conformal radiation in a 1999 pilot study [71]. A potential disadvantage is that the breast is not a stationary target and there is the potential for a geographical miss with external radiation therapy to a small target.

In 2005, the National Surgical Adjuvant Breast and Bowel Project (NSABP) along with RTOG activated a Phase III randomized trial studying whole breast radiation therapy versus partial breast radiation therapy for women with Stages 0, I, and II breast cancer. The trial is expected to accrue 3000 patients over a period of approximately 2–3 years. This trial will be comparing overall survival, recurrence-free survival, distant recurrence-free survival, and quality of life issues between women receiving whole and accelerated partial breast radiation therapy.

Most recently, the American Society for Radiation Oncology (ASTRO) released a consensus statement regarding the use of APBI stating "patients who choose treatment with APBI should be informed that whole-breast irradiation is an established treatment with a much longer track record that has documented long-term effectiveness and safety." A task force composing of experts in breast radiation proposed three groups of patients when considering APBI: 1.) a "suitable" group for whom APBI outside of a clinical trial is acceptable. 2). a "cautionary" group where caution and concern should be applied when considering APBI outside of a clinical trial and 3) an "unsuitable" group for whom APBI outside of a clinical trial is not considered warranted [64]. A breakdown of the

Table 3 Astro's task force consenses tables for: patients approved as "Suitable", "Cautionary" or "Unsutiable" candiates for APBI

Factor	Patients "Suitable" for APBI if all criteria are present Criterion	"Cautionary" group: any of these criteria should invoke caution and concern when considering APBI Criterion	Patients "Unsuitable" for APBI outside of a clinical trial if any these criteria are present Criterion
Patient factors			
Age	≥60 y	50–59 years	<50 years
BRCA 1/2 mutation	Not present		Present
Pathologic factors			
Tumor size	≤2 cm	2.1–3.0 cm	>3 cm
T stage	T1	T0 or T2	T3-4
Margins	Negative by at least 2 mm	Close (<2 mm)	Positive
Grade	Any		
LVSI	No	Limited/focal	Extensive
ER status	Positive	Negative†	
Multicentricity	Unicentric only		Present
Multifocality	Clinically unifocal with total size ≤2.0 cm‡	Clinical unifocal with total size 2.1–3.0 cm ‡	If microscopically multifocal >3 cm in total size or if clicnically multifocal
Histology	Invasive ductal or other favorable subtypes§	Invasive lobular	
Pure DCIS	Not allowed	≤3 cm	If >3 cm in size
EIC	Not allowed	≤3 cm	If >3 cm in size
Associated LCIS	Allowed		
Nodal factors			
N stage	*pNO (¡-, ¡+)*		pN1, pN2, pN3
Nodal surgery	*SN Bx or ALND*		None performed
Treatment factors			
Neoadjuvant therapy	Not allowed		If used

Adaptation From: Smith BD, Arthur DW, Buchholz, TA, et al. "Accelerated partial breast consensus statement from the American Society for Radiation Oncology (ASTRO)." Int J Radiat Oncol Biol Phys 74, no. 4 (July 2009): 987–1001

three groups in listed in Table 3, an adaptation of ASTRO's Task Force Consensus Grouping Tables.

Hypofractionated Whole-Breast Irradiation

Hypofractionated whole-breast irradiation therapy allows radiation therapy to delivery in fewer fractions over a shorter period of time and with less cost. This may be another option for women may not have the time or resources to undergo several weeks of conventional external radiation therapy. This form of treatment delivery was introduced in Canada and the United Kingdom over a decade ago. Randomized trials have shown hypofractionated whole-breast treatments results in equivalent outcome in both local control and cosmesis when compared to conventional whole-breast irradiation [76, 8, 74]. The large Canadian trial involved 1234 patients with T1 or T2 N0 breast cancer randomized to whole breast irradiation 50 Gy in 25 fractions (standard arm) versus 42.50 Gy in 16 fractions. Patients were excluded if tumors were >5 cm, more than one tumor, greater than 25 cm breast separation, presence of positive margins, or unknown nodal status. Five-year local recurrence-free survival was 97.2% in the hypofractionated arm and 96.8% in the standard arm [74]. The ten-year follow-up data was presented at the 50th annual ASTRO meeting in Boston plenary session. Local recurrence was 6.2% in the hypofractionated arm and 6.7% in the standard arm. Cosmesis at 10 years was rated excellent in 70% of the hypofractionated arm and 71% in the standard arm. Of note, a "boost" treatment was not given in either arms to reduce confounding variables.

