Primary Systemic Therapy of Breast Cancer

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Key Words. Primary systemic therapy • Pathologic complete response • Anthracycline • Taxane

ABSTRACT

Primary systemic therapy (PST) or neoadjuvant therapy is used in nonmetastatic breast cancer to treat systemic disease earlier, decrease tumor bulk ideally to a complete pathological response (pCR), and reduce the extent of surgery. The multitude of clinical trials using PST in breast cancer patients has not proven the fundamental hypotheses of improved overall survival and disease-free survival that drove the investigation of PST. The other potential advantages of PST, which include increasing the rate of breast-conserving surgery and predicting outcome to a particular chemotherapy regimen, are also not conclusively established. We examined the published literature on PST for breast cancer and predominantly focused our review on data from large, randomized clinical trials comparing primary systemic chemotherapy with adjuvant chemotherapy, different primary systemic chemotherapy regimens, primary systemic chemotherapy with hormonal therapy, and different preoperative hormonal therapies. Although the optimal neoadjuvant chemotherapy regimen has not been established, a combination of four cycles of an anthracycline followed by four cycles of a taxane appears to produce the highest pCR rate (22%–31%). In patients with HER-2-positive breast cancer, concurrent use of neoadjuvant trastuzumab with an anthracycline–taxane combination has produced provocative results that require further confirmatory studies. Preoperative hormonal therapy is associated with low pCR rates and should be reserved for patients who are poor candidates for systemic chemotherapy. The optimal management of patients with residual disease after the administration of maximum neoadjuvant therapy remains to be defined. The surgical approach, including the role of sentinel node biopsy and delivery of radiation therapy after PST in breast cancer patients, is evolving. Ongoing clinical trials will help identify the subset of patients who would most benefit from the use of PST, establish the most effective PST regimen, and determine the optimal multidisciplinary approach in the management of breast cancer. The Oncologist 2006;11:574–589

Learning Objectives

After completing this course, the reader will be able to:

1. Describe the rationale for using primary systemic therapy (PST) in the treatment of nonmetastatic breast cancer.
2. Discuss the pathologic complete response (pCR) rate as a surrogate marker of PST benefit.
3. Select the most appropriate regimen for a patient with breast cancer considered for PST.
4. Explain the role of sentinel node biopsy and delivery of radiation therapy after PST in breast cancer patients.
**INTRODUCTION**

Increasingly over the past 15 years, primary systemic therapy (PST) has been used in patients with nonmetastatic breast cancers. The concept of primary chemotherapy for operable breast tumors evolved from experience in locally advanced inoperable breast cancer. The goals of PST in breast cancer are to treat occult systemic disease, decrease the tumor bulk (optimally to a complete pathologic response), and reduce the extent of local surgery (Sx) to allow breast-conserving surgery. Four fundamental hypotheses underlie the argument for PST. The first hypothesis is that systemic therapy given prior to surgery might sterilize areas of micrometastases and prevent further cancer growth after the primary tumor is resected. This would be especially true if the second hypothesis was correct, that is, that breast surgery could release tumor cells and stimulate the growth of occult micrometastases through mechanisms such as angiogenesis [1, 2]. The third hypothesis is that PST, by reducing the size of the primary tumor, allows higher rates of breast-conserving surgery and/or reduces local recurrence rates. The fourth hypothesis is that the efficacy of PST can be used as an in vivo assay of drug sensitivity/resistance.

Despite a multitude of clinical trials using PST in breast cancer patients, we are still faced with certain fundamental questions: (a) Is there an advantage in using neoadjuvant versus adjuvant chemotherapy? (b) Which is the most effective PST regimen? (c) Is primary hormonal therapy better than primary systemic chemotherapy in patients with estrogen receptor (ER)/progesterone receptor (PR)-positive tumors? (d) Is response to PST and long-term outcome influenced by tumor histology (invasive lobular carcinoma versus invasive ductal carcinoma)? (e) What are the challenges in performing surgery or delivering radiation therapy (RT) following cytoreductive treatment with PST? (f) What is the role of positron emission tomography (PET) and magnetic resonance imaging (MRI) in predicting response to PST?

In order to examine the evidence to date that addresses the proof of concept of PST and the issues outlined above, we performed a literature search using key words such as “primary systemic therapy,” “neoadjuvant,” “anterior,” “preoperative,” “induction therapy,” and “chemotherapy.” We reviewed the up-to-date literature through 2005 on PST for breast cancer and have relied predominantly on data from large, randomized clinical trials comparing primary systemic chemotherapy with adjuvant chemotherapy, different primary systemic chemotherapy regimens, primary systemic chemotherapy with hormonal therapy, and different preoperative hormonal therapies. Where no randomized, phase III clinical trials were available, we reviewed data from phase II or retrospective studies.

**PST Versus Adjuvant Chemotherapy**

Several phase III randomized clinical trials have compared preoperative chemotherapy with the same regimen of chemotherapy administered postoperatively. The primary end points in most of these studies were overall survival (OS) and disease-free survival (DFS). Results of these studies are shown in Table 1.

The largest of these studies is the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial in which 1,523 patients with T1–3N0–1M0 breast cancer were randomized to receive four cycles of doxorubicin and cyclophosphamide (AC) given either before or after surgery. Tamoxifen was administered in all patients older than 50 and was started at the same time as the chemotherapy. The clinical response rate (cRR), complete clinical response (cCR) rate, and complete pathologic response (pCR) rate in the neoadjuvant group were 80%, 36%, and 13%, respectively. Of the 13% that achieved a pCR, 4% had residual ductal carcinoma in situ (DCIS). The rate of breast-conserving therapy (BCT) was higher among patients treated with PST (67%) than among those receiving adjuvant therapy (60%; \( p = .002 \)). At a 9-year follow-up, there was no difference between neoadjuvant and adjuvant chemotherapy in terms of DFS (55% vs. 53%, nonsignificant [NS]) or OS (69% vs. 70%, NS). Local recurrence rates were higher (15%) in patients requiring chemotherapy in order to undergo BCT than in those patients who were initially considered candidates for BCT (7%). Patients who achieved a pCR had a superior outcome, in terms of 5-year DFS (\( p = .00005 \)), OS (\( p = .0008 \)), and relapse-free survival (RFS) (\( p < .0001 \)) compared with patients in all other groups [3–5].

