Mounting Evidence for Postmastectomy Locoregional Radiation Therapy

August 01, 1999

By Daniel F. Hayes, MD, Matthew J. Ellis, MD, PhD, FRCP, and Claudine Isaacs, MD

Although a substantial number of women will suffer and die from breast cancer during the upcoming years, we clearly have made stepwise progress in treating patients with this cancer over the last 3 decades. Each of these steps of progress has led to

Déjà vu All Over Again?
Although a substantial number of women will suffer and die from breast cancer during the upcoming years, we clearly have made stepwise progress in treating patients with this cancer over the last 3 decades. Each of these steps of progress has led to what are glibly designated “paradigm shifts.” Perhaps the most hotly debated of these paradigms is the local vs systemic nature of early-stage disease.[1] The theory that breast cancer progressed logically from breast to surrounding lymph nodes to distant organs, championed by Halsted during the turn of the last century, dominated both thought and therapy for the next 50 to 75 years.[2]

First Two Paradigm Shifts
The first paradigm shift began in the late 1940s through the early ’80s. During that period, a series of prospective, randomized trials demonstrated that “aggressive” local therapy did not result in superior overall survival when compared to what appeared to be “less aggressive” approaches. These studies compared chest wall radiotherapy after mastectomy to mastectomy alone, radical mastectomy to modified radical mastectomy, and breast-conserving therapy to breast removal. Studies addressing the latter issue included conservative surgery with breast radiation vs mastectomy, and conservative surgery with breast radiation vs conservative surgery alone.[3] Overall survival notwithstanding, a fundamental concept that was established by these trials was that less comprehensive local therapy consistently resulted in higher rates of locoregional recurrence. However, until recently, it was exceedingly difficult to detect survival differences between women who received chest wall radiotherapy and those who did not.

The lack of survival benefit from more aggressive local therapy, coupled with the observed survival benefits conferred by adjuvant systemic therapy, led to the so-called systemic paradigm of breast cancer, supplanting the theory of Halsted and his successors.[1,2] By the late 1980s, standard dogma excluded “adjuvant” locoregional radiotherapy after mastectomy for stage I and II patients. Rather, chest wall radiotherapy was felt to provide only “upfront palliation,” which, in the absence of a survival benefit, was considered to be more efficiently provided to patients if and when they subsequently suffered a relapse.

The ‘Two Wave’ Paradigm
In the late 1970s and early ’80s, several groups of investigators reasoned that reality might fall somewhere between the two paradigms.[4] Stated concisely, they speculated that perhaps breast cancer metastases occur in two “waves”: one prior to detection, stemming from the original primary, and a second arising sometime later from a reservoir of inadequately sterilized locoregional disease. In this case, adjuvant systemic therapy might eradicate the first wave of micrometastases, while locoregional radiotherapy would prevent the second.

To test this hypothesis, a series of prospective, randomized trials was begun in the early to mid 1980s in which all patients were given adjuvant systemic therapy and were randomly assigned to receive or not to receive chest wall radiotherapy after mastectomy. The mature results of at least three of these studies have suggested that this “intermediate” paradigm may be more reflective of breast cancer biology than either extreme.[5-7] Indeed, the proportional reductions in subsequent distant recurrence and death among patients who received chest wall radiation therapy in these studies are similar to those ascribed to adjuvant systemic therapy by earlier prospective, randomized trials. As reviewed by Marks et al, the results of the chest wall radiotherapy studies have resurrected a concept that most clinicians felt was resolved, ie, that more aggressive local therapy
results in improved distant failure and overall survival rates. The consistently observed survival benefits in the recently reported studies, which appear to be similar to those of adjuvant systemic therapy, have led to recommendations, as made by Marks et al, that “all patients with axillary node-positive breast cancer should be considered for postmastectomy locoregional radiation therapy.” Most clinicians agree that the benefits of adjuvant chest wall radiotherapy in patients at exceedingly high risk for locoregional recurrence are sufficient to justify its use in that setting (Figure 1; panel A). However, there is considerable concern over the high risk-benefit ratio for treating patients with better prognoses, such as those with one to three positive, or even negative, nodes.

**Proportional vs Absolute Benefits of Radiation Therapy**

To address this issue, we must consider the difference between the proportional and absolute benefits of the therapy. In general, the proportional reduction in odds of recurrence for all patients due to adjuvant systemic therapy appears to be about 30% over a 10-year period.[8,9] If this proportional reduction is independent of prognosis for stage I-III patients, the absolute benefit of adjuvant systemic therapy for a group of patients depends on the absolute risk of recurrence in the absence of therapy. In other words, the greater a patient’s chance of systemic recurrence, the more likely she could be one of the patients who will benefit from treatment.

In this regard, prognostic factors that determine the risks of relapse and mortality independent of therapy, and predictive factors that “predict” the likelihood of sensitivity and resistance to a specific therapy, can be used to roughly calculate the overall absolute odds of a patient’s benefiting from adjuvant systemic therapy. The decision of whether or not to treat then depends on the risks of therapy.

