The Role of Postmastectomy Radiation in the Treatment of Early Stage Breast Cancer: Back to the Future

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Oncologists once downplayed the adjuvant role of radiotherapy after mastectomy. A decade ago, lacking a survival benefit, studies demonstrating late fatal myocardial infarctions nearly put a stop to any referrals of postoperative high-risk women to radiation oncology. The potential survival benefits of adjuvant radiotherapy may be overshadowed by inadequate technique leading to late cardiac deaths. Is it possible to cover the chest wall, internal mammary lymph chain, supraclavicular, and, where indicated, the axillary nodes and keep the dose to the coronary arteries and the lung to well within tolerance? A modern five-field comprehensive technique can deliver less cardiac and lung irradiation than the standard three-field technique, i.e. supraclavicular field matched to broad tangential fields. Linear accelerators with 4 megavolt (MV) to 6 MV photons, a full spectrum (6 MV to 20 MV) of electron energies, and meticulous computerized treatment planning based on multiple computed tomography planes allow an experienced physics/dosimetry team to treat all target sites while wrapping the dose around critical normal tissues.

Whether to offer postmastectomy radiation to women with one to three positive nodes after adjuvant chemotherapy treatment has been the subject of intense discussion since the publication of two major randomized prospective trials. Although before these studies radiotherapy after mastectomy was an established treatment for women with four or more positive axillary nodes, existing data did not justify its use in patients with less extensive nodal involvement. Now, with results from these studies showing improved survival after radiotherapy in all node-positive premenopausal and perimenopausal women, with perhaps its greatest benefit in women with 1-3 positive nodes, practice patterns are again shifting toward strong consideration of treatment in women with less tumor nodal involvement.

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The Pendulum of Therapeutic Policies

Through the years, one of the most controversial areas in oncology has been the role of postmastectomy chest wall and nodal irradiation in breast cancer. The pendulum has swung one way, then the other, and back again within single institutions as well as in worldwide practice patterns. More than 10 years ago, radiotherapy (RT), if offered at all, was offered only to patients with medial quadrant/central tumors or with four or more positive axillary nodes (1). A decade ago, oncologists were downplaying the adjuvant role of RT after mastectomy: lacking a survival benefit, studies demonstrating late fatal myocardial infarctions nearly put a stop to any referrals of postoperative high-risk women to radiation oncology. Now, as a result of two major randomized prospective clinical trials (2,3), practice patterns have once again shifted dramatically, and RT is now commonly recommended for node-positive women with 1-3 metastatic nodes, as well as other high-risk groups.

Initial trials of postmastectomy RT in the era of inadequate systemic therapy demonstrated improvements in local-regional control but showed little or no impact on survival. This is not surprising; without treatment of the blood, the presence or absence of hematogenous micrometastatic disease determines survival (4). Most of these early studies were also flawed by poor patient selection, such as inclusion of node-negative patients, poor radiation technique, and inadequate statistical power to detect small but significant differences in survival (5).

The first indications that modern megavoltage RT could improve survival came from the Stockholm and Oslo trials (6). Despite the absence of chemotherapy and less than comprehensive coverage in the Oslo trial, a combined study of 1185 patients, a significant improvement in overall and metastasis-free survival rates was noted in node-positive patients. Renewed interest in postoperative RT was spurred by the results of two prospective randomized trials published in 1997 of comprehensive adjuvant chest wall and nodal post-mastectomy RT in high-risk premenopausal women who also received cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy. In a study by the Danish Breast Cancer Group, 1708 premenopausal women demonstrated a 10-year disease-free survival of 48% in the irradiated group vs 34% in the control group as well as a 9% improvement in overall survival in the irradiated group (2). A trial by the British Columbia Cancer Agency reported similar results in 318 premenopausal women treated by mastectomy and CMF chemotherapy (3). These studies, along with positive findings in a subsequent Danish trial of postmenopausal women (7), have pushed the practice pattern pendulum back towards offering RT to node-positive women along with chemotherapy and/or tamoxifen.

