An Update on Randomized Clinical Trials in Breast Cancer

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KEYWORDS
- Breast cancer • Randomized clinical trials (RCT) • Axillary staging
- Lymphadenectomy • Sentinel lymph node (SLN) • Breast conservation therapy (BCT)

KEY POINTS
- Numerous clinical trials reveal new innovations and therapies that continually change the treatment and prevention of breast cancer.
- Earlier trials have changed the standard of care from radical mastectomy to breast conservation therapy and individualized treatment based on tumor-specific biology.
- As research continues and long-term follow-up results become available, updated reviews on randomized clinics trials become exceedingly important in discerning the most effective and oncologically safe therapies to provide optimal outcomes.

INTRODUCTION

In 2016, more than 250,000 women were predicted to be diagnosed with breast cancer. Representing 14.6% of all new cancer cases in the United States, breast cancer is the most common cancer among women. Numerous clinical trials reveal new innovations and therapies that continually change the treatment and prevention of breast cancer. Earlier trials have changed the standard of care from radical mastectomy to breast conservation therapy (BCT) and individualized treatment based on tumor-specific biology. The landmark randomized clinical trials (RCT) in breast cancer were published in the 2002 and 2010 editions of this publication. As research continues and long-term follow-up results become available, updated reviews on randomized clinics trials become exceedingly important in discerning the most effective and oncologically safe therapies to provide optimal outcomes. Many of the published RCTs in the last 7 years have focused on decreasing the overtreatment of breast cancer.

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LEVEL IA EVIDENCE: PROSPECTIVE RANDOMIZED SURGICAL TRIALS AND META-ANALYSES IN BREAST CANCER


Hypothesis

BCT is an oncologically safe treatment of breast cancer.

Published Abstract

Background

The European Organisation for Research and Treatment of Cancer (EORTC) 10801 trial compared BCT with modified radical mastectomy (MRM) in patients with tumors 5 cm or smaller and axillary node-negative or node-positive disease. Compared with BCT, MRM resulted in better local control, but did not affect overall survival (OS) or time to distant metastases. This study reports 20-year follow-up results.

Methods

The EORTC 10801 trial was open for accrual between 1980 and 1986 in 8 centers in the United Kingdom, the Netherlands, Belgium, and South Africa. The trial randomized 448 patients to BCT and 420 to MRM. Randomization was done centrally, stratifying patients by institute, carcinoma stage (I or II), and menopausal status. BCT comprised lumpectomy and complete axillary clearance, followed by breast radiotherapy and a tumor-bed boost. The primary end point was time to distant metastasis. This analysis was done on all eligible patients, as they were randomized.

Findings

After a median follow-up of 22.1 years (interquartile range [IQR], 18.5–23.8), 175 patients (42%) had distant metastases in the MRM group versus 207 (46%) in the BCT group. Furthermore, 506 patients (58%) died (232 [55%] in the MRM group and 274 [61%] in the BCT group). No significant difference was observed between BCT and MRM for time to distant metastases (hazard ratio [HR], 1.13; 95% confidence interval [CI], 0.92–1.38; \( P = .23 \)) or for time to death (HR, 1.11; 95% CI, 0.94–1.33; \( P = .23 \)). Cumulative incidence of distant metastases at 20 years was 42.6% (95% CI, 37.8–47.5) in the MRM group and 46.9% (42.2–51.6) in the BCT group. Twenty-year OS was estimated to be 44.5% (95% CI, 39.3–49.5) in the MRM group and 39.1% (34.4–43.9) in the BCT group. There was no difference between the groups in time to distant metastases or OS by age (time to distant metastases: <50 years 1.09 [95% CI, 0.79–1.51] vs ≥50 years 1.16 [0.90–1.50]; OS <50 years 1.17 [0.86–1.59] vs ≥50 years 1.10 [0.89–1.37]).

Interpretation

BCT, including radiotherapy, offered as standard care to patients with early breast cancer seems to be justified, because long-term follow-up in this trial showed similar survival to that after mastectomy.

Editorial comments  RCTs have established the safety of BCT compared with mastectomy. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial compared patients with tumors less than 4 cm undergoing partial mastectomy and axillary node dissection or MRM. At 20 years, there was no difference in OS or disease-free survival (DFS). However, local recurrence was increased in the BCT group compared with the MRM group. Furthermore, results showed ipsilateral breast
tumor recurrence (IBTR) to be higher in the group that underwent partial mastectomy versus partial mastectomy followed by whole-breast radiation. Likewise, the Milan trial compared radical mastectomy with partial mastectomy followed by radiation in women with invasive breast cancer less than 2 cm. The long-term results have reflected those of NSABP B-06 with a significant difference in local recurrence: 8.8% for BCT versus 2.3% for radical mastectomy. Survival outcomes were not significantly different between the two groups. At the time of EORTC 10801 enrollment, patients with breast tumors less than 5 cm were randomized to BCT or MRM. Results have been consistent with the previous similar trials showing an increase in local recurrence, but no significant difference in OS or time to distant metastasis. Death rates were also increased with tumor size greater than 2 cm and lymph node metastasis across both treatment groups, showing the safety of BCT in patients with larger tumors and/or axillary metastasis. Also of consideration is the 48% rate of positive margins in the BCT group when comparing EORTC 10801 with the previously mentioned trials. Local recurrence rates were higher in the EORTC study, supporting that resection to negative margins is essential.

LEVEL IA EVIDENCE: PROSPECTIVE RANDOMIZED TRIALS AND META-ANALYSES ON EVALUATION AND MANAGEMENT OF THE AXILLA IN BREAST CANCER


Hypothesis
Sentinel lymph node (SLN) dissection is equal to axillary lymph node dissection.

Published Abstract

Background
SLN surgery was designed to minimize the side effects of lymph node surgery but still offer outcomes equivalent to axillary lymph node dissection (ALND). The aims of NSABP trial B-32 were to establish whether SLN resection in patients with breast cancer achieves the same survival and regional control as ALND, but with fewer side effects.

Methods
NSABP B-32 was a randomized controlled phase 3 trial done at 80 centers in Canada and the United States between May 1, 1999, and February 29, 2004. Women with invasive breast cancer were randomly assigned to either SLN resection plus ALND (group 1) or to SLN resection alone with ALND only if the SLNs were positive (group 2). Random assignment was done at the NSABP Biostatistical Center (Pittsburgh, PA) with a biased-coin minimization approach in an allocation ratio of 1:1. Stratification variables were age at entry (≤49 years, ≥50 years), clinical tumor size (≤2.0 cm, 2.1–4.0 cm, ≥4.1 cm), and surgical plan (lumpectomy, mastectomy). SLN resection was done with a blue dye and radioactive tracer. Outcome analyses were done in patients who were assessed as having pathologically negative sentinel nodes and for whom follow-up data were available. The primary end point was OS. Analyses were done on an intention-to-treat basis. All deaths, irrespective of cause, were included. The mean time on study for the SLN-negative patients with follow-up information was 95.6 months (range, 70.1–126.7). This study is registered with ClinicalTrials.gov, number NCT00003830.
Findings
A total of 5611 women were randomly assigned to the treatment groups, and 3989 had pathologically negative SLN. Three-hundred and nine deaths were reported in the 3986 SLN-negative patients with follow-up information: 140 of 1975 patients in group 1 and 169 of 2011 in group 2. Log-rank comparison of OS in groups 1 and 2 yielded an unadjusted HR of 1.20 (95% CI, 0.96–1.50; \( P = .12 \)). Eight-year Kaplan-Meier estimates for OS were 91.8% (95% CI, 90.4–93.3) in group 1 and 90.3% (95% CI, 88.8–91.8) in group 2. Treatment comparisons for DFS yielded an unadjusted HR of 1.05 (95% CI, 0.90–1.22; \( P = .54 \)). Eight-year Kaplan-Meier estimates for DFS were 82.4% (95% CI, 80.5–84.4) in group 1 and 81.5% (95% CI, 79.6–83.4) in group 2. There were 8 regional-node recurrences as first events in group 1 and 14 in group 2 (\( P = .22 \)). Patients are continuing follow-up for longer-term assessment of survival and regional control. The most common adverse events were allergic reactions, mostly related to the administration of the blue dye.

Interpretation
OS, DFS, and regional control were statistically equivalent between groups. When the SLN is negative, SLN surgery alone with no further ALND is an appropriate, safe, and effective therapy for patients with breast cancer with clinically negative lymph nodes.

Editorial comments
The results of this large, well-run, and well-supervised trial in terms of the appropriateness, safety, and effectiveness of SLN biopsy (SLNB) in patients with favorable node-negative disease showed equivalence in terms of DFS, OS, and locoregional recurrence but significantly lower risk of lymphedema.


Hypothesis
ALND does not decrease local regional recurrence in SLN-positive patients receiving BCT with 2 or fewer SLNs.

Published Abstract

Background and objective
The early results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial showed no difference in locoregional recurrence for patients with positive SLNs randomized either to ALND or SLN dissection (SLND) alone. This study now reports long-term locoregional recurrence results.

Methods
ACOSOG Z0011 prospectively examined OS of patients with SLN metastases undergoing BCT randomized to undergo ALND after SLND or no further axillary specific treatment. Locoregional recurrence was prospectively evaluated and compared between the groups.

Results
Four-hundred and forty-six patients were randomized to SLND alone and 445 to SLND and ALND. Both groups were similar with respect to age, Bloom-Richardson score, estrogen receptor (ER) status, adjuvant systemic therapy, histology, and tumor size. Patients randomized to ALND had a median of 17 axillary nodes removed compared
with a median of only 2 SLNs removed with SLND alone ($P < .001$). ALND, as expected, also removed more positive lymph nodes ($P < .001$). At a median follow-up of 9.25 years, there was no statistically significant difference in local recurrence-free survival ($P = .13$). The cumulative incidence of nodal recurrences at 10 years was 0.5% in the ALND arm and 1.5% in the SLND alone arm ($P = .28$). Ten-year cumulative locoregional recurrence was 6.2% with ALND and 5.3% with SLND alone ($P = .36$).

**Conclusions**

Despite the potential for residual axillary disease after SLND, SLND without ALND offers excellent regional control for selected patients with early metastatic breast cancer treated with BCT and adjuvant systemic therapy.

**Editorial comments**

This trial was heavily criticized for lack of enrollment, low power, crossover between arms, nonstandardization of radiation therapy, and short follow-up in a very favorable group of patients. This 10-year follow-up shows no difference in survival between ALND or SLND in patients with breast cancer undergoing BCT. However, the original report of this study showed no statistically significant difference in lymphedema between these two randomized arms, perhaps because of x-ray therapy (XRT) to the axilla. This report gives no further insight to that issue.


