



Steve R. Garner. *Trout in the Trees Series #7*. Watercolor, 27" × 35".

*Preoperative endocrine therapy is well tolerated in older patients and can increase the rate of breast-conserving surgery.*

# Preoperative Endocrine Therapy for Older Women With Breast Cancer: Renewed Interest in an Old Idea

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**Background:** *Tamoxifen as sole therapy (primary tamoxifen therapy) was investigated in the 1970s and 1980s as an alternative to surgery for older patients with breast cancer. While the majority of primary breast tumors responded to tamoxifen, long-term local disease control was poor. The use of primary tamoxifen therapy is therefore restricted to frail, elderly, and infirm patients who cannot tolerate surgery. In contrast, short-term preoperative endocrine therapy to downstage estrogen receptor-positive (ER+) tumors is under increasing scrutiny as a nontoxic neoadjuvant approach for older women.*

**Methods:** *The literature on primary tamoxifen therapy and preoperative endocrine therapy was reviewed to construct an opinion piece on the feasibility and safety of preoperative endocrine therapy.*

**Results:** *A review of nine phase II trials and a meta-analysis of two randomized trials suggest that the initial response rates to preoperative endocrine therapy will exceed 50% to 60% for patients with ER+ disease. A short delay in surgery to administer 3 to 4 months of preoperative endocrine therapy is unlikely to compromise long-term outcomes.*

**Conclusions:** *Preoperative endocrine therapy is a logical approach for older patients with ER+ disease as a well-tolerated means to increase the rate of breast-conserving surgery. Several clinical trials comparing tamoxifen with selective aromatase inhibitors in the preoperative setting have been conducted, and the results are expected soon. These studies will determine if a large multicenter national trial of preoperative endocrine therapy should be conducted.*

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*Dr Ellis is a consultant for Novartis Corporation and receives grant support and Speakers Program honoraria. He also receives grant support from AstraZeneca Pharmaceuticals LC.*

## Introduction

Preoperative chemotherapy is well-accepted initial treatment for breast cancers that are too large for breast-conserving surgery. The majority of tumors respond, and breast conservation becomes possible for some patients. In contrast, preoperative endocrine therapy has not been rigorously examined. Studies of primary tamoxifen treatment (tamoxifen alone with surgery only if local progression) have demonstrated that an initial reduction in tumor size can be achieved for the majority of older women with estrogen receptor-positive (ER+) breast cancer, but long-term local disease control is poor. On this basis, preoperative endocrine treatment might be best employed to increase the rate of breast conservation rather than as single-modality treatment.

Current enthusiasm for this idea stems from several factors. First, the number of women aged 65 and older with breast cancer is increasing steadily, yet this population remains understudied. Second, recent comparisons between tamoxifen and aromatase inhibitors or other novel endocrine therapies have employed preoperative trial designs. Third, the response of a primary tumor to endocrine therapy may help to identify older patients with truly estrogen-dependent breast cancer for whom recommendations for multimodality therapy with chemotherapy and radiation might be safely modified. Finally, the opportunity to remove tumor samples after treatment with endocrine therapy allows investigators to study the molecular basis of endocrine therapy action in a clinical setting. This article reviews this field in light of these developments and discusses ongoing and potential future clinical trial designs to further test the clinical value of preoperative endocrine therapy for breast cancer.

## The Increasing Number of Older Women With Breast Cancer

Increasing life expectancy and the rising incidence of carcinoma of the breast have resulted in a steady increase in the number of elderly women with this disease. Of the estimated 175,000 cases of breast cancer diagnosed in 1999, 82,000 (46%) occurred in women over 65 years of age. This proportion will increase progressively in the United States over the next few decades as the average age of women rises. Surveillance, Epidemiology, and End Results (SEER) data indicate that women 65 years of age and older have an incidence rate of 483 per 100,000 compared with 74.5 per 100,000 for those under age 65.<sup>1</sup> Despite these compelling demographic data, recent data from the Southwest Oncology Group<sup>2</sup> reveal that women over age 65

