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# Axillary dissection versus no axillary dissection in older T1N0 breast cancer patients: 15-Year results of trial and out-trial patients

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**Abstract**

*Background*: Our randomized trial found no survival advantage for axillary dissection (AD) compared observation only (no AD) in older patients with early breast cancer and a clinically negative axilla, indicating that AD is unnecessary. We compared characteristics and outcomes in out-trial patients with those in trial patients to provide indications as to whether AD can be safely omitted outside the trial setting.
*Methods*: The trial started in 1996, recruiting 238 patients age 65–80 years with cT1cN0 breast cancer, randomized to conservative surgery with or without AD. Over the recruitment period, 109 eligible patients who refused to participate in the trial, also received conservative breast surgery with or without AD depending on patient preference/surgeon opinion. Trial and out-trial patients received conventionally-fractioned whole breast radiation and tamoxifen for five years. Endpoints were breast cancer mortality, overall survival, and cumulative incidence of axillary disease in patients not receiving AD.
*Results*: After 15 years of follow-up, breast cancer mortality and overall survival did not differ between the AD and no AD arms, in either the trial or out-trial cohorts. The 15-year cumulative incidence of axillary relapse was 6% in the no AD arm of the trial group, and zero in the no AD arm of the out-trial group.
*Conclusions*: Outside the trial setting, older patients with T1N0 breast cancer can be safely treated by conservative surgery, postoperative radiotherapy and tamoxifen for five years (if ER-positive). Axillary surgery is appropriate only for the small proportion of patients who develop overt axillary disease during follow-up.


*Keywords:* Early breast cancer; Older patients; Axillary surgery; Tamoxifen

## Introduction

Breast cancer is the most common cancer of women in Western countries,[1] where widespread mammographic screening has resulted in earlier diagnosis and progressive increase in the proportion of cases with a clinically uninvolved axilla.[2] In such cases, axillary dissection is no longer a routine part of the surgical treatment of the disease, as it has been superseded by sentinel node biopsy[3–5] – a technique that accurately stages the axilla and spares the morbidity of complete axillary clearance in women with negative sentinel nodes.

However, since publication of the initial results of the NSABP-04 trial in 1977,[6] there has been interest in foregoing all surgical treatment to the axilla in selected groups of women with early, clinically node-negative breast cancer. About 40% of breast cancers are diagnosed in women over 65 years of age[7] and older women tend to develop cancers with favorable prognostic factors,[8] and may therefore be one group that does not benefit from surgical treatment of the axilla. In fact, the 15-year results of our prospective non-randomized study on elderly patients with T1N0 breast

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cancer who underwent breast surgery with or without axillary dissection (AD), showed no outcome advantage for patients who received AD.[9]

To further address this problem, we carried out a single-center randomized controlled trial in older (65–80 years) women. The trial, which started in January 1996. compared AD to observation (no AD) in older T1N0 patients undergoing breast-conserving surgery. After 15 years of follow-up there were no differences in breast cancer mortality or overall survival between the study arms,[10] and the proportions developing distant metastases were also indistinguishable. These findings support the hypothesis that it is the biological behavior of the primary that determines metastatic spread and hence breast cancer mortality, while axillary involvement has little or no influence on metastatic spread, although it may indicate greater risk of such spread. The original trial protocol specified the recruitment of 642 patients, however recruitment was slow in these older patients and we decided to stop accrual after four and a half years (in June 2000). Furthermore approximately one third of eligible patients were treated outside the trial. Hence the results may not reflect outcomes in all patients who fulfilled the inclusion criteria. Therefore our aim in this study was to analyze patients who were treated outside the trial and compare them with trial patients in terms of characteristics, treatments and outcomes, and thus provide indications as to whether AD can be safely omitted in older clinically node-negative breast cancer patients treated outside the trial setting (in normal clinical practice).

## Patients and methods

### *Patients*

The series comprised 238 trial patients aged 65–80 years with primary T1N0 breast cancer, and 109 out-trial patients eligible for recruitment (and with similar characteristics to recruited patients) who refused to take part. Of the 238 randomized patients, 19 were excluded as they were erroneously recruited, and the intention-to-treat analysis was performed on 219 patients. These patients were randomized to conservative surgery with (109 patients) or without (110 patients) AD. The trial was registered at clinicaltrials.gov (NCT00002720). Of the 109 out-trial patients, 71 underwent conservative surgery with AD and 38 conservative surgery without AD. The trial was approved by the scientific and ethical committees of our institute and patients gave written informed consent. Whether or not out-trial patients had AD depended on patient preference and the opinion of the treating surgeon.

### *Treatments*

For all cases that received AD, all three Berg levels were removed. Patients with non-infiltrating disease, bilateral breast cancer, distant metastases at diagnosis, or previous malignancy (except basal cell carcinoma) were excluded from the trial and out-trial series.

In trial and out-trial patients postoperative radiotherapy to the residual breast started within 4 weeks of surgery. A cobalt-60 unit or 6 MeV linear electron accelerator was used to deliver 50 Gray (Gy) to the operated breast in 2 opposing tangential fields over 5 weeks. A supplemental boost of 10 Gy was given to the tumor bed. Axillary, supraclavicular, and internal mammary nodes were not irradiated, however the tangential portals used typically included the lower part of level I of the axilla.[11] Tamoxifen, 20 mg/day for five years, was prescribed after surgery to all patients irrespective of hormone receptor status.

### *Tumor grade and hormone receptor status*

Tumor grade was assessed according to Elston and Ellis.[12] Hormone receptors were determined as described elsewhere.[13] Tumors were considered receptor-positive if over 10% of tumor cell nuclei were immunostained.

### *Follow-up*

Patients were seen every six months for the first five years and yearly thereafter. Mammography and chest X-ray were performed annually. Gynecological examination with pelvic ultrasound was performed twice yearly for the first five years and annually thereafter, because tamoxifen was prescribed. Disease status or cause of death was ascertained from clinical records or by contacting the general practitioners of patients no longer presenting for follow-up. Median follow-up was 150 months for the AD arm and 149 months for the no AD arm of trial patients; and 152 months for the AD, and 148 months for the no AD groups, of out-trial patients.

### *Statistical methods*

The trial was a non-inferiority trial. From data published in the trial[13] the 5-year probability of distant metastasis was 5.5% in the axillary dissection arm, and 5.3% in the no axillary dissection arm. The observed incidence of events was in fact lower than assumed when planning of the trial (17%). With recruitment of 219 patients the power was 0.83, and for a comparison at 5 years this was adequate, assuming a non-inferiority margin of 0.12.

To compare outcomes in trial and out-trial patients, composite endpoints were assessed first, followed by individual endpoints. The two composite endpoints were: death for any cause (classified as breast cancer-related, other malignancy related, or unrelated to cancer) and first event ipsilateral breast recurrence, distant metastasis, overt axillary disease in patients who did not receive AD, contralateral breast cancer, other non-breast malignancy, and death without evidence of neoplastic event. Time to death or first