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The Importance of Systemic Therapy in Minimizing Local Recurrence after Breast-Conserving Surgery: The NSABP Experience

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Abstract

Adjuvant systemic therapy significantly reduces rates of distant recurrence and death. The effect of systemic therapy is not limited to reducing distant recurrences but also extends to reducing loco-regional recurrences, and rates of loco-regional recurrence have steadily declined over the past 25 years. This review focuses on the effect of adjuvant systemic therapy on rates of ipsilateral breast tumor recurrence following lumpectomy plus breast irradiation in several pivotal NSABP trials in early-stage breast cancer.

Keywords

lumpectomy; ipsilateral breast tumor recurrence; adjuvant systemic therapy

INTRODUCTION

The loco-regional treatment of breast cancer has undergone considerable evolution during the past half century as a result of a change in the biologic understanding as well as the clinical presentation of the disease. Starting with the pivotal randomized clinical trials from the NSABP and the Milan group [1–3], radical mastectomy was replaced by modified radical mastectomy and eventually breast-conserving surgery, and breast irradiation became the preferred method of loco-regional management in appropriate candidates [4]. Based on these findings, increasing adoption of breast-conserving surgery was documented in the 1990s, and the rates of breast conservation became a quality indicator for breast cancer programs.

An important measure of the success of breast-conserving surgery is the rate of development of ipsilateral breast tumor recurrence (IBTR). Over the years significant amount of research

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has been conducted in order to identify significant predictors for the development of IBTR and therapeutic interventions to minimize it.

The early pivotal trials evaluating breast-conserving surgery with or without breast irradiation demonstrated long-term rates of IBTR of around 40% with lumpectomy alone, around 15% with lumpectomy plus breast irradiation and around 10% with quadrantectomy plus breast irradiation [2,3]. Based on these findings, the addition of adjuvant breast irradiation became the standard of care for women who undergo breast-conserving surgery.

Since the reporting of the pivotal trials of breast-conserving surgery, there has been a continuous decline in the rates of IBTR. Many factors are responsible for this favorable trend, including a decrease in the size of the primary breast tumors by early detection, improvements in surgical and radiotherapy techniques, and better selection of appropriate candidates for breast-conserving surgery. In addition, the adoption and widespread use of effective adjuvant systemic therapy is arguably one of the most important factors contributing to the decline in IBTR rates

PATIENTS AND METHODS

NSABP adjuvant systemic therapy trials demonstrating significant improvements in disease-free and overall survival were reviewed, and the published results on rates of IBTR and other loco-regional recurrences according to treatment groups are summarized. Trials evaluating systemic therapy for patients with DCIS were also included in this review.

In addition, updated analyses of IBTR rates with longer follow-up were performed for patients treated with lumpectomy plus breast irradiation in several of these NSABP trials. The primary end point for these analyses was time to first IBTR. Other loco-regional recurrences, distant recurrences, second primary cancers, and deaths before IBTR were treated as competing events. Aalen-Johansen estimates were used to determine the cumulative incidence of IBTR for patients in each treatment arm. Treatment comparisons of time to first IBTR were based on log-rank tests. A P-value <0.05 for the log-rank test was considered statistically significant.

RESULTS

Effect of Systemic Therapy on Ipsilateral Breast Tumor Recurrence: The NSABP Experience

In early-stage breast cancer, there is ample information on the correlation between loco-regional recurrence and systemic recurrence. Both events share the same risk factors such as tumor size, grade, and nodal involvement. Thus, given the significant effect of adjuvant systemic therapy in reducing the rates of distant recurrence, it is reasonable to expect a similar effect of adjuvant systemic therapy in reducing the rates of loco-regional recurrence and, by extension, rates of IBTR after breast-conserving surgery plus breast irradiation.

The earliest observation on the effect of systemic therapy on the rates of IBTR came from the NSABP B-06 trial [2]. In that trial, the cumulative incidence of IBTR 20 years after surgery was 39.2% in patients who underwent lumpectomy alone and 14.3% in those who

underwent lumpectomy plus breast irradiation ($P < 0.001$). In patients with negative nodes, 36.2% of those who did not receive breast irradiation and 17.0% of those who did had an IBTR within 20 years (53% reduction, $P < 0.001$). In patients with positive nodes, 44.2% of those who did not receive breast irradiation and 8.8% of those who did had an IBTR (80% reduction, $P < 0.001$). Thus, the effect of breast irradiation was more pronounced in patients with positive lymph nodes, who also received adjuvant chemotherapy per protocol specification.