Another trial, the European Organization for Research and Treatment of Cancer (EORTC) 10902 trial [6], randomized 698 patients with T1c–4b breast cancer to four cycles of 5-fluorouracil (5-FU), epirubicin (60 mg/m²), and cyclophosphamide (the FEC regimen) given before or after surgery. The cRR, cCR rate, and pCR rate were 49%, 7%, and 4%, respectively. Achieving a pCR again was associated with better survival. OS, progression-free survival, and locoregional recurrence were similar between the two groups. However, in a nonrandomized comparison, OS was lower in patients who were planned for mastectomy but underwent BCT because of downstaging of the tumor compared with patients who were initially planned to receive BCT (hazard ratio [HR], 2.53; \( p = .04 \)). This suggests that initial Tumor, Nodes, Metastases (TNM) stage remains an important factor in patient prognosis. Also, clinical downstaging after neoadjuvant chemotherapy does not provide definitive evidence that the tumor size has actually decreased, and therefore, performing BCT in this circumstance may result in a higher rate of misleadingly “clear” surgical margins and, later, in a higher rate of local recurrence.
Gianni et al. [7, 8] randomized 1,355 patients with breast cancers >2 cm to three groups: adjuvant doxorubicin (A) followed by cyclophosphamide, methotrexate, and 5-FU (CMF) (Sx → A → CMF); adjuvant doxorubicin and paclitaxel (AT) followed by CMF (Sx → AT → CMF); and neoadjuvant AT followed by CMF (AT → CMF → Sx). pCR rates in the neoadjuvant arm were 23% in breast only and 20% in breast plus axilla patients. The BCT rate was also better in this arm (65% vs. 34%; p < .001). At 5 years of follow-up, adjuvant chemotherapy was similar to PST in terms of freedom from progression (p = .24) and OS (p = .81) [7, 8]. Other smaller randomized phase III trials of neoadjuvant versus adjuvant chemotherapy (Table 1) used different chemotherapy combinations and, similar to the larger studies, did not find any survival benefit for the neoadjuvant group [9–12].

A recent meta-analysis addressed directly the question of neoadjuvant versus adjuvant chemotherapy. Nine randomized clinical trials involving 3,946 patients were included. pCR rates were highly variable among these trials. Six trials had a higher rate of BCT after PST. No difference was observed between the two arms for death, disease progression, or distant recurrence. Surprisingly, neoadjuvant chemotherapy was associated with a higher locoregional recurrence (risk ratio, [RR] 1.22; p = .015). This greater risk was largely attributed to those trials in which RT alone without surgery was used in patients who achieved a cCR to neoadjuvant chemotherapy (RR, 1.53; p = .009) [13].

The evidence-based literature to date does not support the hypothesis that PST results in better outcomes. Survival and DFS are similar with neoadjuvant and adjuvant therapy for nonmetastatic breast cancer. PST might result in modestly higher BCT rates, but at the cost of a possible slightly higher rate of locoregional recurrence.

### Randomized Phase III Trials of Neoadjuvant Chemotherapy Regimens

The anthracycline-containing regimens have been proven to be superior to the nonanthracycline regimens in the adjuvant treatment of breast cancer patients [14]. Combinations of anthracyclines and taxanes have been used in the adjuvant setting and have become a standard of care [15–17]. The benefit and also the best schedule of administration (sequentially vs. concurrently, weekly vs. every 3 weeks) of neoadjuvant taxanes are being investigated. Results of several randomized trials exploring different neoadjuvant chemotherapy combinations are shown in Table 2.

### Neoadjuvant Taxanes: Is There a Benefit?

NSABP B-27 is the largest of the studies comparing a neoadjuvant anthracycline regimen with an anthracycline–taxane combination. Two thousand four hundred eleven patients with T1c–3N0 or T1–3N1 breast cancer were randomized to three groups: four cycles of preoperative AC (AC → Sx, arm I), four cycles of AC followed by four cycles of docetaxel (D) followed by surgery (AC → D → Sx, arm II), and four cycles of AC followed by surgery followed by four cycles of docetaxel (AC → Sx → D, arm III). All patients were started on tamoxifen on the first day of chemotherapy. The addition of preoperative docetaxel (arm II) was associated with a higher cRR (91% vs. 85%; p < .001), cCR (64% vs. 40%; p < .001), and

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**Table 1. Randomized phase III trials comparing neoadjuvant with adjuvant therapy using the same chemotherapy regimen**

<table>
<thead>
<tr>
<th>Study</th>
<th>n (stage and size)</th>
<th>Chemotherapy regimen</th>
<th>cRR (%)</th>
<th>pCR (%)</th>
<th>DFS benefit</th>
<th>OS benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher et al. [3, 4], Wolmark et al. [5], NSABP B-18</td>
<td>1,523 (operable)</td>
<td>AC</td>
<td>80</td>
<td>13</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Van der Hage et al. [6], EORTC 10902</td>
<td>698 (T1c–4bN0–1)</td>
<td>FEC</td>
<td>49</td>
<td>4</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Gianni et al. [7, 8], ECTO</td>
<td>1,355</td>
<td>AT → CMF</td>
<td>78</td>
<td>23</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Mauriac et al. [9]</td>
<td>272 (&gt;3 cm)</td>
<td>EMV/MTV</td>
<td>81</td>
<td>NA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Scholl et al. [10], Broet et al. [11]</td>
<td>414 (T2–3N0–1)</td>
<td>FAC</td>
<td>85</td>
<td>NA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Makris et al. [12]</td>
<td>309 (operable)</td>
<td>MM(M)+Tam</td>
<td>84</td>
<td>10</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: AC, doxorubicin and cyclophosphamide; AT, doxorubicin and paclitaxel; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; cRR, clinical response rate; DFS, disease-free survival; EMV, epirubicin, methotrexate, and vincristine; ECTO, European Cooperative Trial in Operable Breast Cancer; EORTC, European Organization for Research and Treatment of Cancer; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; MM(M)+Tam, mitomycin C, methotrexate, mitoxantrone, and tamoxifen; MTV, mitomycin C, thiopeta, and vindesine; NA, not available; NSABP, National Surgical Adjuvant Breast and Bowel Project; OS, overall survival; pCR, complete pathologic response.
pCR in breast rate (26% vs. 14%; \( p < .001 \)) when compared with the group of patients who received only AC prior to surgery (arm I + III). There was no difference in the BCT rate (63% in the neoadjuvant D arm vs. 62% in the neo-adiuvant AC only arms). The addition of D to AC did not significantly impact DFS or OS. However, in the subset of patients with a CPR to AC, the addition of preoperative D, but not postoperative D, resulted in a significantly longer DFS than with AC alone (HR, 0.71; \( p = .007 \)). Achieving a pCR was again associated with a better OS (HR, 0.33; \( p < .0001 \)) and DFS (HR, 0.45; \( p < .0001 \)) [18, 19].

