Review

Can Locoregionally Recurrent Breast Cancer Be Cured?

Arati Rani Chand,[1] M. Firdos Ziauddin,[2] Shou-Ching Tang[1,3]

Abstract

Locoregional recurrence (LRR) of breast cancer can occur after multidisciplinary treatment of a primary breast cancer. With modern multidisciplinary breast cancer treatment, the incidence of isolated LRR is decreasing. Improvements in systemic therapy are driving the decrease in LRR. LRR does still occur, however. LRR reflects biology of the cancer, as does systemic recurrence. LRR of breast cancer is frequently associated with systemic disease recurrence and poor prognosis. Given this associated poor prognosis, historically, it has been unclear whether patients with LRR would benefit from aggressive therapy with curative intent. Findings in retrospective studies suggest that prognosis for patients with LRR is not universally poor, and some patients may benefit from aggressive locoregional and systemic therapy. The challenge remains to assess prognosis and appropriately treat patients with locoregional breast cancer recurrence.

Clinical Breast Cancer, Vol. ■, No. ■, ■-■
Keywords: Locoregional recurrence, Prognosis, Radiation, Surgery, Systemic therapy

Introduction

After treatment of early stage breast cancer, disease recurrence can occur locally in the ipsilateral breast or chest wall, regionally in draining lymph nodes, or at distant sites. Distant recurrence is associated with poor prognosis and generally considered incurable. Treatment of patients with distant recurrence is palliative. Understanding of the significance of locoregional recurrence (LRR), however, has evolved.

On the basis of results of the landmark National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 and B-06 trials, investigators concluded that systemic disease is the principal determinant of outcome. Locoregional disease and the extent of locoregional treatment were thought to not affect survival significantly.[1,2] In the NSABP B-06 trial, patients with breast cancer were randomized to treatment with lumpectomy, lumpectomy with adjuvant radiation, or mastectomy.[2] In-breast tumor recurrence (IBTR) was found to be associated with increased risk of distant recurrence (relative risk, 3.41, 95% confidence interval [CI], 2.70-4.30).[3] While patients who were treated with lumpectomy alone had a greater IBTR rate than patients treated with mastectomy or patients treated with lumpectomy plus radiation, all 3 groups had equivalent outcomes in terms of overall survival (OS), disease-free survival (DFS), and distant DFS. On the basis of these findings, LRR was deemed a marker for, but not a cause of, increased risk of distant recurrence.[3] One may conclude from these findings that survival would not be impacted by locoregional therapies which would reduce local recurrence risk. This conclusion was not supported, however, by analysis of multiple randomized trials of local therapy of early stage breast cancer by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). This analysis resulted in the finding that a reduction in the LRR rate by 20% over 5 years is associated with a 15-year reduction in mortality of 5.2%.[4,5] Locoregional therapies such as adjuvant radiation, which reduce local recurrence rates, may impact survival.

While the effect of LRR on survival has been debated, there has been general agreement that LRR is a harbinger of risk of distant disease recurrence. Given the association of LRR with distant recurrence, it is important to assess whether patients who develop LRR should be treated with curative or palliative intent.

Incidence of LRR of Breast Cancer

On the basis of data from randomized trials of treatment of early stage breast cancer, the 10-year incidence of LRR historically has been 3% to 8% after mastectomy and about 10% to 12% after breast-conserving therapy (BCT).[4] Most recurrences occur within the first 5 years after initial treatment.[4,6]

The incidence of local recurrence has been decreasing over time. An examination of 33 studies to evaluate the effect of resection margin width on local recurrence yielded the finding that more

[1]Division of Hematology/Oncology
[2]Department of Surgery, Georgia Cancer Center, Medical College of Georgia, Augusta University, Augusta, GA
[3]Tianjin Medical University Cancer Institute and Hospital, Tianjin, PR China

Submitted: Nov 27, 2016; Revised: Jan 22, 2017; Accepted: Feb 23, 2017

Address for correspondence: Shou-Ching Tang, MD, PhD, FACP, FRCPC, Georgia Cancer Center, Division of Hematology/Oncology, Medical College of Georgia, Augusta University, 1411 Laney Walker Boulevard, Augusta, GA 30912
E-mail contact: Shou.stang@augusta.edu

1526-8209/$ - see frontmatter
http://dx.doi.org/10.1016/j.clbc.2017.02.007

Table 1 Effect of Systemic Therapy on Local Recurrence of Breast Cancer in NSABP Trials[11]

Study Years	NSABP Study	Follow-up (y)	Intervention	Did Not Receive Intervention, Local Recurrence (%)	Received Intervention, Local Recurrence (%)
1976-1984	B-06	20	Adjuvant radiation after lumpectomy	39.2	14.3
1976-1984	B-06	20	Adjuvant radiation and chemotherapy after lumpectomy in node-positive patients	44.2	8.8
1981-1988	B-13	16.1	Adjuvant methotrexate, 5-FU, and leucovorin	19.9	6.3
1982-1988	B-14	19.1	Adjuvant tamoxifen in patients with node-negative, ER-positive cancer	19	10.8
1988-1990	B-19	15.7	Cyclophosphamide in addition to methotrexate and 5-FU	11.9	7.1
1988-1993	B-20	14.5	Adjuvant chemotherapy in addition to tamoxifen in patients with node-negative, ER-positive cancer	12.5	MF 9.7, CMF 4.6
2000-2005	B-31 and NCCTG N9831	10	Trastuzumab in addition to chemotherapy: doxorubicin, cyclophosphamide, paclitaxel	5.9	4

Abbreviations: 5-FU = 5-fluorouracil; C = cyclophosphamide; ER = estrogen receptor; F = 5-fluorouracil; M = methotrexate; NSABP = National Surgical Adjuvant Breast and Bowel Project.

recent studies have reported significantly lower local recurrence rates.[7] Two recent randomized control trials of regional nodal radiation reported LRR rates. The Canadian MA.20 study was conducted from 2000 to 2007 and randomized patients treated with BCT and adjuvant systemic therapy to whole-breast radiation versus whole breast and regional nodal radiation.[8] Ten-year LRR rates in the absence of distant metastasis were 6.8% and 4.3% among patients who had whole-breast radiation and whole breast and regional nodal radiation, respectively. In the European Organization for Research and Treatment of Cancer (EORTC) 22,922 study conducted from 1996 to 2004, patients with breast cancer treated by breast-conserving surgery (BCS) or mastectomy were treated with whole-breast radiation or chest wall radiation, respectively, and were randomized to either receive or not receive nodal irradiation.[9] A total of 76.1% of the patients were treated with BCS. With a median follow-up of 10.9 years, the LRR rate was 9.5% in the control group and 8.3% in the group treated with nodal irradiation.

According to a review of breast cancer randomized phase 3 trials of adjuvant treatment, LRRs have been decreasing as a proportion of all breast cancer recurrences. In 53 trials published between 1990 and 2011 involving 86,598 patients, the proportion of breast cancer recurrences that were locoregional decreased from 30% to 15%. This decreasing proportion of LRR correlated with systemic therapy rather than with locoregional therapy, with greater correlation with chemotherapy than with endocrine therapy.[10] This finding highlights the impact of systemic therapy on locoregional disease. In a review of NSABP randomized trials of systemic therapy agents, addition of chemotherapy and targeted biologic therapy resulted not only in lower rates of distant recurrence but also improved locoregional disease control[11] (Table 1).