**Hypothesis**

Axillary dissection is overtreatment of patients with SLN micrometastases.

**Published Abstract**

**Background**

For patients with breast cancer and metastases in the sentinel nodes, axillary dissection has been standard treatment. However, for patients with limited sentinel node involvement, axillary dissection might be overtreatment. The IBCSG (International Breast Cancer Study Group) trial 23-01 was designed to determine whether no axillary dissection was noninferior to axillary dissection in patients with 1 or more micrometastatic ($< 2$ mm) sentinel nodes and tumors of a maximum 5 cm.

**Methods**

In this multicenter, randomized, noninferiority, phase 3 trial, patients were eligible if they had clinically nonpalpable axillary lymph nodes and a primary tumor of 5 cm or less and who, after sentinel node biopsy, had 1 or more micrometastatic ($≤ 2$ mm) SLNs with no extracapsular extension. Patients were randomly assigned (in a 1:1 ratio) to either undergo axillary dissection or not to undergo axillary dissection. Randomization was stratified by center and menopausal status. Treatment assignment was not masked. The primary end point was DFS. Noninferiority was defined as an HR of less than 1.25 for no axillary dissection versus axillary dissection. The analysis was by intention to treat. Per protocol, disease and survival information continue to be collected yearly. This trial is registered with ClinicalTrials.gov, NCT00072293.

**Findings**

Between April 1, 2001, and February 28, 2010, 465 patients were randomly assigned to axillary dissection and 469 to no axillary dissection. After the exclusion of 3 patients, 464 patients were in the axillary dissection group and 467 patients were in the no
axillary dissection group. After a median follow-up of 5.0 (IQR, 3.6–7.3) years, we recorded 69 DFS events in the axillary dissection group and 55 events in the no axillary dissection group. Breast cancer–related events were recorded in 48 patients in the axillary dissection group and 47 in the no axillary dissection group (10 local recurrences in the axillary dissection group and 8 in the no axillary dissection group; 3 and 9 contralateral breast cancers; 1 and 5 [corrected] regional recurrences; and 34 and 25 distant relapses). Other non–breast cancer events were recorded in 21 patients in the axillary dissection group and 8 in the no axillary dissection group (20 and 6 second nonbreast malignancies; and 1 and 2 deaths not caused by a cancer event). Five-year DFS was 87.8% (95% CI, 84.4–91.2) in the group without axillary dissection and 84.4% (95% CI, 80.7–88.1) in the group with axillary dissection (log-rank \( P = .16 \); HR for no axillary dissection vs axillary dissection was 0.78, 95% CI, 0.55–1.11; noninferiority \( P = .0042 \)).

Patients with reported long-term surgical events (grade 3–4) included 1 sensory neuropathy (grade 3), 3 lymphedema (2 grade 3 and 1 grade 4), and 3 motor neuropathy (grade 3), all in the group that underwent axillary dissection, and 1 grade 3 motor neuropathy in the group without axillary dissection. One serious adverse event was reported: a postoperative infection in the axilla in the group with axillary dissection.

Interpretation
Axillary dissection could be avoided in patients with early breast cancer and limited sentinel node involvement, thus eliminating complications of axillary surgery with no adverse effect on survival.

Editorial comments
Similar to Z-0011, IBCSG 23091 supports the finding that ALND can safely be omitted in selected patients who are clinically node negative. In contrast with Z-0011, in this study all SLN metastases were less than 2 mm, 28% of patients receiving BCT received intraoperative partial breast irradiation (PBI), and 9% of the patients had a mastectomy, connoting the possibility of extended indications to PBI and mastectomy patients with micrometastasis. In this study, 13% of patients with micrometastatic SLNs had additional involved lymph nodes on ALND. The present National Comprehensive Cancer Network (NCCN) guidelines recommend considering using tumor molecular markers (Oncotype DX, Genomic Health Redwood City, CA) for determination of systemic treatment when micrometastatic disease only is present. Whether ALND is needed to determine which patients have truly N1 disease and would benefit from more aggressive systemic treatment is unknown from this study. The results of the ALND compared with SLNB showed no effect of the rate of administration of chemotherapy. Overall, sequelae from ALND were worse than those from SLNB.


Hypothesis
Axillary radiation provides equal control compared with axillary node dissection in patients with nodal metastases.

Published Abstract

Background
If treatment of the axilla is indicated in patients with breast cancer who have a positive sentinel node, ALND is the present standard. Although ALND provides excellent regional control, it is associated with harmful side effects. The study aimed to assess
whether axillary radiotherapy provides comparable regional control with fewer side effects.

Methods
Patients with T1 to T2 primary breast cancer and no palpable lymphadenopathy were enrolled in the randomized, multicenter, open-label, phase 3 noninferiority EORTC 10981-22023 after mapping of the axilla: radiotherapy or surgery (AMAROS) trial. Patients were randomly assigned (1:1) by a computer-generated allocation schedule to receive either ALND or axillary radiotherapy in case of a positive sentinel node, stratified by institution. The primary end point was noninferiority of 5-year axillary recurrence, considered to be not more than 4% for the axillary radiotherapy group compared with an expected 2% in the ALND group. Analyses were by intention to treat and per protocol. The AMAROS trial is registered with ClinicalTrials.gov, number NCT00014612.

Findings
Between February 19, 2001, and April 29, 2010, 4823 patients were enrolled at 34 centers from 9 European countries, of whom 4806 were eligible for randomization. The study randomly assigned 2402 patients to receive ALND and 2404 to receive axillary radiotherapy. Of the 1425 patients with a positive sentinel node, 744 had been randomly assigned to ALND and 681 to axillary radiotherapy; these patients constituted the intention-to-treat population. Median follow-up was 6.1 years (IQR, 4.1–8.0) for the patients with positive SLNs. In the ALND group, 220 (33%) of 672 patients who underwent ALND had additional positive nodes. Axillary recurrence occurred in 4 of 744 patients in the ALND group and 7 of 681 in the axillary radiotherapy group. Five-year axillary recurrence was 0.43% (95% CI, 0.00–0.92) after ALND versus 1.19% (95% CI, 0.31–2.08) after axillary radiotherapy. The planned noninferiority test was underpowered because of the low number of events. The 1-sided 95% CI for the underpowered noninferiority test on the HR was 0.00 to 5.27, with a noninferiority margin of 2. Lymphedema in the ipsilateral arm was noted significantly more often after ALND than after axillary radiotherapy at 1 year, 3 years, and 5 years.

Interpretation
ALND and axillary radiotherapy after a positive sentinel node provide excellent and comparable axillary control for patients with T1 to T2 primary breast cancer and no palpable lymphadenopathy. Axillary radiotherapy results in significantly less morbidity.

Editorial comments
The AMAROS trial, although underpowered for a noninferiority test, showed equivalent survival as well as axillary recurrence compared with axillary XRT in SLN-positive patients. Lymphedema by arm circumference at 5 years was significant higher for ALND (13%) versus XRT (6%), although this was not true of shoulder function or quality of life. “10%” at the beginning of a sentence? of the randomized patients did not have an ALND and nearly 10% of XRT patients crossed over to the ALND group; two-thirds of these had additional positive nodes. In addition, 6% of patients in the ALND group and 2% of patients in the XRT group receive both ALND and XRT. Regardless of the problems with the trial and in light of the results of the preceding trials ACO-SOG Z0011 and IBCSG 23-01, most of these patients could have been treated with no further axillary treatment. Most patient (77%) had only 1 positive lymph node and 40% only micrometastatic disease or isolated tumor cells. As such, caution should be exercised in applying these data to patients with more aggressive disease in order to avoid additional toxicity and cost to patient care. Nevertheless, knowledge of full ALND contents did not seem to affect administration of chemotherapy. In addition, the AMAROS
trial excluded patients treated with neoadjuvant chemotherapy and thus the results are awaited of Alliance 11202 (NCT01901094), which randomizes patients receiving neoadjuvant chemotherapy and who are SLN positive to ALND or axillary XRT.


**Hypothesis**

Using dual mapping (blue dye and radioactivity) to excise the SLNs in patients having undergone neoadjuvant chemotherapy, the false-negative rate (FNR) would be acceptably low (<10%).

**Published Abstract**

**Importance**

SLN surgery provides reliable nodal staging information with less morbidity than ALND for patients with clinically node-negative (cN0) breast cancer. The application of SLN surgery for staging the axilla following chemotherapy for women who initially had node-positive cN1 breast cancer is unclear because of high false-negative results reported in previous studies.

**Objective**

To determine the FNR for SLN surgery following chemotherapy in women initially presenting with biopsy-proven cN1 breast cancer.

**Design, setting, and patients**

The ACOSOG Z1071 trial enrolled women from 136 institutions from July 2009 to June 2011 who had clinical T0 through T4, N1 through N2, and M0 breast cancer and were receiving neoadjuvant chemotherapy. Following chemotherapy, patients underwent both SLN surgery and ALND. SLN surgery using both blue dye (isosulfan blue or methylene blue), and a radiolabeled colloid mapping agent was encouraged.

**Main outcomes and measures**

The primary end point was the FNR of SLN surgery after chemotherapy in women who presented with cN1 disease. The Study evaluated the likelihood that the FNR in patients with 2 or more SLNs examined was greater than 10%, which is the rate expected for women undergoing SLN surgery who present with cN0 disease.

**Results**

Seven-hundred and fifty-six women were enrolled in the study. Of 663 evaluable patients with cN1 disease, 649 underwent chemotherapy followed by both SLN surgery and ALND. An SLN could not be identified in 46 patients (7.1%). Only 1 SLN was excised in 78 patients (12.0%). Of the remaining 525 patients with 2 or more SLNs removed, no cancer was identified in the axillary lymph nodes of 215 patients, yielding a pathologic complete nodal response of 41.0% (95% CI, 36.7%–45.3%). In 39 patients, cancer was not identified in the SLNs but was found in lymph nodes obtained with ALND, resulting in an FNR of 12.6% (90% bayesian credible interval, 9.85%–16.05%).

**Conclusions and relevance**

Among women with cN1 breast cancer receiving neoadjuvant chemotherapy who had 2 or more SLNs examined, the FNR was not found to be 10% or less. Given this FNR threshold, changes in approach and patient selection that result in greater sensitivity would be necessary to support the use of SLN surgery as an alternative to ALND.
Editorial comments In ACOSOG Z1071 the FNR for SLNB in patients with cN1 breast cancer receiving neoadjuvant chemotherapy (CTX) was unacceptably high. Patient factors, tumor factors, pathologic nodal response to chemotherapy, and site of tracer injection did not affect SLN FNR. However, further analysis of this study showed that the FNR could be reduced by using dual tracer (10.8% vs 20.3%) and examination of at least 3 nodes (9.1% vs 21.1%). In a subsequent analyses, obtaining the clip with the SLN reduced the FNR to 6.8%.12,13


Hypothesis
SLN biopsy can be performed reliably after neoadjuvant chemotherapy.