In the Aberdeen trial, 162 patients with tumors >3 cm or T3–4N2 were treated with four cycles of cyclophosphamide, vincristine, doxorubicin, and prednisone (CVAP). Responding patients were randomized to four additional cycles of CVAP (52 patients) or to four cycles of D (52 patients). Patients failing to respond to CVAP \( \times 4 \) received D in a nonrandomized arm (54 patients). The overall response rate (ORR) after the first four cycles of CVAP was 66% (CR, 14%; PR, 52%). In those patients who achieved a clinical response to CVAP \( \times 4 \), changing to D produced a much higher response rate (85% vs. 64%; \( p = .03 \)), pCR rate (31% vs. 15%; \( p = .06 \)), 5-year DFS rate (90% vs. 72%; \( p = .04 \)), 5-year OS rate (97% vs. 78%; \( p = .04 \)), and BCT rate (67% vs. 48%; \( p = .01 \)), than continuing CVAP. Of note, even those patients who did not respond to CVAP \( \times 4 \) had a good response to D, with an ORR of 47% (CR, 11%; PR, 36%) [20, 21].

Similar to the Aberdeen trial design, the German Preoperative Adriamycin and Docetaxel Study III (GEPAR-TRIO) study treated more than 2,050 women with operable breast cancer, tumor size \( \geq 2 \) cm or locally advanced disease (T4 or N3), with two cycles of neoadjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC). If tumor reduction was >50% according to breast ultrasound, patients were randomized to receive either four or six additional cycles of TAC. Nonresponders were randomized to either an additional four cycles of TAC or four cycles of vinorelbine and capcitabine (NX). Results on the 627 nonresponding patients were reported at the 2005 San Antonio Breast Conference and revealed that there was no difference between the two arms (TAC vs. NX) in terms of ultrasound response, clinical response, pathological response, and BCT rate. The pCR rate appeared to be very low for both arms (7% vs. 6%), consistent with the results of the Aberdeen trial. High ER and PR levels appeared to correlate with a low pCR rate. NX (without G-CSF) was associated with a better toxicity profile than TAC (with G-CSF). Results from the patients who responded to two cycles of TAC and were further randomized to receive four or six additional cycles of TAC have not been published [22].

The Anglo-Celtic Cooperative Oncology Group (ACCOG) trial randomized 363 patients with primary tumors >3 cm or inflammatory or locally advanced breast cancer to six cycles of preoperative AC or doxorubicin plus docetaxel (AD). At a 32-month follow-up, there was no statistically significant difference between AC and AD in terms of the ORR (61% vs. 70%), cCR rate (17% vs. 20%), BCT rate (20% vs. 20%), pCR rate (24% vs. 21%, breast invasive only), or relapse rate (31% vs. 25%) [23].

### Table 2. Randomized trials comparing different neoadjuvant chemotherapy regimens

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>( n )</th>
<th>Chemotherapy regimen</th>
<th>pCR (%)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-27 [18, 19]</td>
<td>2,411</td>
<td>AC ( \times 4 ) vs. AC ( \times 4 ) ( \rightarrow ) D ( \times 4 )</td>
<td>14</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ECTO [7, 8]</td>
<td>451</td>
<td>AT ( \times 4 ) ( \rightarrow ) CMF ( \times 4 )</td>
<td>23</td>
<td>NA</td>
</tr>
<tr>
<td>Aberdeen [20, 21]</td>
<td>162</td>
<td>CVAP ( \times 8 ) vs. CVAP ( \times 4 ) ( \rightarrow ) D ( \times 4 )</td>
<td>15</td>
<td>.06</td>
</tr>
<tr>
<td>GEPPAR-DUO [31]</td>
<td>913</td>
<td>AC ( \times 4 ) ( \rightarrow ) D ( \times 4 ) vs. 2wAD ( \times 4 )</td>
<td>22</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ACCOG [23]</td>
<td>632</td>
<td>AC ( \times 6 ) vs. AD ( \times 6 )</td>
<td>24</td>
<td>.61</td>
</tr>
<tr>
<td>AGO [33]</td>
<td>631</td>
<td>2wE ( \times 3 ) ( \rightarrow ) 2wT ( \times 3 ) vs. ET ( \times 4 )</td>
<td>18</td>
<td>.03</td>
</tr>
<tr>
<td>MDACC [34]</td>
<td>258</td>
<td>3wT ( \times 4 ) ( \rightarrow ) FAC ( \times 4 ) vs. wT ( \times 12 ) ( \rightarrow ) FAC ( \times 4 )</td>
<td>14</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Abbreviations: 2w, every 2 weeks; 3w, every 3 weeks; A, doxorubicin; AC, doxorubicin and cyclophosphamide; ACCOG, Anglo-Celtic Cooperative Oncology Group; AD, doxorubicin and docetaxel; AGO, Arbeitsgemeinschaft Gastroenterologische Onkologie; AT, doxorubicin and paclitaxel; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; CVAP, cyclophosphamide, vincristine, doxorubicin, and prednisone; D, docetaxel; E, epirubicin; ECTO, European Cooperative Trial in operable breast cancer; ET, epirubicin and paclitaxel; GEPPAR-DUO, German Preoperative Adriamycin and Docetaxel study II; MDACC, M.D. Anderson Cancer Center; NA, not available; NSABP, National Surgical Adjuvant Breast and Bowel Project; pCR, complete pathologic response in breast only (ductal carcinoma in situ allowed); T, paclitaxel.
We believe that these data support the use of both an anthracycline and a taxane for treating those patients who receive preoperative therapy. However, it is clear that there is a group of low-risk patients in whom the addition of a taxane in the neoadjuvant or adjuvant setting has minimal benefit. Identifying reliable prognostic factors that could help in individualizing the chemotherapy regimen is a work in progress. So far, data from the adjuvant and neoadjuvant settings have shown that breast tumors with a low ER expression level and high proliferation have a better response to chemotherapy [14, 24–29]. More recently, a pCR predictor nomogram based on clinical and pathologic features of the primary tumor was proposed [30].

Neoadjuvant Anthracycline–Taxane Combinations: Sequentially Versus Concurrently, Weekly Versus Every 3 Weeks?
Several trials have addressed the question of how best to incorporate a taxane into a neoadjuvant regimen. Some studies investigated a combination of an anthracycline and a taxane given concurrently versus sequentially. Others have examined weekly versus every-3-weeks taxane administration. pCR rates obtained from different randomized clinical trials of anthracycline with or without a taxane combinations are shown in Table 3.