Since the reporting of the results of the B-06 trial, there have been numerous clinical trials that have confirmed a robust effect of adjuvant systemic therapy on the rates of IBTR after lumpectomy and breast irradiation.

Starting in the 1980s, the NSABP conducted several randomized clinical trials evaluating adjuvant tamoxifen, adjuvant chemotherapy or the combination of both in patients with node-negative invasive breast cancer as well as in those with ductal carcinoma in situ. These studies provide an opportunity to assess the effects of systemic therapy on the rates of loco-regional recurrence in general and on IBTR in particular as they relate to this review. Additional trials that evaluated neoadjuvant chemotherapy and targeted biologics such as trastuzumab are also included.

Effect of Tamoxifen in Patients with Ductal Carcinoma In Situ (NSABP B-24)

The NSABP B-24 trial was designed to evaluate the role of tamoxifen after lumpectomy and breast irradiation in patients with ductal carcinoma in situ (DCIS). Between 1991 and 1994, 1,804 women with DCIS treated with lumpectomy were randomly assigned to receive postoperative radiotherapy and either 5 years of tamoxifen or 5 years of placebo. Patients were eligible whether the lumpectomy margins were free, involved, or unknown. Results from this trial have been published on several occasions [5–7]. At 5 years, women in the tamoxifen group had fewer breast cancer events compared to those taking placebo (8.2% vs. 13.4%, $P = 0.0009$). The risk of ipsilateral breast cancer was lower in the tamoxifen group even when sample margins contained tumor and when DCIS was associated with comedonecrosis [5]. With 7 years of follow-up [6] the addition of tamoxifen significantly reduced the incidence of invasive and noninvasive breast cancer events in the ipsilateral as well as in the contralateral breast. The cumulative incidence of all ipsilateral and contralateral breast cancer events was reduced by 39%, from 16.0% in the placebo group to 10.0% in the tamoxifen group ($P = 0.0003$) [6]. Tamoxifen reduced the rate of all invasive breast cancer events by 45% ($P = 0.0009$) and the rate of noninvasive breast cancer events by 27% ($P = 0.11$). When the effect of tamoxifen was examined according to the location of the first event, the cumulative incidence of ipsilateral breast cancers was reduced by 31% (11.1% with tamoxifen vs. 7.7% with placebo, $P = 0.02$) and the cumulative incidence of contralateral breast cancers was reduced by 47% (4.9% vs. 2.3%, $P = 0.010$). More updated results with 163 months of median follow-up [7] demonstrated that the addition of tamoxifen to breast irradiation significantly reduced the rates of invasive IBTR by 32% ($P = 0.025$). The 15-year cumulative incidence of invasive IBTR was 10.0% for lumpectomy plus breast irradiation and 8.5% with lumpectomy plus breast irradiation plus tamoxifen. Tamoxifen also reduced the 15-year cumulative incidence of all contralateral breast cancers

(10.8% for lumpectomy + breast irradiation + placebo vs. 7.3% for lumpectomy + breast irradiation + tamoxifen).

When the benefit of tamoxifen in NSABP B-24 was examined according to hormone-receptor status of the DCIS [8], patients with ER-positive DCIS treated with tamoxifen (vs. placebo) showed significant decreases in subsequent breast cancer both at 10 years (HR: 0.49; $P < 0.001$) and at overall follow-up (HR, 0.60; $P = 0.003$), which remained significant in multivariable analysis (overall HR, 0.64; $P = 0.003$). Results were similar, but less significant, when subsequent ipsilateral and contralateral, invasive and noninvasive, breast cancers were considered separately. No significant benefit was observed in ER-negative DCIS.

Current Directions in Further Reducing IBTR in Patients with DCIS

Two additional systemic therapy approaches have been utilized in an attempt to further reduce the rates of IBTR (and possibly contralateral breast cancer events) in patients with DCIS.

The first approach evaluates the aromatase inhibitor anastrozole versus tamoxifen in the NSABP B-35 trial. This phase III trial randomly assigned postmenopausal patients with localized, ER-positive and/or PgR-positive DCIS treated with lumpectomy plus breast irradiation to tamoxifen versus anastrozole for 5 years. The primary aim of the trial is to evaluate the effectiveness of anastrozole compared to tamoxifen in preventing the subsequent occurrence of breast cancer (local, regional and distant recurrences, and contralateral breast cancer). This protocol has completed its accrual goal after accruing over 3,100 patients and is currently awaiting maturation of follow-up data.

