Review

Can Locoregionally Recurrent Breast Cancer Be Cured?

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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.

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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

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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.

margin width on local recurrence yielded the finding that more 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]