Table 3. Complete pathologic response rates (breast invasive only) with different neoadjuvant anthracycline combinations with or without a taxane

<table>
<thead>
<tr>
<th>Sequential anthracycline–taxane</th>
<th>pCR</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC × 4 → AD × 4</td>
<td>22%–26%</td>
<td>[18, 19, 31]</td>
</tr>
<tr>
<td>CVAP × 4 → D × 4</td>
<td>31%</td>
<td>[20, 21]</td>
</tr>
<tr>
<td>ddE × 3 → ddT × 3</td>
<td>18%</td>
<td>[33]</td>
</tr>
<tr>
<td>T × 4 → FAC × 4</td>
<td>14%</td>
<td>[34]</td>
</tr>
<tr>
<td>Tx 12 wks → FAC × 4</td>
<td>29%</td>
<td>[34]</td>
</tr>
<tr>
<td>Concurrent anthracycline–taxane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ddAD × 4</td>
<td>11%</td>
<td>[31]</td>
</tr>
<tr>
<td>AD × 6</td>
<td>21%</td>
<td>[23]</td>
</tr>
<tr>
<td>ET × 4</td>
<td>10%</td>
<td>[33]</td>
</tr>
<tr>
<td>AT × 4 → CMF × 4</td>
<td>23%</td>
<td>[7, 8]</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVAP × 8</td>
<td>15%</td>
<td>[20, 21]</td>
</tr>
<tr>
<td>AC × 4</td>
<td>14%</td>
<td>[3–5, 18, 19]</td>
</tr>
<tr>
<td>AC × 6</td>
<td>24%</td>
<td>[23]</td>
</tr>
</tbody>
</table>

Abbreviations: AC, doxorubicin and cyclophosphamide; AD, doxorubicin and docetaxel; AT, doxorubicin and paclitaxel; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; CVAP, cyclophosphamide, vincristine, doxorubicin, and prednisone; ddAD, dose-dense doxorubicin and docetaxel; ddE, dose-dense epirubicin; ddT, dose-dense paclitaxel; ET, epirubicin and paclitaxel; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; T, paclitaxel.

The German Preoperative Adriamycin and Docetaxel study II (GEPAR-DUO) randomized 913 patients with T2–3N0–2M0 breast cancer to four cycles of preoperative AD every 2 weeks (dose-dense [dd]AD × 4) or four cycles of AC every 3 weeks followed by four cycles of D (AC × 4 → D × 4). Sequential AC → D was associated with a higher cRR (85% vs. 75%; p < .001), pCR (22% vs. 11%; p < .001, breast invasive only), and BCT rate (75% vs. 66%; p < .005) than concurrent ddAD [31]. Conceivably, the addition of cyclophosphamide in arm II may have resulted in the superior outcome. Alternatively, this may reflect the impact of administration schedule on outcome. Furthermore, recent data indicate that AD is a regimen associated with significant myelosuppression and toxicity [32].

In the Arbeitsgemeinschaft Gastroenterologische Onkologie (AGO) study, 631 patients with breast cancer were randomized to receive three cycles of dose-dense (every-2-weeks) epirubicin followed by three cycles of dose-dense paclitaxel (ddE × 3 → ddT × 3) or four cycles of epirubicin and paclitaxel (ET) every 3 weeks (ET × 4). Sequential ddE → ddT was associated with a higher pCR rate (18% vs. 10%; p = .03) and BCT rate (66% vs. 55%; p = .016) than concurrent ET [33].

Green et al. [34] randomized 258 breast cancer patients to 12 weeks of paclitaxel given either weekly or every 3 weeks, followed by four cycles of 5-FU, doxorubicin, and cyclophosphamide (FAC). The weekly paclitaxel schedule was associated with higher pCR (28% vs. 16%; p = .02) and BCT (p = .05) rates.

These studies suggest that the sequential use of an anthracycline with a taxane is associated with better results than their concurrent use. However, it is impossible to determine whether the observed benefit is a result of the sequential use or because of differences in total delivered dose of chemotherapy (higher in the sequential arm) or treatment duration (longer in the sequential arm). Similar to the results seen in patients with metastatic breast cancer [35], the neoadjuvant data show that paclitaxel is more active in the weekly schedule. The role of weekly paclitaxel in the adjuvant setting is being investigated in several ongoing trials (the Eastern Cooperative Oncology Group [ECOG] 1199 trial and the Southwest Oncology Group [SWOG] S0221 trial).

Neoadjuvant Chemotherapy in HER-2-Positive Breast Cancer
Human epidermal growth factor (HER-2) receptor is over-expressed in 15%–25% of breast cancers. Trastuzumab, a humanized receptor antibody directed against HER-2, in combination with chemotherapy has been proven to improve DFS and OS in metastatic breast cancer [35, 36] and, more
recently, in the adjuvant setting [37–39] in patients with HER-2-positive breast cancer. A number of small phase II trials have studied different combinations of preoperative trastuzumab and chemotherapy. In these studies, the pCR rates ranged from 12%–45% [40–47].

So far, only one randomized, phase III trial has assessed the use of preoperative trastuzumab in conjunction with chemotherapy. Buzdar et al. [48] compared a 6-month course of preoperative chemotherapy consisting of four cycles of paclitaxel followed by four cycles of FEC with the same chemotherapy with simultaneous weekly trastuzumab for 24 weeks in noninflammatory stage II and IIIA, HER-2-positive breast cancer patients. The study was closed early, after the accrual of only 42 of the 164 planned patients, because of the superiority of the trastuzumab plus chemotherapy arm. Patients who received concurrent preoperative chemotherapy and trastuzumab had a significantly higher pCR rate (65%) than those who received chemotherapy alone (26%; p = .016). There was no difference in the BCT rate between the two groups (57% vs. 53%). No patient developed clinical congestive heart failure, although there was a >10% decrease in cardiac ejection fraction in five and seven patients in the chemotherapy alone and trastuzumab plus chemotherapy arms, respectively. What caused the very high pCR rate seen with neoadjuvant trastuzumab in this study? A favorable patient population, a more prolonged administration of trastuzumab (24 weeks), and the concurrent use of an anthracycline and trastuzumab all may have contributed to these excellent results [48].

In patients with HER-2-positive breast cancers contemplating neoadjuvant chemotherapy, trastuzumab can be considered after risks (cardiac toxicity, interstitial pneumonitis, infections, etc.) and benefits have been assessed for a given patient. It remains unknown whether neoadjuvant trastuzumab is better than adjuvant trastuzumab, or whether the use of trastuzumab earlier in treatment will impact survival.

**Preoperative Hormonal Therapy**

Most studies of PST in breast cancer have used chemotherapy, although several small clinical trials have studied preoperative hormonal therapy. The influence of ER/PR status on response to adjuvant chemotherapy remains unclear.

