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Clinical Target Volume: The Third Front

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Of the three basic target volumes—the gross tumor volume (GTV), the clinical target volume (CTV), and the planning target volume (PTV)—we have seen great advances in 2: the PTV and GTV. Image guided therapy and adaptive therapy have contributed to the reduction and customization of the PTV, and we may soon be able to dispense with the PTV altogether in favor of addressing uncertainties during inverse planning (1). Multimodality imaging and biomarkers continue to change the way we define and dose the GTV. Research programs broadly devoted to these 2 target volumes are widespread and thriving.

What about the CTV? Unlike the PTV, we cannot easily measure it. Unlike the GTV, we cannot easily see it. We may broadly define our CTVs as “at-risk” anatomic regions (eg, nodal target volumes) or as an expansion of a GTV, using a margin inferred from pathology or local failure data. But we do not really know the location of microscopic disease requiring radiation. We do not really know how much of it there is, if any. We have to treat it, and, not being able to see it, we overtreat. Reduction of CTVs on the indirect basis of clinical experience, as has happened in lymphoma and non—small cell lung cancer, requires great caution given the possibility of treatment failure. It is hard to make steady, systematic progress on something we cannot see, and the sophistication of our treatment delivery has arguably overtaken our ability to take meaningful advantage of it. For in the face of the invisible, what does it mean to be conformal and accurate?

We have lagged on the CTV front, because studying it is laborious and relies heavily on expertise outside our field. In breast radiation, for example, we still invoke a study that is 30 years old when discussing target volumes (2). The best current work on the CTV is being performed, we believe, at the Netherlands Cancer Institute (3–5), but it required years of pathology work on lung and breast tumors that, in the end, still yielded a relatively small but fruitful dataset. Advances in defining and treating PTVs and GTVs can be connected to

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widespread availability of advanced imaging. It stands to reason that making strides on the CTV front will require the same. More than 10 years ago, in a “conceptual” article, Chao et al (6) wrote, “an innovative technical breakthrough is needed to gather detailed 3D pathologic information.” Working with our colleagues in biomedical imaging, we should be seeking this break-through. We want a method that will get us data we need: large quantities of readily analyzed volumetric images of microscopic disease, so that we can complete the picture of what and how we should irradiate.

Our own group’s first small steps in this direction involve one possible approach: optical coherence tomography (OCT). Optical coherence tomography is a noninvasive, high-resolution (approximately 10 μm), high-speed (approximately 15 seconds for a $5 \times 5 \times 3\text{-mm}^3$ volume) imaging modality that does not require special labeling or contrast agents. Optical coherence tomography is conceptually analogous to ultrasound, but instead of sound, OCT measures infrared light scattered from subsurface microstructures. Difference in scatter may be used to differentiate tissue types, including cancer, in an OCT image (7). Optical coherence tomography imaging is already established in medical fields such as ophthalmology, and results of a multicenter, prospective, blinded study of its use for intraoperative margin assessment during breast-conserving surgery were recently reported (8). Optical coherence tomography has limited imaging depth (approximately 2 mm), but we believe it can be used to image a complete set of pathology blocks or sections, resulting in high-resolution, 3D images amenable to quantitative analysis (Figs. 1 and 2).

We have lagged on the third target-volume front, the CTV, and there are meaningful gains to be made there. In some ways, the CTV is where the PTV was years ago. It is ripe for customization and reduction, not only in volume but in dose as well. In a 2011 article, for example, Jin et al (9) showed that decreasing dose linearly from a GTV would effectively treat microscopic disease, if microscopic disease decreases exponentially with distance from the GTV. It is a theoretical demonstration—they did not really know how microscopic disease behaves—but it suggests we could look at using inverse planning and dose painting to optimize gradients in the CTV and PTV rather than focus on dose uniformity and conformality. The recent reports out of the Netherlands Cancer Institute have shown some of the many fruits made possible by having real data: improved CTV margin design and tumor control probability modeling, as well as new insights into old problems such as the effect of age in breast-conserving therapy. We hope other groups will be motivated to work on high-resolution imaging on the CTV front to improve target definition, tumor control probability modeling, treatment planning and prescription, and, finally, clinical outcomes.

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Fig. 1.
Slice extracted at depth from a 3-dimensional optical coherence tomography image of a breast lumpectomy tissue block. The block is left intact and undisturbed by the imaging procedure.

Fig. 2.
Hematoxylin and eosin slide at corresponding depth.