

Comparison of Radical Mastectomy and Alternative Treatments for Primary Breast Cancer¹ (1971-1974)

Purpose

- Primary research question(s):
 - Is total mastectomy followed by axillary dissection of those patients who subsequently develop positive nodes as effective a therapy as is radical mastectomy in patients with clinically negative axillary nodes?
 - Is total mastectomy with postoperative regional radiation as effective as radical mastectomy or total mastectomy with postponement of axillary dissection until positive nodes occur?
 - Are radical mastectomy and total mastectomy with radiation equivalent procedures in patients with clinically positive nodes?
 - Is there biological significance to be gained that confirms or repudiates the worth of *en bloc* dissection in cancer surgery?
- Primary outcomes:
 - Treatment failure – defined as the presence of tumor in local, regional or distant sites
 - Survival
 - Morbidity
- Perceived clinical importance:
 - More than 200,000 women diagnosed each year with breast cancer.
 - About 40,000 women die from the disease each year.
 - Breast Cancer is the leading cause of malignancy in women.

Background and Context

- Radical mastectomy was standard of care for breast cancer and one of its biggest proponents was William H. Halsted from Johns Hopkins. He trained many surgeons in this technique, which involved removing the affected breast, underarm lymph nodes and both underlying chest muscles (*en bloc* dissection). He published data in 1895 reporting recurrence in only 3 out of 50 patients.
- Two divergent hypotheses existed regarding tumor biology. Most believed that cancer was a local/regional disease spread by the lymph system to distant sites. Others proposed that breast

cancer was a systemic disease better treated by systemic therapy.

- Anecdotal evidence in the mid-1960s led some surgeons to advocate more extensive surgery and others to promote more limited operations than the radical mastectomy.
- During the 1970s, social pressure/advocacy groups were starting to raise awareness of breast cancer, advocating research and promoting less disfiguring surgery. These advocates served on cooperative group committees for clinical trials in breast cancer.
- The trial took almost a decade to plan because of the great controversy in surgical opinions and ethical considerations.

Date and Place Conducted:

- Location: United States and Canada
 - 34 NSABP member institutions in Canada and the United States
- Recruitment Dates: July 1971 - September 1974.

Principal Investigators:

- The NSABP Investigators (34) from Canada and the United States

Sponsored by/source of funding:

- Supported by a Breast Cancer Task Force Contract (NIH-N01-CB 23876), a grant (CA-12027) from the U.S. Public Health Service and a grant (RC013B) from the American Cancer Society

Size and Design:

- Number randomized: 1,765. Of the 1,765 randomized, 1,159 were randomized to the three clinical node negative groups and 606 to the two clinical node positive groups
- Number of participants eligible for follow-up: 1,665.
- The percentage of participants by race were: 72.6% White, 24.9% Black and 2.5% other. There was a higher proportion of blacks in the clinically positive node group than in the clinically negative node group.
- Participant characteristics: Eligible participants included women with primary operable, potentially curable breast cancer for which

- tumors confined to the breast or breast and axilla,
- tumors movable in relation to the underlying muscle and chest wall
- axillary nodes movable in relation to the chest wall and neurovascular bundle
- no arm edema
- patient consented to participate
- Women were considered ineligible if:
 - pregnant or lactating
 - previously treated for their current neoplasm or had a prior or concomitant cancer other than an effectively managed basal or squamous cell skin tumor
 - existence of bilateral breast cancer or the tumor was other than a carcinoma
 - the tumor was inflammatory or there was skin ulceration >2 cm
 - peau d'orange involving more than one-third of the skin of the breast or if satellite or parasternal nodules were present
 - a fixation of axillary lymph nodes (over 2 cm) or there were lymph nodes elsewhere suspected of containing tumor unproved by biopsy to be negative
 - poor surgical risks precluding their being subject to any of the treatment options
 - presence or non-malignant systemic disease made prolonged follow-up unlikely.
- Design: prospective randomized clinical trial. Randomized to one of three groups after designation of nodal status and the subjects deemed clinically negative:
 - one-third to radical mastectomy,
 - one-third to total mastectomy and regional radiation, and
 - one-third to total mastectomy alone.The subjects with clinically positive axillary nodes were randomized to two groups:
 - one-half received radical mastectomy and
 - one-half total mastectomy and regional radiation.

Issues Encountered During the Trial:

- A total of 5.6% of all patients were judged ineligible after randomization. Almost all had been randomized prior to biopsy and at biopsy were found to have no cancer. This procedure was discontinued later in the study. Other reasons for ineligibility included:
 - ineligible tumor type, disease too advanced, moved, did not cooperative, surgery elsewhere, bilateral malignancy, prior treatment, history of cancer, and concomitant disease.

