Oophorectomy and Tamoxifen Adjuvant Therapy in Premenopausal Vietnamese and Chinese Women With Operable Breast Cancer

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Purpose: In 1992, the Early Breast Cancer Trialists' Collaborative Group reported that a meta-analysis of six randomized trials in European and North American women begun from 1948 to 1972 demonstrated disease-free and overall survival benefit from adjuvant ovarian ablation. Approximately 350,000 new cases of breast cancer are diagnosed annually in premenopausal Asian women who have lower levels of estrogen than western women.

Patients and Methods: From 1993 to 1999, we recruited 709 premenopausal women with operable breast cancer (652 from Vietnam, 47 from China) to a randomized clinical trial of adjuvant oophorectomy and tamoxifen (20 mg orally every day) for 5 years or observation and this combined hormonal treatment on recurrence. At later dates estrogen- and progesterone-receptor protein assays by immunohistochemistry were performed for 470 of the cases (66%).

Results: Treatment arms were well balanced. With a median follow-up of 3.6 years, there have been 84 events and 69 deaths in the adjuvant treatment group and 127 events and 91 deaths in the observation group, with 5-year disease-free survival rates of 75% and 58% (*P* = .0003 unadjusted; *P* = .0075 adjusted), and overall survival rates of 78% and 70% (*P* = .041 unadjusted) for the adjuvant and observation groups, respectively. Only patients with hormone receptor–positive tumors benefited from the adjuvant treatment. In Vietnam, for women unselected for hormone receptor status, a cost-effectiveness analysis suggests that this intervention costs $350 per year of life saved.

Conclusion: Vietnamese and Chinese women with hormone receptor–positive operable breast cancer benefit from adjuvant treatment with surgical oophorectomy and tamoxifen.

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E ACH YEAR APPROXIMATELY one million women are diagnosed with breast cancer; approximately 350,000 of these are premenopausal women who live in Asia, predominantly in South, Southeast, and East Asia.[1,2] For a large fraction of these women, absence of medical resources, limited economic resources, and competing health care problems make any adjuvant treatment unobtainable or impractical. Additionally, there are few rigorous data about the risks and benefits of specific adjuvant therapies in Asian women and limited and conflicting data about the frequency of predictive markers such as hormone-receptor proteins. Reports available in 1992 suggested lower frequency of estrogen-receptor (ER) proteins in Asian patients with breast cancer than in western women.[3-5] Until recently, assessment of estrogen and progesterone proteins has been performed in only specialized centers in Asia.

In 1992, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported that a meta-analysis of six randomized clinical trials, in European and North American women begun from 1948 to 1972, showed benefit from adjuvant ovarian ablation equivalent to that found from cytotoxic chemotherapy.[6] These trials were in patients uncharacterized with respect to hormone receptor status of the tumors, involved surgical or radiotherapeutic ovarian ablation, and had one third to one half of patients who had axillary node-negative tumors.[6-13] The EBCTCG publication renewed interest in ovarian ablation as adjuvant treatment for breast cancer. One particular aspect of this treat-

ment is data suggesting lower hormonal levels in premenopausal Japanese and Chinese women compared with British and North American women.[14-17] These data suggest that the impact of oophorectomy might be less in East Asian women, and that this hormonal milieu in these women might contribute to different tumor hormonal biology. Additionally, one report had noted lower levels of ER protein expression in normal breast tissue in nonwhite women.[18]