The response of ER/PR-positive tumors to neoadjuvant chemotherapy has been reported in several studies (Table 4). Buzdar et al. [49] evaluated 1,292 patients prospectively treated in different neoadjuvant studies at the M.D. Anderson Cancer Center. Patients with ER-positive tumors had pCR rates significantly lower than those with ER-negative tumors, regardless of drug regimen or duration of chemotherapy. The overall pCR rate after neoadjuvant chemotherapy for ER-negative tumors was 21%, versus 5% for the ER-positive ones [49]. The European Cooperative Trial in Operable Breast Cancer (ECTO) study also provides relevant data on tumor response after neoadjuvant AT CMF. A pCR was achieved in 42% of patients with ER-negative tumors, versus 12% of ER-positive patients [7, 8]. In a different study by Gianni et al. [50], 89 patients were treated with neoadjuvant AT for three cycles, followed by 12 weekly cycles of paclitaxel. ER-negative tumors again had a higher pCR rate than ER-positive tumors (23% vs. 8%, respectively) [50]. In the NSABP B-27 trial, pCR rates after AC × 4 were 14% in ER-negative and 6% in ER-positive tumors, and 23% and 14%, respectively, after AC × 4 D × 4 [18,19].

Very few studies have reported the pCR rate with preoperative tamoxifen or aromatase inhibitors (AIs) in ER-positive breast tumors. Nevertheless, it appears that this rate is very low: 0%–2% with tamoxifen [51–53], 2% after 3 months of letrozole [51, 52], 3% after 3 months of anastrazole [53], and 5%–7% after 3–6 months of exemestane [53, 54].

A randomized trial by Semiglazov et al. [53] compared neoadjuvant chemotherapy (AT × 4) with 3 months of preoperative hormonal therapy (anastrozole or exemestane) in 121 patients with ER-positive breast cancer. Results were similar between the two groups, with a similar cCR (76% vs. 79%), mammographic response rate (62% vs. 67%), and pCR rate (7% vs. 5%). While the neoadjuvant chemotherapy used in that trial may not be the most active regimen available, the findings do indicate the potential role of neoadjuvant hormonal therapy [53].

Despite the lack of phase III trials comparing preoperative chemotherapy with hormonal therapy in ER/PR-positive breast cancer patients, the neoadjuvant chemotherapy regimens appear to be associated with a higher pCR rate. Preoperative hormonal therapy represents an alternative to neoadjuvant chemotherapy, especially in elderly patients, patients with poor performance status, and those with multiple comorbidities.

**Neoadjuvant Tamoxifen Versus AIs**

In postmenopausal women with ER/PR-positive breast tumors, AIs have been proven to be superior to tamoxifen by improving time to progression in the metastatic setting [55–57] and DFS in the adjuvant setting [58–60]. Several randomized trials have compared preoperative AIs with tamoxifen.

The Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) study [61] compared 3 months of preoperative anastrozole with tamoxifen or a combination of both administered to 330 postmenopausal women with ER/PR-positive breast cancer.
Clinical response rates were similar: 37% for anastrozole, 36% for tamoxifen, and 39% for the combination. In patients considered to require mastectomy at baseline, 46% treated with anastrozole were deemed candidates for BCT by their surgeon, compared with 22% receiving tamoxifen ($p = .03$). Another study compared 3 months of neoadjuvant anastrozole with tamoxifen with or without chemotherapy in 451 postmenopausal women. In hormonal therapy-only patients ($n = 314$), feasible surgery at baseline improved after 3 months in 43% of patients receiving anastrozole and 31% receiving tamoxifen ($p = .04$) [62].

Study P024 compared 4 months of preoperative letrozole with tamoxifen in 337 postmenopausal women with ER- and/or PR-positive breast cancer ineligible for BCT. Letrozole was more effective than tamoxifen in terms of both the response rate (60% vs. 41%; $p = .004$) and BCT rate (41% vs. 36%; $p = .036$) [51, 52].

Neoadjuvant exemestane also performed better than tamoxifen in a study of 151 postmenopausal breast cancer patients treated for 3 months. The cRR and BCT rate on exemestane were 76% and 37%, respectively, versus 40% and 20%, respectively, on tamoxifen ($p < .05$) [63].

There are data suggesting that a longer administration (>3 months) of neoadjuvant hormonal therapy could be associated with a higher cRR and BCT rate [54, 64, 65]. Patients with breast cancer who received neoadjuvant tamoxifen had a mean time to best ever response of 5.2 months (range, 3–56 months). Patients who received 6 months of tamoxifen had a higher response than those who received only 3 months of tamoxifen [65]. However, this longer preoperative hormonal therapy does not seem to be associated with a higher pCR rate.

Studies to date suggest that tumors expressing HER-2 have a better response to AIs than to tamoxifen, but there are limited numbers of ER- and HER-2-positive patients, and analyses are underpowered [52, 61]. In the P024 study [52], only 36 patients expressed HER-1/2 and ER. Fifteen of 17 patients (88%) in the anastrozole group had a response, versus 4 of 19 patients (21%) treated with tamoxifen. And although the difference was significant (odds ratio for response, 28; $p = .0004$), the numbers were too small and the analysis was underpowered. In the IMPACT study [61], only 34 of 239 patients (14%) were HER-2 positive. Objective responses were observed in 7 of 12 patients (58%) with anastrozole and in 2 of 9 patients (22%) with tamoxifen.

### Table 4. Complete pathologic response rates with various chemotherapy regimens based on estrogen receptor (ER) status

