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LOCALLY ADVANCED BREAST CANCER

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Summary of Literature Review

Introduction/Background

In this document, locally advanced breast cancer (LABC) includes bulky primary breast tumors (large tumors or those involving the skin or chest wall) and breast cancers with extensive lymphadenopathy, as defined by the American Joint Committee on Cancer staging system [1]. Patients with LABC have historically had a poor prognosis, and some are initially inoperable. They include patients with clinical T3 and T4 and evidence of multiple (≥4) or matted axillary lymph nodes (N2) and/or involvement of the second-echelon nodal basins including infraclavicular, supraclavicular, and internal mammary lymph nodes (IMN). A clinically distinct but similarly high-risk type of LABC is inflammatory breast cancer (IBC). This definition for LABC was chosen as a way to integrate with the ACR Appropriateness Criteria® topics on "Local Regional Recurrence and Salvage Surgery — Breast Cancer [2]" and "Postmastectomy Radiotherapy [3]." The discussion for this topic is limited to avoid significant overlap with the other 2 topics.

Overall, LABC is recognized to be a heterogeneous group with wide variability in the disease presentation at diagnosis, ie, large primary tumor with/without involvement of skin and/or chest wall and metastases to lymph nodes ranging from minimal to extensive regional nodal burden. Within the different groups of LABC, there are also prognostically distinguishable biologic subtypes with varied response to systemic therapy. Finally, LABC is associated with a significant risk for systemic disease. Therefore, treatment of LABC must include 2 major goals: control of locoregional disease and eradication of occult systemic metastases. Hence, management of LABC requires a multimodality approach and therapy tailored to risk.

Accurate staging of the extent of the primary cancer, regional node involvement, and distant disease is an important initial step in the management of LABC. Breast imaging is important to determine the extent of primary disease and to evaluate for multifocal, multicentric, or contralateral breast cancer. A bilateral diagnostic mammogram with compression or magnification views if needed is essential for all breast cancer patients. Ultrasound (US) may provide additional information regarding breast malignancy and can also be used to evaluate the axilla. US-guided biopsy can be performed for enlarged lymph nodes or lymph nodes demonstrating architectural distortion. The sensitivity of US is low, and therefore patients with negative axillary lymph nodes by US will still require surgical evaluation with sentinel lymph node biopsy or axillary lymph node dissection. Magnetic resonance imaging has been increasingly used and recognized as an important tool in evaluating the extent of disease for LABC. It is useful for detecting abnormal lymph nodes, involvement or proximity to chest wall, and contralateral disease, and it may aid in evaluating response to neoadjuvant chemotherapy and determining if a mastectomy is feasible without neoadjuvant therapy [4-8]. Because of the high probability of metastatic disease in patients with LABC, imaging studies including bone scan and computed tomography (CT) of the upper abdomen and chest are useful. For patients with LABC, positron emission tomography (PET) is increasingly used in lieu of CT of the chest and abdomen and sometimes bone scan is used [9-12].

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Historical results of LABC with surgery and/or radiation alone were poor. A publication in 1951 by Haagensen and Stout [13] noted no benefit with radical mastectomy in patients with skin ulceration, skin edema (peau d'orange) or erythema, satellite skin nodules, or fixation to the chest wall musculature. Patients with operable disease were commonly treated by mastectomy with or without radiation therapy (RT), and inoperable disease was treated by RT alone [14-16]. The local control in these patients ranged from 50%–70%. Most of the patients succumbed due to distant metastases. However, there were still 20%–50% 5-year survivors when the patients were treated using definitive radiation with various systemic adjuvant chemotherapies [4,17]. Retrospective studies suggested that better local-regional control (LRC) and disease-free survival (DFS) results were obtained with trimodality therapy than with any other combination of therapies [18,19]. In attempts to improve survival and LRC, a multidisciplinary approach to managing LABC is widely accepted. However, the optimal sequencing of therapies remains an important subject of continued research.

Operable Locally Advanced Breast Cancer With Postmastectomy Radiation Therapy

Patients with clinical T3 tumor size and a clinical N0-N1 axilla may be initially resectable and candidates for mastectomy. For operable patients undergoing mastectomy without irradiation, certain subgroups at higher risk for recurrence were identified. The patterns and risk of locoregional recurrence (LRR) after mastectomy are functions most strongly of the size of the primary tumor and degree of regional nodal involvement [20,21]. Other factors affecting risk for LRR are the presence or absence of skin or chest wall involvement and the type of surgical procedure performed, margin status [22,23], lymphatic vessel invasion [24], Oncotype DX score [25], biologic subtypes of the cancer [26], and response to neoadjuvant chemotherapy [11,25,27,28]. Patients having 4 or more nodes involved at mastectomy have a high risk for LRR (>20%). An increasing number of involved lymph nodes is a powerful predictor of LRR and metastasis. Patients with T3 tumor size and 1–3 positive nodes also have a high risk for LRR. There are some reports that selected patients with T3 tumor size, including negative nodes and absence of lymphatic-vascular invasion, may have a low (<10%) risk for LRR [29,30].