are markedly underrepresented in breast cancer studies. Inadequate clinical trial data lead to inappropriate therapy since the biology of breast cancer and the benefits and risks of adjuvant therapy for older women are different for younger women. One way to address this issue is to develop breast cancer research protocols dedicated to the treatment of older women.<sup>3</sup> A prominent factor for older women is that mortality from other causes (principally cardiovascular disease) diminishes the absolute benefit of adjuvant therapy for breast cancer.<sup>4</sup> Furthermore, breast cancer in older women may be more estrogen-dependent<sup>5</sup> and may not always require "multimodality" treatment.<sup>6</sup> Of note, the value of adjuvant chemotherapy for postmenopausal women with ER+ breast cancer is modest. Only small gains, if any, in overall survival were seen when chemotherapy was added to adjuvant tamoxifen treatment for this category of breast cancer.<sup>7-10</sup> Furthermore, age and comorbid conditions may prevent the administration of chemotherapy, radiation, and even the general anesthesia necessary for mastectomy.<sup>11</sup> Finally, immobility and frailty may preclude regular travel to a cancer center for treatment with daily radiation or to manage and administer intravenous chemotherapy. All of these issues emphasize a critical need to rationalize and define the optimal treatment of older women with breast cancer.

## Primary Tamoxifen Treatment

Administration of tamoxifen alone to treat breast cancer has been investigated extensively as an alternative to initial surgery for the treatment of women over 70 years of age (primary tamoxifen therapy). Clinical response rates (complete response [CR] plus partial response [PR]) in phase II studies of primary tamoxifen therapy ranged from 41% to 81%, and the median time to achieve a response was 3 to 5 months. As expected, the treatment was well tolerated.<sup>11</sup> The Table summarizes data on several of these investigations.<sup>12-20</sup> The earliest randomized studies compared surgery (without tamoxifen) against primary tamoxifen without initial surgery in older patients.<sup>21,22</sup> However, when the adjuvant benefits of tamoxifen became apparent, studies were conducted that compared primary tamoxifen therapy with immediate surgery followed by adjuvant tamoxifen. Two large randomized studies were conducted, one by the Group for Research on Endocrine Therapy in the Elderly (GRETA), an Italian group,<sup>23</sup> and the other by the Cancer Research Campaign (CRC) in the United Kingdom.<sup>24</sup> In the GRETA investigation,<sup>23</sup> the clinical CR plus PR rate for patients receiving primary tamoxifen therapy was 37%. With prolonged follow-up, the majority of patients who received tamoxifen alone eventually required surgery.

Study	Patient/Tumor Characteristics	Correlation With ER?	Number of Patients	Response Rate	Comments
Preece et al, 1982 <sup>12</sup>	Age >75, T2-4	no	67	ORR 73%	
Helleberg et al, 1982 <sup>13</sup>	Age >65, T1-2	no	26	CR 75%	
Bradbeer and Kyngdon 1983 <sup>14</sup>	Age >70, T1-3	no	161	CR 27%, PR 34%	
Allan et al, 1985 <sup>15</sup>	Age >60, T1-3	no	53	CR 55%, PR 26%	
Anderson et al, 1989 <sup>16</sup>	Pre- and post-menopausal	yes	43	ORR 41%	60% if tumor ER $\geq$ 20 fmol/mg
Akhtar et al, 1991 <sup>17</sup>	Mean age = 76.3	yes	100	CR 40%, PR 28%	Response 74% if "ER rich"
Bergman et al, 1995 <sup>18</sup>	Age >75, T1-4	no	85	CR 14%, PR 23%	
Ciatto et al, 1996 <sup>19</sup>	Age >70	yes	120	CR 10%, PR 44%	Progression in only 6% if >60% ER+
Soubeyran et al, 1996 <sup>20</sup>	Mean age 72	yes	208	CR 10.5%, PR 42%	Response 62% if ER+ and pS2+

ORR = overall response rate  
CR = complete response  
PR = partial response  
ER = estrogen receptor

At 3 years, the local progression rate was 25% for primary tamoxifen therapy vs 6% for surgery and tamoxifen. Similar figures were seen in the CRC trial with a 23% local progression rate in the primary tamoxifen treatment arm at 34 months.<sup>24</sup> Kenny et al<sup>25</sup> reported long-term results (12 years) for primary tamoxifen therapy in 66 patients with an eventual local recurrence rate of 81%. In all these studies, overall survival was not compromised by delayed surgery, despite a higher incidence of local recurrence.

