

Review Article

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## Adjuvant Surgical Oophorectomy Plus Tamoxifen: New Efficacy and Secondary Effects Data

Richard R. Love\*

Department of Computer science, Marquette University, Milwaukee, WI

**\*Corresponding author:** Richard R. Love, Department of Computer science, Marquette University, Milwaukee, WI, Email: richardibcrf@gmail.com

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### Abstract

Recent publication of the 8-year update of the SOFT and TEXT trials indirectly calls attention to the leading role that surgical oophorectomy plus tamoxifen (SO+T) should now play in global breast cancer care. The here-reviewed breadth of its therapeutic effects, and its practicality, distinguish this treatment from GnRH plus tamoxifen treatment.

Ovarian function suppression, whether by surgery or by GnRH treatment, in combination with tamoxifen, has been repeatedly and now conclusively with the TEXT and SOFT results-- demonstrated to be more effective as adjuvant therapy than tamoxifen alone. The magnitude of this benefit should be greater absolutely in more commonly higher-risk cases seen in low- and middle-income countries.

SO+T has additional benefits on rates of cardiovascular disease and lung and ovarian cancers, which significantly outweigh minor increases in endometrial cancers and thromboembolism. The bone loss toxicity profile of SO+T is unique and salutary: no loss of hip bone mineral density in the first two years and modest loss only in the first year in the lumbar spine.

In contrast, multiple clinical issues compromise the efficacy in clinical practice, safety and practicality of GnRH + tamoxifen treatment, and long-term effects on cardiovascular events and rates of other cancers are unknown.

In achieving potential population benefits, surgical oophorectomy plus tamoxifen is an optimal therapy---the surgery can be obtained by the majority of global patients with very low complication rates, tamoxifen is inexpensive, and the drop out from any hormonal treatment is reduced.

**Key words:** Adjuvant therapy;Surgical oophorectomy;Tamoxifen; Secondary effects;

“The right measure for successful health care isn’t about the maximum possible for a few, but the average for everyone...and the minimum opportunities available to even those with the fewest resources and privileges [1].”

Globally, an ever-increasing majority (now  $\frac{3}{4}$ ) of premenopausal women with hormone receptor positive breast cancer lives in low- and middle-income countries. This broad category of affected women, accounts for one third of all new

annual cases. These circumstances make clarity about population-effective treatment important. New data about the major benefits of combined hormonal treatments, the biology of surgical oophorectomy, the side effects of different hormonal therapies and their implications for other adjuvant therapies, and information about treatment drop-out with attendant loss of potential benefit, are critical to defining a guideline that surgical oophorectomy plus tamoxifen should be a global standard of care. This communication focuses on the breadth of data which strongly make this case.

New efficacy information: SOFT and TEXT trial data on relative benefits of tamoxifen alone, oophorectomy (mostly medical) plus tamoxifen, and oophorectomy (mostly medical) plus exemestane [2, 3, 4]

The new SOFT and TEXT trial data, which now demonstrate the definitively greater benefits of combined ovarian suppression or ablation plus tamoxifen over tamoxifen alone as adjuvant therapy, deserve detailed review because there are a number of issues which should temper understanding for their application in clinical practice (Table 1) [2, 3, 4].

**Table 1: Background issues with SOFT/TEXT trial data interpretation**

Patient selection and self-selection
Combination of initially separate trial data
Confounding by adoption of non-assigned treatments
In-adherence to/drop-out from assigned treatment
Biology of cessation of GnRH treatment and delayed surgical oophorectomy at variable times during the 5-year treatment period
Absence of prescribed post-5-year treatment

First, regarding patient selection: in SOFT the criteria applied to patients selected for chemotherapy or not, are unclear, but non-chemotherapy patients had smaller, and less-likely-to-be Her-2/neu- positive tumors [2, 3].

In general, in both trials, the patients were older and enjoyed better prognoses than were anticipated [2, 3]. The absolute levels of benefits seen need to be understood in light of these observations. The Her-2/neu positive tumor patient inclusion is of particular importance for reasons to be discussed below.