Randomized trials and the Oxford meta-analysis have shown that adjuvant RT has resulted in lower recurrence rates and increased survival. In the most recent Oxford meta-analysis, the addition of RT also showed significant improvement in overall survival (OS) [31]. However, the trials in the meta-analysis included mostly early-stage breast cancer patients. Few randomized studies have also included patients with stage III disease. Evidence-based clinical guidelines have helped define the role of postmastectomy RT (PMRT) [32] (see Variant 1 and Variant 2).

Neoadjuvant Systemic Therapy Followed by Mastectomy + Radiation Therapy

The earliest reports of induction chemotherapy were published in the 1970s. The sequence of treatment has varied, although mastectomy often precedes other therapy for operable patients. Many institutions have preferred to use preoperative systemic or RT or both [33,34]. This may improve resectability for LABC with N2 or N3 adenopathy or tumors involving skin or chest wall. Several studies have long suggested acceptable results concerning LRC and DFS with trimodality therapy [35-37].

Trials comparing the combination of chemotherapy with either RT or surgery as local monotherapy in patients with advanced breast cancer have reported high local recurrence (LR) rates (25%–30%) [38-42]. In multivariate analysis, adjuvant RT independently contributed to better LRC and cause-specific survival. In a study by Huang et al [43] patients who received neoadjuvant chemotherapy with mastectomy alone were compared with those who also received PMRT. Over 67% of patients were stage III in the study. Even when patients achieved complete pathologic response after neoadjuvant chemotherapy, there was a high rate of LRR (33% at 10 years). The addition of RT further reduced that rate to 3% at 10 years. In a small group of patients who were inoperable and resistant to anthracycline-based chemotherapy, preoperative RT was able to convert over 80% of patients to operable status and allow them to undergo mastectomy [43]. Nearly half of these patients were alive at 5 years, with 64% local control. In patients with clinical T3N0 undergoing neoadjuvant chemotherapy and mastectomy without radiation, LRR was 24% without and 4% with radiation at 5 years [44].

In 1997, the Eastern Cooperative Oncology Group reported the results of its trial of postmastectomy locoregional RT in technically resectable LABC. All 312 patients received chemohormonotherapy consisting of cyclophosphamide, doxorubicin, 5-fluorouracil, tamoxifen, and fluoxymesterone for 6 cycles. The patients were then randomized to adjuvant RT or delayed RT until LRR. The patients in the adjuvant RT arm had lower LRR (15% versus 24%) but higher distant metastasis (DM) rates (50% versus 35%) as first site of failure compared to patients in the delayed RT arm. The study population had high competing risk for DM. There were no differences

in OS rate or time to overall relapse. Of note, 30 of 164 patients in the adjuvant RT arm did not actually receive radiation; 11 of these patients had LRR as first site of failure [45].

A randomized trial in stage III breast cancer patients from Helsinki has clearly shown the efficacy of combining all 3 therapeutic modalities of surgery, chemotherapy, and RT. In this trial, 120 patients with stage IIIA breast cancer were randomized to 1 of 3 arms after modified radical mastectomy: locoregional irradiation alone, systemic VAC (vincristine, adriamycin, cyclophosphamide) chemotherapy (with or without levamisole), or both VAC and irradiation. At both 3 and 5 years, RT reduced local failures relative to the chemotherapy arm, whereas VAC reduced the number of distant failures. The best DFS and local control rates were seen in the combined-modality arm [46].

In the Danish Breast Cooperative Group trials (82b and 82c), adjuvant RT improved OS in patients who underwent modified radical mastectomy and systemic chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil if premenopausal or with tamoxifen if postmenopausal [47,48]. However, in those studies, only 12%–14% of the studied patients had T3 primary tumors or skin invasion and unspecified patients and had clinical N2 or N3 disease. A subsequent publication by Kyndi et al [49] evaluated the role of PMRT by the importance of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) in 1000 of the 3083 high-risk breast cancer patients randomly assigned to PMRT in the Danish Breast Cancer Cooperative Group protocols 82b and 82c and suggested that subtypes of breast cancer may be predictive of incremental benefit of locoregional control after PMRT.