Risk Factors for Local Recurrence

Several factors have been associated with risk of local recurrence after BCT or mastectomy. Positive margins, larger primary tumors, nodal metastasis, omission of adjuvant radiation, omission of adjuvant systemic targeted therapy, extensive intraductal component, and young age have all been associated with increased risk of local recurrence.[4,12-14] The most important risk factor for local recurrence is tumor biology, with triple-negative and HER-2/neu amplified cancers having higher local recurrence rates than luminal A and luminal B cancers.[15,16]

With modern multidisciplinary treatment, risk of local recurrence is decreasing, and the type of operative treatment is becoming less impactful in terms of local recurrence risk. In a multi-institutional retrospective review of outcomes of breast cancer patients 40 years old or younger treated with either mastectomy or BCT, LRR rates were found to be significantly lower in more recent years.[17] Furthermore, there was no significant difference in LRR rates between patients treated with mastectomy or BCT. A total of 853 patients 40 years old or younger who were candidates for BCT were included in this study. A total of 295 were treated with BCT, and 558 were treated with mastectomy. The study period was 1975 to 2013. Patients treated with BCT after 2000 had a LRR rate of 5.1% at 10 years compared to a LRR rate of 19.2% among patients treated with BCT before 2000. Among patients treated with mastectomy, the 10-year locoregional rate was 7.9% for patients treated after 2000 compared to 14.2% for patients treated before 2000. For patients treated after 2000, the 10-year local recurrence rate after BCT was 5.1% and after mastectomy was 7.9% ($P = .57$).

Adequate margins of resection are associated with lower local recurrence rates, but over the years, there has been considerable debate regarding adequate margin width in BCS. This question was addressed in a consensus conference which was recently reported.[7,18] A meta-analysis of 33 studies with data regarding margin width and IBTR yielded the finding that no tumor on ink is an adequate definition of clear margins in the setting of multidisciplinary breast cancer treatment. The odds ratio for local recurrence was 2.44 for positive margins compared to negative margins. The risk of local recurrence was not significantly reduced by wider margins.

Prognosis

While LRR of breast cancer is a recognized marker of risk of distant recurrence, the prognosis of LRR can be variable. Understanding the prognosis of differing patterns of recurrence may help guide decisions regarding treatment of LRR. In retrospective analysis, the prognosis of LRR may be related to the time frame and pattern of recurrence.[19-21]

In retrospective studies of outcomes of patients who have LRR after BCT, there is conflicting evidence regarding long-term survival after salvage therapy. In one institutional study of outcomes of 112 patients treated for isolated LRR after BCT, an overall 10-year survival rate of 69% was observed from the time of diagnosis of LRR.[19] A total of 93 patients had invasive recurrence, while 19 patients had recurrence in the form of ductal carcinoma-in-situ (DCIS). The patients with invasive recurrence had an overall 10-year survival rate of 64%. Two of the 19 patients who developed DCIS died of metastatic breast cancer, and the investigators concluded these patients still had risk of metastatic disease related to their initial diagnosis of invasive breast cancer. One hundred patients had IBTR only, and 12 patients had IBTR and regional recurrence. Salvage surgical therapy consisted of mastectomy for all patients and axillary node dissection in 31 patients. The distribution of adjuvant systemic therapy was chemotherapy for 13 patients, endocrine therapy for 8 patients, both chemotherapy and endocrine therapy for 15 patients, and no systemic therapy for 74 patients. Information about systemic therapy was not available for 2 patients. On univariate analysis, time interval from initial diagnosis of breast cancer to LRR and the method of detection of the LRR were significantly associated with survival after LRR. Patients who developed LRR 2 years or sooner after their initial diagnosis, those who developed LRR later than 2 years but at 5 years or earlier after diagnosis, and those who developed recurrence later than 5 years after their initial diagnoses had 5-year survivals of 65%, 84%, and 89%, respectively ($P = .03$). Patients who had recurrence detected by mammography alone, physical examination alone, or by both physical examination and mammography had 5-year survivals of 73%, 91%, and 93%, respectively. On multivariate analysis, only time interval from diagnosis of breast cancer to LRR of ≤ 2 years remained a significant prognostic factor.

In another institutional retrospective study, variables related to prognosis were evaluated for 341 patients initially diagnosed with stage I to II breast cancer and treated with BCT consisting of partial mastectomy and adjuvant radiation. At 5 years after detection of the LRR, OS was 81%, and overall DFS (including freedom from second malignancies) was 65%.[22] A total of 295 of these patients had IBTR only at the time of detection of LRR. A total of 288 patients had invasive recurrence, while 45 patients developed DCIS, and histology of the recurrence was unknown for 8 patients. A total of 276 patients (81%) had salvage mastectomy. Other aspects of salvage therapy, including systemic therapy, lymph node sampling, and radiotherapy, were variable. Patients were evaluated for time from detection of LRR to development of distant failure, second malignancy, or death. Invasive recurrence was found to be a significantly worse prognostic indicator than noninvasive recurrence (hazard ratio [HR] = 4.1, $P < .0001$). For patients who developed invasive recurrence, the most significant prognostic factors were not having local salvage therapy versus having mastectomy or unknown local salvage therapy (HR = 3.5, $P < .0001$), and time to LRR of < 2 years versus > 5 years (HR = 3, $P < .0001$). The 45 patients with noninvasive recurrence had a 5-year actuarial risk of distant failure, second malignancy, or death of 9%.

In a multi-institutional retrospective study of IBTR after BCT that included adjuvant radiation, prognosis of LRR was found to be poor. OS decreased with longer follow-up. A total of 266 patients who had isolated IBTR comprised the study group. A total of 226 patients had an invasive recurrence. The 5-year OS for the patients with invasive recurrence was 61%, but with a median follow-up of 11.2 years, the 10-year OS was found to be 39%.[23,24] On univariate analysis, the mode of detection of the local recurrence (mammography alone vs. presence of signs and symptoms), type and size of the local recurrence (distance from original tumor site, size of the recurrence, and presence or absence of skin involvement), the lymph node status of the primary tumor, and the presence of vascular invasion in the primary tumor were significant prognostic factors related to distant recurrence. On multivariate analysis, examining the end points of distant recurrence, death, and subsequent local recurrence or local progression, lymph node status of the primary tumor, and the type and size of the local recurrence were found to be significant prognostic factors. Skin involvement of the recurrence was found to be the most significant prognostic factor. Time to LRR was not a significant prognostic factor in this study. Four of 25 patients with noninvasive recurrence eventually developed distant metastasis.

These retrospective studies of LRR after BCT highlight the variability in treatment and outcomes of LRR.

The affect of adjuvant chemotherapy on the prognosis of patients who develop LRR was examined in a review of 5 NSABP randomized trials of node-positive patients.[25] In these trials, there were a total of 2669 patients with median time on the study protocol of 13.3 years. All patients in these trials received chemotherapy, except one group who received tamoxifen alone. A total of 424 patients (15.9%) developed LRR as a first event, 259 (9.7%) with IBTR and 165 (6.2%) with other LRR. The adjusted HR for mortality for patients who developed IBTR was 2.58 (95% CI, 2.11-3.15), and for patients who developed other LRR, the HR was 5.85 (95% CI, 4.8-7.13). Patients who developed supraclavicular lymph node recurrences had significantly worse survival compared to patients with axillary recurrences, with a 5-year distant DFS of 12.1% compared to 31.5%.[25] Other negative prognostic indicators included older age, increasing primary tumor size, increasing number of nodes initially involved, and estrogen receptor (ER)-negative primary tumor. The authors concluded that prognosis of patients who developed a local recurrence was as if they had been diagnosed at one stage higher than their stage at initial diagnosis of breast cancer.