Tamoxifen adjuvant therapy also has been under-evaluated in Asian women. In 1992, the benefits of tamoxifen as adjuvant therapy (mostly for 2 years) in premenopausal women were incompletely defined. Although reduction in recurrence with tamoxifen was seen in this group, no mortality benefit was certain, and a beneficial effect of tamoxifen in hormone receptor–negative patients was considered possible.[6] Animal data suggested that tamoxifen works best in a low-estrogen environment.[19] Postmenopausal women benefited more than premenopausal women.[6] Thus in 1992, tamoxifen combined with oophorectomy seemed like a potentially more effective therapy than either intervention alone. Additional considerations in adding tamoxifen to oophorectomy were data showing that tamoxifen prevents bone loss in postmenopausal women,[20] increases bone loss in premenopausal women,[21] and favorably affects total and LDL cholesterol levels.[22] It was judged that if oophorectomy were to be used as adjuvant therapy, combining it with tamoxifen was likely to be a more effective and safer therapy if the symptoms associated with this therapy were acceptable to patients, because tamoxifen could protect against the bone loss and adverse cardiovascular risk-factor effects of early menopause.

In 1992, after establishing that combined oophorectomy and tamoxifen resulted in limited symptoms in Vietnamese women, we designed a randomized clinical trial to evaluate disease-free and overall survival after surgical oophorectomy and tamoxifen in premenopausal Vietnamese women with operable breast cancer. With primary surgical treatment, patients were to receive either oophorectomy and tamoxifen treatment as adjuvant therapy or after observation when metastatic disease developed.

PATIENTS AND METHODS

Design

We conducted an individual-patient randomized, controlled clinical trial at six hospitals in Vietnam and two in China. Initially in 1993, hospitals in Hanoi and Ho Chi Minh City, Vietnam, participated; later in 1995 to 1996, Vietnamese hospitals in Danang, Haiphong, Hue, and Nha Trang joined the study. In 1997, hospitals in Haimen City and Nantong in Jiangsu Province in China joined the study. Eligible participants were women with clinical and cytologic or pathologic

evidence of operable breast cancer. If stage was determined clinically, patients had to have tumors that were greater than or equal to 2 cm in diameter, that is T_2. Stage I patients were ineligible; stage IIA, IIB, and IIIA (tumor-node-metastasis) patients were eligible. Preoperative radiation therapy was permitted as long as the patient had pretreatment disease clinically of these stages. Participants had to have a treatment plan of mastectomy at some time less than 10 weeks from study entry and be premenopausal, which was defined as having had at least one menstrual period in the preceding 12 months. Participants had to have a review of systems and a physical examination, including a gynecologic examination showing no evidence of metastatic cancer within 14 days, a normal chest ray, normal liver function studies, and a normal blood calcium level all within 10 weeks of study entry. Most participants were women with a fine-needle aspirate cytologic diagnosis of breast malignancy for whom mastectomy was planned. After eligibility review, such women entered the study, and if randomized to receive adjuvant oophorectomy, this surgery was performed under the same anesthetic as the mastectomy. Thus, the design allowed lower risk related to anesthesia but created the possibility that some participants with clinical tumors more than 2 cm would be found to have noninvasive breast cancer after oophorectomy had been performed; frozen section intraoperative assessment of tumors was not available in participating institutions.

Randomization at each institution was performed after eligibility review was completed and written informed consent was obtained as described below, by use of sealed envelopes containing the randomized treatment determined using a permuted block design. These were sequentially numbered in eight strata by nodal status: 0, 1 to 3, 4 or more than, or N_x and T_2 or T_3 clinical or pathologic tumor size. If a participant was found on review to have been randomized in the incorrect stratum, the randomized treatment given was not changed. There were 35 such randomization errors. In all multivariate analyses, the correct variables for each participant were used.

Each participant was required to sign a written informed consent document in Vietnamese or Chinese, as appropriate, before randomization and entry onto study. The entire trial and contents of these documents was approved by the institutional (ethical) review committee of the principal investigator's (R.R.L.) local institution in the United States and the Office for Protection of Research Risk of the United States National Institutes of Health, and by the Ministry of Health of Vietnam, Scientific and Technical Council, and by institutional committees at both hospitals in China. After the study was begun, annual written reapprovals by each of these committees (except the Office for Protection of Research Risk) were sought and obtained.