The second approach evaluates trastuzumab as a potential radiosensitizer in patients with HER-2 neu positive DCIS. The NSABP B-43 trial currently randomly assigns HER-2 neu positive DCIS patients treated with lumpectomy to breast irradiation versus breast irradiation plus two doses of trastuzumab, starting on day 1 of breast irradiation and repeated once more 3 weeks later. The primary endpoint of the study is the development of any breast cancer event. Secondary endpoints include in-breast recurrence and development of contralateral breast cancer. This trial will accrue 2,000 patients during a 3.3-year period. Accrual is expected to be completed in 2015.

Effect of Tamoxifen in Patients with Small Invasive Breast Cancer (NSABP B-21)

The NSABP B-21 trial was designed to test whether tamoxifen was as effective as breast irradiation in preventing IBTR in patients with small invasive breast cancers and whether the addition of tamoxifen to breast irradiation would further improve on the local and systemic control of the disease. A total of 1,009 women with node-negative invasive breast cancer <1 cm treated with lumpectomy were randomly assigned to tamoxifen alone for 5 years, breast irradiation plus placebo for 5 years, or breast irradiation plus tamoxifen for 5 years. Results from this trial [9] demonstrated that the addition of breast irradiation resulted in a 49% lower hazard rate of IBTR compared to tamoxifen alone; more importantly, the addition of tamoxifen to breast irradiation resulted in a 63% reduction of the rate of IBTR compared to breast irradiation alone. Cumulative incidence of IBTR through 8 years was 16.5% with

tamoxifen alone, 9.3% with breast irradiation and placebo, and 2.8% with breast irradiation and tamoxifen. Distant disease-free survival and overall survival were not significantly different between the three treatment groups. Thus, this trial demonstrated that in node-negative patients with small invasive tumors treated with lumpectomy, tamoxifen was not as effective as breast irradiation in controlling the disease in the breast but that the addition of tamoxifen to breast irradiation significantly reduced the rates of IBTR.

Additional analyses from this trial with median follow-up at 13.2 years demonstrate that the cumulative incidence of IBTR was 28.4% with tamoxifen alone, 13.8% with breast irradiation and placebo, and 8.3% with breast irradiation and tamoxifen ($P < 0.001$) (NSABP unpublished work; G. Tang, unpublished work).

Effect of Tamoxifen in Node-Negative, ER-Positive Breast Cancer (NSABP B-14)

The NSABP B-14 trial randomly assigned patients with node-negative, ER-positive breast cancer to 5 years of adjuvant tamoxifen or 5 years of placebo. Published results from this trial through 10 and 15 years of follow-up continue to demonstrate a statistically significant disease-free survival and overall survival benefit from tamoxifen [10,11]. In addition to the effects of tamoxifen in reducing distant recurrence and death, the B-14 trial also has consistently demonstrated that treatment with tamoxifen significantly reduced the rates of IBTR following lumpectomy plus breast irradiation. With 42 months of mean follow-up, rates of IBTR were 3.4% in the placebo arm and 1.5% in the tamoxifen arm [12]. These effects have persisted with additional follow-up. With median follow-up of 19.1 years, the cumulative incidence of IBTR was 19.0% in the placebo arm and 10.8% in the tamoxifen arm ($P <0.001$) (NSABP, unpublished work; G. Tang, unpublished work).

Effect of Adjuvant Chemotherapy in Node-Negative, ER-Negative Breast Cancer (NSABP B-13 and B-19)

The NSABP B-13 trial randomly assigned patients with negative nodes and negative estrogen receptors to surgery alone or surgery followed by 12 months of adjuvant chemotherapy with methotrexate and sequentially administered 5-FU (M-F) followed by leucovorin. Findings through 14 years of follow-up [13] continue to demonstrate that the significant improvements in disease-free and overall survival from M-F, previously reported after 5 [14] and 8 [15] years of follow-up, have persisted. In addition to the effects of adjuvant M-F in reducing distant recurrence and death, the B-13 trial also demonstrated that M-F significantly reduced the rates of IBTR following lumpectomy plus breast irradiation. With 42 months of mean follow-up, rates of IBTR were 7.2% in the observation arm and 2.6% in the M-F arm [12]. These effects on reduction of IBTR have persisted with 8 years of follow-up [15], with IBTR rates of 2.6% for patients who received M-F versus 13.4% in those who were treated with surgery alone and no chemotherapy ($P =0.001$) [15]. These effects have persisted with additional follow-up. With median follow-up of 16.1 years, the cumulative incidence of IBTR was 19.9% in the observation arm and 6.3% in the M-F arm ($P < 0.001$).

