

Adjuvant Surgical Oophorectomy Plus Tamoxifen in Vietnamese Patients

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ABSTRACT

Background: Cancer registry data suggest that one third of all annual new cases of breast cancer in Vietnam are in premenopausal women with hormone receptor-positive tumors. There is now an emerging picture of how 80% of these women can be alive after 10 years with cost-effective, limited symptom-associated and beneficial secondary effects treatment.

Methods: We summarize data from 949 premenopausal Vietnamese women data in two randomized clinical trials investigating surgical oophorectomy plus tamoxifen (SO+T) adjuvant therapy (x5 years).

Results: 77% of hormone receptor-positive tumors had high Allred estrogen receptor scores. Despite lower population incidence rates for breast cancer in Vietnam, prognostic factors for recurrence (stage, axillary nodal status, tumor size, age) were the same and of similar magnitudes to those seen in high income-country populations. Almost one-third more of treated women were alive after ten years than women receiving no adjuvant treatment. Her-2/neu positive patients benefitted more from this treatment than Her-2/neu negative patients. Cost-effectiveness analysis suggested this intervention returned \$350/year of life saved. Vasomotor symptoms, elevated in the first year after treatment, were no different than those for untreated women after one year. Few patients suffered blood clots, and none developed endometrial cancer.

Conclusion: By all critical measures, SO+T is the optimal treatment for premenopausal Vietnamese women with hormone receptor-positive tumors, a conclusion consistent with findings from the SOFT/TEXT high-income country trials.

Keywords

Adjuvant therapy, Surgical oophorectomy, Tamoxifen, Vietnamese patient data.

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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 opportunities available to those with the fewest resources and privileges [1]”.

The majority of rigorous data on breast cancer treatments has come from high-income countries [2]. Because of major incidence differences among populations, one might postulate different causes and causal complexes by population, which might be

associated with then different prognostic factors, tumor biology and different responses to treatments. Among Vietnamese women for example, while overall incidence of breast cancer is lower, a higher proportion of women appear to have Her-2/neu positive tumors [3]. Broadly, the greatly improving nutritional status of the population after 1991 might be expected to be playing a role in both incidence increases, and changing patterns of causes.

Two thirds of the highly-literate (>90%) 96 million Vietnamese population lives in rural areas. There has been significant economic growth over the last 25 years such that GDP per capita was \$2300 in 2017. Health expenditures account for 7% of GNP.

Globocan estimates are for 15,230 new cases of breast cancer in Vietnam in 2018 [4]. Hospital registry data from the Vietnam

National cancer hospital have identified 55.3% of new breast cancer cases as premenopausal. In Vietnam, as throughout South Asia, approximately 70% of such cases are hormonal receptor positive (5,895 women/year or 38%) and 80% of these cases are strongly hormonal receptor-positive (by Allred scores, or both estrogen receptor and progesterone receptor positive) (4,716 women or 31%).

In 1991, we began a collaboration (with predecessors and others) to study public health oncology approaches to breast cancer in Vietnam [5,6]. Subsequently, we conducted two moderate size phase III clinical trials (n=709) and (n=740) of adjuvant surgical oophorectomy plus tamoxifen (SO+T). While such combination therapy was not the standard of care in any countries at the time the first trial was begun in 1992, we had just conducted a rigorous study demonstrating the favorable effects of tamoxifen on bone mineral density in postmenopausal women, and together with the suggestive data from the meta-analysis that surgical oophorectomy (SO) was an effective adjuvant treatment, we postulated that a rigorous evaluation of SO was appropriate, but that with the anticipated accompanying loss of bone mineral density following SO in a population most of whom did physical labor for their livelihoods, adding bone density-preserving, fracture-preventing tamoxifen was ethically the right thing to do [2,7].

The current communication focuses on the results for Vietnamese women from these two consecutive phase III clinical trials conducted under long-term RO1 American N.I.H. financial support. 92% of patients in first trial were and 40% of patients in the second trial were Vietnamese. While the main results and other data from these trials have been reported, a complete picture of all of the significant items and implications of these data for Vietnamese women and leaders have not been highlighted, and their overall significance has been magnified by the recent report of the SOFT/TEXT trials showing that ovarian suppression by drug or surgery plus tamoxifen is the most effective adjuvant treatment for this population [8].

Methods

Details of the two trials whose data are addressed in this communication have been presented in the original reports, including those regarding ethical approvals [9-12]. The first trial included patients initially untested for hormonal receptor status; while the second trial enrolled only patients with at least one positive (estrogen or progesterone) hormonal receptor test. As noted above, in the results and discussion which follows, the data from these two trials from Vietnamese patients only are considered.