Perhaps the most surprising finding of the Danish and British Columbia trials was the distinct survival benefit in women with 1-3 positive nodes. A potential survival benefit in women with four or more metastatic nodes was anticipated. Since these women have rates of isolated local-regional recurrence (LRR) without RT ranging from 18% to 36% (5,8,9), lowering the LRR rates to 5% to 10% with comprehensive RT could logically be expected to have a potential impact upon survival. However, women with 1-3 positive nodes have LRR rates ranging from only 5% to 20% without RT (5,8,9). Why would adjuvant RT affect survival in this group of patients with a lower risk of residual subclinical disease after mastectomy and chemotherapy?

The Biologic Basis for a Survival Benefit

With effective systemic therapy, reliable control of local-regional disease becomes of paramount importance, but the influence of chemohormonal therapy on local-regional control is modest and insufficient (8). Theoretically, after a mastectomy, there may be a subset of node-positive women who have hematogenous micrometastatic disease only, and these patients benefit from chemotherapy without RT. Another subset of patients not requiring RT is patients with residual postmastectomy local-regional disease sterilized by systemic therapy. The most important group of patients who can benefit from RT are those with no remaining hematogenous micrometastatic cells after systemic therapy but with local-regional persistence due to tumor burden or viable chemo-resistant breast cancer cells remaining in the mastectomy scar, chest wall, or regional lymphatics. In this group, optimal local-regional control can make the difference between treatment failure and cure. In patients with residual uncontrolled hematogenous disease, adjuvant RT can have a palliative benefit by preventing the disastrous sequelae of uncontrolled local-regional disease in the face of distant metastases (10).

In order to explain the recent data demonstrating a survival benefit to optimal local-regional control, we must assume that the hypotheses presented by both Halsted and Fisher (11) were correct about some aspects of breast cancer biology and incorrect about others. Fisher was right about the importance of hematogenous micrometastases and Halsted about uncontrolled local-regional growth of tumor subsequently spreading to distant sites.

Optimal local-regional control cannot influence survival rates unless hematogenous micrometastatic disease is eradicated. It is likely that chemotherapy eradicates blood-borne disease more reliably and consistently in patients with 1-3 positive nodes because of reduced tumor burden and fewer chemoresistant cells. For the same reasons, this may also apply to the effect of RT in the 1-3 positive node group, allowing more reliable and consistent control of local-regional disease compared with patients with four or more involved nodes.

The Importance of Technique and Technology

The survival benefits of adjuvant RT may be overshadowed by inadequate technique leading to late cardiac deaths. Therefore, *how* the RT is delivered can affect outcomes, in terms of both cure rates and toxicity.

Potential sites of residual subclinical local-regional disease after mastectomy and systemic therapy are the chest wall/mastectomy scar, the axilla, internal mammary nodes, and infra/supraclavicular nodes. If a cure is to be achieved, hematogenous micrometastases must be eradicated and all sites containing persistent carcinoma must be sterilized. In some patients, all these sites may harbor residual malignant cells. In others, one or two sites may be involved. Based upon patterns of recurrence, the chest wall/mastectomy scar has the greatest likelihood of containing residual disease. Although

the axilla is probably the next most likely to harbor residual disease, surgical dissection is adequate therapy for this site based upon the very low recurrence rates occurring without RT after a dissection of levels I and II. The internal mammary nodes are next in probability of involvement. Surgical dissection of the internal mammary nodes in patients with proven involvement of the axilla demonstrates that 20% to 50% of these women will have subclinical metastases to these nodes (4). Because the internal mammary nodes are not customarily treated surgically, irradiation for cure is required if they are involved and chemotherapy is incapable of sterilizing them. The risk of infra/supraclavicular involvement in patients with 1-3 positive axillary nodes is probably in the 5% range (11).

In the Danish, British Columbia, and Stockholm trials, node-positive women were treated with comprehensive chest wall and nodal RT. For example, patients did not receive tangential fields alone or three-fields without internal mammary coverage. Since these studies show a significant survival benefit, comprehensive treatment of patients with positive nodes is indicated until future studies define which, if any, subgroups require less or no therapy. While the role of RT to specific nodal sites cannot be fully determined from the data, it is clear that missing a site harboring malignant cells after surgical and systemic therapy is likely to result in relapse.

