Postmastectomy Radiation Therapy

73

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Key Concepts

- Postmastectomy radiation therapy (PMRT) contributes to both locoregional control and overall survival in appropriately selected cases
- Current indications:
  - Node-positive patients
  - T3N0 disease
  - Patients with T2 disease with high-risk features (lymphovascular invasion, premenopausal status or young age, close margins, high tumor grade)
- Complications:
  - Acute toxicities include generalized fatigue and skin reaction
  - Late cosmetic changes including fibrosis may develop
  - Appropriate sequencing and reconstructive options not yet established
  - Radiation pneumonitis
  - Cardiac toxicity
  - Lymphedema
  - Costochondritis or rib fracture
  - Radiation-induced malignancies

Background

Postmastectomy radiation therapy (PMRT) is an integral component of the curative treatment of breast cancer that contributes to both improved locoregional control and overall survival in appropriately selected cases. Occult disease remaining in the chest wall and/or regional lymph nodes after mastectomy may serve not only as a source of potentially

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morbid locoregional recurrence, but also as an important reservoir from which distant metastases may be seeded or reseeded after the initial elimination of distant disease by sophisticated modern systemic therapies. Therefore, radiation therapy is essential for patients with sufficient risk of harboring an isolated reservoir of residual locoregional disease after mastectomy and systemic therapy.

Brief History, Background, and Indications for Treatment

PMRT has been a subject of considerable controversy over the past several decades. Multiple randomized studies have consistently revealed a substantial reduction in the risk of locoregional recurrence of breast cancer by the use of PMRT. However, in older studies, the benefits of treatment were offset by treatment-related toxicity – especially cardiotoxicity (1). Outdated radiation techniques such as anterior "hockey stick" photon fields led large volumes of the heart to receive high doses of radiation in these older studies. Therefore, the salutary effect of PMRT upon overall survival was not convincingly established until large studies utilizing modern techniques of radiotherapy matured.

The large randomized trials of PMRT from Denmark and British Columbia that were originally published in 1997 have been extremely influential in this regard. The British Columbia trial randomized 318 premenopausal patients with pathologically positive lymph nodes, status post modified radical mastectomy with axillary lymph node dissection, to CMF chemotherapy alone or chemotherapy and PMRT (2). In this study, PMRT both reduced locoregional failure (from 28 to 10%) and improved overall survival (20-year OS improved from 37 to 47%, $p = 0.03$). The Danish 82b trial randomized 1708 premenopausal women with high-risk breast cancer (defined as involvement of the axillary nodes, tumor size >5 cm, or invasion of the skin or pectoral fascia), status post total mastectomy and axillary dissection, to CMF chemotherapy and radiation vs. CMF chemotherapy alone (3). In this study, PMRT also led to both a reduction in locoregional failure (from 32 to 9%) and an improvement in overall survival (10-year OS improved from 45 to 54%, $p < 0.001$). The Danish 82c trial randomized 1375 postmenopausal high-risk breast cancer patients younger than 70 years of age, status post total mastectomy and axillary dissection, to radiation therapy plus tamoxifen vs. tamoxifen alone (4). Again, PMRT reduced locoregional recurrence (from 35 to 8%) and improved overall survival (10-year OS improved from 36 to 45%, $p = 0.03$). Of note, in each of these three trials, PMRT benefited not only patients with four or more axillary nodes involved, but also those with 1–3 nodes positive. Thus, together, these studies provide compelling evidence regarding the impact of PMRT in patients with node-positive disease.

These studies, however, met with certain criticisms. These included concerns about the adequacy of the surgery performed. The median number of lymph nodes removed in the Danish study was only seven, lower than that expected from a standard level I/II axillary dissection, prompting the concern that inadequate regional surgery may have led to the underestimation of the true extent of axillary disease in these patients and possibly also contributed to an increased incidence of locoregional failures. Because locoregional recurrence rates after mastectomy (and without PMRT) in retrospective American series of patients with 1–3 positive lymph nodes have been lower (13% in large series from ECOG

(5) and the NSABP (6)) than those observed in the Danish and British Columbia studies, some have questioned the role of PMRT for American patients with only 1–3 lymph nodes involved. Indeed, consensus panels convened in this country around the turn of the millennium concluded that the evidence to support PMRT was only strong enough to sustain a recommendation for patients with four or more lymph nodes involved. (7) For patients with 1–3 lymph nodes involved, these panels concluded there was insufficient evidence to make suggestions or recommendations for the routine use of PMRT, and practice in the United States became divided between radiation oncologists who routinely treat and those who routinely observe this subgroup of patients (8). Unfortunately, the Intergroup's randomized study designed to assess role of PMRT in U.S. patients with 1–3 positive lymph nodes failed to accrue and closed in 2003.