In general, LABC patients treated with neoadjuvant chemotherapy and mastectomy should have radiation particularly when there is clinical T3-4, clinical N2-N3, or yp node-positive disease. The need for radiation in the subgroup of patients with clinical N1 disease prechemotherapy and pathologic N0 disease at mastectomy postchemotherapy is not certain. There are some reports that there is a low risk of LRR in this select group and radiation may be omitted [25,50,51]. The National Surgical Adjuvant Breast and Bowel Project and the Radiation Therapy Oncology Group are conducting a randomized trial (NSABP B-51/RTOG 1304) that randomizes these patients to observation or PMRT. Outside of a clinical trial, it may be reasonable to individualize the decision for radiation of clinical N1/stage II patients to those with young age, hormone receptor–negative disease, poor response to chemotherapy, close or positive margins, or other factors [50].

Based on the above studies as well as the other studies previously mentioned, it appears that mastectomy and PMRT when used together result in superior local control rates of 80%–90%, and these are significantly higher than what is achieved by mastectomy and chemotherapy without PMRT. This multidisciplinary approach to LABC renders most patients local-regionally disease free [52] (see Variant 3 and Variant 4).

Combined-Modality Breast-Preserving Therapy

In the United States, initial chemotherapy is probably the most common approach to treating inoperable LABC, with response rates an important factor in predicting local control irrespective of the type of surgery required to remove the disease. Although most patients will need mastectomy, breast preservation is feasible in certain LABC patients who have a good response to neoadjuvant chemotherapy. Those with clinical N2/N3 disease and small primary tumors, whose nodal disease responds to neoadjuvant chemotherapy, should be offered breast-preserving therapy. Many patients with large clinical T3 primary tumors may also be treated with breast conservation if a good response to neoadjuvant therapy is achieved [43,53-55]. Trials comparing preoperative and postoperative chemotherapy have reported higher rates of breast-conserving therapy with preoperative chemotherapy, and studies suggest that up to one-quarter of patients with advanced breast cancers can be offered breast preservation [56]. Appropriate patient selection is very important. Patients with multicentric disease or extensive calcifications are not good candidates for breast-conserving therapy following neoadjuvant treatment. All patients undergoing breast-conserving therapy should receive adjuvant whole-breast irradiation. For patients with T4 disease, breast conservation should be used with caution outside of a research study protocol, although a small study suggested its feasibility [57]. There have been some attempts to forgo surgery for patients who responded well to neoadjuvant chemotherapy or hormonal therapy [19]. In a study by Pierce et al [40] only RT was given to those patients who achieved clinical complete response and whose breast biopsy was negative. There was a trend for worse LRC in the RT-alone group compared to those who also had mastectomy and radiation. In a meta-analysis of neoadjuvant versus adjuvant systemic therapy, there was an increased risk for LRR, mostly due to trials in which radiation was given without surgery [58]. Therefore, this strategy should still be considered investigational even in patients with good or complete response to chemotherapy.

Inflammatory Breast Cancer

IBC (T4d) is seen in a small subset of patients but is still a very aggressive disease with worse prognosis than other LABCs [59]. This should be distinguished apart from breast cancer with T4b disease (skin involvement) or locally neglected breast cancer that secondarily develops inflammatory signs. IBC is typically of rapid onset and has erythema or peau d'orange greater than a third of the breast.

Before the era of systemic chemotherapy, 5-year survival rates were in the range of only 5% [16]. Since the use of induction chemotherapy, 5-year survival figures have risen to 30%–50% [60]. Analysis of the Surveillance, Epidemiology, and End Results (SEER) registry by Dawood et al [61] did show improvement in survival over the past 2 decades (1990–2010). Gonzalez-Angulo et al [62] evaluated clinical outcomes of IBC at the University of Texas MD Anderson Cancer Center (MDACC) over a 30-year time span from 1974–2005. Using multivariable models that adjusted for patient and tumor characteristics, increasing year of diagnosis was not associated with a decrease in either the risk of recurrence or death. Seven prospective trials from MDACC in which all patients received local therapy following 3–4 cycles of chemotherapy noted DFS of 30% beyond the 10-year follow-up.

