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By the Metrics Surgical Oophorectomy Plus Tamoxifen is the First Adjuvant Treatment Option for Premenopausal Women with Hormone Receptor Positive Breast Cancer

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“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.

“How you define the problem determines whether you solve it.”²

Outcomes for the majority of women with breast cancer, most of whom, but hardly all, do not live in high-income countries, are poor.³ The breast cancer sub-group of premenopausal women with hormone positive tumors is large: at a minimum: 550,000 total new cases/year, 420,000 of whom come from low- and middle-income countries (LMICs), with 82% of the global population. Based on Globocan estimates for all new breast cancer cases for 2018 at 2.088 million, this subgroup number may be as high as 700,000 cases.³

For this specific population, the impact of optimal treatment is large. The Early Breast Cancer Trialists’ Group found a risk reduction of 25% in death at 10 years with 5 years of tamoxifen treatment.^{4,5} The additional benefits of ovarian suppression or ablation added to tamoxifen suggest risk reductions for death of as much as 42%.⁶⁻⁸ These data suggest that in a premenopausal population of half axillary node-positive patients with a 10-year overall survival of 55-60% without any adjuvant treatment, with optimal 5-year adjuvant endocrine therapy this figure might increase to 75-78%. These estimates, therefore, suggest that 80-100,000 of the 420,000 (minimally) low- and middle-income country women diagnosed annually, at greater absolute risk for death without optimal treatment,

who could be saved for 10 years, instead die.

What is the problem? Among many issues, the following stand out:

- Human rights challenges. In many countries, women do not have permission to seek medical care for themselves. If it were widely known that attainable, affordable, and effective treatment was available, this might mitigate some of these restrictions.⁹
- Barriers to seeking care. Women do not seek interventions for breast problems they know they have. Many women in LMICs don’t seek care because they know that in their medical systems, financial resources will be demanded for diagnosis and treatment, money their families do not have.^{9,10}
- Financial and health system operational issues. Increasingly, health care systems globally operate on business models, with high levels of corruption in many LMICs. For most patients, their systems are byzantine, and time-consuming.⁹

In these broad contexts, for premenopausal women with hormone receptor-positive breast cancer:

- Following from leading cancer organization guidelines, SO (surgical oophorectomy) plus tamoxifen as a treatment choice is not offered.¹¹
- Because of financial barriers and treatment non-adherence, many patients, particularly those in LMICs (the majority), if they have operable disease and do undergo primary surgery, appear not to get any or enough adjuvant treatment to provide maximally achievable outcome benefits: prevention of disease recurrence and death.¹²
- Together with assumptions that SO or ovarian ablation and ovarian function suppression are equivalent clinical treatments, SO and GnRH treatments are inappropriately considered as biologically and therapeutically equivalent.¹¹

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- When offered, there is incomplete consideration of the SO + T option by patients because of no mention by physicians of data regarding multiple key metrics of value and quality of this intervention.¹¹
- Incomplete/immature data on SOFT/TEXT investigated/ recommended treatments regarding key metrics, particularly long-term secondary effects.⁸
- Unrealistic considerations and discussions of host differences about symptoms.
- Much lower clinical practice compliance with treatment programs than in research studies, and limited approaches to treatment in-adherence problems.¹²
- A dominant tumor-biology-focused treatment paradigm exists when there are strong suggestions that a host biology-focused treatment paradigm is also likely.¹³
- Individual patient (in researchers' experiences) versus global public health treatment paradigms, with limited consideration of the equity issues associated with these paradigms.¹⁴

The breadth of these problems as causal explanations emphasize the importance of patient-centric issues in clinical care. In many ways, they are all of a whole. This lengthy introduction has been offered to frame appropriately, constructively, broadly, comprehensively, and for women globally, the rationale and substance of this communication.