These were in most but not all respects not significantly different in each of the trials or from those of the minimal numbers of Chinese patients in the first trial, or the majority of Philippine patients and few Moroccan patients who participated in the second trial. The Vietnamese patients in the second trial were of lower general overall risk than those in the first trial, and then those from other participants in the second trial.

Results

In the first trial, there were 652 Vietnamese patients; in the second trial 297 Vietnamese patients for a total of 949 patients. Among these patients accrued from 1993-2009, 8% were under age 35 and 55% were under age 44. 60% had axillary nodal metastases; tumor median diameters barely exceeded 4 cm; and 23% had histologic grade iii tumors. Of all estrogen receptor positive cases (n=840), 77% had Allred scores of 6-8. 87% of hormonal receptor positive cases were both estrogen and progesterone receptor positive. 20% of hormone receptor positive patients had Her-2/neu positive tumors.

Among these patients, prognostic factors for disease-free and overall survival, were, in order of strength: nodal status (positive versus not; 1-3 nodes versus 4 or more nodes positive), stage (I, II, III), adjuvant radiation therapy (yes or no), tumor size (log of diameter), younger age, and histologic tumor grade (i, ii, iii), in directions and magnitudes very similar to those from studies in high income country populations.

With respect to treatments: approximately 1% of patient assigned surgical oophorectomy did not receive this treatment; 40% of patients received adjuvant radiation therapy; by patients reports very few patients discontinued tamoxifen treatment, while in the first trial greater than 90% of patients had follow up data to ten years, and in the second trial, 96% of patients had follow up data for 5 years.

In the first trial, a randomized study of adjuvant SO+T following primary treatment, versus this treatment on recurrence, 10-year overall survivals were respectively 80% and 51%, with a relative risk reduction for death of 0.59 [10]. In the second trial, the Vietnamese patient 5-year disease-free survival data replicated those from the first trial, suggesting that the 10-year OS data would also be 80%.

In the first trial, we found an interaction of SO+T and Her-2/neu status, with positive status being associated with greater benefit (HR=0.26; p=0.038) [12].

In terms of adverse events, in both trials increased vasomotor symptoms with SO+T declined significantly such that they were no different from those of patients not receiving this treatment after one year or of minimal levels [11,14]. There was no 30-day mortality associated with SO+T. Very few patients suffered blood clots over the first 30 days, despite combined-one anesthesia and thus longer primary breast and SO surgeries. None of these Vietnamese patients developed endometrial malignancies. A large study of bone mineral density changes over two years showed no changes in the femoral neck at all, and modest changes in the lumbar spine in the first year after beginning treatment only [13]. A cost effectiveness analysis showed the SO+T cost \$350 per year of life saved.

Discussion

The two-phase III trials whose Vietnamese data are reviewed here,

provide unusually strong and currently relevant specific-country population treatment information. In broad breast cancer treatment data contexts, the following are critical points:

- Breast cancer characteristic prognostic and predictive factors in premenopausal Vietnamese women are no different from those in women from high income countries.
- Among the hormone receptor positive patients enrolled in these trials who seem representative of all such women with breast cancer in Vietnam, a high fraction was positive for both receptors and was Her-2/neu negative (=of Luminal A phenotype), and very high fractions had high Allred scores predictive of very high levels of favorable response to SO+T treatment.
- The impact of this SO+ T combined hormonal treatment was high with a reduction in odds of death after 10 years of 0.59. This high level of effect must be partially attributable to the facts that almost 100% of patients assigned SO received this surgery, and compliance with long term tamoxifen therapy was also very high. This latter observation must be in part because the symptomatology in this population of these treatments was initially manageable and later minimal. These circumstances and data are in sharp contrast to those showing what has been considered to be critically high levels of vasomotor symptoms among American women undergoing SO +T treatment, and those population data indicating dramatic falls in adherence to tamoxifen or aromatase inhibitor treatment [15,16].
- The suggestion in these studies that Her-2/neu positive tumor-bearing patients benefit significantly from SO+T treatment, a finding also observed in the SOFT/TEXT trial analysis, is of important relevance for the 20% of hormonal receptor positive patients who have Her-2/neu positive tumors (luminal B) [8,12].
- The risks associated with SO+T treatment in this population are remarkably low; surprisingly minimal to bone, low for blood clots and not evident for endometrial cancer.