- Of the 1,665 patients eligible for follow-up, 4 were lost.
- Some treatment variation causing the subjects to be ineligible for analysis occurred in 10.8% of eligible subjects.
 - Incorrect nodal classification occurred in 1.7% of the subjects.
 - Treatment not as assigned
 - Wrong treatment
 - Problem evaluating, starting or continuing radiation
 - Major radiation variation
 - Prophylactic therapy with radiation or chemotherapy
- Major protocol variations of radiation therapy occurred in 9% and 10.8%, respectively in the node negative and node positive specimens.
- Authors stated a methodological concern in analyzing data with regards to intention-to-treat versus treatment received. Therefore analysis performed by:
 - All patients followed
 - All irradiated patients followed excluding those with major variation from protocol specified treatments, except for patients with major radiation variations
 - Patients followed exclusive of all those with major protocol variations

Findings

- Forty-nine (14.2%) of the 344 clinically negative node patients subjected to total mastectomy developed histologically positive nodes and had axillary dissection. Seven patients (2.0%) with clinically positive nodes subjected to axillary dissection and all nodes were histologically negative. The mean time from mastectomy to axillary dissection in those patients with positive nodes was 14 + 8.93 (S.D.) months with a range of 2 to 49 months and a median of 12 months.
- No statistically significant difference in relation to time to treatment failure (disease free interval) was found to exist between the three treatment groups in the clinically negative node patients or clinically positive node patients.
- The probability of remaining disease free was not significantly greater for clinically negative node subjects and the clinically positive node subjects in the three or two treatment groups, respectively.

- No significant differences in distant metastasis were observed.
- Local recurrences were fewer in total mastectomy group receiving radiation.
- No statistically significant difference in relation to time of death was found.
- Probability of survival was not significantly greater for any group within each of the clinical nodal categories.
- A disproportionate number of treatment failures in the total mastectomy group occurred in those requiring subsequent axillary dissection.
- Twenty-five-year findings corroborated earlier results that there is no significant difference in either distant-disease-free survival or overall survival among the groups of women with negative nodes or between the groups of women with positive nodes.

Impact

- Provided evidence that radical mastectomy was no more effective than more limited surgical approaches.
- Provided evidence that positive axillary nodes are not the predecessor of distant tumor spreads but represent one manifestation of disseminated disease.
- Paved the way for other breast conservation trials (e.g. B-06).
- Some surgeons and patients still preferred radical mastectomies due to the perception of risks.
- In June 1979, a Consensus Development Conference was held at NCI which resulted in a consensus statement that total mastectomy with axillary dissection replace the Halsted radical mastectomy as the treatment standard. They also recommended that breast-conservation procedures be vigorously pursued.
- A quote from Bernard Fisher, "...one of the most important advances of the 20th century was taking place: The prospective randomized controlled trial was being introduced into clinical medicine as a mechanism for hypothesis testing, for obtaining natural history information, and for evaluating the worth of a

particular therapy. Replacing anecdotalism with published finding from clinical trials represents a major step in transforming medicine from an art into a science."

Unresolved issues

- 40% of women who underwent mastectomy alone had positive nodes that were not removed during the time of initial surgery. Despite this anomaly, there were no significant differences in outcomes observed among the three groups.
- Lymph nodes were sometimes found in specimens from women who underwent total mastectomy. However the number of nodes in the specimens was less than those in specimens from patients who underwent radical mastectomy.
- Long-term follow-up revealed the need to differentiate between breast cancer deaths and deaths from other causes. During twenty-five-year follow-up a large percentage of deaths were from causes other than breast cancer.
- This study failed to substantiate the belief that unremoved axillary nodes might be immunologically advantageous to the host.
- Variation in radiation was observed despite of the tight controls in the trial leading to the question the variation of radiation therapy in general use.
- At the time the B-04 study began, patients that survived five years were thought to be "cured". Twenty-five year follow-up indicated a need for long-term follow-up because of the high percentage of distal and contralateral cancers that occurred after five years.
- Some commentary questions the power of the study to establish equivalency.

Summary

Total mastectomy was compared to radical mastectomy and it was found that there were no statistical differences in either treatment failure or survival between the two treatment groups for clinical node-negative and node-positive patients. This trial also provided evidence that breast cancer was a systemic disease better treated by systemic therapy as opposed to the prevailing theory that breast cancer was a local disease spread through the lymphatic system.

The results of this study paved the way for studies of breast-conserving surgery (B-06) and studies of systemic therapy. Another direct outcome from this study was the recommendation from the Consensus Development Conference that the total mastectomy replace the Halsted mastectomy as treatment of choice of primary breast cancer.

The social environment around breast cancer trials impacted breast cancer research then and now. One of the more interesting aspects of the breast cancer trials was the formation of many patient advocacy groups that played a role in promoting research, the design of trials, and data safety monitoring.

References

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