Published Abstract

Background
The optimum timing of SLNB for patients with breast cancer treated with neoadjuvant chemotherapy is uncertain. The SENTINA (SENTinel NeoAdjuvant) study was designed to evaluate a specific algorithm for timing of a standardized SLNB procedure in patients who undergo neoadjuvant chemotherapy.

Methods
SENTINA is a 4-arm, prospective, multicenter cohort study undertaken at 103 institutions in Germany and Austria. Women with breast cancer who were scheduled for neoadjuvant chemotherapy were enrolled into the study. Patients with clinically node-negative disease (cN0) underwent SLNB before neoadjuvant chemotherapy (arm A). If the sentinel node was positive (pN1), a second SLNB procedure was done after neoadjuvant chemotherapy (arm B). Women with clinically node-positive disease (cN+) received neoadjuvant chemotherapy. Those who converted to clinically node-negative disease after chemotherapy (ycN0; arm C) were treated with SLNB and axillary dissection. Only patients whose clinical nodal status remained positive (ycN1) underwent axillary dissection without SLNB (arm D). The primary end point was accuracy (FNR) of SLNB after neoadjuvant chemotherapy for patients who converted from cN1 to ycN0 disease during neoadjuvant chemotherapy (arm C). Secondary end points included comparison of the detection rate of SLNB before and after neoadjuvant chemotherapy, and also the FNR and detection rate of SLNB after removal of the SLN. Analyses were done according to treatment received (per protocol).

Findings
Of 1737 patients who received treatment, 1022 women underwent SLNB before neoadjuvant chemotherapy (arms A and B), with a detection rate of 99.1% (95% CI, 98.3–99.6; 1013 of 1022 patients). In patients who converted after neoadjuvant chemotherapy from cN+ to ycN0 (arm C), the detection rate was 80.1% (95% CI, 76.6–83.2; 474 of 592 patients) and FNR was 14.2% (95% CI, 9.9–19.4; 32 of 226 patients). The FNR was 24.3% (17 of 70 patients) for women who had 1 node removed and 18.5% (10 of 54 patients) for those who had 2 sentinel nodes removed (arm C). In patients who had a second SLNB procedure after neoadjuvant chemotherapy (arm B), the detection rate was 60.8% (95% CI, 55.6–65.9; 219 of 360 patients) and the FNR was 51.6% (95% CI, 38.7–64.2; 33 of 64 patients).
**Interpretation**

SLNB is a reliable diagnostic method before neoadjuvant chemotherapy. After systemic treatment or early SLNB, the procedure has a lower detection rate and a higher FNR compared with SLNB done before neoadjuvant chemotherapy. These limitations should be considered if biopsy is planned after neoadjuvant chemotherapy.

**Editorial comments** In this trial, two-thirds of the SLNBs were done using a single tracer. SLN before chemotherapy had a 99% localization rate whether with single or dual tracer. A second SLN after a positive initial SLN had a poor localization rate (80.1%) regardless of the use of lymphoscintigraphy as well as a poor FNR (51.6%). Conversion of a clinically positive node to a clinically negative node (arm C) had an FNR of 16.0% with radiocolloid alone and 8.6% with dual tracer. Overall, FNR reduced with the increased number of SLNs removed. Clips placed in clinically N1 lymph nodes and the impact on FNR were not analyzed. Localization in all groups favored periareolar injection rather than peritumoral or subcutaneous injection. In a subsequent analysis of the ultrasonography data obtained prospectively on the study, Schwentner and colleagues showed that clinical evaluation after neoadjuvant chemotherapy was very poor whether by palpation or ultrasonography. In those patients initially presenting with cN1, the accuracy of nodal evaluation after neoadjuvant chemotherapy by palpation had a sensitivity of 8.3%, specificity of 94.8%, and a negative predictive value (NPV) of 46.6%. Ultrasonography alone revealed a sensitivity of 23.9%, specificity of 91.7%, and an NPV of 50.3%. Palpation and ultrasonography together resulted in a sensitivity of 24.4%, specificity of 91.4%, and an NPV of 50.3%. Placement of clips in cN1(by ultrasonography) patients followed by chemotherapy and then SLNB clearly gives patients the best chance for the least morbid procedure because as many as 40% of these patients convert to node-negative status. An SLNB ahead of time if positive predetermines these patients for an ALND or XRT because the accuracy of a second SLN is so poor.

**LEVEL IA EVIDENCE: PROSPECTIVE RANDOMIZED TRIALS AND META-ANALYSES ON RADIATION IN BREAST CANCER**


**Hypothesis**

In NSABP studies on ductal carcinoma in situ (DCIS), IBTR would negatively affect survival.

**Published Abstract**

**Background**

IBTR is the most common failure event after lumpectomy for DCIS. This study evaluated invasive IBTR (I-IBTR) and its influence on survival among participants in 2 NSABP randomized trials for DCIS.

**Methods**

In the NSABP B-17 trial (accrual period: October 1, 1985, to December 31, 1990), patients with localized DCIS were randomly assigned to the lumpectomy only (LO; n = 403) group or to the lumpectomy followed by radiotherapy (LRT; n = 410) group. In the NSABP B-24 double-blinded, placebo-controlled trial (accrual period: May 9, 1991, to April 13, 1994), all accrued patients were randomly assigned to LRT.
plus placebo \((n = 900)\) or LRT plus tamoxifen \((TAM; n = 899)\). End points included I-IBTR, DCIS-IBTR, contralateral breast cancers, overall and breast cancer–specific survival, and survival after I-IBTR. Median follow-up was 207 months for the B-17 trial \((N = 813\) patients) and 163 months for the B-24 trial \((N = 1799\) patients).

**Results**

Of 490 IBTR events, 263 \((53.7\%\) were invasive. Radiation reduced I-IBTR by 52\% in the LRT group compared with LO \((B-17; HR of risk of I-IBTR = 0.48; 95\% CI, 0.33–0.69; \(P<.001\)). LRT plus TAM reduced I-IBTR by 32\% compared with LRT plus placebo \((B-24; HR of risk of I-IBTR = 0.68, 95\% CI, 0.49–0.95, \(P = .025\)). The 15-year cumulative incidence of I-IBTR was 19.4\% for LO, 8.9\% for LRT \((B-17), 10.0\% for LRT plus placebo \((B-24), and 8.5\% for LRT plus TAM. The 15-year cumulative incidence of all contralateral breast cancers was 10.3\% for LO, 10.2\% for LRT \((B-17), 10.8\% for LRT plus placebo \((B-24), and 7.3\% for LRT plus TAM. I-IBTR was associated with increased mortality risk \((HR of death = 1.75; 95\% CI, 1.45–2.96; \(P<.001\)), whereas recurrence of DCIS was not. Twenty-two of 39 deaths after I-IBTR were attributed to breast cancer. Among all patients \((with or without I-IBTR), the 15-year cumulative incidence of breast cancer death was 3.1\% for LO, 4.7\% for LRT \((B-17), 2.7\% for LRT plus placebo \((B-24), and 2.3\% for LRT plus TAM.

**Conclusions**

Although I-IBTR increased the risk for breast cancer–related death, radiation therapy and tamoxifen reduced I-IBTR, and long-term prognosis remained excellent after breast-conserving surgery for DCIS.

**Editorial comments**

As expected, a recurrence of DCIS does not affect survival. An invasive recurrence would be expected to affect survival, and the relative risk is 1.75. Long-term prognosis with lumpectomy alone versus lumpectomy plus tamoxifen plus XRT is less than 5\% and virtually the same regardless of treatment. However, the psychosocial impact of any recurrence should not be underestimated.


**Hypothesis**

Adjuvant radiation does not provide meaningful benefit in a specific subgroup with favorable tumor biology.

**Published Abstract**

**Purpose**

To determine whether there is a benefit to adjuvant radiation therapy after breast-conserving surgery and tamoxifen in women aged 70 years and older with early-stage breast cancer.

**Methods**

Between July 1994 and February 1999, 636 women \((aged \geq 70\) years) who had clinical stage I \((T1N0M0\ according to TNM [tumor, node, metastasis] classification) ER (ER)–positive breast carcinoma treated by lumpectomy were randomly assigned to receive tamoxifen plus radiation therapy \((TamRT; 317\) women) or tamoxifen alone \((Tam; 319\) women). Primary end points were time to local or regional recurrence, frequency of mastectomy, breast cancer–specific survival, time to distant metastasis, and OS.
Results
Median follow-up for treated patients is now 12.6 years. At 10 years, 98% of patients receiving TamRT (95% CI, 96%–99%) compared with 90% of those receiving Tam (95% CI, 85%–93%) were free from local and regional recurrences. There were no significant differences in time to mastectomy, time to distant metastasis, breast cancer-specific survival, or OS between the two groups. Ten-year OS was 67% (95% CI, 62%–72%) and 66% (95% CI, 61%–71%) in the TamRT and Tam groups, respectively.

Conclusions
With long-term follow-up, the previously observed small improvement in locoregional recurrence with the addition of radiation therapy remains. However, this does not translate into an advantage in OS, distant DFS, or breast preservation. Depending on the value placed on local recurrence, Tam remains a reasonable option for women aged 70 years or older with ER-positive early-stage breast cancer.

Editorial comments
This study of patients aged 70 years or older with early-stage favorable breast cancer originally published a 5-year follow-up that showed no significant difference in locoregional recurrence rate, which was highly touted. Because recurrence steadily increases over time, especially with favorable tumors, the most recent publication shows an 8% locoregional recurrence-free advantage with XRT and tamoxifen versus tamoxifen alone. Again, the psychosocial impact of any recurrence should not be underestimated but this study does give room for patient choice and for less morbid alternatives, such as intracavitary hyperthermia.


Hypothesis
The benefit of radiation may vary by tumor and patient characteristics.

Published Abstract

Background
After breast-conserving surgery, radiotherapy reduces recurrence and breast cancer death, but it may do so more for some groups of women than for others. This study describes the absolute magnitude of these reductions according to various prognostic and other patient characteristics, and relates the absolute reduction in 15-year risk of breast cancer death to the absolute reduction in 10-year recurrence risk.

