

## American College of Radiology ACR Appropriateness Criteria®

### LOCALLY ADVANCED BREAST CANCER

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#### **Summary of Literature Review**

The treatment of locally advanced breast cancer (LABC) must include two major goals: control of locoregional disease and eradication of occult systemic metastases. The patterns and risk of locoregional recurrence after mastectomy are functions of the size of the primary tumor, the degree of regional nodal involvement, the presence or absence of skin or chest wall involvement, and the type of surgical procedure performed.

In this document, 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 (AJCC) staging system [1]. LABC includes clinical T3, T4, N2, or N3 disease. Patients with LABC have historically had a poor prognosis, and some are initially inoperable. They include patients with evidence of multiple ( $\geq 4$ ) or matted axillary lymph nodes or involvement of the second-echelon nodal basins of the infraclavicular [2], supraclavicular [3], and internal mammary lymph nodes (IMN). A clinically distinct but similarly high-risk type of LABC is inflammatory breast cancer. Overall, LABC is very heterogeneous, with highly variable tumor sizes and nodal status. This definition was chosen in a way to integrate with the ACR Appropriateness Criteria® topics on “[Local Regional Recurrence and Salvage Surgery — Breast Cancer](#)” and “[Postmastectomy Radiotherapy](#).” The discussion for this

topic is limited to avoid significant overlap with the other two topics.

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 magnifications views if needed is essential for all breast cancer patients. Ultrasound (US) may provide additional information regarding breast malignancy and may also be used to evaluate the axilla. US-guided biopsy may 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 (MRI) 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 and contralateral disease, and it may aid in determining if a mastectomy is feasible without neoadjuvant therapy [4-9]. MRI can also be used for evaluating response to neoadjuvant chemotherapy [10-12]. 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. Positron emission tomography (PET) is sometimes used in lieu of CT of the chest and abdomen, and sometimes bone scan, although there is not universal agreement on which of these modalities may be preferred [13-14].

Bloom et al [15] reporting the outcome of untreated patients diagnosed with breast cancer, found a median survival time of 2.7 years. The median 5-year overall survival (OS) rate was 18%, and the median 10-year OS rate was 4%. Local therapy improved on these numbers in many cases, even in patients with advanced breast cancer. After Haagensen and Stout [16] showed 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, only patients with operable disease were treated by mastectomy, with or without radiotherapy, while inoperable disease was treated by radiotherapy alone [17-19]. 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 [4,20-23]. The local control in these patients ranged from 50%-70%.

For operable patients undergoing mastectomy without irradiation, certain subgroups at higher risk for recurrence were identified. The clinical and pathologic status of axillary nodes was found to be an important indicator of

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the risk of both subsequent local recurrence (LR) and distant metastasis (DM) [24-25]. Patients having four or more nodes involved at mastectomy had locoregional recurrence rates (LRR) of 22%-38% and were at significant risk of locoregional recurrence regardless of the primary tumor size [16,18,26-27]. An increasing number of involved lymph nodes are a powerful predictor of locoregional recurrence and metastasis. (See [Variant 1](#) and [Variant 2](#).)

In attempts to improve survival and local-regional control (LRC), adjuvant radiation was initially added to definitive surgeries [3,28-29]. With this combination of therapies, Strom et al [30] reported a 10-year LRC of 82% and a 10-year disease-specific, recurrence-free survival rate (DSRFS) of 40%. Even after adjuvant radiation, a higher number of involved axillary lymph nodes predicted worse LRC and DSRFS. In a study by Toonkel et al [29] definitive surgery rather than lesser surgeries was needed, along with adjuvant radiation, to have better OS, RFS, and LRC. Initial mastectomy is not indicated in patients with stage IIIB disease [16] and should be avoided in lower stages of disease unless the tumor can be completely resected. The value of subtotal tumor excision has not been demonstrated.

### **Combined Modality Therapy — Mastectomy**

The earliest reports of induction chemotherapy were published in the 1970s. The sequence of treatment has varied; mastectomy often precedes other therapy for operable patients [31-33], although many institutions have preferred to use preoperative systemic or radiation therapy (RT) or both [34-36]. Randomized trials and the Oxford meta-analysis have shown that adjuvant systemic therapy has resulted in lower recurrence rates and increased survival [37].

In the most recent Oxford meta-analysis, the addition of RT also showed significant improvement in OS [38]. However, the trials in the meta-analysis included mostly early-stage breast cancer patients. Few randomized studies have evaluated only stage III disease, and these have mostly excluded patients with inoperable disease.

Trials comparing the combination of chemotherapy with either RT or surgery as local monotherapy in patients with advanced breast cancer have reported high (25%-30%) local recurrence rates [39-43]. Retrospective studies suggested that better LRC and DFS results were obtained with trimodality therapy than with any other combination of therapies [41,44-50]. In Huang et al [51] patients who received neoadjuvant chemotherapy with mastectomy alone were compared with those who also received postmastectomy RT. Over 67% of patients were stage III in the study. In multivariate analysis, adjuvant RT independently contributed to better LRC and cause-specific survival. 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 [51]. Nearly half of these patients were alive at 5 years, with 64% local control.

In 1997, the Eastern Cooperative Oncology Group (ECOG) reported the results of its trial of postmastectomy locoregional RT in technically resectable LABC. All 312 patients received chemohormonotherapy consisting of CAFTH 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% vs 24%) but higher DM rates (50% vs 35%) as first site of failure compared to patients in the delayed RT arm. The study population had high competing risk for DM. There was no difference 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 [52].

A randomized trial in stage III breast cancer patients from Helsinki has clearly shown the efficacy of combining all three therapeutic modalities of surgery, chemotherapy, and RT. In this trial, 120 patients with stage IIIA breast cancer were randomized to one of three 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 [53].

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 CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) if premenopausal or with tamoxifen if postmenopausal [54-55]. However, in those studies, only 12%-14% of the studied patients had T3 primary tumors or skin invasion and unspecified patients and clinical N2 or N3 disease. Similarly, the British Columbia randomized trial that showed improved LRC and breast-cancer-specific survival with the addition of adjuvant RT to modified radical mastectomy and CMF, had very few LABCs [56]. Therefore, interpretation of those results to LABC is difficult.

Based on the above studies as well as the other studies previously mentioned, it appears that surgery and RT produce essentially equivalent local control rates when used alone with systemic therapy, but these control rates are only in the range of 60%-70%, whereas when they are used together, superior local control rates of 80%-90% can be achieved. This multidisciplinary approach to LABC renders most patients local regionally disease free [57]. (See [Variant 3](#) and [Variant 4](#).)

### **Combined-Modality Breast-Preserving Therapy**

Breast preservation is feasible in certain LABC patients. 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 primary tumors may also be treated with breast conservation if a good response to neoadjuvant therapy is achieved [51,58-67]. 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 [68-70]. 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 offered as part of the study protocol, although a small study suggested its feasibility [71]. In the U.S., initial chemotherapy is probably the most common approach to treating inoperable LABC, with response rates an important factor in predicting local control [65,72-73] irrespective of the type of surgery required to remove the disease. Patients with inflammatory breast cancer should not be considered candidates for breast-conserving therapy.

There have been some attempts to forgo surgery for patients who responded well to neoadjuvant chemotherapy or hormonal therapy [41,47]. In a study by Pierce et al [41] 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. Therefore, this strategy should still be considered investigational.

### **Inflammatory Breast Cancer**

Inflammatory breast cancer (T4d) is seen in a small subset of patients, but is still a very aggressive disease with worse prognosis than other LABCs [74]. Before the era of systemic chemotherapy, 5-year survival rates were in the range of only 5% [18]. Since the use of induction chemotherapy, 5-year survival figures have risen to 30%-50% [75-77].

Trimodality therapy should be considered the standard approach for patients with inflammatory breast cancer. 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 [4,78-81]. However, Fields et al [82] reported significantly improved LRC and OS rates for patients receiving surgery as part of initial treatment: LRR (19% vs 70%,  $P<0.0001$ ) and 5-year OS (37% vs 7%,  $P=0.0004$ ). This may have been a reflection of the favorable outcome of patients who respond to chemotherapy, because other series have shown that the initial responders will also have the best survival rates. For instance, Hennessey et al [83] reported 5-year OS of 83% in patients with pathologic complete disease remission in the axillary lymph nodes, while the same rate dropped to 37% if tumor was still detected in the lymph nodes after chemotherapy.

