

## Short Commentary

# Surgical Oophorectomy Plus Tamoxifen Provides the Optimal Systemic Treatment for Pre-Menopausal Women with Hormone Sensitive Breast Cancer

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## Abstract

Surgical oophorectomy should have a major place in treatment of pre-menopausal women with hormone-receptor positive breast cancer. New data on increasing efficacy and multiple measures of quality of care suggest this surgery should be part of optimal treatment.

From the time of Beatson in the late 1800s through the 1970s-surgical oophorectomy had a major place in the treatment of women with metastatic breast cancer. Small adjuvant trials began in the latter years of this period, but the discovery of the estrogen receptor and the development of systemic treatments with cytotoxic drugs and the oral anti-estrogenic agent tamoxifen, pushed surgical oophorectomy aside as a common treatment option. In the early 1990s, a meta-analysis of the adjuvant trials suggested strongly that in fact ovarian ablation whether by surgery or radiation, had long term survival benefits in women unselected for tumor hormonal receptor status. By this time ovarian function-suppressing drugs-luteinizing hormone releasing hormone (LHRH)agonists-had been developed, and short-term treatment with these agents was deemed a more convenient and reversible approach in women with hormone receptor positive tumors. The operating biological model from that time until the present has been that chronically suppressed estrogen levels leave hormone sensitive tumors starved of growth stimulation. Over the 1990s however, it became increasingly evident that hormone receptor positive breast cancer is a chronic disease and that longer term suppressive hormonal therapy gives better disease control. The evidence that combined hormonal therapy with surgical oophorectomy or ovarian suppression with LHRH agonists plus tamoxifen is of greater benefit than each of these therapies alone, in women in both metastatic and adjuvant situations is, in aggregate while limited, conclusive and sufficient [1-4], and thus at present in such premenopausal women adjuvant treatment with LHRH agonists plus tamoxifen for 5 years is standard [1,4]. At the same time over the last 15 years the Institute of Medicine has proposed that to decrease use of health services which are wasteful and unethical, quality of care must be assessed at multiple levels: efficacy, safety, cost-effectiveness and value, patient-centeredness, timeliness and global equity [5]. Additionally, there have been developed new data about these metrics for surgical oophorectomy, particularly provocative data about selecting patients for greater efficacy, and together these metrics and data suggest that now there is again a major role for surgical oophorectomy in treatment of women worldwide.

Assessing Surgical Oophorectomy + Tamoxifen by The Institute Of MedicineMetric<sup>s5</sup>

## Efficacy

Equivalent efficacy of SO+T to other standard combined hormonal treatments (for example LHRH +T) is widely accepted [3,4]. New data however suggest that superior efficacy of SO+T can be achieved both in patients with metastatic cancer and in operable patients [6,7]. These data are from two phase III trials I have conducted with colleagues in Asia over the past decade. In the adjuvant trial, women in historical luteal phase, but with low progesterone levels consistent with anovulatory status, benefited little from SO+T [6]. Specifically, among these anovulatory women, only 52% had no recurrence of their cancers at 5 years, while in women in the first half of their cycle by history and by blood tests, 72% had no recurrence at this time, a statistically significant difference [3]. In the metastatic trial the same subgroup-of anovulatory luteal phase history-low progesterone women- had much poorer survival; in fact, their median survival was 10 months less than either the low progesterone-confirmed follicular or high progesterone-confirmed luteal history women; this difference showed a strong trend statistically [7]. These consistent results from two studies suggest that if among an average, but high risk group of women with operable breast cancer receiving SO (+T) (without paying any attention to their menstrual cycle history and blood levels of progesterone), 65% have no recurrence in 5 years; if patients have their SO in the first half of their menstrual cycles by history and with confirmation showing low progesterone blood levels, 72% will have no recurrence in 5 years [3].

## Safety

In our studies, among 1083 patients with operable breast cancer, treated in low- and middle-income countries (LMIC) with SO+T, very small numbers of women suffered serious complications following surgery and none died in the first 30 days after surgery [6]. Hormonal and chemotherapy treatments for breast cancer adversely affect bone mineral density and increase risk for bone fractures. Unlike for all other combinations of these therapies, a detailed study of the effects of SO+T on bone mineral density showed no adverse effects at all at the hip over two years, and an adverse effect on the lumbar spine vertebrae for one year only [8]. Because of the adverse effects on bone from all usual therapies, treatment additionally with bisphosphonate drugs is recommended. These drugs have their own side effects and financial costs. This treatment is not needed with SO+T treatment.

## Cost-Effectiveness and Value

The recommended high-income country monthly injections LHRH for at least 5 years cost an average of \$150 a month in LMIC and three or more times this figure in high-income countries; everywhere there are administrative costs also [3]. SO can usually be done as part of the surgical management of breast cancer, and so for women everywhere who usually have to pay out of pocket

for pharmaceuticals, this treatment is obtainable. In these circumstances SO+T is a remarkably cost-effective and high-value treatment, by comparison with currently recommended high-income country approaches.

## Patient-Centered

This refers to patient participation in decision making about her care choices and practicality. In a 20-year-old American study in which women were given the choice of SO or LHRH injections for 5 years, 42% elected SO and 36% injections [9]. The indirect costs of monthly injections for 5 years-missing work and travel for examples, are high for all patients getting this treatment. There are downsides to the SO approach. First, it involves surgery which for some women is not wanted. Second, there are in the first year, more symptom side effects from SO+T than from injections of LHRH +T [9]. Third, SO is perceived as “old-fashioned” treatment. Finally, clearly for young women who would like to become pregnant in the future, SO is not an appropriate choice. The numbers of women diagnosed with breast cancer under 35 or under 40 are fortunately low around the world.

## Timeliness

SO is a practical treatment that can be completed with one small operation (often in many countries by laparoscopy). In the studies reported, this surgery was accomplished under the same anesthesia at the same time the definitive breast surgery was done [6]. As noted, guideline-directed treatments involve monthly visits to physicians for at least 5 years [1,4].

## Equitability/Fairness

The IOM states that “The quality of medical care must be consistent across all patients, irrespective of gender, ethnicity, socioeconomic status, and other personal characteristics [5]”. Women in LMIC (but also in high-income countries) do not seek or get care for breast cancer because of unaffordability and cultural and health system barriers. Widely promoted and applied SO+T could change these circumstances, and save 100,000 women a year. Social justice demands that urgent efforts be made to meet this quality-of-care-for-all measure. Surgical oophorectomy plus tamoxifen should be the first option for hormonal treatment in premenopausal women with hormone sensitive tumors worldwide.

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