Methods
The study undertook a meta-analysis of individual patient data for 10,801 women in 17 randomized trials of radiotherapy versus no radiotherapy after breast-conserving surgery, 8337 of whom had pathologically confirmed node-negative (pN0) or node-positive (pN+) disease.

Findings
Overall, radiotherapy reduced the 10-year risk of any (ie, locoregional or distant) first recurrence from 35.0% to 19.3% (absolute reduction, 15.7%; 95% CI, 13.7–17.7; 2-sided significance level [2P]<.00001) and reduced the 15-year risk of breast cancer death from 25.2% to 21.4% (absolute reduction, 3.8%; 95% CI, 1.6–6.0; 2P = .00005). In women with pN0 disease (n = 7287), radiotherapy reduced these risks from
31.0% to 15.6% (absolute recurrence reduction 15.4%, 13.2–17.6, \(2P<0.0001\)) and from 20.5% to 17.2% (absolute mortality reduction, 3.3%; 0.8–5.8; \(2P = .005\)), respectively. In these women with pN0 disease, the absolute recurrence reduction varied according to age, grade, ER status, tamoxifen use, and extent of surgery, and these characteristics were used to predict large (≥20%), intermediate (10%–19%), or lower (<10%) absolute reductions in the 10-year recurrence risk. Absolute reductions in 15-year risk of breast cancer death in these 3 prediction categories were 7.8% (95% CI, 3.1–12.5), 1.1% (95% CI, −2.0 to 4.2), and 0.1% (95% CI, −7.5 to 7.7) respectively (trend in absolute mortality reduction, \(2P = .03\)). In the few women with pN+ disease (n=1050), radiotherapy reduced the 10-year recurrence risk from 63.7% to 42.5% (absolute reduction, 21.2%; 95% CI, 14.5–27.9; \(2P<.00001\)) and the 15-year risk of breast cancer death from 51.3% to 42.8% (absolute reduction, 8.5%; 95% CI, 1.8–15.2; \(2P = .01\)). Overall, about 1 breast cancer death was avoided by year 15 for every 4 recurrences avoided by year 10, and the mortality reduction did not differ significantly from this overall relationship in any of the 3 prediction categories for pN0 disease or for pN+ disease.

**Interpretation**

After breast-conserving surgery, radiotherapy to the conserved breast halves the rate at which the disease recurs and reduces the breast cancer death rate by about a sixth. These proportional benefits vary little between different groups of women. By contrast, the absolute benefits from radiotherapy vary substantially according to the characteristics of the patient and they can be predicted at the time when treatment decisions need to be made.

**Editorial comments** In this meta-analysis of cooperative trials in more than 10,000 patients treated with BCT with or without XRT the investigators show a 16% decrease (19% vs 35%) in the risk of breast cancer recurrence and a 4% decrease in the risk of death with adjuvant XRT. The study shows a 50% proportional reduction in 10-year recurrence, greater than that of systemic therapy, which highlights the importance of local control. The reduction of recurrence depends on biological subtype, with the benefit of XRT twice as great for ER-positive disease as for ER-negative disease. The benefit for XRT is greater in earlier-stage favorable disease (ER positive, node negative) than later because the likelihood of systemic spread is less and local control is more important. This finding is supported by this meta-analysis showing that, for every 4 local recurrences avoided by 10 years, approximately 1 breast cancer–related death is avoided by 15 years.


**Hypothesis**

Postmastectomy radiation decreases recurrence and mortality in patients with 1 to 3 positive nodes.

**Published Abstract**

**Background**

Postmastectomy radiotherapy was shown in previous meta-analyses to reduce the risks of both recurrence and breast cancer mortality in all women with node-positive disease considered together. However, the benefit in women with
only 1 to 3 positive lymph nodes is uncertain. This study aimed to assess the effect of radiotherapy in these women after mastectomy and axillary dissection.

Methods
The study involved a meta-analysis of individual data for 8135 women randomly assigned to treatment groups during 1964 to 1986 in 22 trials of radiotherapy to the chest wall and regional lymph nodes after mastectomy and axillary surgery versus the same surgery but no radiotherapy. Follow-up lasted 10 years for recurrence and to January 1, 2009, for mortality. Analyses were stratified by trial, individual follow-up year, age at entry, and pathologic nodal status.

Findings
A total of 3786 women had axillary dissection to at least level II and had 0, 1 to 3, or 4 or more positive nodes. All were in trials in which radiotherapy included the chest wall, supraclavicular or axillary fossa (or both), and internal mammary chain. For 700 women with axillary dissection and no positive nodes, radiotherapy had no significant effect on locoregional recurrence (2\(P\) > .1), overall recurrence (rate ratio [RR], irradiated vs not, 1.06; 95% CI, 0.76–1.48; 2\(P\) > .1), or breast cancer mortality (RR, 1.18; 95% CI, 0.89–1.55; 2\(P\) > .1). For 1314 women with axillary dissection and 1 to 3 positive nodes, radiotherapy reduced locoregional recurrence (2\(P\) < .00001), overall recurrence (RR, 0.68; 95% CI, 0.57–0.82; 2\(P\) = .00006), and breast cancer mortality (RR, 0.80; 95% CI, 0.67–0.95; 2\(P\) = .01). Of these 1314 women, 1133 were in trials in which systemic therapy (cyclophosphamide, methotrexate, fluorouracil, or tamoxifen) was given in both trial groups and, for them, radiotherapy again reduced locoregional recurrence (2\(P\) < .00001), overall recurrence (RR, 0.67; 95% CI, 0.55–0.82; 2\(P\) = .00009), and breast cancer mortality (RR, 0.78; 95% CI, 0.64–0.94; 2\(P\) = .01). For 1772 women with axillary dissection and 4 or more positive nodes, radiotherapy reduced locoregional recurrence (2\(P\) < .00001), overall recurrence (RR, 0.79; 95% CI, 0.69–0.90; 2\(P\) = .0003), and breast cancer mortality (RR, 0.87; 95% CI, 0.77–0.99; 2\(P\) = .04).

Interpretation
After mastectomy and axillary dissection, radiotherapy reduced both recurrence and breast cancer mortality in the women with 1 to 3 positive lymph nodes in these trials even when systemic therapy was given. For women, who in many countries are at lower risk of recurrence, absolute gains might currently be smaller but proportional gains might be larger because of more effective radiotherapy.

Editorial comments Postmastectomy XRT improved locoregional DFS, overall DFS, and breast cancer–specific survival, independent of systemic therapy, in patents with any metastases to the axillary nodes. Local control depends on the multimodality therapy chosen, its extent (nodal sampling vs axillary node dissection), and its effectiveness as well as the extent and aggressiveness of the disease. In this meta-analysis of postmastectomy XRT, 1 breast cancer death is avoided for every 15 recurrences avoided at 10 years.


Hypothesis
In patients with node-positive breast cancer undergoing BCT and systemic therapy, the addition of regional nodal irradiation (RNI) would improve locoregional recurrence and survival.
**Published Abstract**

**Background**
Most women with breast cancer who undergo breast-conserving surgery receive whole-breast irradiation. This study examined whether the addition of RNI to whole-breast irradiation improved outcomes.

**Methods**
The study randomly assigned women with node-positive or high-risk node-negative breast cancer who were treated with breast-conserving surgery and adjuvant systemic therapy to undergo either whole-breast irradiation plus RNI (including internal mammary, supraclavicular, and axillary lymph nodes; nodal-irradiation group) or whole-breast irradiation alone (control group). The primary outcome was OS. Secondary outcomes were DFS, isolated locoregional DFS, and distant DFS.

**Results**
Between March 2000 and February 2007, a total of 1832 women were assigned to the nodal-irradiation group or the control group (916 women in each group). The median follow-up was 9.5 years. At the 10-year follow-up, there was no significant between-group difference in survival, with a rate of 82.8% in the nodal-irradiation group and 81.8% in the control group (HR, 0.91; 95% CI, 0.72–1.13; *P* = .38). The rates of DFS were 82.0% in the nodal-irradiation group and 77.0% in the control group (HR, 0.76; 95% CI, 0.61–0.94; *P* = .01). Patients in the nodal-irradiation group had higher rates of grade 2 or greater acute pneumonitis (1.2% vs 0.2%; *P* = .01) and lymphedema (8.4% vs 4.5%; *P* = .001).

**Conclusions**
Among women with node-positive or high-risk node-negative breast cancer, the addition of RNI to whole-breast irradiation did not improve OS but reduced the rate of breast cancer recurrence. (Funded by the Canadian Cancer Society Research Institute and others; MA.20 ClinicalTrials.gov number, NCT00005957.)

**Editorial comments**
The MA.20 study failed to show a survival advantage and reported higher rates of lymphedema but lower rates of local regional recurrence. A similar RCT by Poortmans and colleagues that studied adding RNI to whole breast or thoracic chest wall after surgery in more than 4000 patients did not a benefit in OS but did show a 2.1% benefit in breast cancer–related mortality. The number needed to treat to avoid on death from breast cancer was 39. Because RNI has a small risk of cardiac toxicity, careful selection of the patients who would benefit the most is advised.


**Hypothesis**
That a delay in XRT until after systemic therapy is finished does not affect local control or survival.

**Published Abstract**

**Purpose**
To update the previous report from 2 RCTs, now with a median follow-up of 16 years, to analyze the effect of radiation therapy timing on local failure and DFS.
Patients and methods
From July 1986 to April 1993, International Breast Cancer Study Group trial VI randomly assigned 1475 premenopausal/perimenopausal women with node-positive breast cancer to receive 3 or 6 cycles of initial chemotherapy. International Breast Cancer Study Group trial VII randomly assigned 1212 postmenopausal women with node-positive breast cancer to receive tamoxifen for 5 years, or tamoxifen for 5 years with 3 early cycles of initial chemotherapy. For patients who received breast-conserving surgery (BCS), radiation therapy (RT) was delayed until initial chemotherapy was completed; 4 or 7 months after BCS for trial VI and 2 or 4 months for trial VII. The study compared RT timing groups among 433 patients on trial VI and 285 patients on trial VII who received BCS plus RT. End points were local failure, regional/distant failure, and DFS.

Results
Among premenopausal/perimenopausal patients there were no significant differences in disease-related outcomes. The 15-year DFS was 48.2% in the group allocated 3 months of initial chemotherapy and 44.9% in the group allocated 6 months of initial chemotherapy (HR, 1.12; 95% CI, 0.87–1.45). Among postmenopausal patients, the 15-year DFS was 46.1% in the no-initial-chemotherapy group and 43.3% in the group allocated 3 months of initial chemotherapy (HR, 1.11; 95% CI, 0.82–1.51). Corresponding HRs for local failures were 0.94 (95% CI, 0.61–1.46) in trial VI and 1.51 (95% CI, 0.77–2.97) in trial VII. For regional/distant failures, the respective HRs were 1.15 (95% CI, 0.80–1.63) and 1.08 (95% CI, 0.69–1.68).