The question of whether patients who initially present with node-negative disease fare differently after LRR was examined in a review of 5 National Surgical Adjuvant Breast and Bowel Project (NSABP) randomized trials of node-negative patients.[26] In these studies, there were 3799 patients with median time on the study protocol of 16.1 years. A total of 419 patients (11%) developed LRR as a first event, 342 (9%) with IBTR and 77 (2%) with other LRR. The adjusted HR for mortality for patients who developed IBTR was 3.04 (95% CI, 2.42-3.81). Five-year OS was 76.6% for patients who developed IBTR versus 34.9% for patients who developed other LRR. The adjusted HR for mortality for patients with ER-negative primary cancers (HR = 4.49, 95% CI, 3.29-6.13) was worse than for patients with ER-positive primary cancers (HR = 2.32, 95% CI, 1.72-3.14) ($P = .002$). Age > 50 at entry into the trials, African American race, high body mass index, and primary tumor size > 2.1 cm were also significant negative prognostic factors. Time

to local failure was also a significant prognostic factor. Patients who developed IBTR or other LRR $\leq$ 24 months after their initial diagnosis of breast cancer had 5-year OSs of 38.9% and 19.5%, respectively. Patients who developed IBTR or other LRR $>$ 60 months after their initial diagnosis of breast cancer had 5-year OSs of 87.7% and 49.1%, respectively. The investigators concluded that outcomes are significantly worse for patients with LRR after BCS and adjuvant therapy, whether they initially present with node-positive or node-negative disease.

Prognosis for patients who have LRR after mastectomy has also been examined in retrospective studies. These studies have small numbers of patients, and as in reviews of LRR after BCT, there is variability in recurrence patterns and in treatment. In an instructional retrospective study, outcomes of 90 patients who had isolated LRR after mastectomy were evaluated.[27] These patients were treated for their LRRs with chest wall radiation between 1968 and 1978. Fifty-four of the patients had been treated for their primary cancers with radical mastectomy, and 36 had been treated with modified radical mastectomy (MRM). For treatment of the LRRs, the investigators describe a typical treatment of 45 Gy in 20 fractions over 5 weeks applied to the chest wall and/or draining lymph node basins. Eighty-seven (97%) of 90 patients experienced clinical complete response. Median follow-up was 81 months. Patients developed distant metastasis at the rate of 20% annually. Actuarial local control rates were 42% at 5 years and 35% at 10 years. Only 17 patients were evaluable for local recurrence at 5 years. OS was 50% at 5 years and 26% at 10 years. The disease-free interval (DFI) from the time of mastectomy to LRR was the only significant prognostic factor evaluated. Patients who had DFIs of $\geq$ 2 years had 5-year survival of 58% and 10-year survival of 36%, while patients who had DFIs of $<$ 2 years had 5- and 10-year survivals of 33% and 7%, respectively ($P = .04$ for comparison at 5 years, and $P = .007$ for comparison at 10 years). The investigators concluded that local treatment does not cure patients who have LRR after mastectomy and that effective systemic therapy is important to improve outcomes for these patients.

In another retrospective institutional review, outcomes were examined in patients who had been treated after initial diagnosis of breast cancer with radical mastectomy or MRM and various adjuvant systemic and locoregional therapies.[28] A total of 145 patients with LRR were treated for their recurrence between 1979 and 1992. The distribution of recurrences was as follows: chest wall 59%, axillary lymph nodes 11%, supraclavicular nodes 11%, chest wall and axillary lymph nodes 8%, and a combination of these sites in 11%. The authors examined the association of several patient and tumor and treatment variables with outcomes and identified a subgroup of patients who had good outcomes. The 100% 5-year survival and 69% 10-year survival were observed in patients older than 50 years of age who had a single chest wall or axillary recurrent nodule, a DFI of 1 year or more, a pT1-2N0 primary tumor, and no tumor necrosis, and whose recurrence was locally controlled.

In another examination of the question of whether LRR after BCT versus LRR after mastectomy have differing biologic significance and prognosis, investigators retrospectively reviewed LRR and related prognosis in 2 European randomized trials of BCT versus mastectomy.[29] Because these trials were randomized, comparable groups of patients had BCT or mastectomy. A total of 1807 patients were randomized between 1980 and 1989 to MRM or BCT. A total of 133 patients developed LRR as a first event. Salvage therapy varied. A total of 72% of patients who had LRR after MRM were treated with radiotherapy with or without excision of the recurrent tumor. A total of 73% of patients who had LRR after BCT were treated with mastectomy with or without radiation. Adjuvant systemic therapy was provided to 26 patients (39%) in the MRM group and 18 patients (27%) in the BCT group. Five-year survival rates after treatment of LRR were 58% and 59% in the MRM and BCT groups, respectively. The type of treatment for the primary cancer, whether MRM or BCT, was not a significant prognostic factor. On multivariate analysis, nodal status of the primary tumor, primary tumor stage, and presence of vascular invasion in the primary tumor were significant prognostic factors associated with mortality in the patients who developed LRR. The investigators concluded that early LRR is associated with an aggressive tumor biology and poor prognosis, regardless of its occurrence after mastectomy or BCT.

Variability in prognosis of IBTR may be related to whether the tumor is a new primary (NP) lesion or a true recurrence (TR). There are no standardized criteria to distinguish between TR and NP. Retrospective studies have evaluated the question of whether prognostic differences can be identified by classifying recurrent tumors as NP versus TR.[30-33] Criteria used to classify IBTR as NP or TR include proximity of the recurrent tumor to the primary tumor site and histologic subtype of the recurrence. Tumors located close to the primary tumor site and of the same histologic subtype as the primary tumor may be classified as TRs, while tumors distant from the primary site and of a different histologic subtype may be classified as NPs.[30,32] The presence of an intraductal component or change in receptor status or flow cytometry may indicate a NP.[30,31,33] Consistently in these studies, IBTR classified as NP was found to be associated with a better prognosis than a TR, possibly because the tumors classified as NPs were early stage breast cancers.[30] In one study that classified IBTR as TR if the recurrent tumor was within 3 cm of the primary tumor site and had the same histology, OS at 10 years was 77% for patients who developed NPs versus 46% for patients who developed TRs ($P = .0002$).[32] This difference in prognosis suggests treatment may need to be different for recurrent tumors meeting these criteria. Furthermore, in some of these studies, the risk of contralateral breast cancer is significantly greater in patients who develop NPs than in patients who develop TRs.[30-32] In one study the difference in contralateral breast cancer risk was 16.3% versus 9.5% ($P = .04$) and in another study the difference was 37% versus 12% ($P = .018$).[30,31] This finding suggests chemoprevention strategies may be important for patients who develop NP tumors.

The biology of the recurrent disease may also affect outcomes. In a small retrospective institutional study, recurrent cancers that were triple negative were associated with worse outcomes.[34] Between 1971 and 2005, 1920 patients were treated with BCS and adjuvant breast irradiation for stage I to II breast cancer. A total of 166 patients experienced an IBTR, of which 47 patients had paraffin-embedded tissue blocks of their recurrent tumors. A total of 25.5% of these 47 tumor samples had the triple-negative phenotype. After a median follow-up of 7.5 years, 5-year distant metastasis-free survival was 90.8% in patients who did not have triple-negative recurrences versus

48.6% in patients whose recurrent tumors were triple negative ($P < .01$). The difference in 5-year OS was 96.9% for patients with recurrent tumors with receptor expression versus 72.7% in patients with triple-negative recurrent tumors ($P = .0002$). By multivariate analysis, triple-negative phenotype of the recurrent tumor was a significant risk factor for distant recurrence (relative risk, 5.91, 95% CI, 1.83-19.01, $P < .01$).