Following completion of the NSABP B-13, a subsequent trial in the same patient population (NSABP B-19) attempted to determine whether the alkylating agent cyclophosphamide

contributed additional benefit when administered with methotrexate and 5-FU (CMF regimen). Over a 6-month period, patients received either six courses of M-F or six courses of CMF. A total of 1,095 patients were randomly assigned. Through 8 years of follow-up [13], just as first reported after 5 years [15], results demonstrated a statistically significant disease-free and overall survival advantage with CMF over M-F. Those advantages were most evident in women aged <50 years although there was no statistically significant interaction between age and treatment effect. In addition to the effects of adjuvant CMF versus methotrexate and 5-FU in reducing distant recurrence and death, the B-19 trial also demonstrated that compared to M-F, treatment with CMF significantly reduced the rates of IBTR following lumpectomy plus breast irradiation. At 5 years, the frequency of IBTR was 5.6% with M-F and 0.6% with CMF (P =0.03) [15]. These effects have persisted with additional follow-up. With median follow-up of 15.7 years, the cumulative incidence of IBTR was 11.9% in the M-F arm and 7.1% in the CMF arm (P =0.07) (NSABP, unpublished work; G. Tang, unpublished work).

Effect of Adjuvant Chemotherapy in Addition to Tamoxifen in Node-Negative, ER-Positive Breast Cancer NSABP B-20 Trial)

The NSABP B-20 trial [16] was conducted to determine whether chemotherapy plus tamoxifen would be of greater benefit than tamoxifen alone in patients with axillary lymph node-negative, estrogen receptor-positive breast cancer. Between 1988 and 1993, 2,363 patients were randomly assigned to receive either tamoxifen for 5 years, or tamoxifen plus six cycles of sequential methotrexate and 5-FU followed by leucovorin (M-FT) or tamoxifen plus six cycles of cyclophosphamide, methotrexate, and 5-FU (CMFT). Through 5 years and subsequently 8 years of follow-up, the combination of chemotherapy plus tamoxifen resulted in significantly improved disease-free survival and overall survival over tamoxifen alone [13,16]. The reduction in recurrence and mortality was greatest in patients aged <50 years. The most recent update with 12 years of follow-up continues to demonstrate a statistically significant improvement in disease-free survival and a borderline statistically significant improvement in overall survival with the addition of chemotherapy [11]. Similarly to what has been shown in the previous node-negative, ER-negative NSABP trials evaluating adjuvant chemotherapy, the rate of IBTR following lumpectomy plus breast irradiation was significantly reduced with the addition of chemotherapy to tamoxifen and more so with CMFT than with M-FT. The annual rate of IBTR per 100 patients/year was 0.88 with tamoxifen alone, 0.48 with M-FT, and 0.22 with CMFT (P < 0.025) [16]. These effects have persisted with additional follow-up. With median follow-up of 14.5 years, the cumulative incidence of IBTR was 12.5% with tamoxifen alone, 9.7% with M-FT, and 4.6% with CMFT (P =0.009) (NSABP, unpublished work; G. Tang, unpublished work).

Effect of Neoadjuvant Chemotherapy in Reducing IBTR: Role of Pathologic Complete Response

For patients with early-stage breast cancer who receive surgery as their initial treatment, there is abundant information on rates and predictors of loco-regional recurrence (LRR) and IBTR, with or without adjuvant systemic therapy [17–20]. In contrast, there is limited information on rates and predictors of LRR and IBTR for patients who receive neoadjuvant chemotherapy. In the 1980s and 1990s, the NSABP conducted two neoadjuvant

