PRACTICE CHANGING TRIALS IN BREAST CANCER SURGERY

Rachel Adams Greenup, MD, MPH
Departments of Surgery and Population Health Sciences
Duke University School of Medicine
July 17, 2019
OVERVIEW

• Mastectomy versus breast conservation
• Surgical management of the Axilla
• Preoperative versus post-operative systemic therapy
• Surgery of the primary tumor in stage IV disease
• Contemporary reductions in overtreatment
Mastectomy versus breast conservation
• Father of breast cancer surgery

• “More is better”

• En bloc resection of breast, chest wall muscles, axillary nodes levels I-III, internal mammary nodes (extended radical mastectomy)

• Survival in surgical patients was 2x that of non-surgical patients.
FIGURE 16–12. In the same patient, contraction of the intact pectoralis major muscle can be seen on the left. This photograph demonstrates the difference in the axilla and chest wall defects associated with the two operations.

Harris, et al.; Breast Diseases, 2nd Ed. 1991; J.B. Lippincott Co., Pennsylvania
NSABP B-04

• Radical mastectomy was standard of care (1970’s).
• Divided into clinically node-negative and node-positive.
• N= 1,079 clinically node-negative patients
  • Radical mastectomy (362)
  • Total mastectomy with axillary RT (352)
  • Total mastectomy without axillary treatment (365)
• N= 586 clinically node-positive patients
  • Radical mastectomy (292)
  • Total mastectomy with RT (294)

No difference in survival among treatment arms.
Operable Breast Cancer

Initiated in 1971

Clinically Node-Negative

Radical Mastectomy I,II,III ALND

Total Mastectomy

Total Mastectomy + Irradiation

Clinically Node-Positive

Radical Mastectomy

Total Mastectomy + Irradiation

NO ROLE FOR RADICAL MASTECTOMY!!
Modified radical mastectomy: breast tissue + nodes
NSABP B-06

• Compared lumpectomy +/- ALND with or without irradiation with or without irradiation VS. modified radical mastectomy
• Tumors ≤4cm
• 1976-1984
• N= 2163 clinically node-negative patients
  • Modified radical mastectomy (10% risk of recurrence)
  • Lumpectomy + ALND + RT (14% risk of recurrence)
  • Lumpectomy + ALND + no RT (39% risk of recurrence)

No survival difference between treatment arms at 20 yrs
BCT is preferred treatment for invasive breast cancer
Breast conservation: lumpectomy + radiation
NSABP B-21

• Compared adjuvant therapy after lumpectomy + ALND in women with node-negative tumors ≤1cm:
  • *Is tamoxifen as good as radiation after BCT?*
  • *Is tamoxifen plus radiation superior to RT alone?*

• N= 1009 patients after lumpectomy (8 yr follow-up)
  • Tamoxifen alone (16.5% risk of recurrence)
  • Radiation + placebo (9.3% risk of recurrence)
  • Tamoxifen + Radiation (2.8% risk of recurrence)

  Tamoxifen + radiation = lowest LRR
  Tamoxifen reduced contralateral breast cancer risk.
  No difference in overall survival (94-95%) because distant recurrence risk was low.
NSABP B-17

• NSABP B-17 compared patients with DCIS treated by lumpectomy to no further therapy versus adjuvant radiation:
  • Radiation reduced ipsilateral breast cancer recurrences invasive (17% vs. 8%) and non-invasive (15% vs. 8%).
  • No difference in overall survival was observed and 2/3rds of deaths in DCIS cohort were not related to breast cancer.

• NSABP B-24 randomized women to lumpectomy and radiation with placebo versus tamoxifen:
  • Addition of tamoxifen improved in-breast recurrences AND disease-free and overall survival related to ipsilateral and contralateral invasive cancers (50% reduction).
NSABP B-18

• Compared adjuvant therapy after lumpectomy + ALND in women with node-negative tumors ≤1cm:
  - is tamoxifen as good as radiation after BCT?
  - Is tamoxifen plus radiation superior to RT alone?

• N= 1009 patients after lumpectomy (8 yr follow-up)
  - Tamoxifen alone (16.5% risk of recurrence)
  - Radiation + placebo (9.3% risk of recurrence)
  - Tamoxifen + Radiation (2.8% risk of recurrence)

  Tamoxifen reduced contralateral breast cancer risk.
  No difference in overall survival (94-95%)
NSABP B-32

• Clinically node-negative cancers.
• Randomized to SLNB+ALND versus SLNB alone.