The conduct of the trial was reviewed at annual intervals by an independent data monitoring committee of five experts. Written annual approvals of the data monitoring committee to the institutional review committee of the principal investigator's institution were required and provided.

Treatments

All participants in this trial had surgery with mastectomy and axillary node clearance. Patients receiving radiation, which was at individual physician's discretion, were treated with a 60 Co unit, using 1.8 or 2 Gy/d fraction size to a total dose of approximately 50 Gy. For the majority of patients entered onto the study, if no positive nodes were found at mastectomy, the chest wall only was treated using opposed tangent fields. If positive lymph nodes were found, a third field was added, covering the supraclavicular region, with dose calculated at 3-cm depth.

Ovarian ablation was performed surgically, and confirmation of normal ovaries by pathologic examinations was required. In two patients, radiation therapy ovarian ablation was performed. This treatment was of 20 Gy given in 10 fractions; field details were prescribed.

Tamoxifen (Nolvadex) was provided at cost by ICI Pharma Singapore and provided free to participants in 3- to 6-month supplies of 10-mg tablets with instructions to take two tablets daily. Tamoxifen was provided for 5 years to adjuvant-treated subjects and indefinitely to observation patients with recurrent disease.

Follow-Up

Participants were seen at 3-month intervals for the first 3 years, questioned about symptoms and examined. After 3 years, examinations at 6-month intervals were required. At each visit a separate paper record was made. During the first 2 years, a chest x-ray was required at 6-month intervals because of concern with reactivation of tuberculosis in irradiated women. As inducements to return for follow-up, each participant was paid a nominal amount and given daily multivitamin tablets.

Quality Control

Hospital and clinical medical records and x-rays were reviewed by the principal investigator for all primary study data in a randomly selected fashion, so that 40% of all cases was audited completely. The principal investigator visited each participating institution to review study progress and follow-up and to collect new case and follow-up data for all cases every 3 to 6 months during the study. These visits, combined with required pathology and chest x-ray studies, ancillary studies, and detailed reviews of all patients with missing information or recurrent disease, resulted in partial audits for the majority of cases.

Definitions

Recurrence of disease was defined as definitive evidence of metastatic cancer considered to be from breast cancer, documented and confirmed where practical by cytologic or surgical biopsy. Disease-free survival was defined as date of study entry to date of recurrence of disease or death if before recurrence. Overall survival was defined as date of entry onto study to date of death or date of last follow-up.

Pathology Studies

Histopathologic confirmation of breast cancer by institutional pathologists was sought in all cases.

Evaluations of ER and Progesterone-Receptor (PR) Proteins

ER and PR were assessed 2 to 7 years after diagnosis by immunohistochemical methods on histologic sections of formalin-fixed paraffin-embedded tissue by previously validated methodology[23,24] with the following modifications: Heat-induced antigen retrieval was achieved by boiling slides in 0.1 M TrisHCl buffer at pH 9 for 5 minutes at 120°C in a pressure cooker. Endogenous peroxidase activity was blocked with 3% H_2O_2 in TrisHCL. Nonspecific biotin activity was blocked with excess avidin masked by free biotin (Avidin/Biotin Blocking Kit; Vector, Burlingame, CA). A cocktail of two monoclonal anti-ER antibodies was used, including 6F11 at 1:100 (Vector) and 1D5 at 1:50 (Dako, Carpenteria, CA). The cocktail was necessary to increase sensitivity to acceptable levels in these generally suboptimally preserved tumor samples. The monoclonal anti-PR antibody designated

1294 (Dako) was used at a dilution of 1:1000, which was sufficiently sensitive alone. The sensitivity of the detection system was also enhanced by increasing the dilution of the biotinylated linking antibody (Dako) to 1:100 for both ER and PR. Only cases deemed to have satisfactory preservation were immunostained for ER and PR (83% of samples with available paraffin blocks), based on prior microscopic evaluation of hematoxylin and eosin–stained slides. The most common reasons for cases to be omitted as unsatisfactory were extremely poor fixation, extensive necrosis, and very rare tumor cells.