chemotherapy trials (NSABP B-18 and NSABP B-27) that provide us with useful information on the rates and patterns of loco-regional recurrence in patients treated with neoadjuvant chemotherapy and allow us to identify independent predictors of LRR in this setting [21]. In a combined analysis of all patients who received neoadjuvant chemotherapy in these two trials, the 10-year cumulative incidence of LRR was 12.3% for mastectomy patients (8.9% chest wall/3.4% regional-nodal) and 10.3% for lumpectomy plus breast radiotherapy patients (8.1% IBTR/2.2% regional-nodal). There was a significant reduction in the 10-year cumulative incidence of LRR with the addition of neoadjuvant docetaxel to neoadjuvant AC versus AC alone in B-27 (8.5% vs. 12.2%, P = 0.02) and a nearly statistically significant reduction with the addition of adjuvant docetaxel to neoadjuvant AC versus the AC-alone arm in B-27 (9.5% vs. 12.2%, P = 0.08). Independent predictors of LRR in lumpectomy patients were age, clinical nodal status (before neoadjuvant chemotherapy), and pathologic breast tumor response/nodal status. By using these independent predictors, groups at low, intermediate, and high risk of LRR could be identified. For patients treated with lumpectomy plus breast radiotherapy, the majority of LRRs were IBTRs. For patients >50 years of age the rates of IBTR ranged between 5.2% and 6.7% for those who presented with clinically negative axillary lymph nodes and between 6.5% and 8.7% for those who presented with clinically positive axillary lymph nodes and there was no observable trend towards lower IBTR rates for patients who had pathologic complete response (pCR) in the breast and negative axillary nodes compared to those with residual disease in the breast and/or positive axillary nodes. However, for patients <50 years of age, there was a trend of increasing IBTR rates with decreasing pathologic breast tumor response and positive pathologic nodal status. For clinically node-negative patients, IBTR rates were 6.9% for those with pCR in the breast and pathologically negative nodes, 8% for those with residual disease and pathologically negative nodes and 10.5% for those with pathologically positive nodes. For clinically node-positive patients the respective IBTR rates were 7%, 10%, and 13.6% [21]. These findings suggest that, in patients treated with neoadjuvant chemotherapy, the achievement of pCR in the breast diminishes the adverse effects of age and clinical nodal status on the rates of IBTR.

Effect of Trastuzumab in Reducing Loco-Regional Recurrence NSABP B-31/NCCTG N9831

In the 1990s a substantial amount of information accumulated on the significant role of HER-2/neu overexpression/amplification in breast cancer both as a predictor of benefit from anthracycline-containing chemotherapy and as a therapeutic target for antibody development [22–26]. In the advanced-disease setting, trastuzumab has demonstrated activity as a single agent [26] and in combination with chemotherapy [25]. However, this improvement was associated with a substantial increase in cardiac toxicity, particularly when an anthracycline-containing regimen was combined with trastuzumab. Based on these findings, the NSABP B-31 trial was designed to evaluate the role of trastuzumab in the adjuvant setting by comparing doxorubicin plus cyclophosphamide followed every 3 weeks by paclitaxel with this same chemotherapy regimen plus 1 year of trastuzumab starting with paclitaxel, in node-positive, HER-2/neu-positive patients. Around the same time, the North Central Cancer Treatment Group conducted a similar trial that compared AC followed by weekly paclitaxel versus the same chemotherapy plus trastuzumab either concurrently with paclitaxel or sequentially for 1 year. Besides node-positive patients, the N9831 trial also

randomly assigned 191 high-risk/node-negative patients. The similarities between the two trials led to the decision to perform a joint analysis by combining the control arms and the concurrent trastuzumab arms from both trials. Interim analysis of the joined data revealed that with a median follow-up of 2 years, adjuvant trastuzumab significantly reduced the risk of treatment failure by 52% and the risk of death by 33% [27]. These significant improvements in disease-free and overall survival have persisted with additional follow-up [28] and were confirmed by other clinical trials of similar design [29,30].

In the first report of the joint analysis of B-31 and N9831 [27], a significant benefit from adding trastuzumab to adjuvant chemotherapy was evident at both local-regional and distant sites. Although not reported separately for IBTR or other loco-regional recurrences, there were 47 loco-regional recurrences in the chemotherapy alone arm versus 27 in the chemotherapy-plus-trastuzumab arm. This reduction in loco-regional recurrence appears to be of the same magnitude as the reduction in distant recurrence from the addition of trastuzumab [27]. This reduction in the rates of loco-regional recurrence with the addition of trastuzumab to chemotherapy has persisted with 10 years of follow-up [chemotherapy-alone-arm: 119 events (5.9%) vs. trastuzumab-plus-chemotherapy arm: 81 events (4.0%) (Perez et al., personal communication)].

DISCUSSION

Several factors have played an important role in the continuous reduction of the rates of IBTR and other loco-regional recurrence observed during the past 25 years. Improvements in breast imaging with digital mammography and breast MRI have helped to better select appropriate lumpectomy candidates. Improvements in surgical technique, pathologic assessment of resection margins, and new developments in radiotherapy have also contributed significantly in reducing rates of IBTR.