Is it possible to cover the chest wall, internal mammary lymph chain, supraclavicular, and, where indicated, axillary nodes with comprehensive RT while restricting the doses to the coronary arteries and the lung to well within tolerance? A modern five-field comprehensive technique (4,12,13) can deliver less cardiac and lung irradiation than the standard three-field technique, i.e. supraclavicular field matched to usual vs. broad tangential fields. Linear accelerators with 4-6 megavolt (MV) photons, a full spectrum (6-20 MV) of electron energies, and meticulous computerized treatment planning based upon multiple computerized tomography (CT) planes allow an experienced physics/dosimetry team to treat all sites while wrapping the dose around critical normal tissues. Three-dimensional conformal radiation therapy with dose-volume histogram target evaluation and critical organ dose delivery represents another technological step forward.

In the next decade, modern CT-planned megavoltage RT must be capable of optimizing comprehensive chest wall and nodal RT while minimizing the dose to the heart and coronary arteries. With improved chemohormonal therapy for breast cancer, local-regional control becomes even more important and may make the difference for individual patients. In order to eradicate subclinical disease safely in the chest wall and nodal sites, attention to the technical details of RT, especially in left breast cancers, is essential for success (see Figure 1).

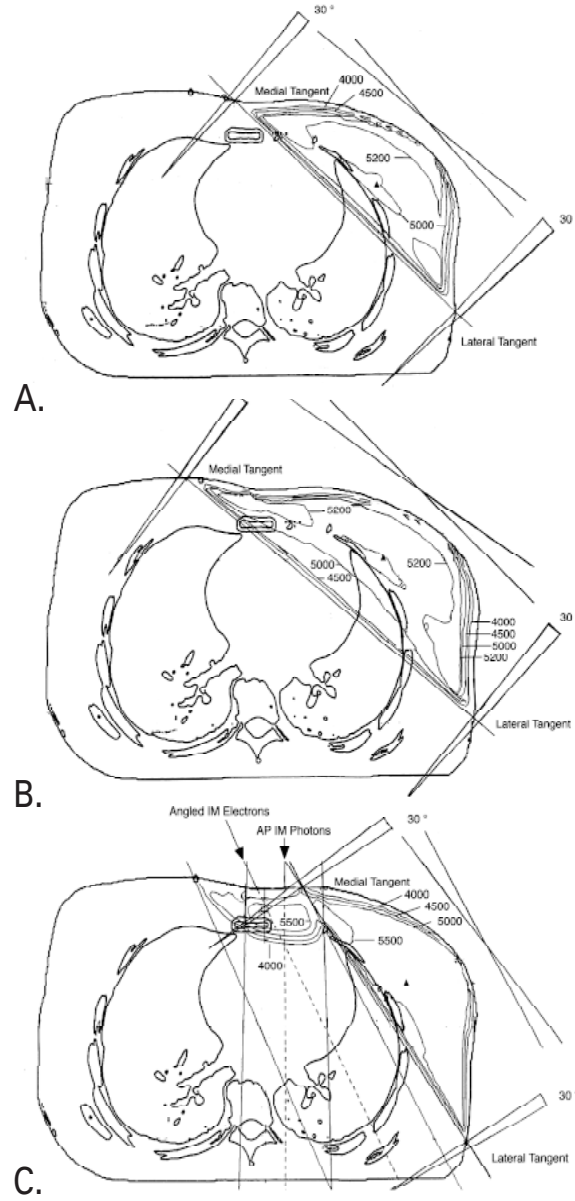

Figure 1. Actual computer-generated dosimetry from CT of a 38-year-old woman with $T_1N_1M_0$ subareolar breast cancer and 10 positive axillary nodes. **A.** Standard left-breast tangential RT fields include a portion of the anterior wall of the left ventricle and fail to encompass the IM lymphatics. **B.** Broad tangential fields encompass IM lymphatics but also include a substantial portion of the left ventricle and 3.5 cm of the lung. **C.** The 5-field technique covers the IM lymphatics with minimal dosage to a very small volume of the heart and lung. The separate IM fields mix 5 anterior 6 MV photon with 23 oblique electron beam fractions of 180 cGy. The usual cold triangle beneath the IM/tangent junction is eliminated by overlapping the antero-posterior IM photons into the medial tangent field by 1 cm, and angling the IM electrons 5° less than the tangents. By choosing an electron energy (here 12 MV) that places the 80% isodose at the pleural surface, the IM nodes are typically at the prescription isodose (90%), and the dose falls off rapidly as it reaches the lung and heart. Multiplane CT planning is a necessity.
CT=computerized tomography, RT= radiotherapy, IM=internal mammary
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Table 1. Indications for Postmastectomy Adjuvant Radiotherapy

1) Must treat:

Primary tumor indicators of high risk;