• Study aims:
  • Accuracy of SLNB
  • Morbidity
  • Long-term disease control and overall survival

• Identification rate of 97.2%
• False-negative rate of 9.8%
• Long-term disease control and DFS and OS pending.
ALMANAC trial

- Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC).
- Surgeons required to demonstrate 90% accuracy and 5% FNR prior to phase II.
- Randomized to SLNB+ALND versus SLNB alone if negative.

Study aims:
- Accuracy of SLNB
  - Long-term axillary recurrence rates
- Identification rate of 96%.
- False-negative rate of 5%.
- Long-term disease control data pending.
Preoperative versus postoperative systemic therapy
Neoadjuvant chemotherapy

- Inflammatory breast cancer
- Locally advanced cancers
- Large primary tumors (>5cm)
- Fixed axillary lymph nodes
- Matted axillary lymph nodes
- Attempt at breast conservation
- Downstage the axilla
- In vivo response to treatment

NSABP B-18 and B-27

- Operable breast cancers.
- Randomized to surgery vs. chemotherapy first (ACx4).
- No difference in survival.
  - 16yr follow-up trends in favor of NCT in women ≤50 yrs.
- pCR (13%) correlated with DFS and OS.
- Improves operability & breast conservation rates
  - Increased eligibility for BCT (67% vs. 60%, p=0.002).
  - Similar rates of in-breast recurrence (8% vs. 6%).
  - Decreased volumes of resected breast tissue.
  - Similar re-excision rates.
  - Decrease in mastectomy rates
  - No difference in surgical complications

Neoadjuvant endocrine trials

- Improves breast conservation (22-46%).
  - Conversion from mastectomy to BCT (P024)
  - Letrozole= 45%, Tamoxifen= 35% (IMPACT trial)
- Aromatase inhibitors >>> tamoxifen.
- Greatest clinical response in HER2+ tumors.
- Similar downstaging as NCT with less toxicity.
- Duration correlates with clinical response (12 weeks).

CALGB 9343: Omission of Radiation in Older Women

- Age 70 +
- Tumor ≤ 2 cm
- Estrogen Receptor-Positive
- Axillary surgery discouraged

Randomize:

- Lumpectomy + Tamoxifen
  - 319 women
- Lumpectomy + Tamoxifen + Radiation
  - 317 women
CALGB 9343

- Lumpectomy plus tamoxifen with and without RT in women ≥70 years with ER+ invasive breast cancer.
- N= T1N0 ER+ invasive cancers.
- 8.2 years of follow-up.
- No survival benefit with addition of radiation.
- Higher risk of local recurrence without RT.
  - At 5 years tamoxifen + RT (1%) versus tamoxifen alone (4%) risk of local recurrence.
  - At 10 years tamoxifen + RT (98%) versus tamoxifen alone (90%) improved disease-free survival.
- Axillary staging did not impact survival.

DCIS

CALGB 40903: Neoadjuvant letrozole for ER(+) Postmenopausal DCIS

For patients who have completed 6 months of letrozole the surgery must be performed within 30 days of the 6 month MRI. Patients who are found to have radiographic progressive disease at month 3 will have the preoperative bilateral mammogram and be scheduled for surgery within 30 days of the second (month 3) MRI central review.
COMET

Patients registered and randomized (n=1200)

GCC Treatment (n=450)
- Surgery +/- radiation
- Endocrine therapy available
- MMG q 6 months x 5 years
  - Usual care for recurrent disease

Declined Participation (n=300)
- GCC or AS treatment
- Follow-up per usual care

AS Treatment (n=450)
- Endocrine therapy available
- MMG q 6 months x 5 years
  - GCC treatment for invasive progression

○ = 50 patients
Clinical T1–T3 N1 M0 breast cancer

NACT

Breast-conserving surgery or mastectomy and sentinel lymph-node surgery

SLN negative

SLN positive

Randomization

ALND plus breast/chest wall and nodal XRT (without XRT to dissected axilla)

No further axillary surgery, but breast/chest wall and nodal XRT

Nature Reviews | Clinical Oncology
"In God we trust. All others must have data."

Bernard Fisher, MD, FACS – Surgeon and Cancer Pioneer