The resulting ER and PR signals were evaluated microscopically and assigned scores estimating the proportion (0 = none; 1 < 1/100; 2 = 1/100 to 1/10; 3 = 1/10 to 1/3; 4 = 1/3 to 2/3; and 5 > 2/3) and intensity (0 = none; 1 = weak; 2 = intermediate; and 3 = strong) of positive staining tumor cells. The scores were summed and positive was defined as more than 2 for both receptors based on calibration to patient outcome in previous studies.[23-25]

Histologic Subtyping and Grading

The histologic subtypes of the breast cancers were assigned based on the terminology and criteria put forth by Page and Anderson.[26] Histologic grading conformed to the system of Scarff-Bloom-Richardson as modified by Elston and Ellis.[27]

Statistical Methods

A study sample size was based on estimates of 50% to 55% 5-year disease-free survival and 60% to 65% overall survival in the observation patients, and on increases of 10% to 12% in disease-free survival and 8% to 9% in overall survival with the studied adjuvant treatment.[6] A sample size of 700 was estimated to provide 82% to 94% power for the expected 5-year disease-free survival difference and 72% to 82% power for the expected 5-year overall survival difference.

The major study objectives of disease-free and overall survival were addressed using Kaplan-Meier methods,[28] and the differences were assessed by means of the log-rank test.[29] The χ^2 test and the Wilcoxon test were used to analyze differences in categorical variables.[30] Multivariate analyses used the Cox proportional hazards model.[31] Subjects were analyzed according to the intent-to-treat principle.

The data were monitored at approximately 6-month intervals by a data and safety monitoring committee. To reduce the likelihood of false-positive results caused by repeated interim analyses, the Lan-DeMets procedure with an O'Brien-Fleming boundary was used.[32,33] For the major study objectives using this procedure, an adjusted P value is reported if a statistically significant value was reached. All computations were performed with SAS software (version 6.12, SAS Institute, Cary, NC). All P values were calculated with two-sided tests of significance.

A preliminary cost-effectiveness analysis of the trial results was performed by modifying the assumptions used in a previously reported natural history model of early-stage breast cancer.[34] The modified model considered a 15-year time horizon and an average patient age of 45 years. The annual cost of tamoxifen was estimated at $90 per year based on the acquisition cost incurred in the trial. The additional cost of oophorectomy at the same time as mastectomy, ie, under the same anesthesia, of $10 was based on local estimates. The relative risk of recurrence used in the model was based on results data. Survival after recurrence was assumed to be 40% greater in the observed patient group. Because no reliable estimate of the cost of recurrence (other than hormonal therapy) was available, it was assumed to be $0, which biased the analysis against the adjuvant oophorectomy/tamoxifen therapy. Costs were discounted at 3% per year.

Table 1. Patient and Tumor Characteristics by Treatment Group

Characteristic	Adjuvant Treatment Group (n = 356)	Observation Group (n = 353)	P for Differences (statistical test)
Age, years, mean ± SD	41.3 ± 5.40	41.3 ± 5.75	.836*
Patients with data, no.	347	349	
Age less than 40, % of total	36.0	35.5	.892†
Age 40 and over, % of total	64	64.4	
Weight, kg ± SD	48.5 ± 7.07	48.12 ± 7.09	.338*
Patients with data, no.	348	349	
Clinical tumor size, cm ± SD	3.9 ± 1.41	4.11 ± 2.16	.153*
Patients with data, no.	347	349	
Pathologic tumor size, cm ± SD	3.22 ± 1.38	3.37 ± 1.28	.0091*
Patients with data, no.	345	348	
Axillary node negative, %	43.6	46	.611†
Axillary node positive, %	53.0	51.7	
Axillary node status unknown, %	3.4	2.3	
No. of axillary nodes positive, mean ± SD	4.24 ± 3.57	4.17 ± 3.26	.913*
No. assessed	186	181	
Radiotherapy postoperatively given, %	70	72	
ER status evaluated, %	67.5	66.6	
ER positive, %	55.7	67.95	.012†
PR status evaluated, %	67.2	66.3	
PR positive, %	63.1	62.1	.812†
Histologic grade			
1, %	24.1	22.4	.562†
2, %	63.0	67.2	
3, %	12.8	10.4	
No. assessable	257	259	

*Wilcoxon rank sum test.
†χ^2 test.