Conclusions
This study confirms that, after more than 15 years of follow-up, it is reasonable to delay RT until after the completion of standard chemotherapy.

Editorial comments
This long-term follow-up for patients randomized to CTX regimens that consequently delayed XRT until the CTX was finished (2, 4, and 7 months) confirms that delaying XRT until after CTX does not affect local failure, DFS, or OS.


Hypothesis
Because most local recurrences in conserved breasts appear in the original tumor bed, intraoperative XRT of the tumor bed should be equivalent in local control to whole-breast XRT.

Published Abstract
Background
The TARGIT-A trial compared risk-adapted radiotherapy using single-dose targeted intraoperative radiotherapy (TARGIT) versus fractionated external beam radiotherapy (EBRT) for breast cancer. The study reported 5-year results for local recurrence and the first analysis of OS.

Methods
TARGIT-A was a randomized, noninferiority trial. Women aged 45 years and older with invasive ductal carcinoma were enrolled and randomly assigned in a 1:1 ratio to receive TARGIT or whole-breast EBRT, with blocks stratified by center and by
timing of delivery of targeted intraoperative radiotherapy: randomization occurred either before lumpectomy (prepathology stratum, TARGIT concurrent with lumpectomy) or after lumpectomy (postpathology stratum, TARGIT given subsequently by reopening the wound). Patients in the TARGIT group received supplemental EBRT (excluding a boost) if unforeseen adverse features were detected on final pathology, thus radiotherapy was risk adapted. The primary outcome was absolute difference in local recurrence in the conserved breast, with a prespecified noninferiority margin of 2.5% at 5 years; prespecified analyses included outcomes as per timing of randomization in relation to lumpectomy. Secondary outcomes included complications and mortality. This study is registered with ClinicalTrials.gov, number NCT00983684.

Findings

Patients were enrolled at 33 centers in 11 countries, between March 24, 2000, and June 25, 2012. The study randomized 1721 patients to TARGIT and 1730 to EBRT. Supplemental EBRT after TARGIT was necessary in 15.2% (239 of 1571) of patients who received TARGIT (21.6% prepathology, 3.6% postpathology). There was a median follow-up of 2 years and 5 months (IQR 12–52 months) in 3451 patients, 2020 of 4 years, and 1222 of 5 years. The 5-year risk for local recurrence in the conserved breast was 3.3% (95% CI, 2.1–5.1) for TARGIT versus 1.3% (0.7–2.5) for EBRT ($P = .042$). TARGIT concurrent with lumpectomy (prepathology, $n = 2298$) had much the same results as EBRT: 2.1% (1.1–4.2) versus 1.1% (0.5–2.5; $P = .31$). With delayed TARGIT (postpathology, $n = 1153$) the between-group difference was larger than 2.5% (TARGIT, 5.4% [3.0–9.7] vs EBRT, 1.7% [0.6–4.9]; $P = .069$). Overall, breast cancer mortality was much the same between groups (2.6% [1.5–4.3] for TARGIT vs 1.9% [1.1–3.2] for EBRT; $P = .56$) but there were significantly fewer non-breast cancer deaths with TARGIT (1.4% [0.8–2.5] vs 3.5% [2.3–5.2]; $P = .0086$), which was attributable to fewer deaths from cardiovascular causes and other cancers. Overall mortality was 3.9% (2.7–5.8) for TARGIT versus 5.3% (3.9–7.3) for EBRT ($P = .099$). Wound-related complications were much the same between groups but grade 3 or 4 skin complications were significantly reduced with TARGIT (4 of 1720 vs 13 of 1731; $P = .029$).

Interpretation

TARGIT concurrent with lumpectomy within a risk-adapted approach should be considered as an option for eligible patients with breast cancer carefully selected as per the TARGIT-A trial protocol, as an alternative to postoperative EBRT.

Editorial comments In this updated publication of the TARGIT-A trial with a median follow-up of 29 months, the external beam arm recurrences have approximately doubled to 11 and, with the TARGIT-A arm, quadrupled to 23 from the prior report. This finding indicates that recurrences in this favorable group of patients have not yet reached the plateau of recurrences. Although these results are encouraging, widespread application should await long-term follow-up. The percentage differences are small and the benefits of using a single procedure are manifold.


Hypothesis

Intraoperative XRT is equivalent to whole-breast XRT to provide local control.
Published Abstract

Background
Intraoperative radiotherapy with electrons allows the substitution of conventional postoperative whole-breast irradiation with 1 session of radiotherapy with the same equivalent dose during surgery. However, its ability to control for recurrence of local disease required confirmation in a randomized controlled trial.

Methods
This study was done at the European Institute of Oncology (Milan, Italy). Women aged 48 to 75 years with early breast cancer, a maximum tumor diameter of up to 2.5 cm, and suitable for BCS were randomly assigned in a 1:1 ratio (using a random permuted block design, stratified for clinical tumor size [<1.0 cm vs 1.0–1.4 cm vs ≥1.5 cm]) to receive either whole-breast external radiotherapy or intraoperative radiotherapy with electrons. Study coordinators, clinicians, and patients were aware of the assignment. Patients in the intraoperative radiotherapy group received 1 dose of 21 Gy to the tumor bed during surgery. Those in the external radiotherapy group received 50 Gy in 25 fractions of 2 Gy, followed by a boost of 10 Gy in 5 fractions. This study was an equivalence trial; the prespecified equivalence margin was local recurrence of 7.5% in the intraoperative radiotherapy group. The primary end point was occurrence of IBTR; OS was a secondary outcome. The main analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01849133.

Findings
The study randomized 1305 patients (654 to external radiotherapy and 651 to intraoperative radiotherapy) between November 20, 2000, and December 27, 2007. After a medium follow-up of 5.8 years (IQR, 4.1–7.7), 35 patients in the intraoperative radiotherapy group and 4 patients in the external radiotherapy group had had an IBTR (P < .0001). The 5-year event rate for IBTR was 4.4% (95% CI, 2.7–6.1) in the intraoperative radiotherapy group and 0.4% (0.0–1.0) in the external radiotherapy group (HR 9.3; 95% CI, 3.3–26.3). During the same period, 34 women allocated to intraoperative radiotherapy and 31 to external radiotherapy died (P = .59). Five-year OS was 96.8% (95% CI, 95.3–98.3) in the intraoperative radiotherapy group and 96.9% (95.5–98.3) in the external radiotherapy group. In patients with data available (n = 464 for intraoperative radiotherapy; n = 412 for external radiotherapy) there were significantly fewer skin side effects in women in the intraoperative radiotherapy group than in those in the external radiotherapy group (P = .0002).

Interpretation
Although the rate of IBTR in the intraoperative radiotherapy group was within the prespecified equivalence margin, the rate was significantly greater than with external radiotherapy, and OS did not differ between groups. Improved selection of patients could reduce the rate of IBTR with intraoperative radiotherapy with electrons.

Editorial comments ELIOT versus external beam radiation had a 10-fold higher local recurrence rate over a median follow-up of 5.8 years, although both arms were low (4.4% vs 0.4%, respectively). However, in a group of low-risk women the 5-year IBTR was 1.5% but 11.3% for those patient with high-risk factors. Regardless, OS was the same. In an era when only ~80% of women with BCT complete their XRT dose, single-dose intraoperative completion provides a lot of advantages for busy and/or noncompliant patients. In addition, patients who live distant to XRT treatment facilities or in rural areas can still undergo BCT. The main drawback with ELIOT is the
LEVEL IA EVIDENCE: PROSPECTIVE RANDOMIZED CHEMOTHERAPY TRIALS AND META-ANALYSES IN BREAST CANCER


Hypothesis

Use of a new nonanthracycline regimen with trastuzumab would have equivalent or improved survival with less toxicity.

Published Abstract

Background

Trastuzumab improves survival in the adjuvant treatment of Human epidermal growth factor receptor (HER)-positive breast cancer, although combined therapy with anthracycline-based regimens has been associated with cardiac toxicity. The study evaluated the efficacy and safety of a new nonanthracycline regimen with trastuzumab.

Methods

The study randomly assigned 3222 women with human epidermal growth factor receptor 2 (HER2)–positive early-stage breast cancer to receive doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks (AC-T), the same regimen plus 52 weeks of trastuzumab (AC-T plus trastuzumab), or docetaxel and carboplatin plus 52 weeks of trastuzumab (TCH). The primary study end point was DFS. Secondary end points were OS and safety.

Results

At a median follow-up of 65 months, 656 events triggered this protocol-specified analysis. The estimated DFS rates at 5 years were 75% among patients receiving AC-T, 84% among those receiving AC-T plus trastuzumab, and 81% among those receiving TCH. Estimated rates of OS were 87%, 92%, and 91%, respectively. No significant differences in efficacy (DFS or OS) were found between the 2 trastuzumab regimens, whereas both were superior to AC-T. The rates of congestive heart failure and cardiac dysfunction were significantly higher in the group receiving AC-T plus trastuzumab than in the TCH group (<.001). Eight cases of acute leukemia were reported: 7 in the groups receiving the anthracycline-based regimens and 1 in the TCH group after receiving an anthracycline outside the study.

Conclusions

The addition of 1 year of adjuvant trastuzumab significantly improved DFS and OS among women with HER2-positive breast cancer. The risk/benefit ratio favored the nonanthracycline TCH regimen rather than AC-T plus trastuzumab, given its similar efficacy, fewer acute toxic effects, and lower risks of cardiotoxicity and leukemia.

Editorial comments

This article by Slamon and colleagues25 from the Breast Cancer International Research Group is the fifth prospective RCT with trastuzumab, all of which showed a substantial increase in DFS and OS with 52-week therapy in patients overexpressing HER2. The critical question here is whether anthracyclines are necessary for the treatment of HER-2–positive breast cancer in order to avoid the cardiotoxicity of anthracyclines. The third group was randomized to a nonanthracycline regimen (docetaxel and
carboplatin with trastuzumab every 3 weeks for 6 cycles) followed by a year of trastuzu-
mab. The non–anthracycline-containing regimen showed equivalency to the stan-
dard regimen in terms of DFS and OS but showed fewer cardiac and leukemia
complications. Further prospective studies are determining just how positive (1+ or
2+) the HER2 oncogene has to be to benefit from trastuzumab. Combined analysis
of NSABP B-31 and the North Central Cancer Treatment Group trials showed a re-
lative reduction in DFS and death rate of 48% and 39% respectively.26 The next RCTs
study combinations of HER tyrosine kinase inhibitors.