Perhaps as importantly, the physician must take into account individual patient choice and value systems.[10] For example, there are some patients whose fear of breast cancer is so great that they would accept the toxicities of treatment for as little as a 1% potential benefit, whereas others fear the treatment to such an extent that they require a much larger possibility of benefit to choose therapy.[11] Many clinicians have suggested that the toxicities of chemotherapy are such that at least 3% to 5% or more of treated patients should benefit (remain alive and disease free) to justify its use.[12]

Can we similarly calculate the odds of benefit from adjuvant chest wall radiotherapy for individual patients? As with adjuvant systemic therapy, this question begs an analysis of risks, both short- and long-term, associated with chest wall radiotherapy. As detailed by Marks et al, the short-term toxicities of modern chest wall radiotherapy are generally acceptable, and the long-term risks appear to be very rare, although occasionally devastating. Therefore, arguably, the major drawbacks to widespread radiation, at least over the short term, are inconvenience and cost.

**Is There a Prognostic Cut-Off for the Risks vs Benefits of Therapy?**

Given these considerations, is there a “prognostic cut-off” below which the risks of treatment-related mortality are likely to exceed the survival benefits? These considerations are diagrammed conceptually in Figure 1. Since so many patients with larger (> 5-cm) tumors and multiple (four or more) positive lymph nodes will suffer a locoregional recurrence, the palliative benefits alone justify the recommendation to treat these patients with radiation, regardless of the survival benefits (Figure 1; panel A).

With decreasing tumor size and/or fewer number of involved nodes, however, an individual’s risk of developing a locoregional relapse, and therefore her absolute chance of deriving a palliative benefit from radiation, become smaller (Figure 1; panel A). In such patients, it is harder to recommend routine treatment for this end point alone. In other words, as one moves to the left on the “prognosis axis” in Figure 1, one must justify treatment based on survival, not local palliation.

**Are Moderate-Risk Patients Most Likely to Benefit?**

The “two wave” paradigm, discussed above, predicts a nonlinear relationship between prognosis and proportional reduction from mortality due to adjuvant local regional radiation. The “two wave” model is therefore distinct from our understanding of the benefits for adjuvant systemic therapy, in which the proportional reductions in systemic recurrence and death appear to be similar for patients of all prognostic categories (stages I to III). If this were the case, the proportional benefits would be the same across prognostic subgroups, and the absolute benefits would decrease with better prognosis, as illustrated by the solid curves in panels B and C of Figure 1.

The “two wave hypothesis” predicts a somewhat unexpected benefit profile. For patients with a high tumor burden at diagnosis, the first wave of metastases is so substantial that locoregional therapy has little effect on mortality. For these women, the systemic theory of breast cancer predominates. On the other hand, for patients with a lower risk of systemic recurrence, the burden of the first wave
is smaller and patients are more likely to survive it. In this situation a second wave of metastatic cells from persistent local disease may contribute to overall mortality. The dashed curves in panels B and C of Figure 1 represent an increasing proportional benefit with better prognosis, and therefore an “optimal” absolute benefit for those patients with an intermediate prognosis. It is these intermediate-risk patients who may stand to derive the greatest survival benefit from locoregional radiotherapy, because the behavior of their disease reflects some elements of the Halsted model. Indeed, a preliminary, extensive subset analysis of the Danish premenopausal trial suggested that the proportional reductions in distant recurrence and death rates appear to be highest in patients with smaller tumors and fewer positive nodes.[M. Overgaard, MD, personal communication] Ironically, of course, this group of patients also includes those more likely to be cured by surgery alone. Therefore, the population as a whole is more likely to suffer any long-term consequences of radiotherapy simply because there are more individuals alive to experience them. At some point on the “prognosis axis,” the odds of a patient experiencing either a first or second “wave” of metastases are so low that these risks outweigh the potential benefits of any adjuvant therapy, local or systemic (Figure 1; panel C).

To make the decision of whether or not to use adjuvant radiation, it would also be helpful to have molecular markers of radiation sensitivity or resistance. To date, there is no satisfactory predictive factor for radiation therapy. Small pilot studies have pointed to certain molecular determinants, such as p53 abnormalities or expression of insulin-like growth factor I (IGFR-I).[13,14] However, withholding radiotherapy from patients whose tumors overexpress these molecular markers is premature and inappropriate.

Summary
In summary, we have reopened what was considered to be a closed issue, or, as Yogi Berra once said, “It’s déjà vu all over again.” As with adjuvant systemic therapy, the decision to recommend chest wall radiotherapy to patients with favorable prognoses is influenced strongly by personal perception of the balance between the inconvenience, costs, and small toxicities vs the patient’s fear of recurrent breast cancer and disease-related mortality. However, if one accepts the two wave paradigm of metastases, the patients most likely to benefit may be those with moderate risks.

Challenges for the Future
The challenge before us is to identify patients with low nodal positivity, or even with negative nodes, who have a sufficiently high risk of harboring a residual locoregional disease “reservoir” to justify postmastectomy radiotherapy. We also need to determine which molecular markers identify those who will not benefit, even if their risk of local relapse is sufficiently high. In addition, we must identify the optimal nodal areas to be irradiated. Furthermore, technologic advances in radiotherapy planning and delivery are required to lessen the long- and short-term toxicities and costs of the therapy. All of these could and should be the focus of prospective, randomized trials.

As a start, we strongly support the soon-to-be-opened US intergroup study that will begin to address at least the first two questions in patients with reasonably good prognoses. This study will enroll patients with one to three positive nodes, precisely the group of patients who may have the most to gain and the most to lose. Moreover, coupled with correlative science studies using specimens from participating patients, this trial will provide a rich source of data from which we should be able to decipher whether prognostic and predictive factors can be used to further refine which patients should be treated.

References:


Source URL:
http://www.physicianspractice.com/review-article/mounting-evidence-postmastectomy-locoregional-radiation-therapy-0

Links: