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LOCAL-REGIONAL RECURRENCE (LRR) AND SALVAGE SURGERY—BREAST CANCER

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Summary of Literature Review

Introduction

For most of the recent decades, the major focus of radiation oncology in the management of breast cancer has been on performing both randomized and nonrandomized trials comparing breast-conserving therapy (BCT) using surgery and radiation with the more traditional modified radical mastectomy (MRM). With data confirming equivalent survival with these 2 local-regional therapies in the management of early-stage breast cancer, attention was then refocused on identifying factors (pathologic, patient, or therapy-oriented) that predicted the success or failure of the local-regional treatment.

Twenty-year rates of local-regional recurrence (LRR) in the intact breast after BCT have been reported to be 8.8% [1]. Similarly low long-term crude recurrence rates (13%) for BCT were reported in the Danish trial as compared with mastectomy (21%) [2]. The relationship of local recurrence to the development of distant failure and death from disease is being well-studied. In early studies, the survival rate with salvage surgery for failures after BCT was 50% or higher at 5 years [3]. These local recurrences were thought less likely to result in subsequent distant disease from local-regional failures when following BCT versus mastectomy, which were readily linked with the development of distant disease and death [3].

Today, any discussion about LRR treatment must be considered in the context of advances of systemic chemotherapy, hormonal therapy, and targeted agents such as trastuzumab in the management of breast cancer with patterns of survival and disease-free survival having changed. Women who decades ago would have died rapidly from distant disease may now exhibit a local-regional failure due to prolonged survival. Outcomes of these LRR failures without distant disease have been re-examined. Analysis of 2 prospective randomized trials from the European Organization for Research and Treatment of Cancer (EORTC) and the Danish Breast Cancer Group comparing mastectomy with BCT in patients of similar stages with similar systemic therapy showed almost identical 5-year actuarial local-regional and survival rates following salvage procedures for early local-only failures in both the breast-conserved arm and the mastectomy arm [4]. Thus, the relationship between local failure and distant failure must be reanalyzed in both patients treated with mastectomy as well as those treated with BCT.

As the radiation oncology field of breast cancer therapy continues to advance with the examination of alternate fractionation schema and methods such as hypofractionation and accelerated partial breast irradiation (APBI), the importance of obtaining local control with initial treatment must remain important, not only to prevent either the loss of the breast in the conserved patients or painful and difficult-to-control local failure in the mastectomy patients, but also to potentially decrease subsequent distant metastases that may be associated with these local failures. Data from the Early Breast Cancer Trialists Collaborative Group (EBCTCG) demonstrate that treatments resulting in improved local control may lead to decrease in breast cancer mortality [5]. The overview analysis also suggests that avoidance of local recurrence after breast-conserving surgery (BCS) and radiation, and avoidance of

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local recurrence elsewhere after mastectomy, such as in the chest wall or regional nodes, are of comparable relevance to 15-year breast cancer mortality. As systemic therapeutic regimens become more effective in reducing the risk of distant disease, the goal of ensuring local-regional control takes on a potentially greater importance.

Randomized trial updates demonstrated the value of postmastectomy radiation therapy (PMRT) in stage II disease with 1 to 3 positive lymph nodes. The Danish Cooperative Breast Cancer Group 82b and 82C trials and the Vancouver British Columbia trial evaluated the local control and survival in mastectomy patients with 1 to 3 positive lymph nodes treated with systemic chemotherapy with or without PMRT [6,7]. Radiation led to both decreased LRR and improved survival. Additional analysis of patients in the Danish trial who underwent a more complete axillary dissection of 8 or more removed lymph nodes also revealed both a significantly lower risk of 15-year LRR and improvement in survival in patients receiving radiation [8]. Likewise, the value of regional nodal irradiation was demonstrated in the results from the MA 20 study in patients undergoing BCT [9].

Recurrence After Breast-Conserving Surgery and Radiation

Predictors for local-regional failure after both BCS and radiation can be divided into 3 broad categories: patient, tumor, and therapeutic factor. Young age at the time of diagnosis (patients in their 30s and 40s), appears to be a strong predictor [10-13].

