

## The use of radiation in the elderly

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**Abstract** Despite the fact that breast cancer is predominantly a disease of postmenopausal women, there have been no uniform recommendations for both locoregional and systemic therapy for women over 70. Until recently, older women have been excluded from clinical trials. This study is the first randomized trial that addresses the use of radiation therapy following lumpectomy in a favorable cohort of elderly women.

**Keywords:** Radiation; lumpectomy; elderly

### Introduction

The standard of care for locoregional treatment of breast cancer, since the time of Halsted, has been the mastectomy. In the 1970s, studies began that would shift the emphasis toward breast conservation. The use of radiation therapy and, more recently, the development of sentinel lymph node biopsy and reliance on tumor markers for prognostic information has led to an array of approaches allowing individualized patient care based on presentation.

Over 30% of women with breast cancer are 70 years of age or older at the time of diagnosis [1]. As the population ages, these numbers will increase. Until recently, older patients were under-represented in clinical trials [2,3] and the treatments for breast cancer in older women were extrapolated from those of their younger counterparts. Physicians were free to base their treatment strategies on anecdotal data and personal experience. The result was that no uniform recommendations existed for the cohort of older women. There were accusations of under-treatment – women who did not undergo axillary dissection at the time

of lumpectomy or radiation postoperatively, or over-treatment – women undergoing mastectomy for small tumors due to fear of, or inaccessibility to, radiation [4,5]. Although it is probable that older women receive fewer types of treatment, it is unclear whether this approach negatively impacts survival [6]. Lack of consensus regarding optimum care and strong adherence to opposing viewpoints were the basis of our study.

### Background

Older women tend to have more comorbid conditions than younger women. The risk/benefit ratio of various therapies shifts to account for the possible exacerbation of unrelated illness or a lower tolerance to complications of treatment. In addition to a more limited physical tolerance to treatment, older women may have a different outlook on treatment options. Quality of life issues place emphasis on self-reliance, independent living, and when inevitable, an easy death. Common sense would dictate that, given equivalent outcomes, most patients would choose less radical and fewer interventions.

Life expectancy in women over 70 years can be substantial, as much as 20 years but is never comparable to that of younger women [7]. The goal of treatment is either cure or control of the disease for a finite time, allowing the patient to succumb to other

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causes. This approach is possible because breast cancer in older women appears to be a more indolent disease. Positive hormone receptors occur more frequently as do lower histologic grade, lower proliferative rates and decreased amplification of HER2/neu [8–10]. Mammograms in older women tend to be easier to read because of involution of breast tissue and increased fat replacement [11]. Coupled with the possibility that tumors in the elderly are more slow growing, with longer doubling times [12], mammographic identification of occult lesions increases the chances of finding cancer at earlier stages.

## Treatment

With over 20 years of follow-up, the National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B06 and other clinical trials have confirmed breast conserving therapy as the standard local treatment for breast cancer. The addition of postlumpectomy radiation reduces in-breast recurrence but does not impact survival [13,14]. Almost as quickly as these treatments were accepted, clinicians began to try to identify subgroups in which radiation could be deferred. Older women with small, well-behaved tumors might be one of these subgroups, deriving less benefit from radiation or, perhaps, achieving increased local benefits from systemic treatment.

The overview analysis of the Early Breast Cancer Trialists Collaborative Group (EBCTG), although including no studies involving women over 70 years, established that 5 years of tamoxifen continued to show a decrease in mortality and a 47% decrease in the rate of contralateral breast cancer throughout 10 years of follow-up [15]. NSABP protocol B14 found a 50% decrease in ipsilateral breast tumor recurrence when tamoxifen was added to radiation therapy [16].

The benefits of axillary dissection are staging, prognostic information used to make treatment decisions, and prevention of axillary recurrence. NSABP protocol B04 suggested that there is no difference in survival between concurrent and delayed axillary dissection at the time of recurrence [17]. If treatment decisions are made based on patient physiology and tumor behavior, regardless of axillary nodal status, then immediate dissection may not be necessary and may, in fact, offer needless complications. The use of sentinel lymph node biopsy is an alternative with low morbidity and may be especially helpful in estrogen receptor negative tumors or those with poor prognostic factors where chemotherapy might offer substantial benefit over hormonal therapy.

The most important question is whether or not radiation therapy can be safely omitted for older women with favorable tumors. Again, the EBCTG has shown that, at 10 years postoperatively, patients who do not

receive radiation have ipsilateral breast tumor recurrence rates of 27.2% while those who do receive radiation recur at a rate of 8.8%, with no impact on survival [14]. Although radiation therapy does not offer significant morbidity, older women often complain of the inconvenience associated with daily treatments. A course of treatment is also costly; an increasingly important consideration as the population ages and health care dollars must cover expanding types of therapies.

To answer these questions, the Cancer and Leukemia Group B (CALGB) in cooperation with the Eastern Cooperative Oncology Group (ECOG) and the Radiation Therapy Oncology Group (RTOG), undertook CALGB protocol 9343, Lumpectomy plus Tamoxifen with or without Irradiation in Women 70 Years of Age or Older with Early Breast Cancer.

## Results

Between July 1994 and February 1999, 636 women 70 years of age or older with clinical stage I breast cancer which was estrogen receptor positive who had been treated with lumpectomy, were randomized to receive tamoxifen and radiation therapy or tamoxifen alone. Axillary dissection was allowed but discouraged. Over 200 patients in each group did not have axillary dissection or sentinel lymph node biopsy. The axilla was not radiated. Primary endpoints were time to locoregional recurrence, frequency of mastectomy for recurrence, breast cancer-specific mortality, time to distant metastases, and all-cause mortality. Secondary endpoints were evaluation of cosmesis and adverse events by physicians and patients.

The only significant difference between the two groups was the rate of locoregional recurrence. In the group receiving radiation therapy followed by tamoxifen, 3 (1%) patients had ipsilateral breast tumor recurrence. In the tamoxifen alone group, 23 (7%) women recurred with 20 (6.3%) breast recurrences and 4 (1.2%) in the axilla. The risk of axillary recurrence without surgery or radiation therapy was 1.5%. There were no significant differences between the two groups with regard to mastectomy for local recurrence, distant disease, all-cause mortality or breast cancer-specific mortality. Physicians and patients uniformly rated the cosmetic results and adverse events to be inferior in the radiation plus tamoxifen group than in the tamoxifen alone group.

## Conclusion

CALGB 9343 is the first randomized trial to specifically address treatment options in women over 70 years with early stage breast cancer. Prior to this study, these women had two choices: modified radical

mastectomy or breast conserving therapy to include axillary sampling and postoperative radiation.

The results of this study were first published in the *New England Journal of Medicine* in September 2004 [18]. At that time, median follow-up was 5 years. Local recurrence in the tamoxifen plus radiation group was 1% and, in the tamoxifen alone group 4%. Although the numbers have changed slightly, the clinical significance at nearly 8 years of follow-up has remained the same. There have been many deaths on each arm of the study, but breast cancer-related deaths have remained few and identical between both groups. As in similar studies, breast radiation following lumpectomy has a significant impact on in-breast recurrence but not on survival. These data support a third choice for older women undergoing breast cancer treatment, that of lumpectomy with adjuvant anti-estrogen therapy and without radiation.

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