Extracranial Stereotactic Body Radiotherapy for Stage I Non-small Cell Lung Cancer

Still Investigational or Standard of Care?

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Once shunned by radiation oncologists when prescribing high dose radiotherapy because of its association with serious late toxicity, hypofractionation seems to be making a comeback. The use of a reduced number of large doses per fraction to deliver radical treatment is increasingly under investigation in early stage breast, prostate and now non-small cell lung cancer.

In stage I non-small cell lung cancer, schedules consisting of 3 or more fractions of 12 to 20 Gy have been tested clinically in phase I and II trials. The delivery of these very large doses has been made possible by greater treatment precision in which a large number of multidirectional static (≥8) or dynamic beams are arranged to intersect at the locus of the tumor. The dose contributed by each beam (and therefore to the normal tissues which it traverses) is relatively small, but within the tumor, the summation of dose can result in biologic effects - tumor ablation - theoretically only achievable with doses up to 180 Gy given using conventional (2 Gy) fractionation. The theory is backed up by encouraging rates of local control reported to be in excess of 85%.

The generic term given to this treatment approach is extracranial stereotactic body radiotherapy (SBRT). It is based on the principles established for the stereotactic irradiation of intracranial tumors. The technical requirements are, however, different as illustrated by the approach used at the Princess Margaret Hospital (PMH) in Toronto and described in this issue of the journal.

The term “stereotactic” implies that the treatment is guided by a set of external three-dimensional coordinates derived from pretreatment localization of the tumor. However, the approach at PMH (as elsewhere) is not so much stereotactic as image guided. That is, the beams are directed not by external coordinates but at the tumor itself which is imaged immediately before each irradiation by a computed tomography scanner attached to the treatment machine. Positional adjustments are then made to ensure that the tumor is still within the high dose envelope as originally planned.

Another difference is that in the chest, unlike the brain, it is critically important to be able to accurately record internal tumor motion secondary to physiological cardioventilatory activity. If significant motion is detected, strategies need to be employed to ensure the tumor does not move in and out of the treatment beam leading to underdosage (“geographic miss”). These strategies include enlarging the target volume to encompass all positions of the tumor during ventilation (but which increases the volume of normal tissue irradiated); limiting the extent of ventilatory excursion, for example by abdominal compression; and ventilatory gating. Although the PMH investigators document internal tumor motion pretreatment (using 4D computed tomography), they found it necessary to apply abdominal compression in fewer than 25% of patients, and like most other SBRT groups, do not use gating at all.
Now that the technical hurdles have been surmounted, SBRT has been implemented both on and off investigational protocols at a number of centers in North America and Europe. Interestingly, this has happened in spite of an absence of supporting randomized phase III data. Given the rapid uptake of this revolutionary new treatment approach, we should pause to reflect on why conventional fractionation came into use in the first place. It is well known that hypofractionated radiotherapy using large doses per fraction is associated with serious late normal tissue injury, and this can be ameliorated by the use of conventional schedules using 2 Gy per fraction. The safety of hypofractionated SBRT came under the spotlight with a report from Indiana University.4 In that study, excessive toxicity was observed in patients with centrally located tumors, with the hypofractionated treatment (60 Gy in 3 fractions) possibly contributing to 6 patient deaths. Chastened by this knowledge, the PMH investigators and others5 have recommended a “gentler” fractionation schedule (for example 60 Gy in 8 fractions) for central tumors near the mediastinum. This is, however, no guarantee that the treatment will be safe, as we have seen radiation necrosis with even “gentler” schedules (42 Gy in 7 fractions) given to small volumes in the treatment of early laryngeal cancer.6 Although the lung is not the larynx, cartilage, one of the tissues at risk, is a major structural component of both organs.

Clinicians intoxicated by the heady mix of new technology and impressive rates of local control can be easily persuaded that exceptional phase II data are sufficient to change practice. However, it is my view that higher level evidence is required before we can regard SBRT as a standard of care. We only need to look at the recent history of consolidation docetaxel in the treatment of locally advanced disease to realize that what seems to be a world-beater in the phase II setting may turn out to be a toxic also-ran when subjected to the rigors of phase III evaluation.7 Let us hope that is not the story of hypofractionated SBRT as well.

REFERENCES