NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer

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Background/Introduction

- The majority of women with early stage breast cancer are managed with breast conserving surgery (BCS) and surgical staging of the axilla, followed by adjuvant systemic therapy as indicated, and whole breast irradiation (WBI). WBI with tangents may treat the low-lying axillary lymph nodes (Levels I and possibly II). Additional regional nodal basins not included in tangent fields include the higher axilla, including Level III, the infra- and supraclavicular regions, and the internal mammary chain (IMNs).
- The addition of regional nodal radiation (RNI) to WBI is recommended for patients with primary tumors > 5 cm, and > 3 positive axillary nodes. RNI in patients with 1-3 + lymph nodes is controversial, and there is considerable variation in the practice of RNI in these patients. For example, inclusion of the IMNs as part of RNI is controversial.
- RNI has the potential to increase treatment-related morbidity including brachial plexopathy, cardiotoxicity, pneumonitis, and lymphedema of the arm.
- Support for RNI in patients undergoing BCS with 1-3 + nodes is extrapolated from the post-mastectomy setting, where randomized trials (British Columbia and Danish trials) have demonstrated that locoregional radiation after mastectomy reduces locoregional recurrence and improves OS in women with node + breast cancer treated with adjuvant chemotherapy, including patients with 1-3 positive nodes.
- The goal of the present study was to determine whether adding RNI to modern systemic therapy improves survival with acceptable limited toxicity in patients treated with breast conservation therapy.

Methods

- Inclusion criteria:
  - Pre- or post-menopausal women who had undergone BCS with axillary dissection, and received either chemotherapy or hormone therapy.
  - Moderate to high risk of regional recurrence, on the basis of:
    - Involved axillary nodes, or
    - Primary tumor > 2 cm in size, having < 10 nodes dissected, and at least one of the following: Grade 3 histology, ER-negative disease, or lymphovascular space invasion, with negative nodes.
- Prior to randomization, patients were stratified for the number of involved nodes (0, 1-3, or >3), number of nodes removed (<10 or ≥10), the type of systemic chemotherapy, and the treatment center.
- Eligible patients were randomized 1:1 to either:
  - WBI (50 Gy in 25 fractions of 2 Gy +/- 10 Gy boost) or
  - WBI plus RNI (delivered as 45 Gy in 25 fractions of 1.8 Gy) targeting the supraclavicular, infraclavicular, ipsilateral IMNs in the first to third interspaces, and high axillary lymph nodes (Level III).
  - The IMNs could be treated with either modified wide tangents, or a mixed photon-electron direct field matched to the tangent.
- The primary outcome was overall survival (OS). Secondary outcomes included locoregional recurrence rates, disease free survival (DFS), distant metastases DFS, toxicity, and cosmetic outcomes.
The study was designed to detect a HR of 0.73 in favor of the RNI group, requiring a minimum of 312 deaths.

The Data Safety Monitoring Committee undertook an interim analysis of relapse patterns, survival and toxicity at 5 years. Upon review of the data, they recommended release of the results.