Trimodality therapy should be considered the standard approach for patients with IBC. Patients with IBC should not be considered candidates for breast-conserving therapy. Mastectomy is required where several series have suggested higher local and regional failure rates when surgery is not included as a component of therapy, although the survival benefit is less clear [4,63]. This may have been a reflection of the favorable outcome of patients who responded to chemotherapy. Other series have also shown that the initial responders will have the best survival rates. For instance, Hennessey et al [64] reported 5-year OS of 83% in patients with pathologic complete disease remission in the axillary lymph nodes, although the same rate dropped to 37% if tumor was still detected in the lymph nodes after chemotherapy.

Combined-modality therapy has been associated with high LRC rates but with little impact on rates of DM and death. As noted by Liao et al [65] the 5-year LRC in patients receiving chemotherapy, mastectomy, and RT was 73%. However, high rates of DM and mortality, with OS of 40% and DFS of 32% at 5 years, were observed. Interestingly, dose escalation with accelerated hyperfractionation (twice a day) seemed to provide improved OS and LRC. Another study from MDACC reported by Bristol et al [66] noted nonmetastatic IBC treated with PMRT delivered in a dose dense twice-daily fractionation to 66 Gy resulted in a 5-year actuarial LRC of 84% and an OS rate of 51%. In a study from Memorial Sloan Kettering Cancer Center with standard fractionation and daily skin bolus after combined-modality therapy including anthracyclines and taxanes in most patients prior to mastectomy, LRC was 87% [67]. It may be reasonable to reserve accelerated or dose-escalated radiation or aggressive use of bolus on an individualized basis, particularly for high-risk patients with less than optimal delivery of chemotherapy or poor response to chemotherapy [68,69].

A deeper understanding of the disease at the molecular level is needed to determine which subtypes of IBC have predictive and prognostic value for guiding treatment intervention. Molecular subtypes in IBC may better guide for treatment intervention [70]. However, further data are needed. It is important to read the literature carefully to determine whether patients with locally advanced noninflammatory cancers are included with those with inflammatory disease or whether the patient group includes those with secondary inflammatory changes that develop after a tumor has been present for some time (frequently >1 year) and eventually invades the skin. Such patients tend to have a more indolent course than those presenting with "classic" inflammatory disease; the "classic" presentation is associated with a rapid growth history and a tendency to involve large areas of skin and the dermal lymphatics. Studies tend to show better treatment results for those types of patients than for those who are confined to the subgroup with classic IBC, and the results should be interpreted accordingly (see Variant 5 and Variant 6).

Timing, Techniques, and Treatment Modalities Under Study

The optimal timing of RT in patients treated with combined-modality treatment as above has not been established by the available data. Although many institutions are delivering locoregional RT sequentially after completion of adjuvant systemic chemotherapy, which can be ≥8 months postmastectomy, there are several favorable reports about using RT (usually with concurrent chemotherapy) early in the patient's treatment course. No study specifically compares these approaches in LABCs. In early-stage breast cancer, sequential therapy has been preferred for avoiding treatment delays or dose reduction due to synergism of acute toxicities.

Preoperative RT with chemotherapy radiosensitizer has been studied in several small prospective studies [71,72]. Formenti et al [18] reported overall response rates of 91% to preoperative RT to 45 Gy with concurrent paclitaxel

chemotherapy. Sixteen percent of patients achieved pathologic complete response. The toxicities in this study appeared to be tolerable. However, this strategy should be examined further under protocol since in other studies radiation-induced pneumonitis rates of up to 25% were observed when paclitaxel was given concurrently with RT [73]. When adjuvant RT was given sequentially after paclitaxel, however, there seemed to be no increased development of clinically relevant radiation pneumonitis [74]. The use of concurrent chemoradiation for breast cancer is an area of active clinical investigation.

There are limited data on the use of hyperthermia to enhance radiation effects in locally advanced and recurrent breast cancer [75,76]. In Welz et al [76] 50 patients with microscopically involved resection margins were treated with radiation to a median dose of 60 Gy and hyperthermia (>41°C for 60 minutes). They observed the 3-year OS and LC rates to be 89% and 80%, respectively, with 28-month median follow-up. Many of the patients in these studies developed toxicities since they were re-irradiated with hyperthermia.

The details of the several radiation techniques used to treat breast cancer after mastectomy are discussed in the ACR Appropriateness Criteria® topic on "Postmastectomy Radiotherapy" [3]. In the major randomized trials of postmastectomy RT for intermediate-stage breast cancer, the targets of treatment, which represent the areas at risk for recurrence, have included nodal volumes (supraclavicular, axillary, and internal mammary) [47] and the chest wall.