Regarding the combination of initially separate trial data, the authors give the impression that this was the plan from the initiation of the trials. In fact, the decision to combine analyses was made essentially after the accrual to the two trials had been completed [2, 5].

Regarding confounding and in-adherence to treatment: 53% of chemotherapy-receiving patients in SOFT had this treatment initially and their hormonal therapies later, so the clock for endpoints started at different times among patients [2]. Since duration of adjuvant hormonal treatments is well-described as affecting their impact, it is difficult to talk about what specific therapy, as far as duration is concerned, the study patients received. 16% of the patients in SOFT assigned to tamoxifen alone received ovarian suppression treatment, and in-adherence to treatment for 5 years was reported in approximately 20% of patients [2, 3]. For tamoxifen alone, this in-adherence figure is much less than has been reported in population-based studies [4]. Again, these observations make interpretation of magnitudes of benefits difficult.

Regarding cessation of treatment or change in form of ovarian suppression therapy from GnRH to surgical oophorectomy, the impacts of timing of these changes and the changes themselves are unconsidered and unknown. Because, in particular, of the strong suggestion that timing of surgical oophorectomy in the menstrual cycle reflecting specific hormonal status, affects its level of efficacy, assuming that these changes have no influence is inappropriate (6, 7, and Love, R.R. unpublished data).

Finally, given data indicating favorable effects of additional tamoxifen treatment after 5 years, the information that 25% of study subject pursued this course, confounds interpretation of 8-year survival data [8, 9].

The implications of these observations are that the treatment group comparisons are not as "clean" comparisons as would be optimal, and critically, that the quantitative differences determined in these trials do not offer information easily translated into clinical practice. Greater impact might be expected with higher percentages of study subjects receiving the assigned treatment and so the reportedly low in-adherence rates in these trials are unlikely to translate into similarly high magnitudes of benefit in general clinical practice [3, 4]. Longer term therapy after 5 years might be expected to fix or increase the relative benefits of oophorectomy + tamoxifen [8, 9].

In evaluating these hormonal therapies, overall survival (OS) is really the optimal endpoint, given the long natural history of hormone receptor positive breast cancer [3, 10]. With respect to the question of efficacy of exemestane plus ovarian suppression vs tamoxifen plus ovarian suppression, in the primary analysis of the combined SOFT/TEXT trials' data, 8-years OSs were 93.4% and 93.3% respectively (N.S.). Results in the two trials were somewhat different, and results for other endpoints were suggestive of greater benefit from exemestane/ovarian suppression. However, in light of the multiple issues previously discussed, it would be very inappropriate to reach any conclusion about the long-term comparative efficacies of these two therapies at this time.

In the primary major analysis of the SOFT trial, comparing tamoxifen versus tamoxifen plus ovarian suppression, 8-year OSs were 91.5% and 93.3% respectively (HR for tamoxifen/ovarian suppression 0.67; (0.48-0.92). In likely higher-risk patents who had received previous chemotherapy, tamoxifen plus ovarian suppression had a survival rate of 89.4% versus 85.1% for tamoxifen alone (HR 0.59; 0.42-0.84). Statistical significance in subset analyses according to Her-2/neu status differed: The Her-2/neu positive patients had an HR of 0.41 (0.22-0.75), while the Her-2/neu negative patients had an HR of 0.72 (0.48-1.07). Vogel dismisses these SOFT results because only a fraction of the Her-2/neu positive patients received trastuzumab (a US current standard-of-care). For most women in the world however, these Her-2/neu findings, which confirm a similar previous observation with surgical oophorectomy plus tamoxifen treatment, are very important in

suggesting an inexpensive alternative to trastuzumab treatment [2, 11]. Vogel's dismissal of the general findings also because of these Her-2 subgroup greater benefits, are challenged by the report's authors [12].