A recent meta-analysis<sup>26</sup> of the GRETA and CRC studies reported that patients randomized to initial surgery did not have a significant advantage in terms of overall survival, although there was a trend (RR 0.86;  $P=0.09$ ). The risk of death from breast cancer, however, was significantly reduced by surgery with a hazard ratio of 0.70 (95% confidence interval, 0.51-0.95). Importantly, ER expression was not required for entry into either of these studies. ER expression is a predictor of responsiveness to primary tamoxifen therapy,<sup>16,27,28</sup> and any future plans to examine the use of tamoxifen in the preoperative setting should exclude patients with ER- tumors. In support of this assumption, a study of 147 patients where ER expression was an eligibility requirement has been reported. The clinical response rate (CR and PR) on the primary tamoxifen arm was 74% with very few patients progressing within the first few months of treatment.<sup>29</sup> The major limiting factor for primary tamoxifen is therefore an unacceptably high local progression rate. Patients

must be followed closely, which is not an optimal recommendation for elderly patients with mobility problems or comorbid illness. The general consensus is that primary tamoxifen treatment is suitable for only the most frail, medically ill, or noncompliant patients.

## Ongoing Preoperative Endocrine Therapy Studies

Despite the disappointing long-term local control rates with primary tamoxifen therapy, these studies have demonstrated that initial response rates to tamoxifen in appropriately selected patients are reasonably high and the treatment is safe, with early progression within 3 to 6 months being uncommon.<sup>29</sup> Therefore, trials that examine the efficacy of endocrine therapy to "down-stage" primary breast cancer in order to increase the rate of breast-conserving surgery have begun to be considered. These investigations differ from the CRC and GRETA investigations because all patients receive surgery, but it is delayed for 3 to 4 months to determine the response of the primary tumor to endocrine therapy. In a phase I/II clinical trial in Scotland,<sup>30</sup> a response rate of 92% was seen in 24 postmenopausal, ER+ patients with locally advanced breast cancer who were treated with the aromatase inhibitor letrozole for 3 months before surgery. Of note, 15 patients who initially required a mastectomy had sufficient tumor regression for a lumpectomy to be effective in excising residual disease.

This study led to the execution of an international randomized, double-blind trial designed to compare the efficacy of preoperative letrozole (2.5 mg daily for 4 months) with preoperative tamoxifen (20 mg daily for 4 months) for postmenopausal women with ER+ and/or PR+ breast cancer. Enrollment for this trial is complete with more than 300 patients entered. All patients had tumors that were large enough for their surgeons to consider them ineligible for breast-conserving surgery. The primary objective of the trial is to compare letrozole and tamoxifen in terms of the primary tumor response rate. The frequency of breast-conserving surgery will also be compared. Preliminary results of this study are now available from meeting abstracts.<sup>31</sup> Fifty-five percent of patients responded clinically to letrozole and 36% to tamoxifen ( $P=0.001$ ). The superior activity of letrozole was associated with a higher rate of breast-conserving surgery (45% with letrozole and 35% with tamoxifen,  $P=0.022$ ). As the largest preoperative endocrine therapy trial conducted to date, the complete results of this study will be pivotal in decisions concerning the future direction of this treatment approach. Similar randomized preoperative endocrine therapy trials comparing anastrozole and tamoxifen have also been conducted and will be reported in the near future.