The Standarisation of Breast Radiotherapy Trial B (START) in the United Kingdom involved over 2215 women with T1-T3a N0-1 breast cancer. Women were randomized after surgery to receiving 50 Gy in 25 fractions or 40 Gy in 15 fractions in 23 centers. At a median follow-up of 6 years, the rate of local relapse at 5 years was 2.2% in the 40 Gy arm and 3.3% in the 50 Gy arm. Late adverse effects were noted to be lower in the 40 Gy arm through photographic and patient self-assessments [8].

Finally, hypofractionated radiation to the breast could certainly be a more cost-effective treatment, reducing staffing needs and equipment time, in addition to making therapy less burdensome for patients since it requires fewer visits. Hypofractionated treatment for such a common malignancy worldwide could significantly reduce healthcare costs. However, more research is needed, particularly looking at long-term results, the use of a "boost" treatment, the impact of chemotherapy, the use of hypofractionation in more locally advanced cases, and the use of hypofractionation in larger sized patients (wider separation).

Conclusion

Improvements have been made in early detection and the treatment of breast cancer in recent years. Advancements in diagnostic imaging allowing better target delineation in radiation therapy planning and in treatment delivery systems will continue to change the way this disease is treated. Multiple radiation treatment techniques are now available for selected patients following breast-conserving surgery. Additional research into providing more conformal and/or faster therapy may one day change the way radiation oncologists manage early-stage breast cancer patients. Whole and partial breast irradiation with varying fractionations schemes will continue to evolve, hopefully to make treatments more economical and fiscally more responsible. Intraoperative breast irradiation delivering one fraction of therapy following surgery is even being studied. Additionally, radiation therapy to the axilla in lieu of surgery is also being explored.

Breast cancer itself is such a heterogeneous disease. There are many risk factors associated with this disease including family history, germ-line mutations, age, hormonal associations, and lifestyle choices. Additionally, this disease can present and vary so differently form one patient to another. Proper patient selection for any type of treatment is vital, ensuring to protect patients from not only under treatment but also overtreatment of this disease. Molecular profiling and clinically assays for radio sensitivity and tumor aggressitivity may 1 day help oncologists decide on not only how to treat, but who to treat.

References

1. American Cancer Society (2008) Cancer facts and figures. American Cancer Society, Atlanta
2. Antonucci J, Wallace M, Goldstein N et al (2009) Differences in patterns of failure in patients treated with accelerated partial breast irradiation versus whole-breast irradiation: a matched-pair analysis with 10-year follow-up. Int J Radiat Oncol Biol Phys 74(2):447–452
3. Arthur D, Winter K, Kuske R et al (2008) A phase II trial of brachytherapy alone after lumpectomy for select breast cancer: tumor control and survival outcomes of RTOG 95–17. Int J Radiat Oncol Biol Phys 72(2):463–473
4. Barnett GC, Wilkinson J, Moody AM et al (2009) A randomised controlled trial of forward-planned radiotherapy (IMRT) for early breast cancer: baseline characteristics and dosimetry results. Radiother Oncol Epub (ahead of publication)
5. Bartelink H, Horiot JC, Poortmans P et al (2001) Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. N Engl J Med 345 (19):1378–1387