When combined modalities were used, high rates of LRC could be reached. Liao et al [72] reported 5-year LRC of 73% in patients who received chemotherapy, mastectomy, and RT. There were still high rates of DM and mortality, with OS of 40% and DFS of 32% at 5 years. Interestingly, dose escalation with accelerated hyperfractionation (BID) seemed to provide improved OS and LRC.

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 more than 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 inflammatory breast cancer, and the results should be interpreted accordingly [75]. (See [Variant 5](#) and [Variant 6](#).)

### **Timing, Techniques, 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. While many institutions are delivering locoregional RT sequentially after completion of adjuvant systemic chemotherapy, which can be eight or more 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 [84-88]. Formenti et al [45] 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 [89-90]. When adjuvant RT was given sequentially after paclitaxel, however, there seemed to be no increased development of clinically relevant radiation pneumonitis [91]. The use of concurrent chemoradiation for breast cancer is an area of active clinical investigation.

Hyperthermia has also been studied to enhance radiation effects in locally advanced and recurrent breast cancer [92-95]. In Welz et al [95] 50 patients with microscopically involved resection margins were treated with radiation to a median dose of 60 Gy and

hyperthermia (>41 degrees 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 reirradiated 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”](#). 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) [54,96-97] 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 insure 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, two 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 (IMC) nodes. In some selected patients, the entire chest wall may be treated with electron beam [98-99]. 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 [4,100]. Unresected lymph node involvement of the IMC, infraclavicular fossa, or supraclavicular fossa receives an additional 10-16 Gy boost. Local recurrence 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 [101].

### **Breast Reconstruction**

For patients undergoing mastectomy, reconstruction offers benefits of improved psychosocial well-being and body image for many patients [102]. Many different types of reconstruction are available, but they can be categorized into two major groups; 1) prosthetic implants, including saline or silicone implants that can be placed in a one-step procedure or with an expander placed at the time of mastectomy and permanent implant placed during a separate surgical procedure, and 2) autologous implants using the patient’s own tissue. What type of reconstruction is chosen depends on several factors, including patient anatomy, comorbidities, need for radiation, and patient preference. The decision to proceed with immediate or delayed reconstruction also depends on several factors, including radiation. Benefits of immediate reconstruction include the need for only one 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 [103-105].

Radiation 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 radiation [106-107]. However, the best type of reconstruction and sequencing of radiation 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 it has an adverse impact on radiation planning and that better cosmesis is achieved when radiation follows TRAM reconstruction [103,108-110].

Prosthetic-based implants are also feasible in the setting of postmastectomy RT. While some studies report feasibility and outcomes with permanent implant placement prior to radiation, many advocate placement of a tissue expander at the time of mastectomy and exchange of the expander for permanent implant following radiation. 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](#) and [Variant 8](#).)

### **Toxicity**

Many common toxicities, such as radiation dermatitis, occur during the course of irradiation for LABC. 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 and/or concurrent chemotherapy, and rates as high as 20% have been reported in patients treated with concurrent paclitaxel and radiation [90,111-112]. Radiation pneumonitis generally resolves without treatment but may require hospitalization or a course of steroids. One major toxicity noted in the older studies was an increase in cardiovascular mortality in patients treated with postmastectomy RT. Analyzing data from the Surveillance, Epidemiology and End Results (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 [113]. 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 [114]. 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 [54,56]. More recent postmastectomy studies using modern techniques and fractionation schedules have demonstrated survival benefits and no increase in cardiac toxicity [115-116]. 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 Herceptin, particularly when used in combination, are known to increase the risk of cardiac disease [117-118]. These agents were not included in the chemotherapeutic regimens used in the aforementioned trials. Currently, Doxorubicin and Herceptin are both included in standard chemotherapeutic regimens and are often administered in combination [119]. It is not known how RT in the setting of these agents will affect cardiovascular outcomes. Maximal cardiac sparing achieved through proton therapy has the potential to decrease this risk.

### Summary

- Patients with LABC have a high risk of both LR and DM.
- Proper initial imaging of the breast and nodal beds is essential for both staging and RT planning.
- Only a few randomized trials specifically examined the role of radiation in LABC 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 a good response to neoadjuvant chemotherapy.