In LABC, treatment planning should take into account the detailed distribution of disease at presentation. For example, in patients with known supraclavicular, infraclavicular, or internal mammary nodal disease, care should be taken to ensure adequate coverage and dose to tumors that may not have been addressed surgically at standard mastectomy. This frequently requires modification of the "standard" radiation techniques used for earlier-stage disease. For the chest wall, 2 common techniques include using only tangents to treat the entire chest wall (or "partially wide tangents" to treat the chest wall and IMN) and using tangents to treat lateral chest wall with matched electron field to treat the medial chest wall and internal mammary chain nodes. In some selected patients, the entire chest wall may be treated with electron beam [77]. The supraclavicular fossa is typically treated with a single-photon field. The specified dose to the chest wall and undissected lymph nodes is at least 50 Gy, and many centers will boost the operative flaps or incision with an additional 10–16 Gy. There are limited data to suggest improved locoregional control with the higher doses [4]. Unresected lymph node involvement of the IMN, infraclavicular fossa, or supraclavicular fossa receives an additional 10- to 16-Gy boost. LR rates after full axillary dissection are probably low, and specific targeting of the low axilla is not necessary for most patients undergoing an adequate lymph node dissection [78].

Breast Reconstruction

For patients undergoing mastectomy, immediate or delayed reconstruction offers benefits of improved psychosocial well-being and body image for many patients. The various types of available reconstructions fall into 2 major groups: 1) prosthetic implants, including saline or silicone implants that can be placed immediately at time of mastectomy (1-stage procedure) or with an expander placed at the time of mastectomy and permanent implant placed during a separate surgical procedure (2-stage procedure), and 2) autologous implants using the patient's own tissue. What type of reconstruction is selected for a given patient depends on several factors, including patient anatomy, comorbidities, need for PMRT, and patient preference. Further, the decision on timing for reconstruction—immediate or delayed—depends largely on the indications for PMRT. Benefits of immediate reconstruction include the need for only 1 surgical procedure, psychological benefits, and cost. The potential disadvantages include increasing the length of the surgical procedure and the potential negative impact on radiation planning and perhaps increased radiation complication rate [79-82].

RT has been shown in several studies to have a negative impact on the complication rate of reconstruction when compared to reconstructions performed on patients who do not require RT [83]. However, the best type of reconstruction and sequencing of RT and reconstruction remains extremely controversial. Some studies indicate that the pedicled transverse rectus abdominis myocutaneous flap (TRAM) tolerates postmastectomy RT very well, but others indicate that achieving optimal radiation dosimetry is difficult, and RT may have an adverse impact on the TRAM, thereby suggesting that better cosmesis is achieved when TRAM reconstruction follows RT [79,84,85]. A study evaluating timing of PMRT in 363 flaps with autologous breast reconstruction reported no significant differences in complication rates or number of revisions based on the type of free flap regardless of preoperative or postoperative RT [86]. Prosthetic-based implants are also feasible in the setting of postmastectomy RT. Although some studies report feasibility and outcomes with permanent implant placement

prior to RT, many advocate placement of a tissue expander at the time of mastectomy and exchange of the expander for permanent implant following RT. There remains controversy on the timing of RT with implant-based breast reconstruction. In one study Nava et al [81] observed the effects of radiation on temporary expanders, finding that RT during tissue expansion may compromise the outcome of implant-based breast reconstruction, and suggested administering PMRT after placement of permanent implants. Coverage of the expanders by serratus muscle or acellular dermal matrix may be particularly important to reduce complications in the setting of skin-sparing mastectomy [87]. All patients with LABC should be evaluated by a radiation oncologist prior to surgery to facilitate the most appropriate reconstructive plan for the patient (see Variant 7, Variant 8, and Variant 9).

Toxicity

Common acute toxicities, such as varying degrees of radiation dermatitis in the irradiated field, occur during the course of treatment. The subacute side effect of radiation pneumonitis is reported in approximately 1%–4% of patients treated for breast cancer. However, the risk of radiation pneumonitis has been shown to increase with treatment of the regional lymph nodes [88] and/or concurrent chemotherapy, and rates as high as 20% have been reported in patients treated with concurrent paclitaxel and radiation [89]. Radiation pneumonitis generally resolves without treatment but may require hospitalization or a course of steroids. Increased cardiac toxicity has been associated with postmastectomy RT. Analyzing data from the SEER database in early breast cancer patients, patients who were treated to the left breast had progressively increasing risk for ischemic mortality with longer time interval from the RT [90]. This risk was only significant for patients treated before 1982. No difference in 15-year mortality from ischemic events was seen between patients who received left breast versus right breast RT when the radiation was delivered after 1980 [91]. Darby et al [90] estimated risk of cardiac disease among women treated for breast cancer between 1958 and 2001. They reported rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per Gy ($P<0.001$), with no apparent threshold. The increase started within the first 5 years after RT and continued into the third decade after RT. The proportional increase in the rate of major coronary events per Gy was similar in women with and without cardiac risk factors at the time of RT. The major limitation of the study is that the estimated cardiac dose was calculated from virtual simulations of individual RT plan on CT scanning of patients with "typical anatomy."