6. Benitez P, Keisch M, Vicini F et al (2007) Five-year results: the initial clinical trial of MammosSite balloon brachytherapy for partial breast irradiation in early-stage breast cancer. Am J Surg 194(4):456–462
7. Benson JR, Jotoi I, Keisch M et al (2009) Early breast cancer. Lancet 373:1463–1479
8. Bentzen SM, Agrawal RK, Aird EG et al (2008) The UK Standarisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet 371(9618):1098–1107
9. Beral V, Hermon C, Reeves G et al (1995) Sudden fall in breast cancer death rates in England and Wales. Lancet 356(8965):1670–1674
10. Beriwal S, Coon D, Kim H et al (2008) Multicatheter hybrid breast brachytherapy: a potential alternative for patients with inadequate skin distance. Brachytherapy 7(4):301–304
11. Blichert-Toft M, Nielsen M, During M et al (2008) Long-term results of breast conserving surgery vs. mastectomy for early stage breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol. Acta Oncol 47(4):672–681
12. Borghero YO, Salehpuor M, McNeese MD et al (2007) Multileaf field-in-field forward-planned intensity-modulated dose compensation for whole-breast irradiation is associated with reduced contralateral breast dose: a phantom model comparison. Radiother Oncol 82(3):324–328
13. Brown S, McLaughlin M, Pope K et al (2009) Initial radiation experience evaluating early tolerance and toxicities in patients undergoing accelerated partial breast irradiationusing the Contura Multi-Lumen Balloon breast brachytherapy catheter. Brachytherapy 8(2):227–233
14. Buchholz TA (2009) Radiation therapy for early-stage breast cancer after breast-conserving surgery. N Engl J Med 360(1):63–70
15. Buchholz TA, Tucker SL, Erwin J et al (2001) Impact of systemic treatment on local control for patients with lymph node-negative breast cancer treated with breats-conservation therapy. J Clin Oncol 19(8):2240–2246
16. Cabioglu N, Hunt KK, Buchholz TA et al (2005) Improving local control with breast-conserving therapy: a 27-year single-institution experience. Cancer 104(1):20–29
17. Cady B, Stone MD, Schuler JG et al (1996) The new era in breast cancer: invasion, size, and nodal involvement dramatically decreasing as a result of mammographic screening. Arch Surg 131(3):201–308
18. Cady B (2007) Local therapy and survival in breast cancer (comment to editor). N Engl J Med 357(10):1051
19. Clarke DH, Le MG, Sarrazin D et al (1985) Analysis of local-regional relapses in patients with early breast cancer treated by excision and radiotherapy: experience of the Institut Gustave-Roussy. Int J Radiat Oncol Biol Phys 11(1):137–145
20. Clarke M, Collins R, Darby S et al (2005) Effects of radiotherapy and of differences in the extent of surgery for earl breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 366(9503):2087–2106
21. Delouche G, Bachelot F, Premont M et al (1987) Conservation treatment of early stage breast cancer: long term results and complications. Int J Oncol Biol Phys 13(1):29–34
22. Dickler A (2009) Xoft Axxent electronic brachytherapy: a new device for delivering brachytherapy to the breast. Nat Clin Pract Oncol 6(3):138–142
23. Dickler A, Seif N, Kirk M et al (2009) A dosimetric comparison of MammoSite and ClearPath high-dose-rate brachytherapy devices. Brachytherapy 8(1):14–18
