SUPPLEMENTARY METHODS

Treatment. Participating institutions and investigators agreed to make every effort to perform combined surgical oophorectomy and mastectomy surgeries within the randomized or assigned time windows, which for two thirds of women could be estimated to be 1-6 days from date of registration on study. Because the order of these surgeries in the hypothesis-generating study had been oophorectomy followed by mastectomy, this order was prescribed in this study [1]. Tamoxifen (Nolvadex) 20 mg. tablets (Nolvadex, provided by Astrazeneca Pharmaceutical Co.) were provided to all participants and begun within 6 days of surgeries. Compliance with tamoxifen consumption is estimated to be high over the five years of treatment because of a requirement for regular 3-6 monthly visits to obtain the study-provided medication, and to undergo symptom assessment and physical examination. Adjuvant radiation therapy was given at investigators' discretion. When administered, this was usually three or four field treatment given over 5 weeks for a total dose of 50Gy. Aspirin or bisphosphonate drugs were not prescribed nor regularly taken by any study patients.

Laboratory studies. On the day of patient surgeries 10ml of blood was drawn prior to any anesthesia or drugs, and the sera was separated and frozen. At the time of mastectomy surgery when the breast specimen was removed, it was immediately brought to a study pathologist who dissected out two one-gram specimens of tumor tissue if such tissue was obviously present.. These tissue specimens were immediately frozen in cryogenic vials in liquid nitrogen. Every effort was made to limit the time from patient-vascular removal to freezing to 15 minutes. At later dates, in batches, without any episodes of thawing, the serum and tissue specimens were shipped frozen to the investigators' US institution sample bank.

The estrogen and progesterone (ER and PR) hormonal receptor immuno-histochemistry (IHC) studies which are the basis for the current report are those reported for the individual clinical sites using diagnostic core biopsies. The data on Her-2/neu immuno-histochemistry, histologic type, histologic grade, and the ER and PR immune-histochemical data used in the definition of phenotypic Luminal A type tumors, all come from central laboratory studies done on paraffin or flash frozen tumor tissues created from the mastectomy specimens 3-9 years from the time of their creation (laboratory of DCA). Because in particular tissue fixation procedures for these paraffin specimens may destroy the hormonal receptor proteins, the numbers of cases used in some of the analyses are less than those included in intent-to-treat analyses although those registered on study all had hormone estrogen or progesterone receptor positive tumors based on core biopsy IHC analyses [2]. Histological subtyping of invasive breast cancers (IBCs) was performed on whole H&E-stained tissue sections by the criteria of Page and Anderson [3]. The Scarff-Bloom-Richardson method as modified by Elston-Ellis was used for histological grading of IBCs, with grades 1, 2 and 3 corresponding to well, intermediate, and poorly differentiated, respectively [4, 5]. Samples were evaluated for estrogen receptor (ER; antibody 6F11), progesterone receptor (PgR; antibody 1294), and erbB2 (antibody SP3) on tissue microarrays (single 2 mm core/case) using validated IHC methodology as previously described [6-10]. ER and PgR were quantified and interpreted by the Allred Score (range 0-8) and "positive" was defined as scores ≥ 3. erbB2 was quantified by the HercepTest score (range 0-3+) as described in the Dako HercepTest Interpretation guides, and "positive was defined as 3+ [10]. Serum progesterone values were determined using an enzyme immunoassay modified from Munro et al. [11] and further modified from Saltzman et al. [12]. Estradiol levels were determined according to standard laboratory practice.

Of 740 patients registered on the trial, 578 patients had paraffin blocks or flash frozen tissue from the breast tumor resected at surgery which allowed creation of high quality tumor sections (78% of registered cases).

Quality Control. Initially, case report forms were used to gather study data completed by clinical site investigator teams and after the initial three years of the study, all case data were entered by site investigators into a secure web-based system. During audits, monitors sought to verify key treatment, safety and efficacy data against study on-site paper and hospital records. Annual data and safety monitoring committee meetings were based on detailed study data reports, particularly on treatment compliance and adverse events.

Recruitment

Complete descriptive summaries of the patients recruited for this study but not enrolled were available only for the major site. At that clinical site with 322/740 cases (44%) accrued, 807 patients were initially assessed as study eligible and had core biopsy hormonal receptor tests performed. 564 patients (70%) were determined to be hormonal receptor positive (a percentage consistent with expected frequency of hormonal receptor positive tumors in the population). 336 of these patients returned for further evaluation (leaving 228 who did not return); 11 were screened as study ineligible, 3 were found study eligible but refused study participation, and 322 were found study eligible, provided informed consent and were registered on study. That 228 patients (40%) did not return for further evaluation and treatment is consistent with general experience in patients with malignancy in this institution.

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