Consider then with the six Institute of Medicine (IOM) quality of health care metrics, relevant SO + T data from the author's two phase III randomized clinical trials (and peripherally one additional trial in metastatic disease in consideration of one issue -- host paradigms), an ECOG trial, and the updated SOFT/TEXT trial report.^{4, 5, 8, 14-18} Additionally, note data from other earlier adjuvant trials where SO has been a treatment: the very first adjuvant trials considered in meta-analysis, and Scottish, Danish, and French trials.^{4,5,19-21}

The six IOM quality of care metrics are efficacy, safety, efficiency, patient-centeredness, timeliness, and equity.²² Addressing the data about these measures with respect to SO+T in order:

A. Efficacy/Effectiveness

A data-supported place for SO in the adjuvant therapy of breast cancer was created by the EBCCTG meta-analysis which included 4 trials, first individually reported on beginning in 1970.^{4, 5} The individual patient data from these trials and those involving radiation to the ovaries, with what would be considered significantly less-than-rigorous methodologies today, and in the absence of patient tumoral hormone receptor data, looked at together, suggested that ovarian function ablation or suppression with radiation, conferred long-term recurrence free (DFS) and overall survival (OS)

benefits.^{4,5}

A Scottish trial in women with axillary node positive breast cancer, found ovarian ablation provided equivalent outcome benefits to those from CMF chemotherapy.²¹ In the sub-set of patients whose tumors were later assessed for hormonal receptors, those patients with hormone receptor positive tumors benefitted more from ovarian ablation. A Danish trial in hormone receptor positive patients found ovarian ablation and CMF to be equivalent therapies in efficacy.¹⁹

A trial in premenopausal women in Vietnam and China with operable breast cancer, 52% of whom were axillary node positive, unselected for hormone receptor status at the time of primary treatment, found that in the patients subsequently determined to be estrogen receptor positive, there were 7 year disease-free and overall survival risk reductions of 0.46 and 0.54, respectively.^{6,17}

A French trial in axillary node-positive, tumor hormone receptor- positive patients found ovarian ablation plus tamoxifen to be superior to FAC chemotherapy.²⁰

An underpowered American Intergroup study in axillary node negative, hormone receptor positive patients found SO plus tamoxifen to give better overall survival at 5 years than tamoxifen alone with a risk reduction of 0.5 (OS 97.6% versus 95.2%) (N.S.).¹⁶

A trial in hormone receptor positive Vietnamese and Philippine women found, in explanatory analyses, that patients with true follicular or luteal menstrual phase status confirmed by blood progesterone testing, had significantly better DFS and OS compared to patients with unconfirmed luteal (or prolonged follicular or anovulatory) status (history of luteal phase, but low progesterone levels).¹⁵ This same observation was made in a SO plus tamoxifen study in women with hormone receptor positive metastatic breast cancer.¹⁸

In the recently updated SOFT/TEXT trials analyses of ovarian suppression by GnRH agonist treatment plus tamoxifen or GnRH treatment followed by SO plus tamoxifen, versus tamoxifen alone, 8-year OS risk reductions of 0.33 without, and 0.41 with chemotherapy (higher risk patients), were observed with the combined ovarian plus tamoxifen treatments, for both p=0.01.⁸

In two trial data sets, the combination of SO or GnRH plus tamoxifen has been suggested to be more beneficial in Her-2neu positive patients.^{8,23}

It is self-evident, but important to note that assigned SO in all of the above trials was received by practically all of the studied patients, while in the SOFT/TEXT trials early discontinuation of the GNRH plus tamoxifen treatment occurred in 19.3% of participating subjects in contexts where treatment for 5 years was being studied.⁸ Based on data about nonadherence to tamoxifen alone treatment (see



below), in non-research settings early discontinuation rates might be expected to be even higher.¹² This is but one of several differences between patients treated with GnRH therapies versus SO. In the SOFT/TEXT trials' interventions, GnRH was given as noted for variable periods less than the planned 5 years. There is no ability to monitor for GnRH efficacy in individual patients, so there is no certainty from month to month of biological effect. GnRH followed by SO beyond 6 months was a treatment option in SOFT/TEXT trials, but SO was done variable times over the 5 years with unspecified treatment gaps between treatments and with uncertain hormonal signaling effects. The duration of follow up in the SOFT/TEXT trials provided limited long-term all-cause mortality information.⁸