Results

- The study accrued 1832 patients between 2000 and 2007, with 916 randomized to each arm.
- Median follow up was 62 months.
- Patients were well-matched in terms of their baseline characteristics:
  - Mean age was 53 years,
  - A median of 12 nodes were removed at axillary lymph node dissection,
  - 85% of patients had 1-3 positive nodes, 10% were node negative, and 5% had > 4 positive nodes.
  - 91% of patients received adjuvant chemotherapy, and 71% received adjuvant hormonal therapy.
- Isolated locoregional DFS: The addition of RNI to WBI was associated with a decrease in isolated locoregional recurrence (LRR) from 48 in the WBI arm to 29 in the WBI+RNI arm.
  - The local-only recurrence rates were similar between the 2 groups, while there was a marked reduction in regional recurrences, with 21 in the WBI arm versus only 4 in the WBI+RNI arm.
  - 67% of these isolated regional recurrences were in the axilla, and there was only 1 isolated recurrence in the IMNs.
  - This translated into an improvement in isolated locoregional DFS from 94.5% to 96.8%, HR = 0.59, (p = .02)
- DFS: There were 144 events in the WBI arm, and 102 events in the WBI+RNI arm, leading to an improvement in 5-year DFS from 84.0% to 89.7% favoring the WBI+RNI arm, with a HR of 0.68 (p .003)
- Distant DFS: Of note, there was a relatively early benefit in terms of distant metastases DFS. There were 116 events in the WBI arm, versus 77 in the WBI+RNI arm; there were decreases in metastases both as a first event, and subsequent to locoregional recurrence.
  - Distant DFS at 5 years was 92.4% for WBI+RNI and 87.0% for WBI alone (HR=.64, p=.002)
- Overall Survival: There was a strong trend towards improved OS with the addition of RNI, with 5-year OS of 92.3% versus 90.7% for WBI alone (HR=.76, p=.07). The OS curves appear to separate at 5 years.
- Toxicity: The addition of RNI to WBI was associated with an increase in grade 2 or greater pneumonitis (1.3% and 0.2% respectively, p=.01), and lymphedema (7.3% and 4.1% respectively, p=.004).
- Adverse cosmetic outcomes (patient reported as “fair” or “poor” cosmesis), increased with time in both groups of patients, but more so in those patients treated with RNI.

Authors' Conclusions

- The addition of regional nodal irradiation to whole breast irradiation in women undergoing breast conservation therapy with 1-3 + nodes improved disease free survival by reducing both locoregional recurrence and distant recurrence. In addition, a trend towards improved overall survival with the addition of RNI was observed. This was achieved without a significant increase in morbidity.
- The implication of this study is that all women with node positive disease should be treated with RNI in addition to WBI.

Clinical/Scientific Implications

- The MA.20 trial represents a landmark, practice changing trial for the treatment of patients with early stage, node positive breast cancer managed with breast conservation therapy. There is controversy as to whether patients with 1-3 + nodes should be treated with regional nodal irradiation in addition to whole breast irradiation, especially as these patients receive chemotherapy and/or hormonal therapy. Many clinicians justify RNI based on the natural history of breast cancer, and by extrapolation from the post-mastectomy setting. The MA.20 trial provides strong evidence that this subset of patients benefits from RNI.
- Perhaps somewhat surprisingly, not only did RNI lead to improved locoregional control, but also to improved distant metastases DFS.
This was over and above the benefit that patients had already derived from adjuvant chemotherapy and/or hormonal therapy.

- The absolute magnitude of the distant DFS benefit (4.3%) was larger than the absolute benefit in locoregional control (2.3%).
- The distant DFS benefit became apparent relatively early on, between 1-5 years after randomization.
- There was a decrease in metastases both as a first event, and subsequent to locoregional recurrence.
- Taken together, these observations support the hypothesis that in patients undergoing BCS with node positive disease, there may be residual regional nodal disease that has the potential to metastasize early, and which may not be adequately addressed by chemotherapy.

While this abstract reports an improvement in DFS, with additional follow-up it is likely that there will be a benefit in terms of OS.

This trial has implications for the post-mastectomy setting, and extrapolation suggests that patients with 1-3 + nodes should receive post-mastectomy RT, which is somewhat controversial.

There are several interesting questions that this trial does not completely answer:

- Is it necessary to radiate the IMNs? In this trial, all patients received radiation to the IMNs, so it is reasonable to assert that this is the new standard of care. Nevertheless, only 1 patient treated with WBI alone relapsed in the IMNs, a finding consistent with recurrence patterns found in other studies conducted in the modern era. IMN treatment may be associated with increased radiation dose to heart and lung, which may be clinically significant as documented in this study by increased pneumonitis risk. The question of IMN radiotherapy remains unanswered at this point, and is an issue that requires further directed study.

- Patients with 1-3 + nodes represent a heterogeneous group, with some patients having only microscopic disease in one node — should all of these women receive RNI? Recent data from the Z11 trial, in which patients did not receive RNI or completion axillary dissection after detection of 1-2 positive sentinel lymph nodes, suggests that in patients with low volume axillary disease, WBI alone may suffice. Further study is necessary to determine whether low risk 1-3 + node women will benefit from RNI.