One of the major considerations in evaluating dosimetry is documenting the mean heart dose. A University of Michigan study [92] reported the average mean dose to the heart was 2.82 Gy fractionated in small daily dose exposure when the heart volume is outside the incident (ie, primary beam). They reported no clinically significant defects after RT. Further, no correlation was found for low doses delivered to cardiac structures and perfusion, the summed stress defect scores, or ejection fraction. Boekel et al [93] described 10,468 women with ductal carcinoma in situ treated between 1989 and 2004, of whom 28% received RT. After a median follow-up of 10 years, the diagnosis of cardiovascular disease was similar between patients receiving surgery alone (9%) or surgery plus RT (8%) and between patients who received left-sided RT (7%) versus right-sided (8%).

In large randomized trials such as the Danish Breast Cancer Cooperative Group trial and the British Columbia trial, no significant difference was seen between left- and right-sided RT [47]. More recent postmastectomy studies using modern techniques and fractionation schedules have demonstrated survival benefits and no increase in cardiac toxicity [94,95]. However, the increased use of cardiotoxic chemotherapy over the past several years adds yet another confounding factor to determining the effect of RT on cardiac outcomes. Doxorubicin and trastuzumab, particularly when used in combination, are known to increase the risk of cardiac disease [96,97]. These agents were not included in the chemotherapeutic regimens used in the aforementioned trials. Currently, doxorubicin and trastuzumab are both included in standard chemotherapeutic regimens and are often administered in combination [98]. It is not known how RT in the setting of these agents will affect cardiovascular outcomes. Modern RT techniques include various strategies for maximal cardiac sparing, including use of cardiac block, breath-hold technique [99], intensity-modulated RT technique, and potential role of proton therapy for PMRT.

The risk of lymphedema is present among patients undergoing axillary dissection but it is increased in patients treated with RT to regional nodes following axillary dissection [100]. The risk of lymphedema is also increased by factors such as patient body mass index, extent/number of nodes dissected, use of posterior axillary RT field, and dose of RT delivered.

Also, there is the rare complication of secondary cancers developing in the irradiated field that needs to be discussed with the patient. Patients should be counseled on survivorship plans, with emphasis on the impact of lifestyle factors and smoking cessation on reducing risk of cancer and improving outcomes in the long run.

Summary of Recommendations

- Patients with LABC have a high risk of both LR and DM.
- Proper initial imaging of the breast and nodal beds is essential for staging, determining response to neoadjuvant therapy, and RT planning.
- Only a few randomized trials specifically examined the role of radiation in LABC patients but it is recommended after mastectomy in most patients.
- Preferred techniques and clinical target volumes and the optimum doses to these regions have not been prospectively studied for treating advanced breast cancer.
- Trimodality therapy with chemotherapy, surgery, and radiation seems to accomplish the best outcome.
- Breast conservation can be achieved in a select population of patients who have noninflammatory LABC and a good response to neoadjuvant chemotherapy.

Summary of Evidence

Of the 100 references cited in the *ACR Appropriateness Criteria® Locally Advanced Breast Cancer* document, 89 are categorized as therapeutic references including 22 well designed studies, 42 good quality studies, and 2 quality studies that may have design limitations. Additionally, 9 references are categorized as diagnostic references including 1 well designed study, 2 good quality studies, and 3 quality studies that may have design limitations. There are 26 references that may not be useful as primary evidence. There are 2 references that are meta-analysis studies.

The 100 references cited in the *ACR Appropriateness Criteria® Locally Advanced Breast Cancer* document were published from 1951-2015.