<table>
<thead>
<tr>
<th>Chemotherapy regimen (Reference)</th>
<th>n</th>
<th>ER-negative</th>
<th>ER-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MDACC [49]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAC × 3</td>
<td>532</td>
<td>15%</td>
<td>1%</td>
</tr>
<tr>
<td>FAC × 4</td>
<td>78</td>
<td>29%</td>
<td>6%</td>
</tr>
<tr>
<td>T × 4</td>
<td>81</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>3wT × 4 → FAC × 4</td>
<td>127</td>
<td>31%</td>
<td>6%</td>
</tr>
<tr>
<td>wT × 12 → FAC × 4</td>
<td>128</td>
<td>55%</td>
<td>15%</td>
</tr>
<tr>
<td>AD × 4</td>
<td>72</td>
<td>16%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1,018</td>
<td>21%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>ECTO [7, 8]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AT → CMF</td>
<td>451</td>
<td>42%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>NSABP B-27 [18, 19]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC × 4</td>
<td>1,533</td>
<td>14%</td>
<td>6%</td>
</tr>
<tr>
<td>AC × 4 → D × 4</td>
<td>722</td>
<td>23%</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Colleoni et al. [27]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>399</td>
<td>33%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Ring et al. [28]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Six cycles of chemotherapy</td>
<td>435</td>
<td>22%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Gianni et al. [24]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AT × 3 → wT × 12</td>
<td>89</td>
<td>23%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Abbreviations: 3w, every 3 weeks; AC, doxorubicin and cyclophosphamide; AD, doxorubicin and docetaxel; AT, doxorubicin and paclitaxel; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; D, docetaxel; ECTO, European Cooperative Trial in operable breast cancer; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; MDACC, M.D. Anderson Cancer Center; NSABP, National Surgical Adjuvant Breast and Bowel Project; pCR, complete pathologic response; T, paclitaxel; w, weekly.
This difference between anastrozole and tamoxifen was not significant \( (p = .18) \) and the study was also underpowered. Larger studies are needed to clearly prove the benefit of AIs over tamoxifen in this setting.

In sum, preoperative AIs appear to be more active (higher cRR and BCT rate) than tamoxifen in postmenopausal women with ER/PR-positive breast tumors. The response to preoperative hormonal therapy is slow, and a longer duration of treatment (>3 months) might be associated with a better response.

**IMPACT OF HISTOLOGIC SUBTYPE ON RESPONSE TO NEOADJUVANT CHEMOTHERAPY**

Invasive lobular carcinoma (ILC) accounts for 10%–15% of all breast cancers. Mammographically and clinically ILC tends to produce more subtle findings than invasive ductal carcinoma (IDC) and as a result ILC appears to be larger than IDC at diagnosis. Lobular carcinomas are also more likely to occur in older patients, to be ER- and PR-positive and HER-2 negative, and to have a propensity for multifocal and multicentric distribution and for bilaterality. Recurrence and survival rates appear to be similar between ILC and IDC, despite the less aggressive biologic phenotype of ILC [66].

Cristofanilli et al. [67] reported on a retrospective analysis of the role of primary systemic chemotherapy in patients with ILC. Of the 1,034 breast cancer patients included, 12% had ILC, and 88% had IDC. Patients with ILC tended to be older and have more ER- and PR-positive tumors, lower nuclear grade, higher stage, and a greater chance of lymph node involvement at diagnosis. The ILC patients were less likely to have a pCR (3% vs. 15%; \( p = .001 \)) but tended to have longer recurrence-free survival (\( p = .004 \)) and OS (\( p = .001 \)) than IDC patients. The difference in the pCR rate between ILC and IDC persisted even after adjusting for hormone-receptor status [67]. Chaturvedi et al. [68] have reported similar data regarding the effectiveness of neoadjuvant chemotherapy in ILC. In that series, the pCR rate to primary chemotherapy was 0% in the ILC patients versus 17% in IDC patients.

In conclusion, in patients with lobular carcinoma, pCR rates are very low, but this dose not appear to impact OS in a negative way.

**CHALLENGES OF SURGICAL APPROACH AFTER PST**

In early-stage disease, sentinel lymph node biopsy (SLNB) in lieu of axillary lymph node dissection (ALND) is a widely accepted method of staging the axilla prior to chemotherapy. In this setting, SLNB has an identification rate of 86%–93% and a false-negative rate (FNR) of 7%–13% [69–71]. However, the feasibility of SLNB and the accuracy of this procedure as a predictor of the status of the lymphatic basin following PST are questionable. One of the hypotheses is that neoadjuvant chemotherapy might sterilize first the SLN, and only later the non-SLNs, and therefore SLNB after neoadjuvant chemotherapy could have a higher FNR. However, this is counterintuitive if one assumes that systemic therapy is hematogenously distributed and not lymphatically distributed.

Single-institution studies of SLNB after neoadjuvant chemotherapy have shown variable success rates of SLN identification in the range of 84%–94% and FNRs in the range of 0%–33% [72–78]. The effect of a learning curve becomes apparent, with the newer studies reporting lower FNRs. Further data are provided from the NSABP B-27 trial, which compared preoperative chemotherapy with AC with the same regimen followed by four cycles of docetaxel in early-stage breast cancer. During the conduct of this study, 428 patients had an SLNB with a concomitant ALND following PST. The success rate for the identification and removal of an SLN was 85%. The SLNs were the only positive nodes in 56% of patients. SLNB after neoadjuvant chemotherapy had an FNR of 11%, overall accuracy of 96%, and negative predictive value of 93% [79]. These results are comparable with those obtained when SLNB is performed before systemic therapy and suggest that the sentinel node technique is applicable following neoadjuvant chemotherapy.

Standard of care would require ALND after neoadjuvant chemotherapy in those patients with clinically positive ALNs or cytologically documented node-positive disease at presentation. However, primary systemic chemotherapy sterilizes axillary metastases approximately 25% of the time, and this can result in unnecessary ALND. Can we use SLNB to identify patients who might be spared an ALND in this setting? In a study by Lang et al. [80], the SLN identification rate and SLN FNR after PST appeared to correlate with clinical nodal status at presentation. Clinically N1 patients had an SLN identification rate of 91% and an FNR of 9%, versus 97% and 0%, respectively, in N0 patients [80]. In another study, by Shen et al. [81], SLNB following PST in patients with cytologically documented node-positive disease at presentation had a good identification rate (93%) but appeared to have a very high FNR (26%). In conclusion, SLNB following neoadjuvant chemotherapy is not an appropriate method for evaluating the axilla in patients with clinically or cytologically positive axillary lymph nodes at presentation.

Another important question relates to the timing of axillary staging, before or after PST. A recently reported, small, single-institution study showed that SLN identification rates were significantly better when mapping was performed before rather than after neoadjuvant chemo-
therapy (100% vs. 81%, respectively). Failure to map after chemotherapy was correlated with clinically positive nodal disease at presentation and residual disease at ALND. The FNR of postneoadjuvant chemotherapy SLNB was 11% [82]. Although performing an SLNB with or without an ALND prior to PST will commit the patient to two different surgical procedures, many surgeons suggest that axillary staging be done before initiating systemic therapy so that it will not be confounded by it. Axillary staging prior to PST would probably not change the plans for systemic therapy but might impact the management of the regional lymph nodes by changing the radiation oncology planning.

But does ALND improve survival in this setting? The retrospective evidence from the adjuvant setting shows that ALND may be associated with a small survival benefit, which appears to be related to the number of nodes removed. The use of systemic adjuvant therapy may overcome this effect [83, 84]. Prospective data from the NSABP B-32 and American College of Surgeons Oncology Group (ACOSOG) Z11 trials will hopefully answer these questions and help resolve the debate on survival and morbidity of SLNB and ALND in patients with breast cancer.