As demonstrated above, adjuvant systemic therapy has also had a profound impact in further reducing the risk for IBTR and other loco-regional recurrence. As shown by the IBTR data according to nodal status in the B-06 trial, it appears that adjuvant systemic therapy has a synergistic effect with breast irradiation, because the reduction in IBTR with breast irradiation in node-positive patients in that study (who also received adjuvant chemotherapy) was of larger magnitude than that observed in node-negative patients (no chemotherapy).

The NSABP experience on the rates of IBTR and other loco-regional recurrence and on outcomes following the development of these events was collectively reported in two publications [31,32] that underscore the continuous reduction in the rates of IBTR and other loco-regional recurrence and provide further insight on the biologic significance of these events.

The first publication [31] focused on several of the pivotal NSABP trials evaluating systemic therapy in node-negative early-stage breast cancer. It included 3,799 women randomly assigned to five NSABP protocols of node-negative disease (B-13, B-14, B-19, B-20, and B-23) who underwent lumpectomy and whole breast irradiation with or without adjuvant systemic therapy. Cumulative incidences of IBTR and other loco-regional recurrence were

calculated, along with distant-disease-free interval and overall survival following these events. Four hundred nineteen patients (11.0%) experienced loco-regional recurrence: 342 (9.0%) experienced IBTR, and 77 (2.0%) experienced other loco-regional recurrence. The 12-year cumulative incidences of IBTR and other loco-regional recurrence in patients treated with adjuvant systemic therapy were 6.6% and 1.8%, respectively. Overall, 37.1% of IBTRs and 72.7% of other loco-regional recurrences occurred within 5 years of diagnosis. Older age, black race, higher body mass index, larger tumors, and occurrence of IBTR or other loco-regional recurrence were significantly associated with increased mortality. The 5-year overall survival after IBTR and other loco-regional recurrence were 76.6% and 34.9%, respectively. Adjusted hazard ratios for mortality associated with IBTR and other loco-regional recurrence were significantly higher in estrogen receptor (ER)-negative patients than in ER-positive patients. Patients with early loco-regional recurrence had worse overall survival and distant disease-free interval than those with later-occurring loco-regional recurrence. These findings suggest that although IBTR and other loco-regional recurrence is uncommon in patients with node-negative breast cancer who are treated with lumpectomy, breast irradiation, and adjuvant systemic therapy, those who do develop these events have substantially worse overall survival and distant disease-free interval.

The second publication [32] focused on several of the pivotal NSABP trials evaluating systemic therapy in node-positive early-stage breast cancer. It included 2,669 women randomly assigned to five NSABP node-positive protocols (B-15, B-16, B-18, B-22, and B-25), who were treated with lumpectomy, whole-breast irradiation, and adjuvant systemic therapy. Four hundred twenty-four patients (15.9%) experienced loco-regional recurrence: 259 (9.7%) experienced IBTR, and 165 (6.2%) experienced other loco-regional recurrence. The 10-year cumulative incidence of IBTR and other loco-regional recurrence was 8.7% and 6.0%, respectively. Most loco-regional recurrences occurred within 5 years (62.2% for IBTR and 80.6% for other loco-regional recurrence). The 5-year distant disease-free survival rates after IBTR and other loco-regional recurrence were 51.4% and 18.8%, respectively. The 5-year overall survival rates after IBTR and other loco-regional recurrence were 59.9% and 24.1%, respectively. These findings, similarly to the ones from the node-negative patients, suggest that node-positive breast cancer patients who developed IBTR or other loco-regional recurrence had significantly poorer prognoses than patients who did not experience these events.

The above findings confirmed prior observations from the NSABP B-06 trial [33] on the biologic significance of IBTR and other loco-regional recurrence as an indicator rather than an instigator of increased risk for distant disease [31–33]. This is an important step in better understanding breast cancer biology and has significant clinical implications [34]. As a result of these findings, the effect of systemic chemotherapy at the time of IBTR or other loco-regional recurrence was formally evaluated in a randomized clinical trial (CALOR trial), which demonstrated significant improvement in disease-free survival and overall survival with the use of chemotherapy in this poor-prognosis group of patients [35].

Increasing use of neoadjuvant chemotherapy, development of more active neoadjuvant chemotherapy regimens (with the addition of biologics), and better selection of appropriate candidates, also hold great promise for further reducing the rates of IBTR and other loco-

regional recurrence. In addition, the ability to document primary tumor and nodal response to neoadjuvant chemotherapy provides an opportunity to potentially further tailor the use of loco-regional therapy modalities or even to possibly eliminate one or both of these interventions (surgery or breast irradiation).

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