While there are references that report on studies with design limitations, 67 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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Clinical Condition: **Locally Advanced Breast Cancer**

Variant 1: **57-year-old woman, triple-negative invasive ductal carcinoma (IDC), status postmastectomy: 3.5-cm inner quadrant primary, 7/12 lymph nodes (LN) (+). Focally positive deep margin. PET (+) IMN and supraclavicular nodes. Adjuvant anthracycline and taxane, with normalization of PET findings. Metastatic workup negative.**

Treatment	Rating	Comments
Radiation Volumes		
Chest wall only ± boost	1	
Supraclavicular + apical nodes (assumes chest wall RT also)	9	
Full axilla (assumes chest wall RT also)	7	
Internal mammary nodes (assumes chest wall RT)	9	
Boost to IMN	8	
Boost supraclavicular nodes	8	
Radiation Doses		
Total dose to chest wall: 45–50 Gy (no boost)	8	
Total dose to chest wall: 60 Gy (no boost)	5	
Total dose to chest wall including boost to focally positive margin: 50–66 Gy	8	
Total dose to supraclavicular fossa including boost: 45–50 Gy	8	
Total dose to pre-chemotherapy, PET (+), supraclavicular fossa: 60–66 Gy	6	
Total dose to entire IMN chain: 45–50 Gy	8	
Total dose to pre-chemotherapy, PET (+) internal mammary node, 60–66 Gy	7	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 2: **55-year-old woman with neglected primary. Large fungating lesion and matted axilla. ER (−)/PR (+), Her2 (−). Metastatic workup negative. Not operable after 3 chemotherapy regimens, including anthracyclines and taxanes.**

Treatment	Rating	Comments
Principles of Treatment		
Switch to endocrine therapy	9	
Preoperative RT (50–54 Gy)	8	
Concurrent chemoradiation	6	This option may be appropriate in selected clinical circumstances.
Definitive RT 60–64 Gy	5	This option may be appropriate in selected clinical circumstances and if no other options are available. The risk of brachial plexopathy increases if this dose is delivered to supraclavicular region.
Switch to 4th line chemotherapy	3	This option is appropriate in a phase I clinical trial.
Debulking surgery with anticipated + margins	3	
Palliative radiation (30–45 Gy)	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Locally Advanced Breast Cancer**

Variant 3: **40-year-old woman, 4-cm primary with diffuse suspicious microcalcifications in breast, direct skin invasion, satellite skin nodule, matted axilla (N2), ER (+)/PR (−), Her2 (−). Metastatic workup negative.**

Treatment	Rating	Comments
Principles of Treatment		
Initial chemotherapy	9	
Mastectomy if response to initial chemotherapy	9	
Initial endocrine therapy	2	This option is appropriate only if cytotoxic therapy is contraindicated or on a clinical trial.
Initial surgery	1	
Initial breast and nodal RT	1	
BCT if response to initial chemotherapy	1	
Radiation Volumes (assume chemotherapy, mastectomy, axillary dissection level I-II, 3/16 LN+)		
Chest wall only ± boost (no nodal RT)	1	
Chest wall, supraclavicular and apical nodes	9	
Chest wall, supraclavicular fossa + full axilla	7	
Internal mammary nodes (assumes chest wall RT)	8	
Boost to chest wall	7	
Radiation Doses (1.8–2.0 Gy/day unless specified otherwise) (assume chemotherapy, mastectomy, clear margins, and axilla dissection level I-II, 3/16 LN+)		
Chest wall: 45–50 Gy	9	
Total dose to chest wall including boost: 60–66 Gy	7	
Supraclavicular and axillary nodes: 45–50 Gy	9	
Full axilla: 45–50 Gy	7	
IMN: 45–50 Gy	7	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 4: **80-year-old woman, 4-cm primary, direct skin invasion, satellite nodule, matted axilla (N2), strongly ER/PR (+), Her2 (−). Metastatic workup negative. Medically fit.**

Treatment	Rating	Comments
Treatment Modalities		
Initial endocrine therapy	9	Both initial endocrine therapy and initial chemotherapy are considered equally appropriate.
Initial chemotherapy	9	Both initial endocrine therapy and initial chemotherapy are considered equally appropriate.
Initial surgery	1	
Initial breast and nodal RT	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Locally Advanced Breast Cancer**

Variant 5: **45-year-old premenopausal woman, 4.5-cm IDC left breast, ER/PR (−), Her2 amplified, PET (+) in breast, axilla, and medial infraclavicular fossa. Palpable nodes in high axilla. Metastatic workup negative. Patient desires breast conservation.**