While the SOFT/TEXT trials investigated the issue of ovarian suppression plus aromatase inhibitor treatment, at 8 years there was no significant difference in overall survival compared with ovarian suppression plus tamoxifen treatment, this at a timepoint 3 years after completion of the adjuvant therapies.⁸

Finally, regarding efficacy of SO plus tamoxifen in the contexts described above, population data on tamoxifen nonadherence strongly suggest that in clinical practice tamoxifen consumption falls dramatically over the 5 years currently prescribed period, and that perhaps but 1/3rd of women, even in high-income countries, take the medication for this period.¹² Further, regarding absolute overall benefits of adjuvant hormonal therapies, these have to be understood in the contexts now of additional benefits to these patients from adjuvant radiation therapy, and long term (between year 5 and 10) hormonal therapies, particularly tamoxifen.²⁴⁻²⁶

Conclusions regarding efficacy of SO+T

The above reviewed specific SO studies demonstrate a consistent overall, and within-several-studies-consistent picture of efficacy from SO plus T greater than that from SO alone or tamoxifen alone, and equivalent or perhaps with

some twists (timing of surgery, for example; or better treatment adherence), efficacy to standard widely available chemotherapy regimens. These superior benefits are seen in node positive as well as node negative patients. Over the first 10 years following diagnosis and treatment, SO plus tamoxifen is clearly and significantly an optimally effective treatment, in major part, at the population level, because when chosen, surgical oophorectomy is always received.

B. Safety and toxicity side effects

In high-income country studies, with often limited follow-up periods of 5-10 years, immediate symptomatic side effects are well-reported, but long-term clinical outcomes are less documented. For the symptoms data, what is important to note is that particularly the vasomotor symptoms vary in frequency, intensity, and duration among populations. In Asian populations, the intensity and duration of vasomotor symptoms following SO plus tamoxifen were indistinguishable from these metrics in untreated women after one year.²⁷ In contrast, in American and European populations, these symptoms were more significant.^{8,16}

For bone mineral density, SO plus tamoxifen causes bone loss at only the lumbar spine site, for one year, and is associated with no significant loss at the hip at all.²⁸ This is a significant salutary benefit, suggesting that such treatment does not need to be supplemented with bisphosphonate therapies with their own financial costs and toxicities. This is not the case with GnRH plus tamoxifen or aromatase treatments.²⁸

Because of the use of tamoxifen in postmenopausal women with breast cancer and as a chemoprevention drug, there are considerable data to allow estimates of the long-term secondary effects of SO plus tamoxifen, summarized in Table 1.

As can be read here, these data are remarkably reassuring that this treatment has long-term overall benefits which far exceed those often overemphasized for endometrial cancer and thromboembolism. What

Table 1. Estimated long-term secondary effects of SO+T*

All-cause mortality	Decreased ²⁹
CHD mortality**	Decreased ^{29, 30}
Myocardial infarction	Decreased ^{29, 31} (in 2/5 studies)
Stroke	Decreased ³¹ (in 3/6 studies)
VTE/PE***	Limited in women under age 50 ^{5, 17, 32}
Lung cancer	Decreased ²⁹
Colon cancer	No impact ³³
Endometrial cancer	Excess affecting 0.2%/ year with very rare deaths ^{15, 17, 34, 35}
Ovarian cancer	Decreased

*Based on studies of tamoxifen in postmenopausal women

** C.H.D.=Coronary Heart Disease

***Venous thromboembolism, pulmonary embolism



is also clear is that at present such long-term data are not available for GnRH plus tamoxifen or aromatase inhibitor treatments, and also that there are multiple reasons to expect that when available data on the outcomes listed in Table 1, will offer a much less favorable picture for GnRH treatments than those for SO plus tamoxifen.

Other than vasomotor symptoms, other specific side effects of SO should be noted. Among 1101 patients who received SO in two adjuvant studies primarily in Vietnam, China, and the Philippines, there was no 30-day mortality, and 4 patients only developed pneumonia (2) or deep vein thromboses (2).^{15,17} Most of these SO procedures were done under the anesthesia done also for the primary breast surgery. All of these patients were fully informed of the irreversible nature of this procedure on their menopausal status and ability to conceive, and provided written informed consent.^{15,17} In one major clinical trial site in Manila, 3 patients of 336 (<1%), refused SO plus tamoxifen treatment, possibly because of irreversible and inability-to-conceive treatment consequences.