Another important aspect of surgical evaluation after PST is establishing the operability criteria for the primary tumor that would identify candidates for breast conservation versus mastectomy. With the help of both clinical findings and imaging studies, the size and extent of the primary tumor can be measured. However, one hypothesis is that tumor response to chemotherapy can be patchy and not concentric. And as the tumor volume removed is usually less than the gross volume originally occupied by the cancer, this could cause falsely negative tumor-free margins. That is, if the breast tissue was evaluated beyond the surgical margins, one could find additional malignant tissue. In addition, there are other variables that influence the decision for BCT or mastectomy, including subjective operator-related bias and consideration toward patient preference. Because of all these confounding factors, it is difficult to standardize the surgical criteria for operability of the primary tumor among patients receiving PST. For women who are candidates for BCT at presentation, the use of PST may not offer any benefit in terms of local recurrence and might actually render the surgical approach more problematic.

At our institution, we perform an axillary evaluation on all patients prior to PST. In those patients with clinically/ultrasound suspicious ALNs, cytological diagnosis is obtained by fine-needle aspiration. Patients with clinically/cytologically negative ALNs undergo SLNB prior to PST. After completion of PST, ALND at the time of definitive surgery is performed only on those patients who had a positive axilla prechemotherapy.

### Challenges of RT After PST

#### BCT after PST in Locally Advanced Breast Cancer

One of the potential advantages of PST is that it may result in decreasing the size of the primary tumor, making BCT feasible. In published studies, approximately 23%–32% of patients for whom the initial surgery would be a mastectomy are able to undergo BCT following PST [3–6, 85]. In the NSABP B-18 trial, 67% of patients underwent BCT after neoadjuvant chemotherapy, compared with 60% of the group that received postoperative adjuvant treatment [3–5]. In a study from the M.D. Anderson Cancer Center, 17% of patients potentially eligible for BCT were actually treated with mastectomy [86]. Kuske et al. [87] reported that the mastectomy specimen after PST showed a marked regression of the invasive component, whereas whenever an intraductal component was present, its margins extended across a volume similar to the original tumor. As noted in the surgical section, there are no established criteria that define eligibility for BCT. For the most part, tumor size after response to PST is used in selecting patients for BCT. Extrapolating from the adjuvant setting, assessment of the status of the margins and the excision specimen size are used in selecting patients for RT. There are no firm recommendations on the impact of histologic subtype on the selection of patients for BCT in this patient population.

In the NSABP B-18 trial, there was a trend toward a higher breast cancer local recurrence rate in the subset of patients made eligible for BCT only after undergoing PST (16%), compared with those who were candidates for BCT at diagnosis (10%; p = .14) [5]. In the published literature, local recurrence rates after BCT in locally advanced cancer appear to increase with increasing follow-up. With short follow-up, recurrence rates of 5% or less are observed. However, studies with follow-up of 52 months, 85.5 months, and 124 months reported recurrence rates of 14%, 19%, and 23%, respectively [9, 85, 88].

#### Postmastectomy RT

A large study [89] reported on 2,016 patients enrolled in four randomized trials conducted by the ECOG. For patients with 1–3 ALNs positive for metastases, the risk for locoregional failure was 13% at 10 years, and for patients with four or more nodes with metastatic disease, it was 29%. Multivariate analysis noted tumor size, number of positive lymph nodes, ER status, and number of lymph nodes examined as significant prognostic factors. Accordingly, for patients with large tumors and/or four or more positive ALNs, postoperative RT is routinely recommended. Another retrospective study assessed 676
patients treated in six consecutive institutional prospective trials with neoadjuvant chemotherapy and mastectomy, with or without RT. Local control and survival rates were again higher for those patients who received RT and had clinical T3 tumors, stage III–IV disease, and four or more positive nodes [90].

Buchholz et al. [91] reported on 150 women treated with neoadjuvant chemotherapy and mastectomy without post-mastectomy RT. The 10-year actuarial rate of locoregional recurrence was reported at 27%. On further analysis, clinical stage IIIB or greater, pathologic involvement of more than four lymph nodes, and no use of tamoxifen were all independent predictors of recurrence. Of specific interest is the outcome of the 18 patients who achieved a pCR of both the primary tumor and the lymph nodes. In this subset, the locoregional recurrence rate was 19%, illustrating that pCR does not exclude the need for locoregional RT [91].

The locoregional control rates for patients treated with PST, mastectomy, and RT are reported to be in the range of 85%–90% [92–94]. It has been suggested that the initial response to PST may influence the eventual local control rate achieved by the multidisciplinary application of surgery and RT. In a study by Singletary et al. [86], the recurrence rates observed after PST, mastectomy, and RT were correlated with the degree of response. Among patients who had a sufficient response and hypothetically could have been candidates for BCT, 0% recurrence was noted, compared with a 15% recurrence rate among those patients with an insufficient response to potentially categorize them as candidates for BCT [86].

The risk for locoregional recurrence is lower following a good response to PST. However, the pattern of failure in the published experience does not identify any subset of women, including patients with pCR, for whom RT may be omitted. Postmastectomy RT is routinely indicated for all patients presenting with large tumors and/or four or more positive lymph nodes.

An important implication of PST is defining the appropriate RT fields with regard to treating the regional lymph nodes. In all instances of positive nodes at presentation, it would be ideal that the status of the axilla be known up front. In these patients, the target volume encompassed by the RT field should include regional lymph node irradiation. PST changes the status of the lymph nodes involved, compromising our ability to judge the true value of adding RT to the findings of an ALND performed following PST. As we strive to apply strategies to minimize toxicity from combined surgery and RT, the question of whether axillary RT can substitute for routine lymph node dissection in patients with positive SLNs after PST is currently being addressed in an ongoing study at M.D. Anderson Cancer Center.

Managing patients after locoregional failure is not only a challenging clinical problem but also one that has a detrimental impact on the patient’s quality of life and OS. RT plays a critical role in the overall management of patients with locally advanced breast cancer by significantly decreasing locoregional failures.