Several studies have found that positive microscopic margins, gross multifocality, and an extensive intraductal component are associated with a higher risk of recurrence in the conserved breast. Additionally, larger tumor size and lymphatic vessel invasion have been reported as risk factors for ipsilateral breast tumor recurrence (IBTR) [10,13-15]. Newer studies suggest that the molecular subtype may also impact local recurrence, with both triple negative (ER- [estrogen receptor], PR- [progesterone receptor] and HER-2-neu-) and HER-2-enriched (HER-2+) subtypes associated with a higher rate of local and regional relapse [16,17].

The third category of risk factors for IBTR consists of therapeutic factors, most importantly the omission of breast radiation. Numerous studies have demonstrated that radiation therapy (RT) significantly reduces the risk of recurrence in the breast [18-20]. Patients receiving systemic chemotherapy or hormone therapy appear to have higher local control rates, all else being equal, than those who do not [14,19,21]. The addition of a radiation boost to the lumpectomy cavity may decrease the incidence of a recurrence in the conserved breast, particularly in women younger than 40 [11].

An increasing number of women are treated with APBI with either interstitial or balloon brachytherapy or external beam treatment. A limited long-term follow-up study regarding pattern of failure in breast or nodal regions is generally lacking. However, existing data do suggest that the rate of IBTR is comparable to whole-breast irradiation (WBI), with 10-year recurrence rates reported to be up to 6% [17,22-25]. An update of the American Society of Breast Surgeons MammoSite brachytherapy trial evaluated patients treated with balloon brachytherapy APBI. With a median of 53.5 months of follow-up, the 5-year actuarial IBTR rates were 2.59%, 5.43%, and 5.28%, respectively for "suitable," "cautionary," and "unsuitable" as defined by the ASTRO consensus panel on APBI (P=.1884). The only factor on univariate analysis associated with the development of an IBTR was receptor-negative disease [26]. A matched pair analysis of 199 patients receiving interstitial APBI versus WBI showed no differences in 12-year rates of local recurrences (3.8% versus 5%), regional recurrences (0% versus 1.1%), or cause-specific survival (78% versus 71%) [27].

Neoadjuvant therapy is increasingly used in breast cancer patients in whom it is known that systemic therapy will be needed in an adjuvant setting or to increase chances of success with BCS. Data suggest that BCT can be used after neoadjuvant therapy with acceptable local control [28,29]. In the NeOAdjuvant Herceptin trial of 235 patients with HER-2 positive locally advanced or inflammatory breast cancer were randomized to treatment with neoadjuvant trastuzumab plus chemotherapy or chemotherapy alone. Only 6 of 235 patients (2.5%) experienced either an IBTR or chest wall relapse with a median follow-up time of 3.2 years with the rate being similar in both BCT and mastectomy groups. None of the 4 patients undergoing BCT after chemotherapy with trastuzumab experienced an IBTR [30].

Following an IBTR in patients undergoing BCT, the 5-year survival rate is 76.6% for node-negative patients and 59.9% for node-positive patients [31,32]. The generally recommended treatment for locally recurrent breast cancer after BCT using WBI is salvage mastectomy, although a repeat attempt at breast conservation may also be possible in select cases. The phase II trial 1014 is currently ongoing to evaluate repeat BCS followed by 3-D conformal partial breast reirradiation. (See Variant 1.)

Limited data exist on salvage of patients who develop IBTR after APBI. Repeat BCS or mastectomy has been shown to produce excellent salvage rates comparable to the low rate of failures after WBI, but patient numbers are small [23,24]. The rate of IBTR at 5 years was shown to be 3.6% for invasive breast cancer and 3.3 % for DCIS out of 1,440 patients treated with balloon brachytherapy APBI. The 3-year disease-free survival and overall survival rate of 58% and 80%, respectively, after salvage mastectomy or repeat breast conservation. In this trial, 74% underwent salvage mastectomy, and 26% received BCT [33].

The incidence of any nodal recurrence in breast-conserving series is low [34]. However, involvement of the nodes has significant impact on outcome; therefore, assessment of the axillary status for an invasive local recurrence of the breast should be considered. The role of sentinel lymph node biopsy (SLNB) in this scenario remains to be defined. Preliminary data indicate that SLNB may be performed at the time of salvage surgery, as previous breast conservation or axillary surgery may not be a contraindication to SLNB [35]. Because of the relationship between local recurrence and distant failure, systemic therapy must also be considered in the treatment program for this patient group. (See Variant 2.)