In summary, with respect to the IOM safety metric, SO plus tamoxifen is comprehensively described over short and long terms and the overall impact on women's health is very favorable.

C. Cost efficacy/efficiency/net benefit for cost

For patients, SO plus tamoxifen is much more cost-effective or gives more net health benefit for much lower patient payment, than GnRH plus tamoxifen. SO plus tamoxifen treatment maximizes the impact of available medical resources, when both indirect and direct costs for both providers and patients are considered. Perhaps more so in low- and middle-income than in high-income countries, financial issues come to the fore in treatment decisions. A breast self-examination trial in the Philippines was abandoned because patients who had breast tumors did not seek care because they assessed that they did not have the financial resources to have treatment.³⁶ In the United States, the American Society of Clinical Oncology considers delivering value to be a major driver of change in health care delivery, and has expressed concerns regarding the financial toxicity of expensive cancer therapies.³⁷ The cost -efficacy of SO plus tamoxifen treatment

has been estimated at \$351 per year of life saved, a level of return comparable to those suggested for very effective vaccinations.¹⁷

SO plus tamoxifen requires inpatient surgery accomplishable in most settings globally together with the primary breast surgery, with financial costs covered. Tamoxifen, in most settings, requires out of pocket costs for patients, but of manageable levels. No additional therapies are required in particular because of an absence of bone loss toxicity. In contrast, GnRH therapies require monthly (recommended) or 3 monthly physician visits with associated significant direct and indirect patient costs, and as noted above, 5 years of treatment are the standard of care.

D. Patient-centeredness

This important metric addresses tailoring treatment to patient needs, values, and preferences. SO treatment absolutely requires open discussion with patients about this option in detail, and as such, if chosen by patients, meets the metric requirements. In contrast, full exposition of GnRH treatment with all its components, clearly is not well patient-centered, and is significantly impractical.

E. Timeliness

SO, treatment is a one-time intervention done together with primary surgery. Once completed, patients must incur the benefits. There are no delays in treatment associated with unavailability of medicines and finances, or schedules of patients and caregivers, as occur regularly with GnRH treatments. This "one stop" metric of SO makes it a better treatment than GnRH.

F. Equity

Essentially all women globally can get SO treatment, which meets the need offered by Tufeki for successful health care.¹ SO treatment limits corruption factors which play out over time with GnRH treatments. SO plus, tamoxifen treatment provides consistent quality of care to all patients and is a socially just treatment. With GnRH treatments, major financial issues and dysfunctional health systems interfere with delivering this treatment to populations for their maximal benefit. Table 2 summarizes the fore-presented data on IOM metrics.

Table 2. Summary: Adjuvant SO+T by the 6 IOM metrics

Efficacy: When taken for prescribed 5 years, efficacy is equivalent to (or possibly significantly better) than guideline-recommended GnRH plus tamoxifen treatment. Globally, SO as a treatment is practical and when chosen by patients is always received.

Safety: The organ and tissues effects of SO+T are well-known and more favorable than those for any other hormonal therapies. The symptomatic effects vary among patients, and dissipate over one year.

Cost efficacy: With SO performed together with primary breast surgery and generic tamoxifen, cost/year of life saved is remarkably low. Value as a treatment is high to patients and for medical systems.

Patient-centeredness: SO plus tamoxifen treatment is practical.

Timeliness: No delay in getting some adjuvant treatment administered.

Equity: SO+ T is a consistent, high-quality achievable intervention for women everywhere. Socially just.



Globally, all 550,000-700,000 women annually (1/3rd of all new cases) for whom adjuvant hormonal therapies are strongly indicated, should be provided information on the 6 metrics of quality of care for adjuvant treatments, and given the option of SO plus tamoxifen treatment. Treatment standards are local not global; thus, particular circumstances, both patient and medical system may determine whether SO+T is a reasonable option.³⁸

Conflict of Interest

The author reports no conflicts of interest.

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