RESULTS

From early 1993 through mid-1999, 709 women were entered onto this clinical trial at seven institutions, six in Vietnam and one in Haimen, China. An eighth institution in Nantong, China entered an additional 26 patients; on audit of these cases, 14 were found ineligible, and 14 were found to have received unreported chemotherapy treatment, and the data monitoring committee recommended removing all 26 cases from this institution from the analysis. The analysis reported is thus based on 709 cases. Among these entered cases, eight patients received no primary treatment for their cancers, and eight cases were found on audit to be ineligible. Twenty-three participants (3.2%) are considered lost to follow-up because their status has been unknown for over 6 months. Only seven of these are in the adjuvant group. On pathology review, 34 (4.9%) of the 701 cases have been found to have no evidence of invasive breast cancer. Twelve of these cases were in the observation group (P = .08).

The current report is based on evaluations to March 1, 2001. At this timepoint, the median follow-up is 3.6 years.

Patient and tumor characteristics are listed in Table 1. Pathologic tumor size is statistically greater in the observation group, whereas the adjuvant group had a significantly lower percentage of cases evaluated that were ER positive (P = .012). Of 66% of cases whose primary tumors were available and assessable for ER and PR proteins, 62% were ER positive, and 62% were PR positive. Eight percent were ER positive and PR negative, and 8% were ER negative and PR positive.

Among patients in the group assigned adjuvant therapy (n = 356), 93.0% underwent oophorectomy and tamoxifen therapy; 3.9% received tamoxifen alone, and 3.1% received neither oophorectomy nor tamoxifen. Thus, 97% of these patients received some adjuvant hormonal therapy. In the observation group of women developing recurrent breast cancer to date (n = 124), 23% have been treated with oophorectomy and tamoxifen, one has had oophorectomy alone (1%); 52% have received tamoxifen; 19% have received neither hormonal treatment for metastatic disease; and for 5%, the treatment is unknown. Data from treating physicians indicated that of the patients with recurrence not treated with oophorectomy and tamoxifen, in approximately half, the treating physician felt the patient was not an appropriate candidate for surgical oophorectomy, and in the remaining half, the patients refused surgical or radiation oophorectomy.

To date, no patients have died postoperatively, and none have developed major morbidity after oophorectomy surgery and tamoxifen; specifically, no patients have developed deep vein thrombosis, pulmonary embolism, or endometrial cancer. The symptoms associated with oophorectomy and tamoxifen treatment have been limited, and no patients have stopped tamoxifen treatment because of symptoms. These have been previously reported.[35]

There have been 84 events and 69 deaths among the 356 entered women in the adjuvant treatment group and 127 events and 90 deaths in the observation group of 353. Of 11 deaths without recurrence (eight treatment, three observation; $P = .13$), two have been a result of well-documented non–breast cancer, non–treatment-related causes. In an intent-to-treat analysis of all entered cases, disease-free and overall survival are significantly greater in the adjuvant treatment group ($P = .0003$ and $P = .0477$ unadjusted, respectively; and $P = .0075$ adjusted for interim analyses for disease-free survival) (Fig 1). In explanatory post hoc analyses, positive ER or PR status was associated with improved disease-free survival in the adjuvant treatment group (Figs 2 and 3), whereas negative hormonal status was associated with no benefit from adjuvant treatment. Axillary node-negative and -positive groups benefited from adjuvant oophorectomy and tamoxifen. An analysis excluding the cases with noninvasive disease gave results that were substantially no different. Median survival after recurrence was 391 days in adjuvant cases and 471 days in observation cases.