Outcomes after LRR can be variable and may depend on several variables. Reliable models may allow for better treatment selection to improve outcomes. Tumor genomic profiling needs to be correlated with biology and outcomes.

Treatment of Locoregionally Recurrent Breast Cancer

Local Treatment After IBTR

In patients with IBTR after BCS, salvage mastectomy is the standard treatment.[2,3,19,22,25,26,35,36] There are conflicting data in retrospective studies regarding the efficacy of BCT for IBTR. One study found the HR for distant failure, second malignancy, or death to be 2.0 for patients who had an IBTR after BCT for their primary breast cancer and had salvage therapy with repeat BCT compared to patients who had mastectomy. The authors state that the 2 groups may not be comparable because data regarding the extent of LRR were not available.[22]

Among studies that have retrospectively examined the question of the efficacy of BCT versus mastectomy for IBTR, 2 studies have the largest numbers of patients. In one study, 190 patients with IBTR after BCT were treated for their local recurrences with either another attempt at BCT or mastectomy.[37] A total of 133 patients were treated with mastectomy, and 57 were treated with repeat BCS. These 57 patients were deemed appropriate for BCS, and the patients and surgeons agreed with BCS. There was no significant difference in 5-year OS. Five-year OS was 70% among patients who had mastectomy and 85% among patients who had BCS. Five-year local recurrence, however, was greater among patients who had BCS (19%) versus patients who had mastectomy (4%).

In another retrospective study of 146 patients who had IBTR after BCT, 116 underwent salvage mastectomy, while 30 patients refused mastectomy and had BCS for salvage local therapy.[38] There was no significant difference in 10-year OS between the 2 groups. Ten-year OS was 65.7 ± 5.1% for patients who had mastectomy and 58 ± 9.2% for patients who had BCS. Two patients who had BCS for treatment of IBTR had another IBTR and were treated with salvage mastectomy. Eight patients who had mastectomy had a second local recurrence and were treated with excision, if their disease was resectable, along with adjuvant systemic therapy and/or radiotherapy. The authors also commented that patients with multicentric disease recurrence may be less suitable for BCS. Among patients who had mastectomy, multicentricity of the recurrent tumor was significantly associated with deleterious *BRCA1* and *BRCA2* gene mutations, ER-negative primary tumor, increasing recurrent tumor size, lymph node metastasis at time of IBTR, and detection of recurrence by physical examination.

Local Treatment for Postmastectomy LRR

Postmastectomy LRR historically has been treated with excision, radiation, or both. In a retrospective study, 128 patients were treated between 1967 and 1988 with radiation after postmastectomy LRR.[39] The most common sites of recurrence were chest wall (n = 86) and supraclavicular nodes (n = 20). Excision of the recurrence was done for 78 patients, and incisional biopsy was done for 49 patients. Most patients received chest wall and nodal radiation. Nineteen percent of patients who had isolated chest wall recurrence were treated with radiation to chest wall but not to nodes, and 13% of patients who had isolated nodal recurrence had radiation to nodes but not chest wall. Only 66 patients received systemic therapy. Multivariate analysis yielded findings that a longer DFI, locoregional control after recurrence, and excision of the recurrent tumor before radiation were significantly associated with survival. A subgroup of patients (18% of the entire study population) who had a DFI of 2 years or more and excision of the recurrent tumor and locoregional control had a 5-year survival of 61%.

In the setting of postmastectomy LRR, radiation alone can have therapeutic efficacy. A total of 224 radiotherapy-naive patients with isolated chest wall, regional nodal, or both chest wall and nodal recurrences after mastectomy were treated with radiation with curative intent.[40] A total of 57% of patients treated had locoregional control at 5 years. Locoregional control was best for patients with isolated chest wall recurrences only. At 5 years, 63% of patients with isolated chest wall recurrences, 45% of patients with isolated nodal recurrences, and 27% of patients with both chest wall and nodal recurrences had control of locoregional disease with therapeutic radiation. Radiation to the entire chest wall in the setting of isolated chest wall recurrence had greater efficacy in terms of local control than focusing radiation only on an affected small area. Large-field radiation covering the entire chest wall yielded local control in 75% and 63% of patients at 5 and 10 years, respectively. Small-field radiation focused mainly on the site of recurrent tumor yielded local control rates at 5 and 10 years of 36% and 18% ($P = .0001$). OS for patients in this study was 43% at 5 years and 26% at 10 years. The authors concluded that although most patients with LRR after mastectomy eventually develop distant disease, a significant percentage of patients do live 5 years and may benefit from radiation with curative intent.

One prospective but nonrandomized clinical study showed that complete resection was strongly associated with better local control and also with better OS.[41] Between 1979 and 1989, 120 women were diagnosed with isolated LRR after mastectomy. These patients had no prior chemotherapy nor endocrine therapy. The LRR was excised if possible. Between 1979 and 1983, 61 women were treated with chemotherapy (doxorubicin and cyclophosphamide) and radiation and endocrine therapy (if tumor was ER positive). Between 1983 and 1989, 59 women were treated with radiation and endocrine therapy (if ER positive) and no chemotherapy. The HRs for OS and LRR-free survival favored the group that had excision of the recurrent tumor (HR for OS was 0.55, $P = .019$; HR for LRR-free survival was 0.32, $P = .001$). Patients receiving chemotherapy had better OS at 5 and 10 years, but the difference in OS did not reach statistical significance.

In a retrospective study, chest wall resection was described for chest wall recurrence of breast cancer. Between 1977 and 1995, 44 patients had chest wall resection, 30 with curative intent and 14 with palliative intent.[42] Patients who had palliative resection had either incomplete resection or had distant metastasis. The median

survival in the group who had curative resection was 8.9 years, and 5-year survival was 58%. Palliative resection was associated with a median survival of 2.3 years and a projected 5-year survival of 21% ($P = .008$). There was selection bias in this study, as patients selected for chest wall resection were younger, had longer DFIs, and had less extensive disease. Overall, prognosis was poor with chest wall recurrence.

Regional Nodal Assessment After Local Recurrence

Regional nodal assessment in the setting of local recurrence of breast cancer, as in the setting of a primary breast cancer, is done with the goals of regional disease control and assessment of extent of disease to assess prognosis and guide decisions regarding systemic therapy and radiotherapy.[43-45]

Sentinel lymph node biopsy (SLNB) is feasible after LRR for LRR control and guidance for systemic therapy decisions.[43,46-49] There has been greater success in performing SLNB in the setting of previous BCT and SLNB, but SLNB can also be done after previous mastectomy and axillary lymph node dissection (ALND).[48,50,51] In a meta-analysis of 25 studies involving 692 patients, the overall sentinel lymph node identification rate was 65.3%—much lower than in the setting of initial staging, in which the identification rate is greater than 90%.[52] SLNB was successful in 81% of patients who had previous SLNB, but only in 52.2% of patients who had previous ALND ($P < .0001$). Sixty-two patient who had previous mastectomy were included in this meta-analysis. There was no significant difference in the SLNB success rate between patients who had previous BCT and those who had mastectomy (65.5% vs. 68.9%, respectively). Sentinel lymph node (SLN) metastases were found in 19.2% of patients. A total of 27.5% of these SLN metastases were found in lymphatic basis other than the ipsilateral axilla. Lymphoscintigraphy was found to be of value in the setting of SLNB for LRR. Among patients who had successful lymphoscintigraphy, 43.2% had demonstration of lymphatic drainage pathways toward sites other than the ipsilateral axilla. In studies that stratified aberrant drainage according to previous axillary surgery, lymphoscintigraphy demonstrated aberrant drainage in 25.7% of patients who had previous SLNB versus in 74.2% of patients who had previous ALND ($P < .0001$). In studies that stratified aberrant drainage pathways according to previous breast operation, aberrant drainage was seen on lymphoscintigraphy in 40.1% of patients who had BCT and in 77.4% of patients who had mastectomy ($P < .0001$). In this review, there was limited data regarding false-negative rates. Thirteen of 25 studies reported axillary recurrence rates, and an axillary recurrence rate of 0.2% was calculated among patients who had a reoperative SLNB with no SLN metastases. Given this low axillary recurrence rate, the value of adding the morbidity of ALND to document the false negative rate is questionable.[53]