Robidoux A, Tang G, Rastogi P, et al. Lapatinib as a component of neoadjuvant ther-
apy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label,

Hypothesis

Dual blockade of the HER2 oncogene with lapatinib added to trastuzumab would
increase therapeutic response.

Published Abstract

Background

The authors studied the effect on tumor response to neoadjuvant therapy for the sub-
stitution of lapatinib for trastuzumab in combination with weekly paclitaxel after doxo-
rubicin plus cyclophosphamide treatment, and of the addition of lapatinib and
trastuzumab combined after doxorubicin plus cyclophosphamide treatment in pa-
tients with HER2-positive operable breast cancer to determine whether there would
be a benefit of dual HER2 blockade in these patients.

Methods

For this open-label, randomized phase 3 trial the study recruited women aged 18 years
or older with an ECOG performance status of 0 or 1 with operable HER2-positive
breast cancer. Each received 4 cycles of standard doxorubicin 60 mg/m² and cyclo-
phosphamide 600 mg/m² intravenously on day 1 every 3 weeks followed by 4 cycles of
weekly paclitaxel (80 mg/m²) intravenously on days 1, 8, and 15, every 4 weeks.
Concurrently with weekly paclitaxel, patients received either trastuzumab (4 mg/kg
load, then 2 mg/kg intravenously) weekly until surgery, lapatinib (1250 mg orally)
daily until surgery, or weekly trastuzumab plus lapatinib (750 mg orally) daily until sur-
gery. After surgery, all patients received trastuzumab to complete 52 weeks of
HER2-targeted therapy. Randomization (ratio 1:1:1) was done centrally with stratifica-
tion by clinical tumor size, clinical nodal status, hormone-receptor status, and age.
The primary end point was the pathologic complete response in the breast, and anal-
ysis was performed on an intention-to-treat population.

Findings

Patient accrual started on July 16, 2007, and was completed on June 30, 2011; 529
women were enrolled in the trial. The pathologic response determined in 519 patients.
Breast pathologic complete response was noted in 93 (52.5%; 95% CI, 44.9–59.5) of
177 patients in the trastuzumab group, 91 (53.2%; 45.4–60.3) of 171 patients in the
lapatinib group (P = .9852); and 106 (62.0%; 54.3–68.8) of 171 patients in the combi-
nation group (P = .095). The most common grade 3 and 4 toxic effects were neutro-
penia in 29 patients (16%) in the trastuzumab group (grade 4 in 5 patients [3%]), 28
patients (16%) in the lapatinib group (grade 4 in 8 patients [5%]), and 29 patients
(17%) in the combination group (grade 4 in 9 patients [5%]) and grade 3 diarrhea in
4 patients (2%) in the trastuzumab group, 35 patients (20%) in the lapatinib group,
and 46 patients (27%) in the combination group ($P<.0001$). Symptomatic congestive heart failure, defined as New York Heart Association class III or IV events, occurred in 7 patients (4%) in the trastuzumab group, 7 (4%) in the lapatinib group, and 1 (<1%) in the combination group ($P = .185$).

**Interpretation**

Substitution of lapatinib for trastuzumab in combination with chemotherapy resulted in similar high percentages of pathologic complete response. Combined HER2-targeted therapy produced a numerically but insignificantly higher pathologic complete response percentage than single-agent HER2-directed therapy; these findings are consistent with results from other studies. Trials are being undertaken to further assess these findings in the adjuvant setting.

**Editorial comments**  Lapatinib in combination with trastuzumab was not significantly better than single agent. Anti-HER2 agents under investigation include heat shock protein 90 inhibitors, small molecules that inhibit HER2 tyrosine kinase activity (eg lapatinib), monoclonal antibodies directed at other epitopes of the HER2 extracellular domain (eg, pertuzumab), and antibody-drug conjugates (eg, trastuzumab-DM1), or in combination. These agents are covered in systematic reviews.


**Hypothesis**

Dual blockade of the HER2 oncogene with pertuzumab added to trastuzumab increases therapeutic response.

**Background**

Primary results from the randomized, double-blind, phase 3 study CLEOPATRA showed significantly improved median progression-free survival (PFS) with pertuzumab plus trastuzumab plus docetaxel versus placebo plus trastuzumab plus docetaxel in patients with HER2-positive first-line metastatic breast cancer (MBC). OS data at the primary analysis showed a strong trend in favor of the pertuzumab arm but did not reach statistical significance. This study reports confirmatory OS results after 1 additional year of follow-up.

**Methods**

Patients were randomly assigned to study treatment. OS and investigator-assessed PFS were analyzed using the Kaplan-Meier approach and log-rank tests stratified by geographic region and prior treatment status. This trial is registered with ClinicalTrials.gov, NCT00567190.

**Findings**

In the intent-to-treat population (808 patients), 267 deaths had occurred at data cutoff (placebo arm, 154 of 406 [37.9%]; pertuzumab arm, 113 of 402 [28.1%]). Treatment with pertuzumab plus trastuzumab plus docetaxel resulted in a 34% reduction in the risk of death during the course of the study (HR, 0.66; 95% CI, 0.52–0.84; $P = .0008$). Median OS was 37.6 months in the placebo arm and was not yet reached in the pertuzumab arm. A descriptive follow-up analysis of investigator-assessed PFS showed a median PFS of 12.4 and 18.7 months in the placebo versus pertuzumab arm (HR, 0.69; 95% CI, 0.58–0.81). No new safety concerns were identified with 1 additional year of follow-up. Adverse events were similar to those reported at the primary analysis with respect to incidence, severity, and specificity.
**Interpretation**
This OS analysis showed statistically significant and clinically meaningful survival benefit with pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive MBC. Updated analyses of investigator-assessed PFS and safety were consistent with the results from the primary analysis.

**Editorial comments** Adding pertuzumab to the combination of taxanes and trastuzumab significantly reduced risk of death by 34% with acceptable toxicity in metastatic patients. A combination of vinorelbine, pertuzumab, and trastuzumab offers an alternative for patients who cannot receive the standard anthracyclines for first-line treatment of HER2-positive locally advanced or metastatic disease.31


**Hypothesis**
Neoadjuvant chemotherapy containing poly(ADP-ribose) polymerase (PARP) inhibitors would provide improved pathologic complete response.

The genetic and clinical heterogeneity of breast cancer makes the identification of effective therapies challenging. The investigators designed I-SPY 2, a phase 2, multicenter, adaptively randomized trial to screen multiple experimental regimens in combination with standard neoadjuvant chemotherapy for breast cancer. The goal is to match experimental regimens with responding cancer subtypes. The study reports results for veliparib, a PARP inhibitor, combined with carboplatin.

**Methods**
In this ongoing trial, women are eligible for participation if they have stage II or III breast cancer with a tumor 2.5 cm or larger in diameter; cancers are categorized into 8 biomarker subtypes from their status with regard to human epidermal growth factor receptor 2 (HER2), hormone receptors, and a 70-gene assay. Patients undergo adaptive randomization within each biomarker subtype to receive regimens that have better performance than the standard therapy. Regimens are evaluated within 10 biomarker signatures (ie, prospectively defined combinations of biomarker subtypes). Veliparib-carboplatin plus standard therapy was considered for HER2-negative tumors and was therefore evaluated in 3 signatures. The primary end point is pathologic complete response. Tumor volume changes measured by MRI during treatment are used to predict whether a patient will have a pathologic complete response. Regimens move on from phase 2 if they have a high bayesian predictive probability of success in a subsequent phase 3 neoadjuvant trial within the biomarker signature in which they performed well.

**Results**
With regard to triple-negative breast cancer, veliparib-carboplatin had an 88% predicted probability of success in a phase 3 trial. A total of 72 patients were randomly assigned to receive veliparib-carboplatin, and 44 patients were concurrently assigned to receive control therapy; at the completion of chemotherapy, the estimated rates of pathologic complete response in the triple-negative population were 51% (95% bayesian probability interval [PI], 36%–66%) in the veliparib-carboplatin group versus 26% (95% PI, 9%–43%) in the control group. The toxicity of veliparib-carboplatin was greater than that of the control.
Conclusions
The process used in our trial showed that veliparib-carboplatin added to standard therapy resulted in higher rates of pathologic complete response than standard therapy alone specifically in triple-negative breast cancer. (Funded by the QuantumLeap Healthcare Collaborative and others; I-SPY 2 TRIAL ClinicalTrials.gov number, NCT01042379.)

Editorial comments PARP enzymes are essential for processing and repair of DNA breaks. BRCA-1/2 breast cancers, lacking this functionality, have been shown to be highly sensitive to PARP inhibitors. Therefore, the investigators thought that the response in triple-negative breast cancer would be similar. The I-SPY 2 is a phase 2, multicenter, adaptively randomized trial to screen multiple experimental regimens in combination with standard neoadjuvant chemotherapy for breast cancer in order to speed their adoption into practice. From the I-SPY2 came this small phase III trial that showed that neoadjuvant treatment with the PARP inhibitor (veliparib) produced a greater pathologic complete response compared with treatment with carboplatin alone as well as greater toxicity.


Hypothesis
Evaluation by a patient-level meta-analyses of available RCT could detect differences in efficacy between treatment regimens for breast cancer.

Published Abstract

Background
Moderate differences in efficacy between adjuvant chemotherapy regimens for breast cancer are plausible, and could affect treatment choices. This study sought any such differences.

Methods
The study undertook individual-patient-data meta-analyses of the randomized trials comparing any taxane plus anthracycline–based regimen versus the same, or more, nontaxane chemotherapy (n = 44,000); 1 anthracycline-based regimen versus another (n = 7000) or versus cyclophosphamide, methotrexate, and fluorouracil (CMF; n = 18,000); and polychemotherapy versus no chemotherapy (n = 32,000). The scheduled dosages of these 3 drugs and of the anthracyclines doxorubicin (A) and epirubicin (E) were used to define standard CMF, standard four cycles of doxorubicin (4AC), and cyclophosphamide, doxorubicin, fluorouracil (CAF) and cyclophosphamide, epirubicin, fluorouracil (CEF). Log-rank breast cancer mortality ratios (RRs) are reported.