## Preoperative vs Postoperative Endocrine Therapy

The sequence of radiation, chemotherapy, surgery, and endocrine therapy has generated long-standing controversy. With respect to chemotherapy, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18<sup>32,33</sup> supports the conclusion that preoperative chemotherapy increases the rate of breast conservation but does not improve survival. There does not appear to be any compelling reason to think that preoperative endocrine therapy would be any different in this respect. However, one theory suggests that cell biological changes associated with endocrine therapy may reduce the metastatic potential of cells released by surgery, an advantage for preoperative endocrine therapy.<sup>34</sup>

Conversely, there are concerns that preoperative endocrine therapy may select resistant clones within the primary tumor that would not arise if the tumor had been immediately removed. The results of NSABP B-18 suggest that systemic treatment with the primary intact does not increase the number of chemotherapy-resistant clones that are later associated with relapse, but this issue remains a theoretical concern for preoperative endocrine therapy. These issues would be addressed by an NSABP B-18-type design that substitutes endocrine therapy for chemotherapy, targeting an

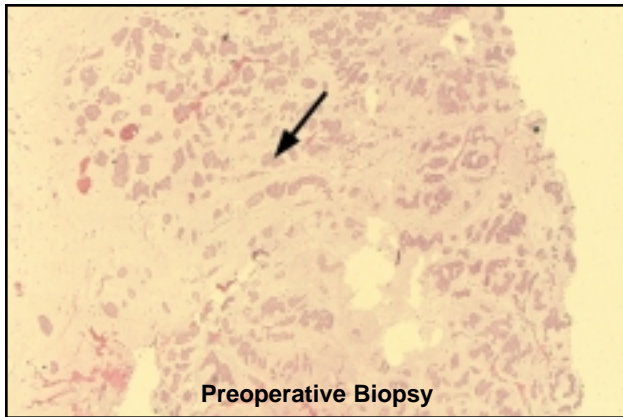
older population with ER+ disease. This design is currently being considered by investigators in the United Kingdom in the context of adjuvant endocrine therapy trials that are comparing aromatase inhibitors or the pure antiestrogen Faslodex with tamoxifen.<sup>35</sup>

## Neoadjuvant Endocrine Therapy

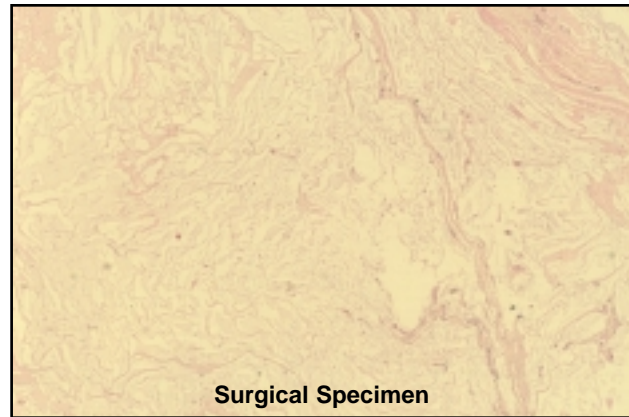
Experience with neoadjuvant chemotherapy has shown that patients with tumors that undergo a pathologic CR in the breast and regional nodes have better long-term outcomes than do patients with residual invasive disease.<sup>33</sup> Kuerer et al<sup>36</sup> recently observed that 90% of tumors that underwent a pathologic CR with chemotherapy were ER-. These results challenge the assumption that chemotherapy is the best approach to preoperative systemic therapy for ER+ disease. Data concerning pathologic status after preoperative endocrine therapy are sparse, although pathologic CRs have been reported with the aromatase inhibitor letrozole.<sup>30</sup>