24. Fisher B, Anderson S (1994) Conservative surgery for the management of invasive and noninvasive carcinoma of the breast: NSABP trials. National Surgical Adjuvant Breast and Bowel Project. World J Surg 18(1):63–69
25. Fisher B, Anderson S, Bryant J et al (2002) Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 347(16):1233–1241
26. Fisher B, Dignam J, Bryant J et al (1996) Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-postive tumors. J Natl Cancer Inst 88(21):1529–1542
27. Fisher B, Stewart JA (2007) Local therapy and survival in breast cancer (comment to editor). N Engl J Med 356(10):1051
28. Fisher BJ, Bryant J, Dignam J et al (2002) Tamoxifen, radiation therapy, or both for the prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. J Clin Oncol 20(20):4141–4149
29. Fowble B, Solin LJ, Schultz DJ et al (1989) Frequency, sites of relapse, and outsome of regional node failures following conservative surgery and radiation for early breast cancer. Int J Radiat Oncol Biol Phys 17(4):703–710
30. Fowble BL, Schultz DJ, Overmoyer B et al (1994) The influence of young on outcome in early stage breast cancer. Int J Radiat Oncol Biol Phys 30(1):23–33
31. Fyles AW, McCready DR, Manchul LA et al (2004) Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med 351(10):963–970
32. Goyal S, Khan AJ, Vicini F, et al (2009) Factors associated with optimal cosmetic results at 36 months in patients treated with accelerated partial breast irradiation (APBI) on the American Society of Breast Surgeons (ASBrS) MammoSite ® Breast Brachytherapy Registry Trial. Ann Surg Oncol [Epub ahead of print]
33. Harris JS, Neill CJ, Rosser PF (2008) A comprehensive clinical 3-dimensional dosimetric analysis of forward planned IMRT and conventional wedge planned wedged techniques for intact breast radiotherapy. Med Dosim 33(1):62–70
34. Holland R, Connolly JL, Gelman R et al (1990) The presence of extensive intraductal component component following a limited excision correlates with prominent residual disease in the remainder of the breast. J Clin Oncol 8(1):113–118
35. Holli K, Saaristo R, Isalo J et al (2001) Lumpectomy with or without postopertive radiotherapy for breast cancer with favorable prognostic features: results of a randomized study. Br J Cancer 84 (2):164–169
36. Hughes KS, Schnaper LA, Berry D et al (2004) Lupectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med 351(10):971–977
37. Keisch M, Vicini F, Kuske R et al (2003) Initial clinical experience with the Mammo Site breast brachytherapy applicator in women with early-stage breast cancer treated with breast-conserving therapy. Int J Radiat Oncol Biol Phys 55 (2):289–293
38. Keynes G (1954) Carcinoma of the breast, the unorthodox view. Proc Cardiff Med Soc 40
39. Kumle M (2008) Declining breast cancer incidence with decreased HRT use. Lancet 372(9639):608–610
40. Kurtz JM, Spitalier JM, Amalric R et al (1988) Mammary recurrences in women younger than forty. Int J Radiat Biol Phys 15(2):271–271
41. Mehta K, Haffty BG (1996) Long-term outcome in patients with four or more positive lymph nodes treated with conservative surgery and radiation therapy. Int J Radiat Oncol Biol Phys 35 (4):679–685
42. Morrow M, Harris JR (2007) Practice guidelines for breast-conserving therapy in the management of invasive breast cancer. J Am Coll Surg 205:362–372
43. Murley R (1986) Breast cancer: Keynes and conservatism. Br J Clin Pract 40:49–58

