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COMMENTARY

Defining Target Volumes in Breast Cancer Radiation Therapy for the Future: Back to Basics

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There is considerable evidence that for many node-positive breast cancer patients, local regional radiation therapy after mastectomy, or regional radiation therapy in addition to breast treatment after lumpectomy, results in improved local control, a more modest but consistent reduction in distant metastases, and absolute improvement in breast cancer survival (1, 2). On the other hand, there is similar substantial evidence that the use of local regional radiation therapy can come with the price of permanent toxicity such as lymphedema (2), and even more serious consequences like cardiac-related mortality (3). It would seem then that this critical balance of potential survival benefit and toxicity risk would be an ideal setting for using advanced radiation treatment planning to conform dose to targets and avoid normal tissues, thereby maximizing the therapeutic ratio. It was with this in mind that members of the Breast Cancer Committee within the Radiation Therapy Oncology Group (RTOG) sought to systematically evaluate advanced treatment planning for breast cancer by integrating questions about its feasibility and effect on outcomes into the radiation therapy treatment arms of clinical trials asking breast cancer questions. However, to transition from planning breast cancer radiation therapy based on a standardized field arrangement to a patient-specific, CT-based, 3-dimensional conformal radiation therapy (3D-CRT) planning, some idea of the anatomic boundaries of the regions of interest were necessary so that targets could be generated and dose–volume analysis (DVA) could be done. In particular, use of DVA was keenly anticipated as an important quality control and analysis tool in breast cancer clinical trials by providing a means to quantify adherence to treatment arms, permit secondary comparisons between radiation therapy methods (3D-CRT, intensity modulated radiation therapy [IMRT], brachytherapy, etc), and allow subsequent exploration to find correlation with cancer control and toxicity outcomes. As had been seen by others (4), significant anatomic heterogeneity was found when 10 radiation oncologists with breast cancer and clinical trial expertise delineated clinical targets for elective radiation therapy to the breast and/or chest wall, and regional nodes on 3 specific cases (5). It was estimated by DVA that this extent of heterogeneity in contoured targets would result in large variations in dose to normal tissue (5). After significant discussion, it was concluded that it was not possible to dictate the precise anatomic border of a clinical target volume (CTV) applicable to every breast cancer patient because this would be expected to vary according to the presence of any gross disease (gross tumor volume or GTV) and by the individual biological risk of the breast cancer in the absence of a GTV. As a result, the RTOG Breast Cancer Atlas emerged in 2009 as consensus definitions for anatomic reference in the regions of interest to reduce interoperator heterogeneity on the same case and was not intended as a "cookie cutter" for CTV in every case. A second run on the same 3 cases was performed by 9 of the original radiation oncologists after the consensus anatomic definitions were developed, and the target volumes delineated had significantly more overlap and less anatomic heterogeneity, supporting the usefulness of the atlas.

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It has been several years since the RTOG Breast Cancer Atlas was posted, and although other disease sites in oncology have fully studied and assimilated advanced treatment planning as a means for delivering conformal radiation therapy (6), more modest integration has occurred in breast cancer radiation therapy. Therefore, the debate generated by these four articles (three published in this issue and one published July 1 2015) of *International Journal of Radiation Oncology, Biology, Physics* regarding the optimal anatomic extent of CTVs for local regional radiation therapy for breast cancer is both welcomed and overdue. Each study challenges whether the RTOG Breast Cancer Atlas is sufficient for guiding CTV delineation. Two of these studies frame this question by examining institutional series of breast cancer patients with gross disease in the supraclavicular region (7, 8), another does so by retrospectively studying preoperative CT scans in patients found to have axillary node metastases on surgical pathology (9), and the fourth does this by reviewing failure patterns on the chest wall after mastectomy (10). These studies provide an opportunity to reflect on some basic concepts in breast cancer radiation therapy treatment planning as the field moves forward: (*1*) What is a CTV?; (*2*) Is the CTV that is used in elective radiation therapy to prevent recurrence expected to be identical in extent to that used in the presence of gross disease (GTV)?; and (*3*) Is the CTV used for adjuvant or elective treatment to prevent recurrence "one size fits all" for breast cancer radiation therapy?