Imperfect, impure, and muddled and quantitatively insecure as the SOFT/TEXT conclusions are by these issues as they apply to general clinical practice, they are confirmatory of direct and indirect data [13 – 17]. It is important to note that the magnitude of expected absolute benefit in a risk population category (e.g. hormone receptor positive patients) is proportional to the general relative risk reduction [13]. Thus, the translation of what may seem to be small absolute benefits from combined ovarian suppression/ablation plus tamoxifen treatment in these SOFT and TEXT results, to generally higher risk women across the world, may be expected to show larger absolute benefits. If for example, in a mixed group of axillary node positive and negative-larger tumor patients, typical of low- and middle-income country (LMIC) presentations, with 8-year OS of 75% for tamoxifen alone, a hazard ratio of 0.67 (which is what was found in SOFT/TEXT) would suggest an OS of 83% for tamoxifen plus ovarian suppression, exactly what was seen in a Vietnam trial [15]. An overall survival benefit of this magnitude at 8 years, must negate any hypothetical long-term secondary or adverse event concerns, which, as will be considered below, in fact are minimal and overwhelmed by other non- breast cancer tissue effect benefits.

### Broader issues in application of hormonal therapies

As above noted, data have accumulated to clearly show that hormone receptor-positive breast cancer is a chronic disease, with distant recurrent disease appearing at a steady rate for at least 15 years after adjuvant endocrine treatment of 5 years [10]. These data have provided the rationale for studies of longer-term tamoxifen treatment after 5 years, which investigations have demonstrated the expected benefits [8, 9]. In the contexts then of these data, permanent ovarian suppression=ovarian ablation with surgical oophorectomy (SO), is a logical treatment because temporary ovarian function suppression does not address the chronicity disease profile. Additionally, 100% of patients agreeing to this SO treatment get it, and its benefits. There is no subsequent dropping out of this ovarian treatment, with expected loss-of-treatment benefit consequences.

Symptomatic toxicities contribute to treatment in-adherence and decreased efficacy [18]. Very surprisingly, early dis-continuation of treatment was in fact lower in the SOFT trial in the combined tamoxifen-ovarian suppression group than in the tamoxifen only group (19.3% versus 22.5%) [2]. The frequencies of vasomotor symptoms with combined tamoxifen-ovarian suppression treatment have been a focus of trial results and editorials [2, 14, 19]. In our Vietnamese patient trial, after one year we found no significant symptom differences in non-treated and adjuvantly-treated patients receiving surgical oophorectomy and tamoxifen

(SO + T) [20]. One must conclude that the symptomatic intermediate and long-term impacts and contribution to long-term in-adherence with ovarian plus tamoxifen treatments versus tamoxifen alone, are not large and may vary remarkably with populations.

### Specific secondary effects of SO+T treatment

Two studies have suggested concern with the long-term impact of oophorectomy, but critically do not address oophorectomy plus tamoxifen treatment. An investigation of women in the Nurses' Health Study found increased all-cause mortality in women undergoing this procedure [21]. A cost-benefit analysis of tamoxifen alone and ovarian ablation and aromatase inhibitor treatment in premenopausal women found tamoxifen only to be the preferred treatment [22]. These studies however only indirectly speak to the question of long-term impact of SO+T, and in fact support the general picture from large data sets and systemic reviews that SO+T has overall long-term mortality benefits outside of those from its impact on breast cancer recurrence and death: Table 2 [23, 24, 25]. The long-term secondary effects of SO+T are reasonably estimated from the effects of tamoxifen alone in post-menopausal women [23-25]. The long-term absolute increased mortality associated with oophorectomy in the Nurses' Health Study was 3.5%, and this was consequent to increased mortality from coronary heart disease (CHD), lung and colon cancer [21]. Estrogen replacement therapy negated the increased mortality from CHD and lung cancer, as the evidence also suggests occurs with tamoxifen [21, 23-25]. The cost-benefit analysis report suggested harm from tamoxifen on rates of fractures and stroke, which specific effects are not supported from other less confounded studies [22, 24 and below]. Overall, consistent with the absolute benefits from tamoxifen in postmenopausal women, OS rates with SO+T are significantly better than with T alone, because the major impact of this therapy is on breast cancer recurrence and death, and the impact on other organs are favorable or in the case of venous thromboembolism or endometrial cancers, numerically small [2].