More recently, however, increasing evidence has accumulated in support of a role for PMRT in patients with 1–3 lymph nodes involved. The Danish studies were pooled and reanalyzed in order to include only the 1,152 node-positive patients with eight or more lymph nodes removed. A survival benefit of the same absolute magnitude (9%) was observed in patients with 1–3 lymph nodes involved as among patients with four or more lymph nodes involved, even though the locoregional recurrence rates were lower among the former group (9). This led the authors to note that the survival benefit of PMRT is likely related to the ability of systemic therapy to eliminate any existing metastatic deposits at the time of diagnosis; therefore, PMRT may be particularly important in the subgroup of patients with less extensive nodal involvement, in whom the burden of distant disease at diagnosis is likely to be less substantial (and potentially more amenable to elimination by systemic therapies) or absent. Further compelling findings have emerged from the Oxford Early Breast Cancer Trialists' Collaborative Group's (EBCTCG) meta-analysis of data from 8,340 node-positive women treated with mastectomy and axillary clearance and enrolled on randomized trials of PMRT. In the most recent update of the Oxford meta-analysis, which included patients enrolled on trials initiated through 1995, the 5-year local recurrence risk was reduced from 22.8 to 5.8%, with 15-year breast cancer mortality risks of 54.7 vs. 60.1% (reduction 5.4%, $2p = 0.0002$) and an overall mortality reduction of 4.4% (64.2 vs. 59.8%, $2p = 0.0009$) (10). Thus, there has now been documented a clear overall survival advantage due to the use of PMRT in node-positive patients, and all node-positive patients should be referred to a radiation oncologist for discussion of the role of PMRT in their management.

In addition, referral to radiation oncology is appropriate for certain high-risk node-negative patients who may also benefit from PMRT. This includes patients with T3N0 disease, patients with involvement of the skin or pectoral fascia, positive margins, and possibly even patients with T2 tumors with multiple adverse features (such as lymphovascular invasion, premenopausal status or young age, close margins, and high tumor grade). While much of the evidence relating to these patient subgroups is drawn from retrospective studies, the consulting radiation oncologist should be able to quantify for the patient the expected risks of locoregional recurrence in the absence of radiation therapy, as well as the reduction in that risk expected from radiation treatment. The radiation oncologist may then extrapolate regarding the potential for effects upon survival based upon models such as that proposed by the EBCTCG, in which a 20% absolute reduction in 5-year local recurrence risk leads to about a 5% absolute reduction in 15-year breast cancer mortality,

or a 4:1 ratio of absolute effects. In this way, radiation oncology consultation can play an essential role in assisting patients facing the complex decision of whether to pursue PMRT.

Techniques

In the large Danish and Canadian trials that revealed the survival benefit of PMRT, the targets of radiation therapy included the chest wall and regional nodal areas, including the supraclavicular, axillary, and internal mammary regions. In the United States, given the more extensive axillary dissections performed in this country and the rarity of axillary recurrences observed, the axilla is generally not included as a target, except in cases with certain high-risk features (such as gross extranodal extension, inadequate nodal dissection, or a particularly high number of lymph nodes involved with tumor). Practice regarding treatment of the internal mammary lymph nodes is divided, largely due to the technical challenges of treating this region while excluding most of the heart from the radiation field, as well as the fact that clinically evident internal mammary recurrences are rare. Nevertheless, given the abilities to minimize dose to the heart using modern treatment techniques, the fact that most internal mammary recurrences are likely to be subclinical (insofar as this is an area that is infrequently assessed with directed imaging and difficult to monitor on physical examination, unlike the axilla), and the fact that extended radical mastectomy specimens have revealed relatively high rates of internal mammary involvement in patients with positive axillary nodes (22% among patients with positive axillae and lateral tumors, and 37% among patients with positive axillae and medial tumors in one large study conducted in the premammography era (11)), we feel that the internal mammary region was a potentially critical target in the Danish and Canadian studies and an important target for coverage in all node-positive patients, and particularly those with medially located tumors.

The chest wall is typically treated with tangent beams of photons generated by a megavoltage linear accelerator. The supraclavicular and infraclavicular regions may be treated with an anterior photon field (usually obliqued slightly medially to avoid the spinal cord), and a monoisocentric approach may be employed to ensure a perfect match between the supraclavicular and tangent fields, or a slight couch angle may be employed to eliminate the cranial divergence of the tangent fields into the supraclavicular field. If the axilla requires treatment, a posterior axillary boost field may be necessary to ensure adequate coverage of these nodes, which lie deeper than the supraclavicular and infraclavicular nodes. Finally, the internal mammary region may be encompassed with a "wide" or "deep" tangent technique, in which the medial border of the tangent field is placed beyond the midline to allow the parasternal region at the levels of the first three intercostal spaces to be included within the tangential fields, with blocking inferiorly to exclude the heart and lung. If this technique does not allow for sufficient blocking of normal structures, as determined by analysis of a dose-volume histogram or normal tissue complication probability model, a separate electron (or mixed photon/electron) beam may be employed to treat the internal mammary region, angled slightly away from the medial border of the tangent field, to which it is matched on the skin, several centimeters away from the midline on the ipsilateral

side of the chest wall. Finally, the mastectomy scar is typically treated with en face electrons for an additional boost dose, as this is the region at greatest risk for recurrence.