In the meta-analysis of 25 studies of reoperative SLNB, 9 studies reported whether results of the SLNB affected recommendations regarding radiotherapy or systemic therapy. Among patients who had successful SLNB, the findings affected treatment recommendations for 17.9% of patients.[52] Although feasible and in some cases relevant to treatment decisions, the necessity of SLNB in the setting of local recurrence has been questioned. In a retrospective institutional study of 83 patients with initial negative SLNB (1997-2000) and invasive recurrence with clinically negative nodes, 47 patients had reoperative SLNB, while 36 did not.[54] There were no significant differences in treatment strategies between the 2 groups. Furthermore, there were no significant differences in outcomes. Axillary failure rate in 5 years after the local recurrence occurred was 0 in the patients who had axillary surgery and 5.9% (2 events) among patients who did not have axillary surgery. After the diagnosis of local recurrence, the 5-year incidence of distant metastasis was 14.7% among patients who had axillary surgery and 10.1% among patients who did not have axillary surgery. Two of the patients (4.3%) who had axillary surgery died within 5 years after diagnosis of local recurrence, while 4 patients (3.8%) who did not have axillary surgery died within 5 years. The authors also pointed to prognosis data and results of randomized trials to suggest that systemic therapy decisions may not be affected by repeat axillary staging.

Role of Radiation

After adjuvant breast or chest wall radiation for treatment of the primary breast cancer, there is concern for tissue toxicity from radiation delivered to treat a local recurrence. There is evidence, however, that radiotherapy may be safely delivered to previously irradiated tissue. While salvage mastectomy has been considered the standard local therapy for IBTR after BCT, there is interest in a second attempt of BCT after IBTR. In one study, a single radiation oncologist reported his experience treating IBTR with excision and repeat irradiation after previous treatment of an ipsilateral breast cancer with BCT that included adjuvant whole-breast radiation.[55] A total of 39 patients with IBTR without skin involvement were treated. Thirty-one patients had invasive breast cancer and 8 had DCIS. Initial treatment had been lumpectomy with or without ALND, followed by adjuvant whole-breast radiation. Thirty-two of the patients had received 5000 cGy in 25 fractions, while others had been treated with 4500 to 5000 cGy. IBTR was treated with resection, and 34 patients had their recurrent tumors resected with clear margins. Radiotherapy was then delivered to the involved quadrant of the breast with electrons. A total of 5000 cGy was administered in 25 fractions. Thirty-eight of 39 patients completed the radiation (1 patient refused). Patients received various systemic therapy regimens: tamoxifen (n = 19), 3 chemotherapy with or without tamoxifen (n = 3), no systemic therapy (n = 16), or Arimidex (n = 1). There were no late local complications other than skin pigmentation. Thirty-six of 39 patients were evaluated for cosmesis: 27 good to excellent, 9 fair to poor. These patients reported satisfaction that they could keep their breasts. The author thought that cosmesis was more a function of tumor location and surgical therapy than a function of radiotherapy. Eight of 39 patients developed second IBTR. One patient a had mastectomy for suspected recurrence that was not real. Thirty (76.9%) of 39 patients had an intact breast with no tumor. Overall 5-year survival was 77.9% by Kaplan-Meier analysis, similar to rates reported after salvage mastectomy.

In a larger multi-institution study, toxicity of repeat irradiation for local recurrence after BCT or mastectomy was retrospectively examined. Between 1993 and 2005, 81 patients at 8 institutions were treated with adjuvant radiation after resection of their primary breast cancer by either BCS or mastectomy. The median total dose

of radiation was 106 Gy. A total of 54% of the patients were treated with concurrent hyperthermia as a radiosensitizer. A total of 54% of patients were treated concurrently with chemotherapy. The median follow-up for the patients was 12 months. A total of 25 patients had follow-up for greater than 20 months. Grade 1 or 2 toxicities were induration and fibrosis (n = 16), skin infection (n = 6), lymphedema (13), soft tissue necrosis (n = 4), fracture (n = 1), brachial plexopathy (n = 1), and pneumonitis (n = 1). Grade 3 or 4 toxicities were fewer in number: skin infection (n = 1), lymphedema (n = 1), dermatitis (n = 1), induration/fibrosis (n = 1), lymphedema (n = 1), and pneumonitis (n = 1). The complete response rate was 57%, with a trend toward a greater complete response rate with hyperthermia, 67% versus 39% ($P = .08$). The 1-year local DFS rate for patients with gross disease was 53% compared to 100% for those without gross disease ($P < .0001$).[56]

There has been a limited experience with partial breast irradiation in the setting of local recurrence after BCT. Studies of partial breast irradiation in this setting are small, with 17 to 69 patients. Local control rates of 0% to 43.8% and 5-year OS of 50% to 97.2% have been reported.[57] In one study, a retrospective review was done of patients treated with interstitial brachytherapy with iridium-192 wires between 1970 and 1995.[58] A total of 4026 patients were treated for breast cancer with BCT including whole-breast radiation to a total dose of 46 to 50 Gy in 2 Gy fractions, with a total of 50 to 80 Gy (median, 60.5 Gy) of adjuvant radiation to the tumor bed. A total of 97% of patients had a boost delivered to the tumor bed. A total of 473 patients developed IBTR. A total of 69 of these patients refused mastectomy and were treated with BCT with interstitial brachytherapy intraoperatively. A total of 24 patients were treated with a dose of 30 Gy at one center, while 45 patients were treated with 45 to 50 Gy at the other participating center. Median follow-up after interstitial brachytherapy was 50.2 months (range, 2-139 months). Long-term complication rates were related to dose. None of the patients who received 30 Gy had complications related to the brachytherapy, while 28% of patients who received 45 to 46 Gy and 32% of patients who were treated with 50 Gy experienced complications ($P = .01$). Complication rates were also examined in relation to total dose of radiation, including the dose provided as adjuvant therapy for the primary tumor and the brachytherapy dose provided for the recurrence. The incidence of grade 2/3 long-term complications in patients receiving total doses $\leq$ 100 Gy was 4%, but was 30% in patients receiving total doses $\geq$ 100 Gy($P = .008$). There were no long-term complications in 27.5% of the patients, grade 1 complications in 50.7%, grade 2 complications in 11.6%, and grade 3 complications in 10.2%. Complications included fibrosis (n = 16), breast retraction (n = 6), and telangiectasia (n = 5). There were 11 second local recurrences after a median interval of 24.3 months (range, 6-58 months). Sites of local recurrence were at the tumor bed (50.8%), near the tumor bed (34.3%), or in another quadrant (14.9%). On multivariate analysis, factors significantly associated with better local control were greater number of wires used for interstitial brachytherapy (< 5 or ≥ 5, $P = .013$) and interval between diagnosis of primary breast cancer and diagnosis of local recurrence of $\geq$ 36 months ($P = .039$). Overall 5-year survival was 91.8% (95% CI, 82-96.5). Factors significantly associated with improved OS and distant DFS were node-negative primary tumor and local recurrence away from the primary tumor site.