To date, no published series has shown a statistically significant improvement in subsequent outcome with the administration of salvage chemotherapy or hormonal intervention at the time of local recurrence. Factors to be considered in this clinical decision include 1) prior systemic therapy, if any; 2) extent of recurrence; 3) time from initial treatment to recurrence; 4) tumor hormone receptor status; 5) patient age; 6) tumor size; 7) margin status; and 8) general medical condition [31,32].

The National Surgical Adjuvant Breast and Bowel Project (NSABP) is evaluating the benefit of adjuvant chemotherapy following radical resection of recurrent LRR breast cancer. This prospective randomized trial is currently open to accrual [36].

Some patients who present with an IBTR following BCT may have a new primary tumor as opposed to a true local recurrence [37,38]. The IBTR tumor is defined as a new primary if it is distinctly different from the original tumor with respect to histology subtype, if it presents in a different location in the breast, or if it is of different clonality. The time between the original primary and the second tumor is generally considerably greater for new primaries compared to true recurrences (average 55 months versus 33 months) [37]. In patients receiving RT as part of BCT, 10-year overall survival rates (75% versus 55%) and distant disease-free survival rates (85% versus 41%) tend to be much better for patients with new primaries compared to those with true recurrences [38]. Thus, the diagnosis of a new primary as opposed to a true recurrence implies a different natural history and prognosis and has different implications for therapeutic management. Unfortunately, most series addressing breast tumor recurrences do not adequately distinguish between the 2 entities. This may be of particular importance to breast cancer management in young women with BRCA 1/2 gene mutations, who are at increased risk for breast tumor recurrences due to new primaries [39].

Patients with ductal carcinoma in situ (DCIS) who undergo BCT and subsequently sustain a recurrence in the treated breast appear to have an excellent outcome following salvage therapy [40]. In most series, about half of the recurrences are invasive, with the other half recurring as DCIS. Nevertheless, almost all of these patients can be cured by mastectomy.

Analysis of outcomes of IBTR after breast conservation in NSABP B-17 and B-24 trials demonstrated that the 15-year cumulative incidence of invasive IBTR in patients treated with BCS was 19% with lumpectomy alone and 8.9% with lumpectomy and RT in B-17. In B-24, the 15-year cumulative incidence of invasive IBTR in patients treated with lumpectomy alone was 10% in lumpectomy and RT versus 8.5% with lumpectomy and tamoxifen. For noninvasive DCIS, the incidence of IBTR was 15.7% for lumpectomy only and 8.8% for lumpectomy and RT in B-17. In B-24, the incidence of IBTR for lumpectomy and RT was 8.3% and 7.5% with lumpectomy and tamoxifen. The probability of cancer-related death was 10.4% at 10 years after an invasive recurrence versus 2.7% after a noninvasive (DCIS) IBTR [40]. (See Variant 3.)

Recurrence after Mastectomy

Risk factors for local-regional failure following mastectomy can also be divided into clinical, pathological, and treatment-related categories. Young age (<35 years), nodal status, hormone receptor status, tumor size, lymphovascular invasion, multicentricity, and adequacy of nodal dissection as measured by the number of removed lymph nodes are all risk factors for postmastectomy recurrence [41-43]. Elective PMRT reduces this risk [44]. There is controversy regarding the risk of chest wall recurrence in the subgroup of patients with 1 to 3

positive nodes and their need for PMRT due to an unclear impact on survival and potential increased toxicity despite increased local control. (See the Appropriateness Criteria® topic on "Postmastectomy Radiotherapy.")

Systemic therapy appears to have an impact on local-regional control. In the most recent meta-analysis of systemic therapy from the EBCTG, 5 years of tamoxifen therapy reduced the local recurrence rate by about one-half in women with hormone receptor-positive disease (local recurrence ratio of 0.47), whereas, irrespective of hormone receptor status, polychemotherapy reduced it by about one-third (ratios 0.63–0.70 depending on patient age) [45].