In a multivariate Cox model, adjuvant treatment, axillary lymph node positivity, pathologic tumor size, ER positivity, and histologic grade 3 were each related to disease-free survival and overall survival (Table 2), as shown by relative risks for each factor in the presence of the others listed (Table 2). A cost-effectiveness analysis in women unselected for hormone receptor status, using a 15-year time horizon, projects an average benefit of an increased survival of 1.4 current years (3% discounting) and an incremental cost of $351 per life-year gained.

DISCUSSION

By design in this trial, we attempted a more rigorous evaluation of the possible benefits of an adjuvant treatment by prescribing that the treatment for metastatic disease in observation cases should be, whenever possible, the same as that given as adjuvant therapy. Although 97% of adjuvant cases received oophorectomy with tamoxifen or tamoxifen alone, 76% of observation cases with recurrence received hormonal therapy.

The cancellation, loss to follow-up, and ineligibility rates in this trial are acceptably low; the imbalance of 11 more
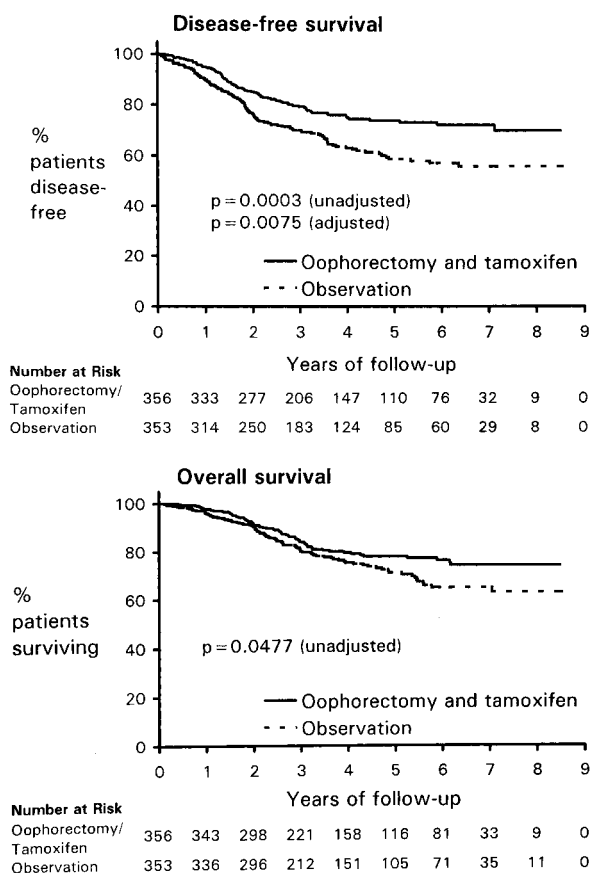
Fig 1. Disease-free and overall survival: All ages. The curves represent the number of patients at risk by treatment arm: adjuvant oophorectomy and tamoxifen (solid line), and observation (dashed line). A disease-free survival event is death or recurrence; an overall survival event is death. Patients without events are censored at time of last known contact.

cases in the observation group lost to follow-up suggests the possibility of greater benefit from adjuvant treatment than the figures demonstrate (because some of these cases have recurred and died). Although statistical significance of the difference in overall survival between the treatment groups at present is by rigorous standards borderline (ie, a significant P value adjusted for repeated measures has not been reached), on the advice of the study data monitoring committee, this report is offered at this time because of the general acceptance of disease-free survival as the primary objective in adjuvant studies.