The importance of examining the pathologic response is illustrated in the Figure. In this example, the regression of the malignant epithelial component of the tumor was dramatic, but the effect on the tumor dimensions was modest because the tumor had a large mucinous component that did not resolve with treatment. A correlation between pathologic response and the long-term outcome of endocrine therapy has not been reported to date, although the letrozole vs tamoxifen preoperative study discussed previously should provide some information in this regard. The assumption that preoperative endocrine therapy "responders" do better than "nonresponders" (based on clinical measurements) is supported by data from primary tamoxifen studies. Horobin and colleagues<sup>37</sup> reported the long-term results of 113 patients over 70 years of age who received primary tamoxifen therapy (unselected on the basis of ER status). The group of patients who had a clinical CR to tamoxifen (approximately one third) had a 5-year survival rate of 92% compared with 49% for the entire study. If tamoxifen responders have a significantly better outcome than nonresponders, modifications in our standard treatment approaches could be investigated in the responding group.

Patients with truly tamoxifen-sensitive tumors may be less likely to benefit from the adjuvant effects of radiation.<sup>38</sup> Brachytherapy could therefore be investigated as a more convenient approach than 6 weeks of external-beam treatment to keep the local recurrence rate at a minimum.<sup>39</sup> For older patients who respond well to preoperative endocrine therapy, radiation may possibly be avoided altogether. The value of



**Preoperative Biopsy**



**Surgical Specimen**

An 80-year-old woman with a T3 mucinous carcinoma of the breast was treated with 4 months of preoperative endocrine therapy (a blinded comparison of letrozole vs tamoxifen). There was a partial response, and a mastectomy was performed. Histopathologic examination revealed that the preoperative endocrine therapy had induced marked regression of the malignant epithelial component of the tumor (arrow) but no change in the mucinous component.

chemotherapy could also be reconsidered in a group of patients with tumors that responded to preoperative endocrine therapy. Since the benefits of adjuvant chemotherapy are small for older patients with ER+ disease, it may be safe to forego or modify this treatment in a subgroup of patients with good prognosis selected on the basis of preoperative tamoxifen response.

## New Predictive Markers for Adjuvant Endocrine Therapy Outcomes

Generally, studies on the mechanism of endocrine therapy resistance have depended on tissue culture and animal models principally due to the difficulty in obtaining tumor samples before and after a period of endocrine therapy treatment. Since tissue sampling can be readily achieved during preoperative endocrine therapy trials, this clinical approach is currently favored by European investigators interested in elucidating the molecular basis of the antitumor action of tamoxifen and, more recently, aromatase inhibitors. For example, Miller et al<sup>40</sup> demonstrated that aromatase inhibitors prevented the production of intratumoral estrogen when an aromatase inhibitor was used as preoperative treatment.

Preoperative endocrine therapy has been shown to induce apoptosis,<sup>41</sup> suppress proliferation,<sup>42</sup> and alter gene expression. Genes modulated by preoperative endocrine therapy include ER, PR, pS2<sup>20</sup> and *bcl-2*.<sup>42</sup> Detection of endocrine-therapy-induced changes in the primary tumor may improve our ability to predict the long-term effectiveness of adjuvant treatment. The recent introduction of technologies that analyze mRNA expression levels for thousands of genes in a single experiment is particularly relevant for this hypothesis (gene microarrays).<sup>43,44</sup> Statistical techniques and computer programs are being adapted to link gene micro-

array information to clinical outcomes. This may allow the detection of gene expression "clusters" that will predict sensitivity or resistance of individual breast cancers to tamoxifen. Samples from preoperative endocrine therapy trials are therefore likely to be a critical component of future gene microarray-based investigations of breast cancer.

## Conclusions

Preoperative endocrine therapy will continue to be investigated in the treatment of older women with ER+ breast cancer. In the United States, endocrine therapy has generally been withheld until all other treatment modalities have been competed. However, an "endocrine therapy first" approach may allow patients to gain additional advantages from this form of treatment, including an increase in breast conservation and the early identification of ER+ endocrine-therapy-resistant tumors that require more intense therapy. These arguments have obvious parallels with prostate cancer. Endocrine therapy is now routinely employed as initial therapy before radiation because this change in the sequence of radiation and endocrine therapy was associated with a significant improvement in the treatment of locally advanced disease.<sup>45</sup>

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