All-cause mortality	Decreased (25)
CHD mortality**	Decreased (23, 25)
Myocardial infarction	Decreased (24 in 2/5 studies, 25)
Stroke	Decreased (24 in 3/6 studies)
VTE/PE***	Limited in women under age 50 (26)
Lung cancer	Decreased (25)
Colon cancer	No impact (27)
Endometrial cancer	Excess affecting 0.2%/ year with very rare deaths (6, 22, 28)
Ovarian cancer	Decreased
*Based on studies of tamoxifen in postmenopausal women ** C.H.D.=Coronary Heart Disease ***Venous thromboembolism, pulmonary embolism	

**Osseous effects of hormonal therapies in premenopausal women**

The major intermediate-term toxicity issue with hormonal and chemotherapy treatments for breast cancer is that they adversely affect bone mineral density and increase risk for bone fractures. However, unlike for all other combinations of these therapies (including tamoxifen alone in premenopausal women), a detailed, large study of the effects of SO+T on bone mineral density showed no adverse effects at all at the hip over two years, and a modest adverse effect on the lumbar spine vertebrae for one year only [29]. Because of the adverse effects on bone from all usual therapies, treatment additionally with bisphosphonate drugs is recommended [19]. These drugs have their own side effects and financial costs: specifically, for women globally, oral health is very poor and this situation would put the overwhelming majority of women at increased risk for jaw osteonecrosis with bisphosphonate treatment, if they could afford it [30, 31]. Bisphosphonate treatment is not needed with SO+T treatment.

**Clinical issues with GNRH plus tamoxifen and SO plus Tamoxifen treatments**

A spectrum of clinical issues with respect to combined GnRH plus tamoxifen and surgical oophorectomy plus tamoxifen

deserve additional consideration (Tables 3 and 4). For the former combined treatment, the summary of issues noted in Table 3 all lead to compromised efficacy, in particular with respect to usual clinical practice, and the additional known safety and practicality/cost issues all contribute to minimal application in global clinical practice and thus minimal global impact. In contrast to the situation with SO+T, where secondary effects can be well estimated from studies of tamoxifen in post-menopausal women, such effects cannot be so estimated with GnRH + tamoxifen treatment. GnRH and the combination with tamoxifen have their own biological secondary effects, whose long-term impacts are mostly unknown. That this combination has different major effects from those of SO+T is best illustrated by the situation for bone. Summarized studies are clear in showing a significantly different adverse profile of bone loss and fracture-increasing effects from GnRH +tamoxifen as compared with SO+T [29].

With respect to combined surgical oophorectomy plus tamoxifen treatment, globally qualified surgeons are generally available and laparoscopic surgery can be safely employed (Table 4). Hospitalization-requiring treatment-surgery- is generally available world-wide at limited costs to patients. In the three SO+T reported studies discussed in this communication, over 1300 patients were treated in 8 low- and middle-income countries with minimal

<b>Table 3: Clinical issues with GnRH+ tamoxifen treatment</b>
<b>Efficacy:</b> Unpredictable/incomplete ovarian function suppression for which individual patient testing is not recommended (32)
Suggestion of limited efficacy in overweight patients (33)
Adherence to treatment declines significantly over time which compromises efficacy (2, 4).
Consequences of cessation of treatment uncertain (and thus ‘advantage’ of reversibility is uncertain).
Optimal choices of treatment after 5 years unclear (3).
Tamoxifen alone after 5 years associated with bone loss (22, 34).
 <b>Compromised efficacy</b>
<b>Safety:</b> Continuous loss of bone mineral density with treatmentà leads to a requirement for bisphosphonate treatment with its own safety and cost issues (29, 30, 31)
Injections site reactions: 8% (2).
Long-term effects on rates of C.H.D., M.I., stroke, lung cancer, colon cancer, and ovarian cancer unknown.
<b>Practicality:</b>
High monthly out-of-pocket cost for most women globally leads to women not seeking or not receiving treatment (35, 36)
Direct and indirect costs of monthly clinic visits for treatment.
 <b>Limited global target population impact</b>

morbidity and only 3 not-unexpected deaths occurred in patients with metastatic cancer within 30 days [6, 7, 15]. We overcame the issues of having breast surgery and surgical oophorectomy done under the same anesthesia, thus at the same time, and at scheduled times in the menstrual cycle, in these trials, at which sites often the leading surgeon did both surgical procedures.