Three-dimensional planning techniques are growing in popularity because they allow for the individualization of treatment plans and detailed assessment of the coverage of important targets as well as requisite shielding of critical normal tissues. Even more sophisticated treatment approaches such as intensity modulated radiation therapy are currently under investigation to determine whether an even more conformal, homogeneous dose distribution may be achieved and may yield clinical benefit.

A common dose and fractionation schedule employed in the United States involves 50 Gy to the chest wall and regional nodal areas followed by a 10-Gy boost to the scar, bringing the total dose to the boosted volume to 60 Gy.

Complications

Normal tissues in the radiation field may develop both acute and late toxicities related to their irradiation. The most common acute toxicities of PMRT include generalized fatigue and skin reaction (which can range from erythema to moist desquamation, depending upon individual patient factors and treatment techniques). Late cosmetic changes, including telangiectasias and scar fibrosis, may ultimately develop. PMRT may also impact upon the cosmetic outcomes of breast reconstruction, and further research is necessary to define better optimal sequencing and reconstructive approaches, particularly in light of the fact that PMRT is now established as a standard and necessary part of the treatment for many patients undergoing mastectomy.

Radiation pneumonitis may develop in patients treated for breast cancer, typically several weeks after the completion of radiation therapy. The volume of lung irradiated is an important predictor of the development of pneumonitis, and three-dimensional planning with careful analysis of dose-volume histograms is important to ensure that rates of pneumonitis remain low, as they should be in this population. Radiation pneumonitis is typically responsive to steroid therapy and rarely results in lasting, clinically significant pulmonary damage.

A number of studies have sought to assess the potential cardiotoxic effects of radiation therapy. As discussed above, older techniques of radiation delivery resulted in very large doses of radiation to the heart, and an increased risk of cardiovascular events in these cases has clearly been established. Population-based studies have suggested that the magnitude of increased cardiac risk related to radiation therapy has decreased in more recent years (12). Still, even when delivered with modern techniques, radiation has been shown to lead to perfusion defects (for which the clinical consequences have yet to be defined) (13). Furthermore, single-institution studies have suggested that there may be an increase in the relative risk of ischemic cardiac events following radiation therapy for left-sided breast cancer, although the absolute magnitude of this increased risk appears to be low (14). Recent studies have also suggested that radiation and other cardiac risk factors, such as hypertension or smoking, may be synergistic in their effects (15, 16).

Lymphedema may occur after axillary dissection alone, and the risk is increased by the addition of radiation therapy to the regional nodes. Brachial plexopathy has been reported,

although it is exceedingly uncommon at the doses and standard fractions commonly used to treat breast cancer in the United States. Costochondritis may occur in some patients following the completion of radiation therapy, and rib fractures occur in approximately 1%.

Finally, radiation-induced secondary malignancies have been reported after treatment of breast cancer. The EBCTCG has reported an excess cancer incidence that mainly involved contralateral breast cancer and lung cancer among patients receiving radiation therapy for breast cancer. Radiation-induced sarcomas have been described, although they are extremely uncommon, with a cumulative incidence of two to three cases per thousand at 10 years (17).

New Developments/Clinical Trials on the Horizon

Several ongoing and recently completed studies seek to clarify further the appropriate patient selection and treatment volumes for PMRT. In the United Kingdom, the SUPREMO study is currently enrolling patients with T1-2N1 or high-risk T2N0 disease in a randomized trial of PMRT to the chest wall alone. In Canada, the MA-20 trial, which completed accrual in early 2007, randomized patients to receive therapy to the breast or chest wall alone vs. more comprehensive treatment fields including the supraclavicular and internal mammary nodal regions. A separate EORTC 22922/10925 study exploring the role of supraclavicular and internal mammary irradiation completed accrual in 2004. Together, these studies will help to inform the selection of appropriate treatment volumes for PMRT.

In addition, studies are ongoing to determine the relative value of recent technical advances in radiation treatment planning. Other areas of active research include the optimal integration of PMRT and breast reconstruction, as well as the proper selection of patients for PMRT after neoadjuvant chemotherapy has been utilized.

It is important to note in conclusion that while important issues will be clarified by ongoing studies, there is already substantial evidence from randomized trials to support the role of PMRT in patients with node-positive disease and suggestive evidence from retrospective analyses that PMRT may also be of value in some patients with high-risk node-negative disease. It has, at long last, been firmly established that local control is integral to the overall outcome of patients with breast cancer, and therefore, the appropriate referral of patients for PMRT is an essential part of the management of this disease.

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