Findings
In trials adding 4 separate cycles of a taxane to a fixed anthracycline–based control regimen, extending treatment duration, breast cancer mortality was reduced (RR, 0.86; standard error [SE], 0.04; 2P = .0005). In trials with 4 such extra cycles of a taxane counterbalanced in controls by extra cycles of other cytotoxic drugs, roughly doubling nontaxane dosage, there was no significant difference (RR, 0.94; SE, 0.06; 2P = .33). Trials with CMF-treated controls showed that standard 4AC and standard CMF were
equivalent (RR, 0.98; SE, 0.05; 2P = .67), but that anthracycline-based regimens with substantially higher cumulative dosage than standard 4AC (eg, CAF or CEF) were super-
ior to standard CMF (RR, 0.78; SE, 0.06; 2P = .0004). Trials versus no chemotherapy also suggested greater mortality reductions with CAF (RR, 0.64; SE, 0.09; 2P<.0001) than with standard 4AC (RR, 0.78; SE, 0.09; 2P = .01) or standard CMF (RR, 0.76; SE, 0.05; 2P<.0001). In all meta-analyses involving taxane-based or anthracycline-
based regimens, proportional risk reductions were little affected by age, nodal status, tumor diameter or differentiation (moderate or poor; few were well differentiated), ER status, or tamoxifen use. Hence, largely independently of age (up to at least 70 years) or the tumor characteristics currently available for the patients selected to be in these trials, some taxane plus anthracycline–based or higher cumulative dosage anthracy-
cline–based regimens (not requiring stem cells) reduced breast cancer mortality by, on average, about one-third. Ten-year overall mortality differences paralleled breast cancer mortality differences, despite taxane, anthracycline, and other toxicities.

**Interpretation**

Ten-year gains from a one-third breast cancer mortality reduction depend on abso-
lute risks without chemotherapy (which, for ER-positive disease, are the risks remaining with appropriate endocrine therapy). Low absolute risk implies low abso-
lute benefit, but information was lacking about tumor gene expression markers or quantitative immunohistochemistry that might help to predict risk, chemosensitivity, or both.

**Editorial comments**  This study clearly shows that polychemotherapy with CMF or stan-
dard 4AC decreases breast cancer mortality and an even greater effect can be seen by increasing the cumulative dose of anthracycline, but with a concomitant increase in car-
diac mortality. An unexpected and important finding is that the proportional reduction in breast cancer mortality with polychemotherapy was independent of receptor status (ER+ vs ER−) or age. A limitation of this meta-analysis is that the effect of molecular het-
erogeneity on the benefits and risks of chemotherapy cannot be assessed.

**LEVEL IA EVIDENCE: PROSPECTIVE RANDOMIZED TRIALS (AND META-ANALYSES) ADDRESSING THE ROLE OF ENDOCRINE THERAPY IN BREAST CANCER PREVENTION AND TREATMENT**


**Hypothesis**

Extending tamoxifen therapy to 10 versus 5 years would reduce breast cancer mortality.

**Published Abstract**

**Background**

For women with ER-positive early breast cancer, treatment with tamoxifen for 5 years substantially reduces the breast cancer mortality throughout the first 15 years after diagnosis. The study aimed to assess the further effects of continuing tamoxifen to 10 years instead of stopping at 5 years.

**Methods**

In the worldwide Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial, 12,894 women with early breast cancer who had completed 5 years of treatment...
with tamoxifen were randomly allocated to continue tamoxifen to 10 years or stop at 5 years (open control). Allocation (1:1) was by central computer, using minimization. After entry (between 1996 and 2005), yearly follow-up forms recorded any recurrence, second cancer, hospital admission, or death. The study reported effects on breast cancer outcomes among the 6846 women with ER-positive disease, and side effects among all women (with positive, negative, or unknown ER status). Long-term follow-up still continues. This study is registered, number ISRCTN19652633.

Findings
Among women with ER-positive disease, allocation to continue tamoxifen reduced the risk of breast cancer recurrence (617 recurrences in 3428 women allocated to continue vs 711 in 3418 controls; \( P = .002 \)), reduced breast cancer mortality (331 deaths vs 397 deaths; \( P = .01 \)), and reduced overall mortality (639 deaths vs 722 deaths; \( P = .01 \)). The reductions in adverse breast cancer outcomes seemed to be less extreme before than after year 10 (recurrence RR 0.90 [95% CI, 0.79–1.02] during years 5 to 9 and 0.75 [95% CI, 0.62–0.90] in later years; breast cancer mortality RR, 0.97 [95% CI, 0.79–1.18] during years 5 to 9 and 0.71 [95% CI, 0.58–0.88] in later years). The cumulative risk of recurrence during years 5 to 14 was 21.4% for women allocated to continue versus 25.1% for controls; breast cancer mortality during years 5 to 14 was 12.2% for women allocated to continue versus 15.0% for controls (absolute mortality reduction 2.8%). Treatment allocation seemed to have no effect on breast cancer outcome among 1248 women with ER-negative disease, and an intermediate effect among 4800 women with unknown ER status. Among all 12,894 women, mortality without recurrence from causes other than breast cancer was little affected (691 deaths without recurrence in 6454 women allocated to continue vs 679 deaths in 6440 controls; RR, 0.99 [0.89–1.10]; \( P = .84 \)). For the incidence (hospitalization or death) rates of specific diseases, RRs were as follows: pulmonary embolus 1.87 (95% CI, 1.13–3.07; \( P = .01 \) [including 0.2% mortality in both treatment groups]), stroke 1.06 (0.83–1.36), ischemic heart disease 0.76 (0.60–0.95; \( P = .02 \)), and endometrial cancer 1.74 (1.30–2.34; \( P = .0002 \)). The cumulative risk of endometrial cancer during years 5 to 14 was 3.1% (mortality 0.4%) for women allocated to continue versus 1.6% (mortality 0.2%) for controls (absolute mortality increase 0.2%).

Interpretation
For women with ER-positive disease, continuing tamoxifen to 10 years rather than stopping at 5 years produces a further reduction in recurrence and mortality, particularly after year 10. These results, taken together with results from previous trials of 5 years of tamoxifen treatment versus none, suggest that 10 years of tamoxifen treatment can approximately halve breast cancer mortality during the second decade after diagnosis.

Editorial comments  ER status is the only recorded factor importantly predictive of the proportional reductions with tamoxifen. Extending treatment beyond 5 years in ER+ patients in the overview analysis significantly improved DFS but also significantly increased the risks of death caused by endometrial cancer and stroke, whereas there was a significant decrease in cardiac mortality.

Hypothesis
Aromatase inhibitors provide superior DFS compared with tamoxifen in estrogen-positive disease.

Published Abstract
Background
The optimal ways of using aromatase inhibitors or tamoxifen as endocrine treatment of early breast cancer remains uncertain.

Methods
The study undertook meta-analyses of individual data on 31,920 postmenopausal women with ER-positive early breast cancer in the randomized trials of 5 years of aromatase inhibitor versus 5 years of tamoxifen; of 5 years of aromatase inhibitor versus 2 to 3 years of tamoxifen then aromatase inhibitor to year 5; and of 2 to 3 years of tamoxifen then aromatase inhibitor to year 5 versus 5 years of tamoxifen. Primary outcomes were any recurrence of breast cancer, breast cancer mortality, death without recurrence, and all-cause mortality. Intention-to-treat log-rank analyses, stratified by age, nodal status, and trial, yielded aromatase inhibitor versus tamoxifen first-event RRs.

Findings
In the comparison of 5 years of aromatase inhibitor versus 5 years of tamoxifen, recurrence RRs favored aromatase inhibitors significantly during years 0 to 1 (RR, 0.64; 95% CI, 0.52–0.78) and 2 to 4 (RR, 0.80; 0.68–0.93), and nonsignificantly thereafter. Ten-year breast cancer mortality was lower with aromatase inhibitors than with tamoxifen (12.1% vs 14.2%; RR, 0.85, 0.75–0.96; 2P = .009). In the comparison of 5 years of aromatase inhibitor versus 2 to 3 years of tamoxifen then aromatase inhibitor to year 5, recurrence RRs favored aromatase inhibitors significantly during years 0 to 1 (RR, 0.74; 0.62–0.89) but not while both groups received aromatase inhibitors during years 2 to 4, or thereafter; overall in these trials there were fewer recurrences with 5 years of aromatase inhibitors than with tamoxifen then aromatase inhibitors (RR, 0.90; 0.81–0.99; 2P = .045), although the breast cancer mortality reduction was not significant (RR, 0.89; 0.78–1.03; 2P = .11). In the comparison of 2 to 3 years of tamoxifen then aromatase inhibitor to year 5 versus 5 years of tamoxifen, recurrence RRs favored aromatase inhibitors significantly during years 2 to 4 (RR, 0.56; 0.46–0.67) but not subsequently, and 10-year breast cancer mortality was lower with switching to aromatase inhibitors than with remaining on tamoxifen (8.7% vs 10.1%; 2P = .015). Aggregating all 3 types of comparison, recurrence RRs favored aromatase inhibitors during periods when treatments differed (RR, 0.70; 0.64–0.77), but not significantly thereafter (RR, 0.93; 0.86–1.01; 2P = .08). Breast cancer mortality was reduced while treatments differed (RR, 0.79; 0.67–0.92), and also subsequently (RR, 0.89; 0.81–0.99), and for all periods combined (RR, 0.86; 0.80–0.94; 2P = .0005). All-cause mortality was also reduced (RR, 0.88; 0.82–0.94; 2P = .0003). RRs differed little by age, body mass index, stage, grade, progesterone receptor status, or HER2 status. There were fewer endometrial cancers with aromatase inhibitors than with tamoxifen (10-year incidence, 0.4% vs 1.2%; RR, 0.33; 0.21–0.51) but more bone fractures (5-year risk, 8.2% vs 5.5%; RR, 1.42; 1.28–1.57); non–breast cancer mortality was similar.

Interpretation
Aromatase inhibitors reduce recurrence rates by about 30% (proportionately) compared with tamoxifen while treatments differ, but not thereafter. Five years of an aromatase inhibitor reduces 10-year breast cancer mortalities by about
15% compared with 5 years of tamoxifen, hence by about 40% (proportionately) compared with no endocrine treatment.

**Editorial comments** Aromatase inhibitors are superior to tamoxifen or combination of the two. There were fewer recurrences with 5 years of aromatase inhibitors than with tamoxifen followed by aromatase inhibitors or tamoxifen alone. There was less endometrial cancer but more bone fractures. Aromatase inhibitors are favored in postmenopausal patients without bone disease. Because more women die of the osteoporosis than breast cancer, tamoxifen should be considered in that setting.


**Hypothesis**

Bisphosphonates, through modification of osteoclastic activity, could reduce the excess production of growth factors in bone, thereby decreasing metastasis, and therefore could improve disease-free survival.