**Role of PET and MRI in Assessing Response to PST**

Assessment of response to PST for breast carcinoma early during therapy is helpful in choosing between maintenance of successful therapy and discontinuation of unsuccessful treatment. However, conventional methods of evaluation of therapy response by means of physical examination, mammography, and ultrasound are suboptimal in accurate assessment [95]. In comparison, several studies have shown the usefulness of PET in the assessment of response [96–100]. Early in the course of chemotherapy, a significant decline in the standardized uptake value (SUV; a parameter that evaluates relative intensity of glucose metabolism semiquantitatively) occurs in responders, in contrast to no change or a slight increase in those who do not respond to treatment [96]. Small studies found that PET-computed tomography could accurately predict pathological response to treatment after neoadjuvant chemotherapy. Fluorodeoxyglucose (FDG) uptake showed minimal change in nonresponding patients, based on surgical/histopathological evaluation, but a marked decrease in most responding patients [100, 101]. Similar results were seen in patients with metastatic disease. In a small study evaluating chemotherapy response in patients with metastatic breast carcinoma, there were both early and overall decreases in SUV values in responders [102]. Studies evaluating patients with metastatic skeletal breast carcinoma showed that the change in SUV values after treatment was in tandem with clinical response and tumor markers [102, 103]. In contrast to the decrease in FDG uptake in chemotherapy responders, responders to antiestrogen therapy, early in the course of treatment, demonstrate an increase in SUV values, so-called “metabolic flare,” as demonstrated in a group of patients who underwent FDG-PET at baseline and again after 7–10 days of tamoxifen treatment [104].

MRI may also be better than traditional methods of mammography or clinical examination in monitoring response to therapy and may help determine early in the treatment if a particular chemotherapy regimen is working for a patient, or if alternative drugs should be used [105]. The morphologic pattern of the breast tumor on MRI is variable and appears to be predictive of response to therapy. Five distinct imaging patterns have been identified (circumscribed mass, nodular tissue infiltration, diffuse tissue...
nosis, after the anthracycline therapy, and after the taxane. An MRI is performed at the time of diag-
nosis after PET. Another consideration is that tumors with poor proliferative potential, such as those with a high proliferation rate (ER negative, high proliferation rate) are associated with a better response to chemotherapy [14, 18, 19, 24–29, 49] and are strong predictors of pCR, despite their high likelihood of recurrence. It is therefore unlikely that achieving a pCR identifies patients with good tumor biology and better prognosis who would have done well even without the addition of chemotherapy.

The BCT rate is not a valid end point for a number of reasons. Unfortunately, it is difficult to prospectively define criteria for breast conservation versus mastectomy. The surgical decision making is complex and hard to objectify. If investigators assume benefits of PST, then they are more likely to opt for breast conservation, when adverse prognostic signs such as tumor size, chest wall invasion, or other factors would have favored a mastectomy. This investigator selection bias most likely accounts for the higher local recurrence rates for patients who received PST versus adjuvant therapy.

Another consideration about PST is implications of ALN staging and treatment. The principle of staging is that patients are evaluated for the extent of disease at the time of presentation when the TNM stage is evidence based. Even though SLN methodology can be extrapolated to the post-PST setting, there are few data to support the prognostic implications of ALN staging after PST. Again, the validity of clinical and pathologic response in ALNs as a surrogate marker of outcome is flawed, as it may not be an independent variable, using an analogous argument that applies for response in the primary tumor. Assuming that the primary value of SLN assessment and ALND is prognostic, then the sequencing is problematic in the setting of PST.

Considerable resources have been committed to clinical trial design to establish optimal regimens for PST. Is there any fundamental reason to think that there are differences among regimens whether or not they are used as PST or adjuvant treatment? The evidence to date supports the assumption that the best regimens for adjuvant therapy are likely the best regimens for PST. The clinical trial emphasis should be on whether one can identify subsets of patients who need a particular regimen rather than another based on molecular features of the cancer and the discovery of innovative approaches to the management of women with nonmetastatic disease independent of whether or not the therapy is adjuvant or PST.

The correlation of pCR with better survival, supported by several studies [3–6, 18, 19, 28, 110, 111], is encouraging as a surrogate marker of PST benefit, but pCR as an end point has limitations. Different clinical trials have reported a wide range of pCR rates (Table 2). In interpreting these results, one needs to be cautious, since pCR is defined differently in many of these studies (breast only vs. breast and axilla, no invasive tumor only vs. no invasive tumor and no DCIS). Another consideration is that tumors with poor prognostic markers (ER negative, high proliferation rate)
of a shorter course of PST, minimizing toxicity. Functional imaging of the primary tumor is emerging as an important biologic end point. PST has advantages for future clinical trials evaluating novel drugs and combinations of drugs in the systemic treatment of breast cancer patients.

Toxicity of systemic therapy is also of important consideration. The concept of QTWiST (Quality-adjusted Time Without Symptoms of disease or Toxicity of treatment) has been used in a number of different clinical settings, and one might even consider QTWiST as a valuable end point in PST trials. This analysis might be applied to the patients with ER/PR positivity that have a lower response to chemotherapy, likely a more chronic disease course, and would have a much better QTWiST with a more prolonged course of PST with hormones rather than chemotherapy [112].

**Recommendations**

At the present time, there is no standard of care regarding the use of preoperative chemotherapy or hormonal therapy. In the absence of an appropriate clinical trial, patients should be offered an anthracycline–taxane combination, preferably four cycles of an anthracycline followed by four cycles of a taxane. In patients with HER-2-positive breast cancer, concurrent use of neoadjuvant trastuzumab with an anthracycline–taxane combination has produced provocative results that require further confirmatory studies. As yet, such treatment should not represent the standard of care. It remains unclear if neoadjuvant trastuzumab will impact more on survival than adjuvant trastuzumab, although it appears that neoadjuvant trastuzumab is associated with higher pCR rates and possibly with higher BCT rates. Preoperative hormonal therapy is associated with a low pCR rate and should be reserved for patients who are poor candidates for systemic chemotherapy (i.e., poor performance status, ongoing comorbidities, elderly, etc.).

Currently, several questions regarding the use of preoperative systemic therapy remain unanswered. For example, the optimal management of patients with residual disease in the breast or axilla after the administration of maximum PST remains unknown. There is no evidence to support additional chemotherapy at this point. Alternatively, the management of patients who do not respond to the initial pre operative chemotherapy or hormonal therapy remains troublesome. Novel agents need to be integrated into the therapy of such patients.

The past decade has witnessed an increased use of PST for the treatment of breast cancer. Studies demonstrate that there is no difference in survival between neoadjuvant and adjuvant chemotherapy. Despite the lack of survival benefit, primary systemic chemotherapy has potential advantages, increasing the rate of BCT and predicting outcome to a particular chemotherapy regimen. Surgery remains an important part of breast cancer management. Current trials will better define the optimal PST and those patients who might best benefit from this therapy.

**Disclosure of Potential Conflicts of Interest**

The authors indicate no potential conflicts of interest.
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