Finally, contextual issues must be noted:

- Long term benefits in terms of reduced coronary heart disease mortality, reduced stroke, reduced lung and ovarian cancers, have been demonstrated with tamoxifen treatment in postmenopausal women (17, 18, 19). These salutary findings can be expected to have important effects in the large fraction of such treated premenopausal women who enjoy long term survival.
- By the Institute of Medicine criteria for assessment of quality of a treatment (efficacy, safety, cost-effectiveness, patient-centeredness, timeliness, and equity), SO+T is a remarkable intervention by all measures, particularly for equity. For approximately the one third of all women each year in the Vietnam who are diagnosed with breast cancer and who are premenopausal with luminal A phenotype tumors, these SO+T findings are very relevant [20].
- Additionally, because some patients in these studies did not receive what is now believed to be useful adjuvant radiation therapy, and tamoxifen treatment beyond 5 years now appears to be useful, these absolute results found in these trials may

yet be improved upon [21,22].

References

1. Tufekci Z. Rich health poor health. *The New York Times Magazine*. 2018; 50.
2. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 1992; 339: 71-85.
3. Niravath P, Bondy M, Hilsenbeck SG. Unique Breast Cancer Features within the Vietnamese Population. *J Health Disparities Research Practice*. 2016; 9: 53-58.
4. <http://gco.iarc.fr/today/data/factsheets/populations/704-vietnam-fact-sheets.pdf>.
5. Love RR. Clinical trials and practice guidelines as educational methods in developing countries. *J Cancer Educ*. 1994; 9: 200-201.
6. Love RR, Ginsburg OM, Coleman NC. Public health oncology a framework for progress in low- and middle-income countries. *Annals Onc*. 2012; 23: 3040-3045.
7. Love RR, Mazess RB, Barden HS, et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med*. 1992; 326: 852-856.
8. Francis PA, Pagani O, Fleming GF, et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *New Engl J Med*. 2018; 379: 122-137.
9. Love RR, Duc NB, Allred DC, et al. Oophorectomy and tamoxifen adjuvant therapy in premenopausal Vietnamese and Chinese women with operable breast cancer *J Clin Oncol*. 2002; 20: 2559-2566.
10. Love RR, Van Dinh N, Quy TT, et al. Survival after adjuvant oophorectomy and tamoxifen in operable breast cancer in premenopausal women. *J Clin Oncol*. 2008; 26: 253-257.
11. Love RR, Laudico AV, Dinh NV, et al. Timing of adjuvant surgical oophorectomy in the menstrual cycle and disease-free and overall survival in premenopausal women with operable breast cancer. *J Nat Cancer Inst*. 2015; 107.
12. Love RR, Duc NB, Havighurst TC, et al. HER-2/neu overexpression and response to oophorectomy plus tamoxifen adjuvant therapy in estrogen receptor-positive premenopausal women with operable breast cancer. *J Clin Oncol*. 2003; 21: 453-457.
13. Love RR, Young GS, Laudico AV, et al. Bone mineral density changes following surgical oophorectomy and tamoxifen adjuvant therapy for breast cancer. *Cancer*. 2013; 119: 3746-3752.
14. Love RR, Ba Duc N, Binh NC, et al. Symptoms associated with oophorectomy and tamoxifen treatment for breast cancer in premenopausal Vietnamese women. *Breast Cancer Res Treat*. 1999; 58: 281-286.
15. Tevaarwerk AJ, Wang M, Zhaon F, et al. Phase III Comparison tamoxifen versus tamoxifen plus ovarian function suppression in premenopausal women with node negative, hormone receptor positive breast cancer E-3193, INT-0142 A trial of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2014;

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- 32: 3948-3958.
16. van Herk-Sukel MP, van de Poll Franse LV, Voogd CA, et al. Half of breast cancer patients discontinue tamoxifen and any endocrine treatment before the end of the recommended treatment period of 5 years a population-based analysis. *Breast Cancer Res Treat.* 2010; 122: 843-851.
 17. Khosrow-Khavar F, Filion KB, Al-Qurashi S, et al. Cardiotoxicity of aromatase inhibitors and tamoxifen in postmenopausal women with breast cancer: a systematic review and meta-analysis of randomized controlled trials. *Ann Oncol.* 2017; 28: 487-496.
 18. Matthews A, Stanway S, Farmer RE, et al. Long-term adjuvant endocrine therapy and risk of cardiovascular disease in female breast cancer survivors: systematic review. *BMJ.* 2018; 363.
 19. <http://www.divaportal.org/smash/get/diva2:763072/FULLTEXT02>
 20. Love RR. Adjuvant endocrine therapy for premenopausal breast cancer. Letter and authors' response. *New Engl J Med.* 2018; 379: 1683-1685.
 21. Gray RG, Rea DW, Handley K, et al. Atom Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early stage breast cancer. *J Clin Oncol.* 2013; 31.
 22. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer. ATLAS, a randomized trial. *Lancet.* 2013; 381: 805-813.