**Published Abstract**

**Background**

Bisphosphonates have profound effects on bone physiology, and could modify the process of metastasis. The study undertook collaborative meta-analyses to clarify the risks and benefits of adjuvant bisphosphonate treatment in breast cancer.

**Methods**

The study sought individual patient data from all unconfounded trials in early breast cancer that randomized between bisphosphonate and control. Primary outcomes were recurrence, distant recurrence, and breast cancer mortality. Primary subgroup investigations were site of first distant recurrence (bone or other), menopausal status (postmenopausal [combining natural and artificial] or not), and bisphosphonate class (aminobisphosphonate [eg, zoledronic acid, ibandronate, pamidronate] or other [ie, clodronate]). Intention-to-treat log-rank methods yielded bisphosphonate versus control first-event RRs.

**Findings**

The study received data on 18,766 women (18,206 [97%] in trials of 2–5 years of bisphosphonate) with median follow-up 5.6 woman-years, 3453 first recurrences, and 2106 subsequent deaths. Overall, the reductions in recurrence (RR, 0.94; 95% CI, 0.87–1.01; 2P = .08), distant recurrence (0.92; 0.85–0.99; 2P = .03), and breast cancer mortality (0.91; 0.83–0.99; 2P = .04) were of only borderline significance, but the reduction in bone recurrence was more definite (0.83; 0.73–0.94; 2P = .004). Among premenopausal women, treatment had no apparent effect on any outcome, but among 11,767 postmenopausal women it produced highly significant reductions in recurrence (RR, 0.86; 95% CI, 0.78–0.94; 2P = .002), distant recurrence (0.82; 0.74–0.92; 2P = .0003), bone recurrence (0.72; 0.60–0.86; 2P = .0002), and breast cancer mortality (0.82; 0.73–0.93; 2P = .002). Even for bone recurrence, the heterogeneity of benefit was barely significant by menopausal status (2P = .06 for trend with menopausal status) or age (2P = .03), and it was nonsignificant by bisphosphonate class, treatment schedule, ER status, nodes, tumor grade, or concomitant chemotherapy. No differences were seen in non-breast cancer mortality. Bone fractures were reduced (RR, 0.85; 95% CI, 0.75–0.97; 2P = .02).
**Interpretation**
Adjuvant bisphosphonates reduce the rate of breast cancer recurrence only in the bone and improve breast cancer survival. There is definite benefit only in women who were postmenopausal when treatment began.

**Editorial interpretation** Bisphosphonates improve DFS by decreasing metastasis to the bone. This decrease was independent of the type or schedule of bisphosphonate, the ER status or stage, and the use of adjuvant systemic chemotherapy. This report should lead to the routine use of bisphosphates in early breast cancer in menopausal patients.


**Hypothesis**
Anastrozole is superior to tamoxifen in DFS when treating patients with DCIS.

**Published Abstract**

**Background**
DCIS is currently managed with excision, radiotherapy, and adjuvant hormone therapy, usually tamoxifen. The study postulated that an aromatase inhibitor would be safer and more effective. The study therefore undertook this trial to compare anastrozole versus tamoxifen in postmenopausal women with DCIS undergoing lumpectomy plus radiotherapy.

**Methods**
The double-blind, randomized, phase 3 NSABP B-35 trial was done in 333 participating NSABP centers in the United States and Canada. Postmenopausal women with hormone-positive DCIS treated by lumpectomy with clear resection margins and whole-breast irradiation were enrolled and randomly assigned (1:1) to receive either oral tamoxifen 20 mg/d (with matching placebo in place of anastrozole) or oral anastrozole 1 mg/d (with matching placebo in place of tamoxifen) for 5 years. Randomization was stratified by age (<60 vs ≥60 years) and patients and investigators were masked to treatment allocation. The primary outcome was breast cancer–free interval, defined as time from randomization to any breast cancer event (local, regional, or distant recurrence, or contralateral breast cancer, invasive disease, or DCIS), analyzed by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00053898, and is complete.

**Findings**
Between January 1, 2003, and June 15, 2006, 3104 eligible patients were enrolled and randomly assigned to the 2 treatment groups (1552 to tamoxifen and 1552 to anastrozole). As of February 28, 2015, follow-up information was available for 3083 patients for OS and 3077 for all other disease-free end points, with median follow-up of 9.0 years (IQR, 8.2–10.0). In total, 212 breast cancer–free interval events occurred: 122 in the tamoxifen group and 90 in the anastrozole group (HR, 0.73; 95% CI, 0.56–0.96; \( P = .0234 \)). A significant time-by-treatment interaction (\( P = .0410 \)) became evident later in the study. There was also a significant interaction between treatment and age group (\( P = .0379 \)), showing that anastrozole is superior only in women younger than 60 years of age. Adverse events did not differ between the groups, except for thrombosis or...
embolism (a known side effect of tamoxifen), for which there were 17 grade 4 or worse events in the tamoxifen group versus 4 in the anastrozole group.

**Interpretation**
Compared with tamoxifen, anastrozole treatment provided a significant improvement in breast cancer–free interval, mainly in women younger than 60 years of age. This finding means that women will benefit from having a choice of effective agents for DCIS.

**Editorial comments** Patients in the 10-year follow-up of NSABP B-24 with ER-positive DCIS receiving adjuvant tamoxifen after standard therapy showed significant reductions in subsequent breast cancer. This study shows that anastrozole improves on DFS. However, when side effects are intolerable, tamoxifen is a good alternative. It is the treatment of choice for premenopausal women with DCIS.

**LEVEL IA EVIDENCE: PROSPECTIVE RANDOMIZED TRIALS AND META-ANALYSES ADDRESSING THE ROLE OF BIOMARKERS IN BREAST CANCER PREVENTION AND TREATMENT**

**Hypothesis**
Intrinsic tumor biology by a 5-biomarker panel would predict disease-free survival in patients with breast cancer undergoing BCS.

**Published Abstract**

**Purpose**
To determine the clinical utility of intrinsic molecular phenotype after BCT with lumpectomy and whole-breast irradiation with or without a cavity boost.

**Patients and methods**
Four-hundred and ninety-eight patients with invasive breast cancer were enrolled into a randomized trial of BCT with or without a tumor bed radiation boost. Tumors were classified by intrinsic molecular phenotype as luminal A or B, HER-2, basal-like, or unclassified using a 5-biomarker panel: ER, progesterone receptor, HER-2, CK5/6, and epidermal growth factor receptor. Kaplan-Meier and Cox proportional hazards methodology were used to ascertain relationships to IBTR, locoregional recurrence, distant DFS (DDFS), and death from breast cancer.

**Results**
Median follow-up was 84 months. Three-hundred and ninety-four patients were classified as luminal A, 23 were luminal B, 52 were basal, 13 were HER-2, and 16 were unclassified. There were 24 IBTR (4.8%), 35 locoregional recurrence (7%), 47 distant metastases (9.4%), and 37 breast cancer deaths (7.4%). The overall 5-year disease-free rates for the whole cohort were IBTR, 97.4%; locoregional recurrence, 95.6%; DDFS, 92.9%; and breast cancer–specific death, 96.3%. A significant difference was observed for survival between subtypes for locoregional recurrence ($P = .012$), DDFS ($P = .0035$), and breast cancer–specific death ($P = .0482$), but not for IBTR ($P = .346$).
Conclusions
The 5-year and 10-year survival rates varied according to molecular subtype. Although this approach provides additional information to predict time to IBTR, locoregional recurrence, DDFS, and death from breast cancer, its predictive power is less than that of traditional pathologic indices. This information may be useful in discussing outcomes and planning management with patients after BCT.

Editorial comments Tumor molecular subtype identifies groups with divergent rates of local regional recurrence, DFS, and OS. However, such classification was not better than traditional pathology variables such as tumor size, grade, hormonal status, lymph node status, lymphatic vascular invasion, and positive margins. The rate of positive margins in this study was very low (2.4%), as was the rate of local recurrence, which would make it difficult to assess the predictive value of any tumor attribute. The Oncotype 21-gene assay is both predictive of recurrence and prognostic for benefit of chemotherapy and survival. This test was validated retrospectively on 2 prospective NSABP trials (B-14 and B-20). The TAILORX trial, which has completed accrual, will prospectively validate the assay. Recurrence score generated from the Oncotype assay is now commonly used and is included in the new staging American Joint Committee on Cancer guidelines, and has significantly decreased the use of chemotherapy. Similarly, prospective-retrospective trials with Oncotype on DCIS have shown that the DCIS score can predict risk of recurrence without XRT.


Hypothesis
PD-L1 is of prognostic significant in breast cancer.

Published Abstract
Programmed cell death 1 ligand 1 (PD-L1) is a promising therapeutic target for cancer immunotherapy. However, the correlation between PD-L1 and breast cancer survival remains unclear. This study presents the first meta-analysis to investigate the prognostic value of PD-L1 in breast cancer. The study searched PubMed, Embase, and Cochrane Central Register of Controlled Trials databases for relevant studies evaluating PD-L1 expression and breast cancer survival. Fixed-effect and random-effect meta-analyses were conducted based on heterogeneity of included studies. Publication bias was evaluated by funnel plot and Beg test. Overall, 9 relevant studies with 8583 patients were included. PD-L1 overexpression was found in 25.8% of patients with breast cancer. PD-L1 (+) associated with several high-risk prognostic indicators, such as ductal cancer (P = .037), high tumor grade (P = .000), ER negativity (P = .000), PR negativity (P = .000), HER2 positivity (P = .001), and aggressive molecular subtypes (HER2 rich and Basal-like; P = .000). PD-L1 overexpression had no significant impact on metastasis-free survival (HR, 0.924; 95% CI, 0.747–1.141; P = .462), DFS (HR, 1.122; 95% CI, 0.878–1.434; P = .357), and overall specific survival (HR, 0.837; 95% CI, 0.640–1.093; P = .191), but significantly correlated with shortened OS (HR, 1.573; 95% CI, 1.010–2.451; P = .045). PD-L1 overexpression in breast cancer associates with multiple clinicopathologic parameters that indicate poor outcome, and may increase the risk for mortality. Further standardization of PD-L1 assessment assay and well-controlled clinical trials are warranted to clarify its prognostic and therapeutic value.
**Editorial comment**

In the new era of checkpoint inhibitors, the findings of these studies were significantly heterogeneous; the results should be interpreted cautiously. Phase I prospective trials using PD-L1 monoclonal antibodies show response rates from 4% to 14% with various drugs, which is higher in aggressive subtypes (HER2+ or triple negative) and with an acceptable safety profile. The higher response rates are thought to be secondary to the higher percentage of expression of the PD-L1 that is seen in the more aggressive subtypes (triple negative and Her2+).

**REFERENCES**