In another smaller study of brachytherapy as a component of repeat BCT, 17 patients with IBTR after BCT were treated with excision of their recurrent tumors followed by pulsed dose brachytherapy.[40] After a median follow-up of 59 months (range, 20-84 months), 12 of the 17 patients had no local recurrence. Complications were limited to mild fibrosis.

Although salvage mastectomy remains the standard treatment for local recurrence after BCT, these studies provide evidence that BCT may be feasible for IBTR after previous BCT that included adjuvant radiation.

For patients who receive postmastectomy radiation as adjuvant therapy for their primary breast cancers, there is similar concern regarding tissue tolerance for additional radiotherapy to treat a local chest wall recurrence. There has been some experience in using radiotherapy to treat chest wall recurrences in the setting of previous postmastectomy radiation. Concurrent hyperthermia may be used as a radiosensitizer in this setting.[59,60] Hyperthermia may allow lower doses of radiation which may result in lower toxicity. There are no standard regimens for a second course of postmastectomy radiation to treat recurrence. Studies evaluating this therapy are varied in their patient populations and study designs.[59] One retrospective study reviewed the experience with 42 patients who were treated with a second course of radiation to treat a LRR of breast cancer.[60] Eighteen of these patients had mastectomy as the initial operative treatment of their primary breast cancers. Patients who were initially treated with BCT, including adjuvant radiation, had a mastectomy before their second courses of radiation. The median dose of radiation the patients in this study received in their first course of adjuvant radiation was 54 Gy. The median time between courses of radiation was 53 months. The median dose for the second radiation treatment was 60 Gy. A total of 29 patients were treated with hyperthermia concurrently with radiation. The median follow-up after the second course of radiation was 41 months. Five-year local control was approximately 62%. Five-year OS was 59%. In cases in which toxicity was observed, 40 patients experienced grade 1 or 2 skin toxicity acutely, while 2 patients experienced grade 3 skin toxicity. The numbers for late skin toxicity were 1 patient with grade 0 toxicity, 7 with grade 1, 26 with grade 2, and 8 with grade 3. Four patients developed grade 1 or 2 pneumonitis. One patient had rib fractures. No patient experienced grade 4 toxicity. These data and data from other studies of reirradiation suggest that a second course of radiation may be safely applied.

Role of Adjuvant Systemic Therapy

Given the association of distant recurrence and poor prognosis in patients with LRR, there is a need for adjuvant systemic therapy in these patients.

One of the earliest trials of adjuvant systemic therapy for LRR was the Swiss Group for Clinical Cancer Research (SAKK) trial.[61] A total of 167 patients were included in this study and were randomized to receive either tamoxifen or observation after local excision of LRR followed by radiotherapy. Patients were eligible for the study if they had isolated LRR expressing ER. If receptor status was unknown, patients were eligible if they had DFI greater than 12 months, and 3 tumor nodules or fewer with each tumor nodule measuring 3 cm or less in greatest dimension. Median follow-up was

11.6 years for surviving patients. Median DFS was 6.5 years in the tamoxifen arm and 2.7 years in the observation arm ($P = .053$). While there was a difference in DFS, OS was not significantly different between the 2 study groups, with a median OS of 11.2 years in the group randomized to observation versus 11.5 years in the group randomized to receive tamoxifen.

Interestingly, analysis by menopausal status showed strikingly different outcomes for pre- and postmenopausal patients. The improved DFS was seen in postmenopausal patients, with 5-year DFS of 61% in postmenopausal patients treated with tamoxifen versus 33% among postmenopausal patients in the observation arm ($P = .006$). Meanwhile, in premenopausal patients, 5-year DFS was 60% in both study arms. In premenopausal women, a better survival was noted in the control arm, although the difference was not statistically significant.

Because now patients are already treated with adjuvant hormone treatment in the primary setting, whether a second adjuvant hormone therapy would be beneficial in patients still remains unknown.

Chemotherapy as adjuvant therapy for LRR was studied by the International Breast Cancer Study Group (IBCSG). The Chemotherapy as Adjuvant for Locally Recurrent breast cancer (CALOR) trial was an international multicenter randomized controlled study examining the value of adjuvant chemotherapy in isolated LRR in breast cancer.[62] Between 2003 and 2010, 162 patients with isolated LRR were randomized to receive or not receive chemotherapy. The chemotherapy regimen was not standardized for the study but left to the discretion of the treating physicians. Patients were eligible for this study if they had complete excision of their LRR. After a median follow-up of 4.9 years, there was a significant difference in 5-year DFS: 57% (95% CI, 44-67) among patients who were not treated with chemotherapy versus 69% (95% CI, 56-79) among patients who were. Five-year OS was not significantly different between the 2 groups: 88% (95% CI, 77-94) for patients who received chemotherapy and 76% (95% CI, 63-85) for patients who did not. A total of 103 of the 110 patients who had hormone receptor−expressing recurrent tumors received adjuvant endocrine therapy. Chemotherapy had a significant impact in improving 5-year DFS among patients with recurrent tumors that expressed hormone receptor, while patients with hormone receptor−negative tumors had no benefit from adjuvant chemotherapy in terms of DFS. The investigators concluded that adjuvant chemotherapy should be recommended to patients with isolated LRR after resection of the recurrent tumor.

Discussion

A LRR of breast cancer after modern multidisciplinary treatment that includes mastectomy or BCT poses a challenge. As in the setting of a primary breast cancer, the prognosis of a locoregionally recurrent breast cancer is largely determined by the risk or presence of systemic disease. Distinguishing the tumor as a NP cancer versus a recurrence may help guide treatment decisions. The treatment of a primary cancer is guided by anatomic staging or assessment of biology through tumor genomic profiling. A similar process may have value in the evaluation and treatment of locoregionally recurrent breast cancer, but there are insufficient data to formulate clear guidelines. Furthermore, in the setting of a NP cancer or recurrent cancer, treatment decisions are complicated by previous locoregional and systemic therapies that may have reduced or exhausted patients' tolerance for repeat therapy.

Locoregional therapies—surgical resection and radiation, either alone or in combination—have evidence for benefit in significant proportions of patients with isolated LRRs in retrospective studies. The challenge is to identify markers of favorable tumor biology that would allow selection of patients for aggressive locoregional therapy. There are several clinical and pathologic models as well as molecular signatures available to prognose early breast cancer. However, none of them has been explored to determine the aggressiveness of the locally recurrent breast cancer. Additional biomarkers may be developed to achieve this goal because the locally recurrent tumor may have different biology from that of the primary breast cancer.

As for SLNB, even though it is feasible in selected patients with isolated local recurrence, its benefits are questionable, and the associated potential morbidity may not be justified. In addition, because LRR is associated with very high incidence of systemic disease and many physicians chose to offer systemic therapy, a negative SLNB or ALND is unlikely to affect the treatment options or outcome.

