Introduction
For the last decade, the behavioral practices of women obtaining screening mammograms have changed significantly. More women than ever are following the American Cancer Society Guidelines of an annual screening mammogram beginning at age 40. This has likely added to the reduction in deaths from breast cancer that was reported for the first time in the last decade. With the increasing number of women getting mammograms on a regular basis, the stage at which women are diagnosed has steadily decreased. Women are more likely than ever to be diagnosed with a stage I breast cancer at the time of their original diagnosis. Stage I breast cancer is defined as those breast cancers that are less than or equal to 2 cm in greatest diameter with no involved axillary lymph nodes and no evidence of metastatic disease (T1, N0, M0). In the International Staging System, T1 breast cancers are further subdivided into three groups. T1a tumors are less than or equal to 0.5 cm, T1b tumors range from greater than 0.5 cm to less than or equal to 1 cm, and T1c tumors range from greater than 1 cm to less than or equal to 2 cm. Prognostic factors have been developed for the eventual risk of developing metastatic breast cancer after the original finding of early breast cancer. The single most important determinate of prognosis is number of lymph nodes involved in the ipsilateral axilla. Other important prognostic factors include tumor size, tumor grade, and hormone receptor status (estrogen or progesterone receptors). Other prognostic factors, such as proliferative growth rates, HER-2/neu gene amplification, and p53 mutations are still the subject of some controversy and research.

Retrospective reports of prognosis of T1a and T1b breast cancers
Lymph node–negative breast cancers that are less than or equal to 1 cm in greatest diameter are considered a group that has a particularly excellent long-term prognosis. This has been based on several long-term retrospective reports from single institutions. The initial long-term study was reported by Rosen et al. [1] from the Memorial Sloan-Kettering Cancer Center in 1993. This oft-quoted paper reported on 767 women from that institution who had been diagnosed with a lymph node–negative breast cancer between 1964 and 1970. Of the 767 women, 171 were diagnosed with tumors less than or equal to 1 cm in greatest diameter. All of these women had either a ductal or lobular histology, and all women underwent either a radical or modified radical mastectomy. The authors reported that the women had a 91% relapse-free survival
(RFS) rate at 10 years and an 86% RFS rate at 20 years. No biologic prognostic information, such as hormone receptor status, proliferative indices, or oncogene amplification, was available on these tumors. Lessons learned from this report were as follows: 1) women with breast cancers less than or equal to 1 cm in diameter have an especially good long-term prognosis when compared with women with lymph node–negative tumors greater than 1 cm; and 2) for those women who do relapse with recurrent breast cancer, two thirds of the relapses will occur in the first decade, but another third will occur between years 11 and 20.

Several other groups also have reported their findings regarding the long-term prognosis of lymph node–negative tumors less than or equal to 1 cm. These reports are comparable in that the numbers of women being reported are relatively small and their long-term prognosis appears similar. They are diverse, however, in that the length of follow-up ranges from 7 to 20 years [2–4]. The literature is hampered by the lack of a prospective trial comparing adjuvant systemic therapy versus no systemic therapy for this group of women. It is also lacking in any long-term relapse data related to any other biologic prognostic data, such as hormone receptor status.

NSABP analysis of outcome of tumors less than or equal to 1 cm in five prospective randomized trials

An important addition to this literature was published in 2001 by the National Surgical Adjuvant Breast and Bowel Project (NSABP). The investigators reported on an analysis of data from five randomized lymph node–negative trials [5––]. A total of 10,302 women were enrolled in one of the following NSABP trials: B-06, B-13, B-14, B-19, and B-20. Two hundred and thirty-five women with estrogen receptor (ER)-negative tumors and 1024 women with ER-positive tumors were identified; all had tumors measuring less than or equal to 1 cm in greatest diameter.

The NSABP B-06 trial was conducted to assess the local and systemic outcomes of women with an invasive breast cancer as influenced by their local therapy: lumpectomy, lumpectomy plus radiation, or mastectomy [6]. No systemic therapy was delivered as part of this trial. The study showed survival equivalence among the three groups, but there was clearly an increased incidence of ipsilateral breast tumor recurrences (IBTRs) in the lumpectomy-alone group compared with those women who were randomized to radiation. For the purposes of the five-study analysis, only those women who had a total mastectomy or lumpectomy plus radiation and whose hormone receptor status was known were included in the analysis. A total of 84 women from NSABP B-06 met these criteria.

Two trials were designed to assess the benefit of systemic therapy in women with lymph node–negative, ER-negative breast cancer. In NSABP B-13, 760 women with ER-negative, lymph node–negative breast cancer were randomly assigned to receive either surgery alone or surgery followed by chemotherapy using the regimen of methotrexate followed by 5-fluorouracil (5-FU) and leucovorin [7]. This trial demonstrated a significant improvement in disease-free survival (DFS) for those women receiving systemic chemotherapy. An additional 356 women who met the same protocol requirements were enrolled in a study by the same investigators to receive surgery, then methotrexate followed by 5-FU. A total of 96 out of these 1116 women met the criteria of having a tumor less than or equal to 1 cm.

Having established that there was a DFS advantage of receiving methotrexate followed by 5-FU after surgery in lymph node–negative, ER-negative breast cancer, the NSABP sought to perform another trial for this group of women that would compare two different chemotherapy regimens: methotrexate followed by 5-FU or CMF (cyclophosphamide, methotrexate, and 5-FU). In B-19, 1095 patients underwent this randomization. The results of this trial suggested that both chemotherapy regimens were effective for this group of women but that CMF was more effective in premenopausal women [7]. From this trial, 114 women had tumors that measured less than or equal to 1 cm.

Two trials, NSABP B-14 and B-20, were performed to assess the benefit of adjuvant systemic therapy in women with lymph node–negative, ER-positive breast cancer. These trials were designed to run concurrently with the hormone receptor–negative trials.

The B-14 trial randomized 2892 women with lymph node–negative, ER-positive invasive breast cancer to either placebo or tamoxifen, 20 mg/d for 5 years. On completion of this accrual, another 1235 women who met the same protocol criteria of the randomized trial were registered in a trial in which they received open-label tamoxifen [8,9]. A total of 633 women from this trial had tumors less than or equal to 1 cm in diameter.

In NSABP B-20, 2363 women who met the above criteria were randomly assigned to one of three arms, all of which included tamoxifen, as this was shown to have a significant benefit in B-14 [10]. The women received either tamoxifen alone or one of the two chemotherapy regimens that were delivered in B-19. Findings of this study showed a significant reduction in recurrences when women received chemotherapy along with the tamoxifen. Among the three arms, there were 332 women with tumors less than or equal to 1 cm.

For the current five-study analysis of the outcome of the women with breast cancers less than or equal to 1 cm in these five trials, the outcome of women was truncated at 8 years. Although some of these studies had longer follow-up, all studies had follow-up times of at least this period of time. Tables 1 and 2 show the 8-year RFS for women in the analysis, according to their hormone receptor status.

The investigators reviewed their data according to RFS and event-free survival (EFS) by hormone receptor status. They also reported on the overall survival of these women and evaluated the relationship between tumor characteristics and recurrence.