44. Nelson J, Beitsch P, Vicini F et al (2009) Four-year clinical update from the American Society of Breast Surgeons MammoSite brachytherapy trial. Am J Surg 198(1):83–91
45. NIH Office of the Director: NIH Concensus Statement (2000) 4: 17
46. Nixon AJ, Neuberg D, Hayes DF et al (1994) Relationship of patient's age to pathologic features of the tumor and prognosis for patient's with stage I or II breast cancer. J Clin Oncol 12(5):888–894
47. Overgaard M, Hansen PS, Overgaard J et al (1997) Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. N Engl J Med 337 (14):945–955
48. Peto R, Boreham J, Clarke M et al (2000) UK and USA breast cancer deaths down 25% in year 2000 at ages 29–69 years. Lancet 355(9217):1822
49. Pierce LJ, Butler JB, Martel MK et al (2002) Postmastectomy radiotherapy of the chest wal: dosimetric comparision of common techniques. Int J Radiat Oncol Biol Phys 52(5):1220–1230
50. Pierce LJ, Levin AM, Rebbeck TR et al (2006) Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA 1/2-associated stage I/II breast cancer. J Clin Oncol 24 (16):2437–2443
51. Poggi MM, Danforth DN, Sciuto LC et al (2003) Eighteen-year results in the treatment of early breast carcinoma with mastectomy versus breast conservation therapy: the National Cancer Institute Randomized Trial. Cancer 98(4):697–702
52. Poortmans PM, Collette L, Bartelink H et al (2008) The addition of a boost dose on the primary tumour bed after lumpectomy in breast conserving treatment for breast cancer. A summary of the results of the EORTC 22881–10882:boost versus no boost trial. Cancer Radiothér 12(6–7):565–570
53. Poortsman PM, Collette L, Horiot JC et al (2009) Impact of boost dose of 10 Gy vesus 26 Gy in patients with early stage breast cancer after a microscopically incomplete lumpectomy: 10-year results of the randomised EORTC boost trial. Radiother Oncol 90 (1):80–85
54. Porter P (2008) Westernizing womens' risks? Breast cancer in lower-income countries. N Engl J Med 358(3):213–216
55. Puglia RS, Morrow M, Harris JR (2007) Local therapy and survival in breast cancer. N Engl J Med 357(10):1051–1052, author reply
56. Punglia RS, Morrow M, Winer EP et al (2007) Local therapy and breast cancer. N Engl J Med 356(23):2399–2405
57. Ragaz J, Olivotto IA, Spinelli JJ et al (2005) Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst 97(2):116–126
58. Recht A, Pierce SM, Abner A et al (1991) Regional nodal failure after conservative surgery and radiotherapy for early-stage breast cancer. J Clin Oncol 9(6):988–996
59. Rutqvist LE, Cedermark B, Glas U et al (1992) Randomized trial of adjuvant tamoxifen in node negative postmenopausal breast cancer. Acta Oncol 31(2):265–270
60. Sarrazin D, Le MG, Arriagada R et al (1989) Ten-year results of a randomized trial comparing a conservative treatment to mastectomy in early breast cancer. Radiother Oncol 14(3):177–184
61. Scanderbeg J, Yashar C, Rice R et al (2009) Clinical implementation of a new brachytherapy device for partial breast irradiation. Radiother Oncol 90(1):36–42
62. Schlembach PJ, Buchholz TA, Ross MI et al (2001) Relationship of sentinel and axillary level I and II lymph nodes to tangential fields used in breast irradiation. Int J Radiat Oncol Biol Phys 51 (3):671–678
63. Singletary SE (2002) Surgical margins in patients with early stage breast cancer treated with breast conservation therapy. Am J Surg 184:383–393
64. Smith BD, Arthur DW, Buchholz TA et al (2009) Accelerated partial breast consensus statement from the American Society for Radiation Oncology (ASTRO). Int J Radiat Oncol Biol Phys 74 (4):987–1001
65. Smith BD, Gross CP, Smith GL et al (2006) Effectiveness of radiation therapy for older women with early breast cancer. J Natl Cancer Inst 98(10):681–690
66. Streeter O, Vicini F, Keisch M et al (2003) MammoSite ® radiation therapy system. Breast 12(6):491–496
67. Taghian AG, Powel SN (1999) The role of radiation therapy for primary breast cancer. Surg Clin North Am 79(5):1091–1115
68. van Dongen JA, Bartelink H, Fentiman IS et al (1992) Randomized clinical trial to assess the value of breast conserving therapy in stage I and II breast cancer, EORTC 10801 trial. J Natl Cancer Inst Monogr: 15–18
69. Veronesi U, Cascinelli N, Mariani L et al (2002) Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 347(16):1227–1232
70. Vicini F, Baglan K, Kestin L et al (2001) Accelerated treatment of breast cancer. J Clin Oncol 19(7):1993–2001
71. Vicini F, Remouchamps V, Wallace M et al (2003) Ongoing clinical experience utilizing 3-D conformal external beam radiotherapy to deliver partial-breast irradiation in patients with early-stage breast cancer treated with breast-conserving surgery. Int J Radiat Oncol Biol Phys 57(5):1247–1253
72. Vicini FA, Recht A, Abner A et al (1992) Recurrence in breast following conservative surgery and radiation therapy for early-stage breast cancer. J Natl Cancer Inst Monogr (11): 33–39
73. Vinh-Hung V, Verschraegen C (2004) Breast-conserving therapy with or without radiotherapy:pooled analysis for risks of ipsilateral breast tumor recurrence and mortality. J Natl Cancer Inst 96 (2):115–121
74. Whelan T, MacKenzie R, Julian J et al (2002) Randomized trial of breast irradiation schedules after lumpectomy in womenwith lymph node-negative breast cancer. J Natl Cancer Inst 94 (15):1143–1150
75. White J, Halberg F, Rabinovitch R et al (2008) American College of Radiology Appropriateness Criteria® on conservation surgery and radiation: stages I and II breast carcinoma. J Am Coll Radiol 5(6):701–713
76. Yarnold J, Ashton A, Bliss J et al (2005) Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trail. Radiother Oncol 75(1):9–17