In patients initially uncharacterized with respect to hormone receptor status in a Scottish trial, ovarian ablation was found equivalent to cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy in women with positive axillary nodes.[36] In a subset of patients who were later found to be hormone receptor positive, disease-free survival
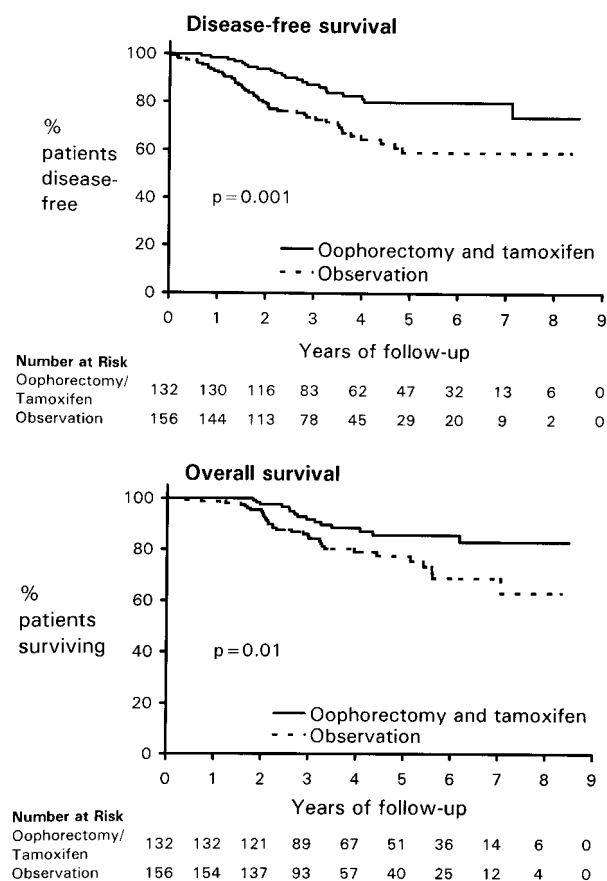
Fig 2. Disease-free and overall survival: ER-positive subset of study patients (n = 288 or 41% of total study sample).
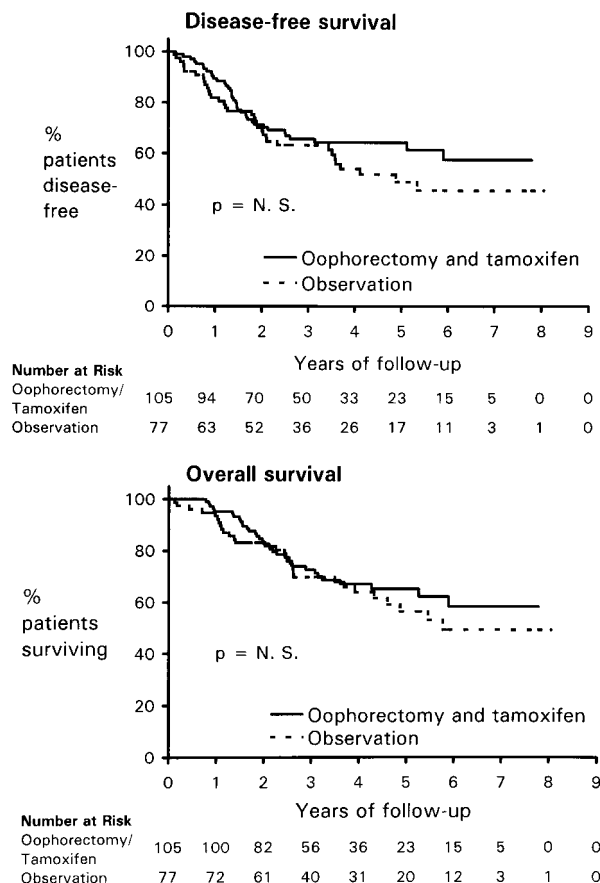

Fig 3. Disease-free and overall survival: ER-negative subset of study patients (n = 182 or 26% of total study sample). There is imbalance in the numbers of cases in the two arms of the study in each of these subsets, as noted in Table 1.