- Tumors >5 cm, node (+)
- Any tumors involving skin or chest wall
- Deep margins (+)

Nodal indicators of high risk;

- 4 or more (+) nodes
- 1-3 (+) axillary nodes with ECE
- An inadequate axillary dissection
  - <6 nodes sampled (Exception: Sentinel node mapping with the node(s) negative)
  - "I left something behind in the high axilla"
- Fixed or matted axillary node(s) or internal mammary node (+)

2) Might treat:

Primary tumor indicators of moderate risk

- Tumor >5 cm, node (-)
- Larger (>2.5 cm?) tumors with 1-3 (+) nodes
- Inner quadrant/central tumors and (-) nodes
- Close deep margin (< 5mm)

Nodal indicators of moderate risk

- 1-3 (+) axillary nodes without ECE
- Outside case referrals where there is doubt (surgical or pathological)

3) Do not treat:

- **Outer quadrant tumors ≤ 2 cm or > 2 cm but < 5 cm with (-) nodes**
- **Small (<2.5cm) inner quadrant or central tumors with (-) nodes**
- **Any patient on NSABP Protocol**

(+) = positive; (-) = negative; ECE = extracapsular axillary nodal extension; NSABP = National Surgical Adjuvant Breast Program

Current Treatment Policies: The Moving Pendulum at One Point in Time

For many medical centers, the only change in treatment policies after publication of the Danish (2) and British Columbia (3) postmastectomy post-systemic therapy trial results was in the treatment of women with 1-3 positive nodes. Most centers were irradiating patients with ≥4 positive nodes, or with tumors >5 cm or involving the deep margin. However, these data compelled radiation oncologists to consider adjuvant RT for women with less extensive nodal involvement, since they suggest that, for a particular patient, it might make the difference between failure and cure. The indications for postmastectomy adjuvant RT are shown in Table 1.

The goal of therapy before the publication of the Danish and British Columbia studies was prevention of local regional recurrence, with treatment given only to higher-risk patients. At that time decisions were easier to make. Now, oncologists cannot discount the Danish finding that women with 1-3 positive nodes had a greater percentage decrease in failure and concomitant increase in survival rates with adjuvant RT than women with more extensive axillary involvement. If the oncology team concludes that women with 1-3 positive nodes require RT based upon the recent data, then the radiation oncologist should comprehensively cover the chest wall and nodal regions, because this technique has produced these favorable outcomes.

Since adjuvant RT after mastectomy was given in the past, stopped, and now is recommended once again, radiation oncology is truly "back to the future," but with deeper purpose and hope for benefitting the lives of our patients.

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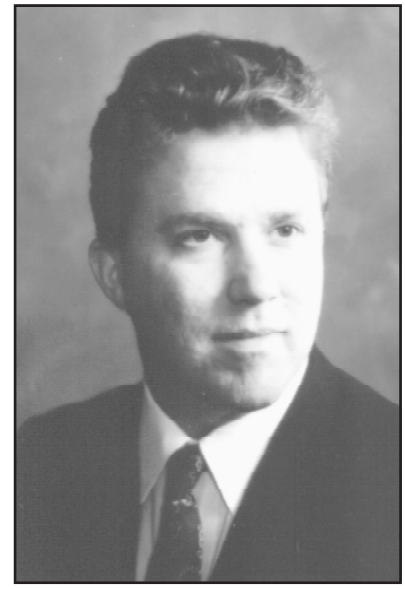

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