Because LRR is a marker for systemic relapse, many physicians choose to offer another systemic therapy or second adjuvant therapy in patients whose local recurrent breast tumor is treated by surgery or radiotherapy. However, there are only limited data that support this practice, including the SAKK trial and the multicenter international CALOR trial. Neither study demonstrated an OS advantage in the treated groups. Furthermore, it is currently unknown what the optimal chemotherapy regimen should be or what the duration of therapy should be. As in the primary breast cancer setting, systemic therapy decisions would be guided by tumor receptor expression. Patients with HER-2/neu amplified tumors would likely be offered anti-HER-2 therapy. Again, the choice of specific anti-HER-2/neu agents depends on the prior drug exposure and the evolving standard therapy in the adjuvant and metastatic setting. Finally, in patients with hormone receptor−positive tumors, systemic endocrine therapy is commonly offered to patients with LRR who receive local therapy either alone or after systemic chemotherapy.

The ultimate goal to treat isolated locoregional recurrent breast cancer is to control the local disease with the available multimodal treatments. Long-term disease control or cure is feasible in certain patient populations. With the further development of novel targeted therapy including immunotherapy in breast cancer, many of these newer agents will be incorporated into the management of the locally recurrent diseases. In addition, the biology of breast cancer dormancy is being actively explored. Novel strategies to target the dormant breast cancer stem cells are under active investigation. They will undoubtedly result in more effective treatment and higher chance of cure for locoregionally recurrent breast cancer.

Conclusions

Advances in systemic therapy have had an impact on locoregional disease, and isolated LRRs of breast cancer are dropping in incidence. The biology of the disease is the most important factor in determining the recurrence risk of the individual cancer and the outcome for the patient. Patients who have LRR without systemic

recurrence may benefit from multimodal therapy with curative intent. Tumor genomic profiling and next-generation sequencing may be important in clarifying individual tumor biology and identifying patients who will benefit from curative versus palliative therapy.

Disclosure

The authors have stated that they have no conflict of interest.

References

1. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med* 2002; 347: 567-75.
2. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; 347: 1233-41.
3. Fisher B, Anderson S, Fisher ER, et al. Significance of ipsilateral breast tumour recurrence after lumpectomy. *Lancet* 1991; 338:327-31.
4. Abe O, Abe R, Enomoto K, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 366:2087-106.
5. Darby S, McGale P, Correa C, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. *Lancet* 2011; 378:1707-16.
6. Van Dongen JA, Voogd AC, Fentiman IS, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst* 2000; 92:1143-50.
7. Houssami N, Macaskill P, Luke Marinovich M, Morrow M. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. *Ann Surg Oncol* 2014; 21:717-30.
8. Whelan TJ, Olivotto IA, Parulekar WR, et al. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med* 2015; 373:307-16.
9. Poortmans PM, Collette S, Kirkove C, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med* 2015; 373:317-27.
10. Bouganim N, Tsvetkova E, Clemons M, Amir E. Evolution of sites of recurrence after early breast cancer over the last 20 years: implications for patient care and future research. *Breast Cancer Res Treat* 2013; 139:603-6.
11. Mamounas EP, Tang G, Liu Q. The importance of systemic therapy in minimizing local recurrence after breast-conserving surgery: the NSABP experience. *J Surg Oncol* 2014; 110:45-50.
12. Huston TL, Simmons RM. Locally recurrent breast cancer after conservation therapy. *Am J Surg* 2005; 189:229-35.
13. Komoike Y, Akiyama F, Iino Y, et al. Ipsilateral breast tumor recurrence (IBTR) after breast-conserving treatment for early breast cancer: risk factors and impact on distant metastases. *Cancer* 2006; 106:35-41.
14. Elkhuisen PHM, Van De Vijver MJ, Hermans J, et al. Local recurrence after breast-conserving therapy for invasive breast cancer: high incidence in young patients and association with poor survival. *Int J Radiat Oncol Biol Phys* 1998; 40: 859-67.
15. Arvold ND, Taghian AG, Niemierko A, et al. Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy. *J Clin Oncol* 2011; 29:3885-91.
16. Tseng YD, Uno H, Hughes ME, et al. Biological subtype predicts risk of locoregional recurrence after mastectomy and impact of postmastectomy radiation in a large national database. *Int J Radiat Oncol Biol Phys* 2015; 93:622-30.
17. Frandsen J, Ly D, Cannon G, et al. In the modern treatment era, is breast conservation equivalent to mastectomy in women younger than 40 years of age? A multi-institution study. *Int J Radiat Oncol Biol Phys* 2015; 93:1096-103.
18. Buchholz TA, Somerfield MR, Griggs JJ, et al. Margins for breast-conserving surgery with whole-breast irradiation in stage I and II invasive breast cancer: American Society of Clinical Oncology Endorsement of the Society of Surgical Oncology/American Society for Radiation Oncology Consensus Guide. *J Clin Oncol* 2014; 32:1502-6.
19. Doyle T, Schultz D, Peters C, Harris E. Long-term results of local recurrence after breast conservation treatment for invasive breast cancer. *Int J Radiat Oncol Biol Phys* 2001; 51:74-80.
20. Wapnir IL, Dignam JJ, Fisher B, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. *J Natl Cancer Inst* 2011; 103:478-88.
21. Moran MS, Haffty BG. Local-regional breast cancer recurrence: prognostic groups based on patterns of failure. *Breast J* 2002; 8:81-7.
22. Galper S, Blood E, Gelman R, et al. Prognosis after local recurrence after conservative surgery and radiation for early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 2005; 61:348-57.
23. Voogd AC, van Tienhoven G, Peterse HL, et al. Local recurrence after breast conservation therapy for early stage breast carcinoma: detection, treatment, and outcome in 266 patients. Dutch Study Group on Local Recurrence after Breast Conservation (BORST). *Cancer* 1999; 85:437-46.
24. Voogd AC, van Oost FJ, Rutgers EJT, et al. Long-term prognosis of patients with local recurrence after conservative surgery and radiotherapy for early breast cancer. *Eur J Cancer* 2005; 41:2637-44.
25. Wapnir IL, Anderson SJ, Mamounas EP, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. *J Clin Oncol* 2006; 24:2028-37.
26. Anderson SJ, Wapnir I, Dignam JJ, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five national surgical adjuvant breast and bowel project protocols of node-negative breast cancer. *J Clin Oncol* 2009; 27:2466-73.
27. Aberizk WJ, Silver B, Henderson IC, Cady B, Harris JR. The use of radiotherapy for treatment of isolated locoregional recurrence of breast carcinoma after mastectomy. *Cancer* 1986; 58:1214-8.
28. Willner J, Kiricuta IC, Kölbl O. Locoregional recurrence of breast cancer following mastectomy: always a fatal event? Results of univariate and multivariate analysis. *Int J Radiat Oncol Biol Phys* 1997; 37:853-63.
29. van Tienhoven G, Voogd AC, Peterse JL, et al. Prognosis after treatment for locoregional recurrence after mastectomy or breast conserving therapy in two randomised trials (EORTC 10801 and DBCG-82TM). EORTC Breast Cancer Cooperative Group and the Danish Breast Cancer Cooperative Group 4029. *Eur J Cancer* 1999; 35:32-8.
30. Yi M, Buchholz TA, Meric-Bernstam F, et al. Classification of ipsilateral breast tumor recurrences after breast conservation therapy can predict patient prognosis and facilitate treatment planning. *Ann Surg* 2011; 253:572-9.
31. Nishimura S, Takahashi K, Akiyama F, et al. Classification of ipsilateral breast tumor recurrence after breast-conserving therapy: new primary cancer allows a good prognosis. *Breast Cancer* 2005; 12:112-7.
32. Huang E, Buchholz TA, Meric F, et al. Classifying local disease recurrences after breast conservation therapy based on location and histology: new primary tumors have more favorable outcomes than true local disease recurrences. *Cancer* 2002; 95: 2059-67.
33. Smith TE, Lee D, Turner BC, Carter D, Haffty BG. True recurrence vs new primary ipsilateral breast tumor relapse: an analysis of clinical and pathologic differences and their implications in natural history, prognoses, and therapeutic management. *Int J Radiat Oncol Biol Phys* 2000; 48:1281-9.
34. Parikh RR, Housman D, Yang Q, Toppmeyer D, Wilson LD, Haffty BG. Prognostic value of triple-negative phenotype at the time of locally recurrent, conservatively treated breast cancer. *Int J Radiat Oncol Biol Phys* 2008; 72:1056-63.
35. Chang JS, Wang F, Ewing C, et al. Chest wall recurrence rates for low risk patients with close/positive margins after mastectomy for breast cancer, treated with reexcision and no postmastectomy radiation therapy (PMRT). *Int J Radiat Oncol Biol Phys* 2015; 93:E49.
36. Abner AL, Recht A, Eberlein T, et al. Prognosis following salvage mastectomy for recurrence in the breast after conservative surgery and radiation therapy for early-stage breast cancer. *J Clin Oncol* 1993; 11:44-8.
37. Salvadori B, Marubini E, Miceli R, et al. Reoperation for locally recurrent breast cancer in patients previously treated with conservative surgery. *Br J Surg* 1999; 86: 84-7.
38. Alpert TE, Kuerer HM, Arthur DW, Lannin DR, Haffty BG. Ipsilateral breast tumor recurrence after breast conservation therapy: outcomes of salvage mastectomy vs salvage breast-conserving surgery and prognostic factors for salvage breast preservation. *Int J Radiat Oncol Biol Phys* 2005; 63:845-51.
39. Schwaibold F, Fowble B, Solin L. The results of radiation therapy for isolated local regional recurrence after mastectomy. *Int J Radiat Oncol Biol Phys* 1991; 21:299-310.
40. Halverson KJ, Perez CA, Kuske RR, Garcia DM, Simpson JR, Fineberg B. Isolated local-regional recurrence of breast cancer following mastectomy: radiotherapeutic management. *Int J Radiat Oncol Biol Phys* 1990; 19:851-8.
41. Haylock BJ, Coppin CM, Jackson J, Basco VE, Wilson KS. Locoregional first recurrence after mastectomy: prospective cohort studies with and without immediate chemotherapy. *Int J Radiat Oncol Biol Phys* 2000; 46:355-62.
42. Faneyte IF, Rutgers EJ, Zoetmulder FA. Chest wall resection in the treatment of locally recurrent breast carcinoma indications and outcome for 44 patients. *Cancer* 1997; 80:886-91.
43. Port ER, Fey J, Gemignani ML, et al. Reoperative sentinel lymph node biopsy: a new option for patients with primary or locally recurrent breast carcinoma. *J Am Coll Surg* 2002; 195:167-72.
44. Derkx F, Maaskant-Braat AJG, van der Sangen MJC, et al. Staging and management of axillary lymph nodes in patients with local recurrence in the breast or chest wall after a previous negative sentinel node procedure. *Eur J Surg Oncol* 2010; 36:646-51.
45. Cajucom CC, Tsangaris TN, Nemoto T, Driscoll D, Penetrante RB, Holyoke ED. Results of salvage mastectomy for local recurrence after breast-conserving surgery without radiation therapy. *Cancer* 1993; 71:1774-9.
46. Taback B, Nguyen P, Hansen N, Edwards GK, Conway K, Giuliano AE. Sentinel lymph node biopsy for local recurrence of breast cancer after breast-conserving therapy. *Ann Surg Oncol* 2006; 13:1099-104.
47. Port ER, Garcia-Etienne CA, Park J, Fey J, Borgen PI, Cody HS. Reoperative sentinel lymph node biopsy: a new frontier in the management of ipsilateral breast tumor recurrence. *Ann Surg Oncol* 2007; 14:2209-14.