The recommended definition of CTV was developed by the International Commission on Radiation Units and Measurement (ICRU) over a series of reports (ICRU 50, 62, and 83). It is defined as a volume of tissue that contains a demonstrable GTV and/or subclinical (microscopic) malignant disease with a certain probability of occurrence considered relevant for therapy. Therefore, it is a construct with both an anatomic and clinical component. The RTOG Breast Cancer Atlas addresses the anatomic component. The definition and contouring of the CTV in the absence of gross disease (GTV), however, depends on knowledge of both the anatomy and the anticipated pattern of breast cancer spread. To address this, Brown et al (7) and Jing et al (8) studied a series of archived breast cancer patients at their respective institutions who had gross supraclavicular disease. In each study, the RTOG Breast Cancer Atlas or other was used to contour a CTV designed for adjuvant supraclavicular nodal treatment on the available or representative CT with gross supraclavicular disease. Not surprisingly, the CTV delineated failed to contain the extent of gross supraclavicular disease in up to 75% of cases. This emphasizes the important fact that the RTOG Breast Cancer Atlas was never intended to redefine the ICRU definition of CTV, which includes gross disease (GTV) when present. Therefore, the appropriate CTV in these studies would have been an expansion on the contoured GTV, and the best role for the RTOG Atlas in this scenario is to assist clinicians in understanding the anatomic component for the CTV expansion.

This then begs the second question, is the extent of the CTV that is used for elective radiation therapy in the adjuvant setting to prevent recurrence expected to be identical in extent to that used in the presence of GTV? Small et al (9) nicely illustrate the difference that can exist in the extent of CTV when gross disease (GTV) is present, versus that expected in the adjuvant setting for axillary nodal radiation therapy. In this study, 25 breast cancer patients were identified who had a preoperative CT scan of the thorax with evidence of axillary adenopathy and had axillary nodal metastases confirmed by axillary dissection. The axillary nodal GTV was delineated on each preoperative thoracic CT scan and fused with the postoperative treatment planning CT scan, which had the axillary CTV contoured for adjuvant radiation therapy with guidance from the RTOG Atlas. In 96%, the nodal GTV on the preoperative diagnostic CT scan extended outside the post−axillary dissection CTV contoured for elective nodal irradiation. This occurred most frequently for axillary nodes identified in levels 1-2, or in the anatomic region removed by the dissection. In current radiation therapy practice, inclusion of the low axilla that has already been anatomically removed by dissection is discouraged, to minimize lymphedema risk. The oncologic safety of this approach is demonstrated by the National Cancer Institute of Canada MA.20 trial, in which axillary recurrences are $<1\%$ in the arm that received nodal radiation therapy. On this arm of the trial all patients had dissection and were treated with supraclavicular−axillary nodal fields, using the coracoid process as the lateral extent excluding axillary levels 1-2 not covered by the breast fields (2). Adding an additional 2-3 cm margin that Small et al state is required for inclusion of the level 1-2 axillary nodes is unlikely to improve this low recurrence rate and could certainly add toxicity. An important point from this study is that 50% of the patients received neoadjuvant chemotherapy for locally advanced breast cancer (T4, N2-3 disease), and if pathologically confirmed gross axillary nodal disease due to progression/poor response persists that is not dissected a GTV should be used based on the patient's individual imaging with a CTV expansion. However, for those with axillary dissection or in clinically node-negative patients who have microscopically positive sentinel nodes, smaller CTV volumes for elective axillary nodal irradiation will likely suffice and avoid excessive inclusion of normal tissue. Similarly, Brown et al (7) and Jing et al (8) call for routine use of a much larger anatomic CTV for elective supraclavicular nodal radiation therapy, on the basis of the extent of gross supraclavicular disease (GTV) in their respective datasets. It is plausible that the larger anatomic distribution of supraclavicular disease in these datasets is the result of lymphatic and vessel disruption from the presence of bulky invasive breast cancer. A study performed by MacDonald et al (11) using lymphotrophic nanoparticle−enhanced (ferumoxtran-10) MRI (LN-MRI) to evaluate lymph node spread in 23 breast cancer patients