Treatment	Rating	Comments
Principles of Treatment		
Initial chemotherapy plus Her2-directed therapy	9	
Breast conservation therapy (BCT) if ≥PR to chemotherapy	8	For some patients with less than a partial response, breast conservation may be appropriate if surgically feasible.
Initial mastectomy and axillary dissection	1	N3 status contraindicates initial surgical approach.
Initial BCT and axillary dissection	1	
Radiation Volumes (assume initial chemotherapy followed by BCT, clear margins, and axilla dissection level I-II, 8/16 LN+, highest node+)		
Whole breast only ± boost (no nodal RT)	1	
Partial breast irradiation (no nodal RT)	1	
Whole breast and supraclavicular + apical axillary nodes	9	
Whole breast and supraclavicular LNs and full axilla	7	This option is probably not required after a standard axillary dissection.
Internal mammary nodes (assumes breast RT given concurrently)	8	This option is appropriate provided caution is taken to minimize cardiac pulmonary volumes.
Boost infraclavicular region	8	Boost is determined by extent of surgical resection and clinical features.
Radiation Doses (1.8–2.0 Gy/day unless specified otherwise) (assume initial chemotherapy followed by BCT, clear margins, and axilla dissection level I-II, 8/16 LN+, highest node+)		
Whole breast: 42.5 Gy (16 fractions)	1	Despite available data for early-stage disease, little data exist for this fractionation scheme in the setting of chemotherapy and postneoadjuvant treatment.
Whole breast: 45–50 Gy	9	
Total dose to breast tumor bed: 45–50 Gy	1	
Total dose to breast tumor bed: 60–66 Gy	9	
Total dose to supraclavicular fossa and axillary apex: 45–50 Gy	9	
Total dose to supraclavicular fossa and axillary apex: 60 Gy	1	
Total dose to medial infraclavicular nodes: ≥60 Gy	8	Gross tumor may require higher doses. Higher doses risk the brachial plexus. CT planning is recommended.
Full axilla: 45–50 Gy	7	
IMN: 45–50 Gy	7	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Locally Advanced Breast Cancer**

Variant 6: **38-year-old woman, T4 inflammatory, N1 disease, no response post 3-cycle multidrug chemotherapy. ER/PR (−), Her2 (−). Metastatic workup negative.**

Treatment	Rating	Comments
Principles of Treatment		
Change chemotherapy; if no response or progressive disease, proceed to RT	9	
Change chemotherapy; if response, mastectomy	9	
Change chemotherapy; if no response, pre-op chemoradiation (radiosensitizing chemotherapy)	7	
Immediate mastectomy/axillary dissection	1	
Radiotherapy (assume sufficient response to be operable with clear margins)		
Standard fractionation (1.8–2.0 Gy)	9	
Accelerated fractionation (1.5 Gy BID)	7	
Dose to central chest wall: 45–50 Gy	9	
Total dose to chest wall including boost: 60–66 Gy	9	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 7: **50-year-old woman, T3N2M0 disease, with clinical CR post 4-cycle multidrug chemotherapy. ER/PR (−), Her2 (−). Patient does not desire BCT.**

Treatment	Rating	Comments
Treatment Modalities		
Mastectomy and axillary dissection	9	
Additional chemotherapy	9	Patient would complete all chemotherapy up front. This option depends on what drugs are used.
Postmastectomy RT	9	
No surgery: RT + chemotherapy	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Locally Advanced Breast Cancer**

Variant 8: **50-year-old woman, stage T3N2M0 disease, with good clinical response following 4 cycles of multidrug neoadjuvant chemotherapy. She does not desire BCT and consents for mastectomy with reconstruction. Pathology from the mastectomy confirms ypT0N0M0 disease.**

Treatment	Rating	Comments
Treatment Modalities		
No postmastectomy RT	2	
Postmastectomy RT with tissue expander in place	9	
Postmastectomy RT after implant exchange with tissue expander	7	
Postmastectomy RT after autologous flap	7	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 9: **42-year-old woman with clinical stage T2N1M0 Her2 amplified left breast cancer. She undergoes a mastectomy with reconstruction and axillary dissection. Pathology notes 3.5-cm invasive cancer mastectomy margins are negative and 11/12 (+) nodes. Patient will receive chemotherapy and trastuzumab for 1 year.**

Treatment	Rating	Comments
Principles of Treatment		
Chest wall RT	9	Try to exclude all heart from RT volume.
Supraclavicular RT	9	Try to exclude all heart from RT volume.
Total RT dose delivery of 50 Gy or 50.4 Gy without boost	8	It is reasonable to deliver radiation at 1.8 Gy per fraction. Because the delivery of a boost is considered controversial, it is very reasonable to omit the boost in this clinical situation.
Total RT dose delivery of 60 Gy including boost	7	
Total RT dose delivery with bolus	8	
Total RT dose delivery without bolus	5	
Full axilla RT	8	
IMN RT	8	
Discontinue trastuzumab during radiotherapy	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		