Value of adjuvant radiation therapy in breast cancer patients with one to three positive lymph nodes undergoing a modified radical mastectomy and systemic therapy

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**Background**
- The Early Breast Cancer Trialists’ Collaborative Group Overview (Lancet 2005), a meta-analysis of 78 randomized trials, including 42,000 women, showed that radiation therapy (RT) after breast-conserving surgery (BCS) and RT after mastectomy with axillary clearance in LN+ disease produced significant absolute improvements in 5-year LR (17-19% benefit) and 15-year breast cancer mortality (5.4% benefit).
  - RT produced similar proportional reductions in LR risk (70% risk reduction) irrespective of age, grade, tumor size, ER status, or amount of LN involvement.
  - Among patients treated with systemic therapy, the absolute benefit of RT on LR and breast cancer mortality were 20% at 5-year and 5.9% at 15-year, respectively.
  - Therefore, better local treatment adds to the effect of systemic therapy on LR, which can translate into a moderate breast cancer mortality benefit (4:1 ratio).
  - Addition of RT improved 15-year OS by 5.3% after BCS and by 4.4% after mastectomy with axillary clearance for LN+ disease.
- 1-3+ LN pts: Controversial
  - There is a ~15% local recurrence at 5-year without RT. With RT, we would have expected 5% OS benefit. The thought behind this is that a reduction in early local recurrence can lead to long term survival benefit.
  - However, there is an estimated 12% LRR at 10-year for this group. Is this enough to treat for measurable benefit on overall survival?
- Based on these results, the absolute benefit gained from post-mastectomy radiation (PMRT) is believed to be greatest for those at high risk of LRF.
  - There is a consensus that PMRT should be delivered in patients with four or more positive axillary lymph nodes, primary tumor size > 5 cm or T4 disease.
    - PMRT is not indicated in patients with node-negative disease or with tumors < 5 cm.
- The potential benefits of PMRT in patients with 1-3 positive axillary nodes remain controversial.
  - The purpose of this study was to determine if adjuvant radiation therapy had an impact on survival for this cohort of patients.

**Materials and Methods**
- This study is a retrospective study in which 4,240 patients with Stage I or II breast cancer patients (T1-2N0-1), diagnosed between 1980-2007, who underwent either mastectomy without adjuvant radiation therapy or segmental mastectomy with adjuvant radiation therapy were identified and compared. The trial was stopped on Dec. 30, 2008.
  - The two groups compared were mastectomy without radiation versus segmental resection with radiation. The groups were chosen this way by the authors as opposed to mastectomy +/- radiation because the historical standard was to not deliver PMRT to 1-3 node + patients. Therefore, the numbers for the mastectomy with radiation group would have been too low for a valid comparison.
Inclusion criteria:
- Female patients
- Diagnosed between 1987-2007
- Had to have surgical assessment of LN’s
- Tumors < 5 cm in size
- Number of Nodes < 4
- T1/T2 tumors

Exclusion criteria:
- Male patients
- > 1 primary breast cancer
- Had mastectomy with radiation treatment
- Had segmental resection without radiation treatment

All patients received systemic treatment.

The primary endpoints of the study were loco-regional disease free survival (LRDFS) and distant disease free survival (DDFS). Secondary endpoint was overall survival (OS).

Overall (OS) and distant disease free survival (DDFS) were estimated using the Kaplan-Meier product method. Cox proportional hazards were used to determine associations between OS/DDFS and type of surgery after controlling for patient and disease characteristics.

Results
- Patients were well-balanced in the two groups with respect to age.
- 1336 (18.8%) had T1N0 disease, 1114 (26.27%) had T2N0 disease, 989 (23.33%) had T1N1 disease and 801 (18.89%) had T2N1 disease.
- 42.37% of patients were in the mastectomy without RT (M+no RT) group and 57.63% of patients were in the segmental resection with RT (S+RT) group.
- The median number of nodes removed in the M+no RT group was 13, while it was 10 in the S+RT group.
- There were a significantly higher number of node positive patients in the mastectomy group.
- The majority of patients received anthracycline-based chemotherapy and about half of patients received taxanes. About 22-24% of all patients received neo-adjuvant chemotherapy.
- Median follow-up was 54 months.
- On multivariate analysis of LRDFS among the LN negative patients, there was no difference seen between the 2 groups (91% vs. 89%). For LN positive patients, there was no difference seen in T1N1 patients, however T1N2 patients demonstrated a 4% difference between the 2 groups (91% for S+RT and 87% for M+no RT; p=0.009). A difference favoring the S+RT was also seen for T2N1 patients.
- 5-year DDFS among women who underwent mastectomy and segmental mastectomy was 81% (95% CI 78%-83%) and 86% (95% CI 84%-87%), respectively (p < 0.0001). In the Cox analysis, patients in the M+no RT group had a significantly increased risk of distant recurrence (HR = 1.38, 95% CI 1.14-1.70, p = 0.0013) compared to patients in the S+RT group.
- No significant difference in DDFS was observed between the two groups in pts with lymph node negative disease.
- However, for patients with 1-3 positive lymph nodes, patients treated with M+no RT had significantly increased risk of distant recurrence compared to the S+RT group (HR=1.614, 95% CI 1.198-2.177, p = 0.002). This difference was most pronounced in the subset of patients with T2N1 disease (HR = 1.794, 95% CI 1.220-2.637, p=0.003), showing 9% difference in DDFS between the groups favoring S+RT (p=sig). Similar trends were observed for OS.

Author’s Conclusions
- This study indicates that patients with tumors less < 5 cm and 1-3 + LN’s have an increased risk of LRR and distant relapse.
- This study provides provocative evidence for benefit of radiation therapy among pts with 1-3 positive axillary lymph nodes who are treated with surgery and systemic therapy, and the highest benefit was seen in the T2N1 group.

Clinical/Scientific Implications
- The use of adjuvant radiation therapy for patients with early stage breast cancer with up to 3 positive axillary lymph nodes
treated with mastectomy and systemic therapy is controversial.

- Therefore, it is important to continue to study this gray area of what do in terms of adjuvant RT for these patients. This study has made a significant attempt to accomplish this goal; however the study has many limitations.

- Limitations of the study:
  - The study is retrospective and an inherent selection bias is present in who was having BCS versus mastectomy. It can be assumed that patients with larger tumors were more likely to have mastectomy and do better that those who would have received BCS alone. Therefore, the addition of RT may have benefited these patients who had BCS alone.
  - The study design did not allow one to adequately compare mastectomy +/- radiation, since the 2 groups studied did not include mastectomy in both groups. The authors acknowledge this limitation, however, this non-ideal comparison has large implications on the ability to generalize the results of this study to mastectomy patients. It is difficult to make clinical decisions regarding post-mastectomy RT based on this study since results for RT in the post-mastectomy setting was not examined in this retrospective study. Only segmental resection + RT was studied.
  - The authors did not address the question of what type of radiation fields were used and whether or not patients received RT to the axilla or supraclavicular fields.
  - For 1-3 positive LN patients, BCT + RT does not yield better outcomes than mastectomy according to the EBCTCG overview and the NSABP studies that were part of this meta-analysis. However, this study leads us to believe that BCT + RT does yield better results than mastectomy alone, especially for T2N1 patients. It is unclear why the results of this retrospective study differ from previously published prospective trials.
  - The authors of this study have made a valiant attempt to address the issue of PMRT in the setting of 1-3 + nodes for T1/T2 breast cancer patients. But this study has many flaws, and the authors have acknowledged these appropriately.
  - For this reason, these data can only be hypothesis generating at this time and need to be confirmed in future prospective trials.