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EDITORIAL COMMENT

Radiation Therapy for Breast Cancer

Buyer Beware*

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> "*People can foresee the future only when it coincides with their own wishes, and the most grossly obvious facts can be ignored when they are unwelcome.*"
>
> —George Orwell, 1945 (1)

New medical therapies typically follow a common trajectory. They are originally tested in high-risk populations, in whom the potential benefits of the intervention are most clearly visible, and in whom the downside of side effects is relatively minimal compared with the upside of treating the disease. After a therapy has been approved, its use is expanded to ever-increasing populations, in whom the benefit is invariably smaller and the relevance of side effects is invariably larger.

There is likely no better example to illustrate this principle than with cancer therapies, often rich in both efficacy and in off-target side effects. Treatment with anthracyclines or trastuzumab is frequently an easy decision in patients with metastatic breast cancer; such patients will almost certainly die of their malignancy and the risk/benefit ratio often clearly favors treatment (2). This becomes a much more difficult question in the young patient with breast cancer with a favorable prognosis, in whom the absolute reduction in mortality is lower, and in whom the relevance of long-term cardiotoxicity is higher (3).

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The principle becomes further muddled when the intervention being considered is radiation therapy. The difficulty arises from the fact that the negative downstream consequences of radiation may not be apparent for decades. Hence, having a true idea of the risk/benefit ratio becomes exceedingly difficult, and by definition, clinicians and patients are committed to using data reflective of therapeutic practices decades out-of-date.

In this issue of the *Journal*, Bouillon et al. (4) present convincing evidence that radiation therapy for breast cancer can be associated with significant increases in long-term cardiovascular mortality. Their study represents an important addition to the literature, due to the long duration of follow-up and their focus on the contribution of radiation therapy to the internal mammary lymph nodes.

Left- versus right-sided breast cancer. One of the more compelling data points has been the difference in cardiovascular outcomes between women treated for left- versus right-sided disease. For obvious anatomical reasons, therapy for left-sided tumors results in a significantly higher radiation dose to the heart. In the current study, patients with left-sided breast cancer had significantly higher rates of cardiac complications, particularly after >10 years from the time of radiation therapy. Even more convincing was the fact that the components of "cardiovascular deaths," which are most plausibly influenced by radiation (heart failure, valvular disease, ischemic disease) were the most dramatically affected, whereas no such findings were seen in other cardiac diseases (e.g., hypertensive disease, "pulmonary heart diseases"), which are less plausibly affected by radiation. Several other studies of >10 to 15 years follow-up have found clear evidence of excess cardiovascular risk in patients treated for left-sided disease (5–7). Increased use of anthracyclines and anti-HER2 therapy over the last 10 to 20 years adds another wrinkle to the equation, as their use likely further increases the cardiac risk (8).

Radiation doses. Despite the fact that substantial improvements in radiation techniques have resulted in less radiation being delivered to the heart, doses remain substantial. Recent studies documented drops in mean dose to the heart from 13.3 to 2.3 Gy and in mean dose to the left anterior descending artery (LAD) from 31.8 to 7.6 Gy over the last 3 decades (9,10). Unfortunately, it is eminently biologically plausible that these current doses of radiation are high enough to have long-term consequences; similar or lower dose whole-heart irradiation from survivors of atomic bombings and from treatment of other malignancies has been linked with increased cardiovascular mortality (11,12). In addition, portions of the heart and LAD continue to receive large doses, with part of the heart receiving >20 Gy and part of the LAD receiving >30 Gy in many breast cancer patients (10).

Whether or not to irradiate the internal mammary chain (IMC) nodes has been a point of pre-existing controversy—and this study should give clinicians even greater pause. Although this nodal chain has a relatively high rate of pathologic involvement, it has been unclear that this involvement affects survival (13). Cardiac radiation exposure with IMC irradiation is substantial, even for right-sided nodes, and the evidence that such irradiation substantially increases cardiovascular events/mortality is convincing (14).

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In the present study, women who received left-sided IMC irradiation had a >2-fold increase in death from cardiovascular disease, and there was a strong trend for women who received right-sided IMC irradiation. Tremendous institutional variation currently exists in the frequency of IMC irradiation, with no clear standard-of-care. Results of 2 international trials intended to "definitively" address the role of IMC irradiation are pending, but even if favorable, will not reflect long-term cardiovascular risks.

Multiple strategies have been proposed that affect the radiation dose to the heart. One trend in Canada and the United Kingdom has been to deliver a lower total radiation dose to the breast over a shorter interval, but at higher doses during each session. Whereas breast cancer outcomes to date have been largely equivalent (15), it is far too early to determine if the long-term cardiac consequences will be less (because of the lower total dose) or more (because of the higher per-session dose). Intensity modulated radiation therapy focuses more of the peak radiation dose toward the intended field, but exposes a larger field to low-dose radiation. Prone positioning can decrease the cardiac radiation dose in some patients, but can increase it in others—as the result is entirely dependent on each patient's individual anatomy.

Current status. So where do we stand in 2010? Radiation therapy has significantly improved outcomes for breast cancer, both in conjunction with breast-conserving therapy and with post-mastectomy chest wall irradiation (5,16). Furthermore, it is impossible to believe that the real advances in radiation techniques over the last 3 decades have not made a difference in acquired cardiac morbidity/mortality. However, the extent of the impact is unknown—and impossible to know—at this point. Disturbingly, to the extent that we have evidence, it points to duration of patient follow-up having a larger effect than the era when the trials were conducted (17). As the 2 are inextricably linked (it is impossible to have a long duration of follow-up in a very recent trial), physicians are left in the unenviable position of making crucial clinical decisions with an incomplete data set.

There are already changes that could be implemented today. A young woman with early-stage breast cancer who has initially opted for breast-conserving therapy and radiation might instead opt for mastectomy if she knew that her anatomy was such that her heart/LAD was likely to receive a substantial radiation dose. Radiation therapy clearly should not be thrown out with the proverbial bathwater—but considering the data, we must approach the issue with eyes wide open. Buyer beware.

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