Five-year survival rates range from 35%–75%, and 10-year survival rates range from 25%–55% after LRR. Long-term control of the local-regional disease is achieved in only 45%–70% of patients. Most patients with early LRR develop distant metastases [46], but a favorable subgroup exists with a lower risk of distant metastases and improved 5- and 10-year survival rates. Prognostic factors include the extent of disease (EOD) initially and at recurrence, the disease-free interval, grade, and the ER status as well as the use of surgical excision, radiation, and hormonal therapy. Patients with uncontrolled local-regional disease are usually symptomatic, are more likely to develop distant metastases, and die sooner than patients who have controlled LRR. Consequently aggressive attempts at controlling the LRR are warranted.

A multidisciplinary approach is required for the management of a chest wall recurrence after mastectomy. (See Variant 4 and Variant 5.)

Surgical resection should be performed if the size and location of the recurrence permit. In patients who have not received prior RT, LRRs are managed with irradiation [41]. LRR after mastectomy is a harbinger of distant metastases, so systemic treatment should also be considered. If the patient is ER-positive, then tamoxifen, an aromatase inhibitor (depending on menopausal status), or ovarian ablation may be used. If the patient is ER-negative, then chemotherapy may be given [36]. Although it is a reasonable treatment, chemotherapy has not historically been proven to impact overall survival after a recurrence. It has not been well studied. However, data from the CALOR trial presented at 2012 at the San Antonio Breast Cancer Symposium show a benefit to chemotherapy, predominantly in ER-negative women.

Treatment Guidelines After Breast-Conserving Therapy

For patients failing BCT that included standard WBI and an axillary node dissection, simple mastectomy is recommended as the local treatment of choice when the failure is confined to the breast parenchyma and is operable [47]. The role of partial breast irradiation in this setting is currently under investigation, and consideration should be given to placing the patient on an available clinical trial. The Radiation Therapy Oncology Group® (RTOG®) phase II trial 1014 is currently open for accrual. It uses 3-D conformal partial breast irradiation for patients with an in-breast local recurrence ≤3 cm and 3 or more positive lymph nodes without extranodal extension.

In the clinical situation involving recurrence in the treated breast, along with a supraclavicular nodal failure, radiation to the untreated supraclavicular area plus chemotherapy is the recommendation. Although this pattern of recurrence is not common, it is viewed as systemic failure based on existing evidence. Similarly, for patients with clear distant metastases as well as local failure, primary systemic management is recommended rather than mastectomy.

In the rare clinical situation of a local recurrence for a patient whose initial treatment consisted only of a wide local excision without radiation or axillary dissection, treatment options include simple excision or lumpectomy, axillary nodal evaluation, and RT in the absence of distant metastasis.

Given the situation of a patient with recurrent DCIS treated initially with lumpectomy plus RT only, simple excision is recommended.

Treatment Guidelines for Local Recurrence After Mastectomy

Treatment Options for LRR following mastectomy include surgery, RT, chemotherapy, hormonal therapy, or a combination of modalities. Patients experiencing LRR after mastectomy should undergo a workup for metastatic disease. In the absence of distant metastases, aggressive attempts at salvage should be entertained. When possible, surgical excision followed by RT to the involved chest wall and regional lymphatics is the standard treatment approach. Haffty et al [48] reported an overall survival after chest wall recurrence of 46% at 5 years and 28% at 10 years for patients treated with full-course external beam irradiation. Ten-year local-regional disease control

was achieved in 79% of patients, with a distant metastasis-free survival rate of 49% at 5 years and 40% at 10 years. In this series, HER-2 status was the only significant factor affecting local-regional progression. Patients with HER-2 positive disease had a local-regional progression-free rate of 59% compared with 92% for patients with HER-2 negative disease. Both PR-positive status and time longer than 2 years from the original diagnosis to chest wall recurrence were associated with favorable distant metastasis-free and long-term survival. Along with disease-free interval, the adequacy of local control for LRR has also been shown to have a favorable impact on long-term survival.

Isolated Axillary and Supraclavicular Nodal Failures

Isolated nodal recurrences in the axillary or supraclavicular nodal regions occur less frequently than chest wall or in-breast recurrences. In a review of 1,614 breast cancer patients undergoing either lumpectomy or mastectomy by Walsh et al [49], only 14 patients (0.9%) developed an ipsilateral nodal recurrence after axillary dissection. Isolated supraclavicular recurrence is similarly uncommon.

If feasible, surgery is usually used as the initial treatment modality. Radiation therapy is generally used after surgery if the patient has not seen prior radiation. Systemic therapy may also be incorporated in the salvage therapy although the role of systemic therapy in this setting is unclear. Surgery, however, may not be technically feasible due to prior axillary dissection. Likewise, supraclavicular disease may not be amendable to surgical resection due to potential postoperative morbidity. In addition, patients who have received prior axillary or supraclavicular RT are usually not candidates for reirradiation. Both isolated axillary and supraclavicular relapses are generally associated with a poor long-term survival due to high rate of subsequent distant metastasis [49,50]. However, subsets of patients with favorable features including a single axillary nodal recurrence, greater than 1-year disease free interval, attainment of local control have been identified with 10 year survivals reported at 69% [51]. In the absence of distant metastasis, aggressive attempts at salvage should be entertained. (See Variant 6.)

Summary

- Five-year actuarial LRR and survival rates following salvage procedures for early local-only failures are similar in patients undergoing mastectomy versus BCT.
- Salvage mastectomy is generally recommended for locally recurrent breast cancer after BCS. Repeat attempts at breast conservation may be considered, preferably through participation in a clinical trial.
- To date, no published series has shown statistically significant improvement in outcome with salvage chemotherapy or hormonal therapy in the case of local recurrence after BCT.
- Multidisciplinary management of chest wall recurrence after mastectomy is warranted, including surgery, RT, and systemic therapy. In the absence of distant metastasis, aggressive attempts at salvage should be entertained.
- Multidisciplinary management of isolated axillary or supraclavicular nodal recurrence is warranted where feasible with surgery and RT, although risk of systemic failure is high. The benefit of systemic therapy in this setting remains to be determined.

Supporting Documents

- ACR Appropriateness Criteria® Overview
- Evidence Table

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Clinical Condition: **Local-Regional Recurrence (LRR) and Salvage Surgery—Breast Cancer**

Variant 1: **52-year-old woman, 0.5-cm LRR in breast, 15 years after BCT with lumpectomy and axillary node dissection + RT for T1bN0 lesion. Biopsy showed invasive ductal carcinoma. ER/PR (+). HER-2 negative/nonamplified. EOD workup negative.**

Treatment	Rating	Comments
Principles of Treatment		
Hormone therapy	6	No trial data exists to support in this setting. One could infer possible benefit from data provided by the SAKK trial, which demonstrated improvement in disease-free survival in the setting of postmastectomy patients. There is no trial that demonstrates benefit in the post lumpectomy LRR setting.
Chemotherapy	1	
Trastuzumab	1	
Simple mastectomy (SM)	8	
SM + sentinel lymph node biopsy (SLNB)	1	This procedure is appropriate if the patient had prior SLND.
SM + LND or modified radical mastectomy	2	
Lumpectomy	3	This procedure is appropriate only in a clinical trial.
Quadrantectomy	3	This procedure is appropriate only in a clinical trial.
Lumpectomy + RT	3	This procedure is appropriate only in a clinical trial.
RT Volumes		
Whole breast +/- boost	1	
Partial breast RT	3	
Chest wall (after mastectomy)	1	
Supraclavicular (adequate LND)	1	

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

Clinical Condition: **Local-Regional Recurrence (LRR) and Salvage Surgery—Breast Cancer**

Variant 2: **42-year-old woman, 3.0-cm LRR in breast 6 years after BCT + chemotherapy for T1cN0 lesion. Biopsy showed invasive ductal carcinoma. ER/PR (–). HER-2 negative/nonamplified. EOD workup positive: liver and multiple bone metastases.**