was greater with ovarian ablation than with CMF treatment.[36] A Danish trial of only hormone receptor–positive patients found CMF and ovarian ablation to be equivalent therapies.[37] A small French study found ovarian ablation plus tamoxifen to be superior to anthracycline-based chemotherapy in double hormone receptor–positive patients.[38] More recent studies have used luteinizing hormone releasing hormone (LHRH) agonist therapy to ablate ovarian function in hormone receptor–positive patients only. A French study found LHRH agonist and tamoxifen to be superior to an anthracycline-based chemotherapy regimen.[39] A large Austrian study found this combined hormonal therapy to be superior to CMF chemotherapy,[40] whereas a small Italian study found these treatments equivalent.[41] Finally, American and Italian studies have found that the addition of both LHRH agonist and tamoxifen together to anthracycline-based chemotherapy improved disease-free survival over treatment with chemotherapy alone.[42,43] A recently reported study of combined LHRH

tamoxifen treatment in metastatic hormone receptor–positive breast cancer compared with LHRH or tamoxifen single-agent therapies found greater survival with combined treatment,[44] and a meta-analysis of four LHRH agonist plus tamoxifen trials also found combined therapy more effective and suggested that this should be the new standard therapy for metastatic hormone receptor–positive premenopausal patients with advanced breast cancer.[45] Together these data suggest that, in hormone receptor–positive patients, adjuvant treatment with oophorectomy (by surgical or LHRH treatment) and tamoxifen is likely to be of equivalent or greater efficacy than either hormonal therapy alone or standard cytotoxic chemotherapy regimens. These data are the basis for the recommendation of the International Consensus panel that oophorectomy plus tamoxifen should be a therapy of choice in receptor-positive premenopausal women.[46]

Table 2. Multivariate COX Proportional Hazards Models for Prognostic Factors

Variable	Risk Ratio	95% Confidence Interval	P
Disease-free survival			
Adjuvant treatment	0.58	0.40-0.84	.0043
Square root of number of positive lymph nodes*	1.35	1.15-1.59	.0003
Pathologic tumor size	1.15	1.03-1.28	.016
ER positivity	0.55	0.38-0.80	.0015
Histologic grade 3	1.78	1.10-2.88	.019
Overall survival			
Adjuvant treatment	0.67	0.44-1.02	.059
Square root of number of positive lymph nodes	1.36	1.12-1.64	.0017
Pathologic tumor size	1.15	1.01-1.30	.029
ER positivity	0.43	0.29-0.66	.0001
Histologic grade 3	1.85	1.07-3.18	.028

*The square root of the number of positive lymph nodes was used because risk of recurrence associated with this variable is not linear.

In magnitude of benefit demonstrated, the current study results are consistent with data from European and North American populations and suggest that, despite a different hormonal profile,[14-16] premenopausal Vietnamese and Chinese women have percentages of estrogen- and receptor-positive tumors similar to those reported in western populations and benefit significantly from adjuvant treatment with combined ovarian ablation and tamoxifen treatment. The disease-free survival relative-risk reduction of 0.52 found in this study of oophorectomy plus tamoxifen compares favorably with that of 0.45 found with tamoxifen alone for 5 years in the EBCTCG meta-analysis.[47] These data support the 1992 meta-analysis conclusion on ovarian ablation[6] and affirm the following conclusions: (1) that if hormone receptor assessments can be performed, benefit from hormonal therapy can be maximized; if a patient's tumor is found to be hormone receptor positive, ovarian ablation and tamoxifen adjuvant therapy should be considered the treatment of choice for Asian women because symptoms are manageable[35] and cost-effectiveness is likely to be high; and (2) that if hormone receptor tests cannot be performed, ovarian ablation and tamoxifen is likely to be as effective if not more effective than standard adjuvant chemotherapy regimens, and again, should be the adjuvant treatment of choice.[6]

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