48. Kaur P, Kiluk JV, Meade T, et al. Sentinel lymph node biopsy in patients with previous ipsilateral complete axillary lymph node dissection. *Ann Surg Oncol* 2011; 18:727-32.
49. Maaskant-Braat AJG, Roumen RMH, Voogd AC, et al. Sentinel node and recurrent breast cancer (SNARB): results of a nationwide registration study. *Ann Surg Oncol* 2013; 20:620-6.
50. Intra M, Viale G, Vila J, et al. Second axillary sentinel lymph node biopsy for breast tumor recurrence: experience of the European Institute of Oncology. *Ann Surg Oncol* 2014; 22:2372-7.
51. Karam A, Stempel M, Cody HS, Port ER. Reoperative sentinel lymph node biopsy after previous mastectomy. *J Am Coll Surg* 2008; 207:543-8.
52. Maaskant-Braat AJG, Voogd AC, Roumen RMH, Nieuwenhuijzen GAP. Repeat sentinel node biopsy in patients with locally recurrent breast cancer: a systematic review and meta-analysis of the literature. *Breast Cancer Res Treat* 2013; 138:13-20.
53. Newman LA. Lymphatic mapping and sentinel lymph node biopsy for locally recurrent breast cancer: new clues to understanding the biology of chest wall relapse [comment]. *Ann Surg Oncol* 2007; 14:2182-4.
54. Ugras S, Matsen C, Eaton A, Stempel M, Morrow M, Cody HS. Reoperative sentinel lymph node biopsy is feasible for locally recurrent breast cancer, but is it worthwhile? *Ann Surg Oncol* 2016; 23:744-8.
55. Deutsch M. Repeat high-dose external beam irradiation for in-breast tumor recurrence after previous lumpectomy and whole breast irradiation. *Int J Radiat Oncol Biol Phys* 2002; 53:687-91.
56. Wahl AO, Rademaker A, Kiel KD, et al. Multi-institutional review of repeat irradiation of chest wall and breast for recurrent breast cancer. *Int J Radiat Oncol Biol Phys* 2008; 70:477-84.
57. Hannoun-Levi JM, Houvenaeghel G, Ellis S, et al. Partial breast irradiation as second conservative treatment for local breast cancer recurrence. *Int J Radiat Oncol Biol Phys* 2004; 60:1385-92.
58. Resch A, Fellner C, Mock U, et al. Locally recurrent breast cancer: pulse dose rate brachytherapy for repeat irradiation following lumpectomy—a second chance to preserve the breast. *Radiology* 2002; 225:713-8.
59. Datta N, Puric E, Klingbiel D, Gomez S, Bodis S. Hyperthermia and radiation therapy in locoregional recurrent breast cancers: a systematic review and meta-analysis. *Int J Radiat Oncol Biol Phys* 2016; 94:1073-87.
60. Müller A, Eckert F, Heinrich V, Bamberg M, Brucker S, Hehr T. Re-surgery and chest wall radiation for recurrent breast cancer—a second curative approach. *BMC Cancer* 2011; 11:197.
61. Waeber M, Castiglione-Gertsch M, Dietrich D, et al. Adjuvant therapy after excision and radiation of isolated postmastectomy locoregional breast cancer recurrence: definitive results of phase III randomized trial (SAKK 23/83) comparing tamoxifen with observation. *Ann Oncol* 2003; 14:1215-21.
62. Aebi S, Gelber S, Anderson SJ, et al. Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial. *Lancet Oncol* 2014; 15: 156-63.