Treatment	Rating	Comments
Principles of Treatment		
Chemotherapy	9	
Simple mastectomy (SM)	2	
SM + LND or modified radical mastectomy	2	
Lumpectomy	2	For this procedure, consider a clinical trial.
Quadrantectomy	2	For this procedure, consider a clinical trial.
Lumpectomy + RT	2	For this procedure, consider a clinical trial.
Hormone therapy	1	
RT Volumes		
Whole breast +/- boost	2	
Partial breast RT	1	
Chest wall (after mastectomy)	2	
Supraclavicular (adequate LND)	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 3: **55-year-old woman, 1.5-cm LRR in breast 7 years after BCT with lumpectomy only + RT for original diagnosis of DCIS, not otherwise specified. Biopsy: invasive ductal carcinoma. ER/PR (–). HER-2 normal. EOD workup negative.**

Treatment	Rating	Comments
Principles of Treatment		
Chemotherapy	8	
SM + LND or modified radical mastectomy	8	
SM + sentinel lymph node biopsy (SLNB)	8	
Simple mastectomy (SM)	2	
Lumpectomy	2	For this procedure, consider a clinical trial.
Quadrantectomy	2	For this procedure, consider a clinical trial.
Lumpectomy + RT	2	For this procedure, consider a clinical trial.
Hormone therapy	2	
RT Volumes		
Whole breast +/- boost	2	
Partial breast RT	2	
Chest wall (after mastectomy)	2	
Supraclavicular (adequate LND)	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Local-Regional Recurrence (LRR) and Salvage Surgery—Breast Cancer**

Variant 4: **55-year-old woman, 7 nodules (1-2 cm in diameter) along MRM scar 3 years after MRM + chemotherapy + adjuvant chest wall/SCL RT (50 Gy). Primary and LRR both ER/PR (–), HER-2 normal.**

Treatment	Rating	Comments
Complete excision of recurrence	8	Perform this procedure if technically possible with primary closure with or without simple advancement flap.
Chemotherapy	7	This treatment can be considered for study.
Radiation therapy	7	For this treatment, use judgment on RT volume.
Hormone therapy	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 5: **60-year-old woman, 2-cm nodule on MRM scar 4 years after MRM + chemotherapy without hormonal therapy for T1N1 [3 lymph nodes (LN) (+)]. Fine-needle aspiration (+). Primary ER/PR (+). Biopsy nodule ER/PR (+) by immunohistochemistry and HER-2 3+. Asymptomatic EOD workup negative.**

Treatment	Rating	Comments
Principles of Treatment		
Complete excision of recurrence	8	
Radiation therapy	8	
Hormone therapy	8	
Chemotherapy	5	If patient recurred while on an aromatase inhibitor, consider a taxane with trastuzumab.
Trastuzumab	6	No clear data exists to support Herceptin but, given risk of distant disease, it could be considered.
RT Volumes		
Chest wall	9	
Supraclavicular fossa	8	
Axilla	2	
Internal mammary nodes (IMN)	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Local-Regional Recurrence (LRR) and Salvage Surgery—Breast Cancer**

Variant 6: **65-year-old woman, 2-cm isolated axillary nodal recurrence detected on PE, confirmed on CT. Initial treatment MRM, chemotherapy, no adjuvant RT for T2N1MO invasive ductal carcinoma, grade 2. LN biopsy (+), invasive ductal carcinoma, ER/PR (+), HER-2 nonamplified. Metastatic workup negative for distant metastases.**

Treatment	Rating	Comments
Principles of Treatment		
Complete excision of recurrence	9	This procedure is appropriate if disease is surgically resectable without significant morbidity.
Radiation therapy	9	
Hormone therapy	9	
Chemotherapy	5	This treatment has no role in ER + disease. Limited data exist on the benefit in ER (–) disease; recent study shows benefit to chemotherapy at the time of recurrence.
Trastuzumab	1	
RT Volumes		
Chest wall	8	
Supraclavicular fossa	9	
Axilla	8	For this treatment, the field extent is dependent on surgical extent, ie axillary dissection versus excision of solitary LN.
Internal mammary nodes (IMN)	5	Strong consideration should be given if IMN are clinically or radiographically involved. Physicians must weigh 0%–2% subsequent recurrence rate in uninvolved IMN when not treated electively versus potential for morbidity from IMN irradiation.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		