**Table 4: Clinical issues with surgical oophorectomy + tamoxifen treatment**

<b>Efficacy:</b> Availability of surgery, Laparoscopic surgery
<b>Safety:</b> Low morbidity/ complications
<b>Practicality:</b> Under same anesthesia as primary breast surgery? Different surgical teams?

## Discussion

The comprehensive breadth of information presented here makes clear that surgical oophorectomy plus tamoxifen (SO +T) should be the hormonal treatment of choice globally for premenopausal women with hormonal receptor positive breast cancer. With now definitive evidence from the SOFT and TEXT trials of greater benefits from combined ovarian suppression/ablation plus tamoxifen treatment, the availability, practicality, likely benefits in Her-2/neu positive patients, better toxicity experience with bone, significant and known non-breast cancer event-reductions for CHD, MI and stroke, and lung and ovarian cancer, and potential greater efficacy with timing in the menstrual cycle of the surgery, combine to make SO+T the cost-effective treatment of choice over GnRH plus tamoxifen [2, 6, 7, 11, 12, 23-25, 29, 36, 37].

For women and treating clinicians world-wide, the issue now is making this option known and providing patients a choice. Before many of the data reviewed here were known, in EST 3193, a majority of women given the choice of SO or LHRH treatment, chose SO (42 versus 36%; total N=174) [14]. Of course, for younger women, multiple complex questions about the risks and benefits of preserving fertility and future pregnancies arise, but fortunately the numbers of these women are not large.

Globally, the challenge is the current omission of this specific SO +T option in guidelines, and discussion of the breadth of these presented data [38]. The emphasis on efficacy alone, and limited or no consideration of all Institute of Medicine recommended quality-of-care metrics is essentially demedicalization of important issues in clinical interventions for this group of patients [39, 40]. Commission of mis-guidance in discussing SO based on perceived or unconsidered limited data seems to have been more feared more than the consequences of omission, but now the case for omission of a SO option is untenable.

Choices going forward are clear. The scientific community should embrace the clear scientific data and population perspectives and encourage SO+T on choice and public health grounds. We should recognize that optimally large numbers of lives could be saved, but

realistically, the advantages in terms of life-saved will be less than maximal: oophorectomies will guarantee an effective breast cancer adjuvant treatment, but adherence to tamoxifen treatment will be suboptimal, more so in younger women, which will compromise some breast cancer and other benefits [3]. Continuing to allow the status quo and guidelines omitting SO and only mentioning suppression treatment, in the face of organizational positions which are not supported by the breadth of evidence and parsimonious public health/global population considerations, are socially unjust [40, 41].

For this population of women globally, the challenge ahead is not what Stearns editorialized in commenting on the TAILORx trial results: “to carefully study the exciting new assays, agents, and emerging technologies...” [42]. No, the immediate challenges are to more justly, equitably and widely apply our known science and data “in the service of man”, and to get our guidelines for treatment of this population of women worldwide in line with our stated values [40]. The major issue in this cancer subset of patients is reflective of the broad issue of our time: social justice. “We must focus on equitable outcomes for all of us...” The right measure for successful health care isn’t about the maximum possible for a few, but the average for everyone...and the minimum opportunities available to even those with the fewest resources and privileges” [1].

If the conservative position is taken with regard to the SO timing hypothesis, that the case that women in prolonged follicular phase with low progesterone levels benefit little from oophorectomy done at this time has but limited support, then the rational approach is to do a clinical trial of timed SO+T (excluding these women) vs. GnRH/LHRH +T. With provision of the drugs, this would not be a difficult trial to do, certainly with low- and middle-income county participation. Additionally, health behavior model-based interventional research addressing hormonal therapy in-adherence should be a priority [44].

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