### Supporting Document(s)

- [ACR Appropriateness Criteria® Overview](#)
- [Evidence Table](#)

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

**Clinical Condition:****Locally Advanced Breast Cancer****Variant 1:**

57-year-old woman, triple negative IDC, status postmastectomy: 3.5 cm inner quadrant primary, 7/12 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
<b>Radiation Volumes</b>		
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 IMC	8	
Boost supraclavicular nodes	8	
<b>Radiation Doses</b>		
Total dose to chest wall including boost: 45-50 Gy	1	
Total dose to chest wall including boost: 60 Gy	2	
Total dose to chest wall including boost: 64-66 Gy	9	Clinical circumstance may require higher dose.
Total dose to supraclavicular fossa including boost: 45-50 Gy	9	
Total dose to supraclavicular fossa including boost: 60-66 Gy	9	
Total dose to entire IMN chain: 45-50 Gy	9	
Total dose to entire IMN chain: 60-66 Gy	9	
<b>Rating Scale:</b> 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 three chemo regimens, including anthracyclines and taxanes.

Treatment	Rating	Comments
<b>Principles of Treatment</b>		
Switch to endocrine therapy	9	
Preoperative RT (50-54 Gy)	8	
Concurrent chemoradiation	6	May be appropriate in selected clinical circumstances.
Definitive RT to ≥70 Gy	5	May be appropriate in selected clinical circumstances and if no other options are available. Risk of brachial plexopathy increases if this dose is delivered to supraclavicular region.
Switch to 4 <sup>th</sup> line chemotherapy	3	Appropriate in phase I clinical trial.
Debulking surgery with anticipated + margins	3	
Palliative radiation (30-45 Gy)	3	
<b>Rating Scale:</b> 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
<b>Principles of Treatment</b>		
Initial chemotherapy	9	
Mastectomy if response to initial chemotherapy	9	
Initial endocrine therapy	2	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	
<b>Radiation Volumes (assume chemotherapy, mastectomy, axillary dissection level I-II, 3/16 LN+)</b>		
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	
<b>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+)</b>		
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	
<b>Rating Scale:</b> 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
<b>Treatment Modalities</b>		
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	
<b>Rating Scale:</b> 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
<b>Principles of Treatment</b>		
Initial chemotherapy plus Her2-directed therapy	9	
Breast conservation therapy (BCT) if $\geq$ 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	
<b>Radiation Volumes (assume initial chemotherapy followed by BCT, clear margins, and axilla dissection level I-II, 8/16 LN+, highest node+)</b>		
Whole breast only $\pm$ 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	Probably not required after a standard axillary dissection.
Internal mammary nodes (assumes breast RT given concurrently)	8	Provided caution is taken to minimize cardiac pulmonary volumes.
Boost infraclavicular region	8	Boost determined by extent of surgical resection and clinical features.
<b>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+)</b>		
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: $\geq$ 60Gy	8	Gross tumor may require higher doses. Higher doses risk brachial plexus. CT planning recommended.
Full axilla: 45-50 Gy	7	
IMN: 45-50 Gy	7	
<b>Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate</b>		

**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
<b>Principles of Treatment</b>		
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	
<b>Radiotherapy (assume sufficient response to be operable with clear margins)</b>		
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	
<b>Rating Scale:</b> 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 (-). Does not desire BCT.

Treatment	Rating	Comments
<b>Treatment Modalities</b>		
Mastectomy and axillary dissection	9	
Additional chemotherapy	9	Would complete all chemotherapy up front. Depends on what drugs are used.
Postmastectomy RT	9	
No surgery: RT + chemotherapy	1	
<b>Rating Scale:</b> 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:****42-year-old woman, T2N1 (clinical), M0 left breast cancer, Her2 amplified. Status postmastectomy with 11/12 (+) nodes and reconstruction plus chemotherapy, no evidence of disease. Margins negative. Will receive trastuzumab for 1 year.**

<b>Treatment</b>	<b>Rating</b>	<b>Comments</b>
<b>Principles of Treatment</b>		
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 50.4Gy without boost	8	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.
Full axilla RT	8	
IMN RT	8	
Discontinue trastuzumab during radiotherapy	1	
<b><u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate</b>		