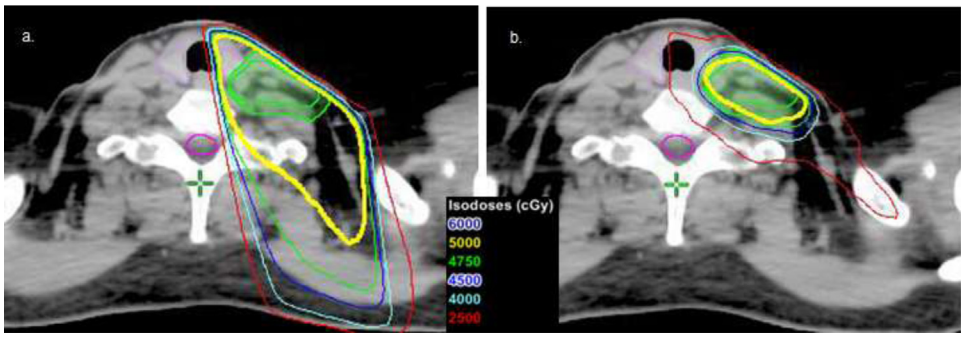

Fig. 1. Axial slice of a CT treatment plan for the same patient that contrasts 3-dimensional conformal radiation therapy (a) and intensity modulated radiation therapy (b) for irradiation of supraclavicular nodal targets.

before surgery supports that there can be more concordance between preoperative nodal volumes on MRI and nodal CTV contoured on CT per the RTOG Atlas. In this study, 89 percent of the nodes detected by LN-MRI were <1 cm in size. For malignant-appearing lymph nodes, 82% of actual (LN MRI−detected) and 85% of sampled (confirmed on pathology report) were within contoured nodal CT volumes, and with a 5-mm margin 96% of these lymph nodes were encompassed. The routine use of larger anatomic supraclavicular volumes for all nodal irradiation is unwarranted in the absence of GTV and will result in the unnecessary exposure of more normal tissue to radiation toxicity.

Last, this leads to the third consideration: should the CTV used in adjuvant treatment to prevent recurrence be "one size fits all" for patients undergoing breast cancer radiation therapy? Vargo et al (10) reviewed 5 publications that reported patterns of failure on the chest wall after mastectomy in response to their participation in the National Surgical Adjuvant Breast and Bowel Program B51/RTOG 1304 phase 3 clinical trial, which is evaluating the benefit of local regional radiation therapy in the post-neoadjuvant chemotherapy setting for patients who down-stage to node negative. These revealed that $\geq$75% of the recurrences occurred in the skin and subcutaneous anterior to the pectoralis muscles and $\leq$25% in the chest wall musculature or deeper. On the basis of this the authors recommend defining the deep border of the chest wall CTV for all postmastectomy radiation therapy as the anterior rib surface. Redefining the deep border of the chest wall CTV as Vargo et al recommend (10) could be insufficient for some percentage of advanced breast cancer where a larger CTV may be needed. It is clear that what is needed is to determine how much of the anatomic extent of the chest wall described by the RTOG Atlas should be included in the chest wall CTV on the basis of the risk of the breast cancer. In particular, as pointed out by these authors, lower-risk patients who do not need the deeper extent of the chest wall included in the CTV may avoid unnecessary cardiac and pulmonary toxicity. This is unlikely to be answered by retrospective analyses in which a CTV is applied after treatment to standardized fields. In particular, as more advanced and conformal treatment planning methods are studied for breast cancer radiation therapy, specific definitions for target CTV become necessary. Take for example the dose distribution in Figure 1 with 3D-CRT versus IMRT for the treatment of the supraclavicular nodes. The dose distribution with 3D-CRT planning (Fig. 1a) includes surrounding soft and vascular tissue that can contribute to permanent toxicity, such as reduced shoulder range of motion, chronic pain, and lymphedema. In contrast, the IMRT dose distribution (Fig. 1b) conforms closely to the target, reducing the amount of normal tissue treated; however, is the target present equally sufficient for cancer control in those with 1-3 axillary nodal metastases as in those with $>$10?

Phenomenal advancement in breast cancer biology and prognosis has occurred over nearly the same time period as an explosion in technology for radiation therapy delivery. Understanding basic steps is necessary to appropriately integrate more conformal and advanced treatment planning technologies effectively in the future. The RTOG Atlas was a first step to understanding the anatomy component of CTV, and these 4 articles highlight the opportunity that exists for future research to define the clinical component necessary for risk-specific CTV delineation for adjuvant regional nodal and chest wall treatment to tailor breast cancer radiation therapy to best fit the specific disease and minimize its morbidity.

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