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EDITORIAL

Using a Bigger Hammer: The Role of Stereotactic Body Radiotherapy in the Management of Oligometastases

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One of the foundations of radiation therapy is fractionation: dividing the total dose into many daily treatments. In a classic experiment performed almost 100 years ago, Regaud and Ferraux[1] demonstrated that by fractionating radiation, the scrotum could be spared severe radiation dermatitis while producing sterilization. Although the concept that this was a model for tumor radiation had flaws, Coutard[2] shortly thereafter successfully used fractionation to control head and neck cancer with decreased normal tissue injury. Additional experimental work elucidated the four Rs of radiation therapy—repopulation, reoxygenation, redistribution, and repair—that contribute to establishing a therapeutic index between tumor killing and normal tissue injury, which permitted the cure of tumors (especially when combined with chemotherapy) with acceptable normal tissue injury.[3]

Stereotactic body radiotherapy (SBRT) turns the concept of fractionation on its head. SBRT uses high-dose, hypofractionated, highly conformal external beam radiotherapy delivered under direct physician supervision using image guidance. Most commonly, it consists of one, three, or five fractions of approximately 10 to 20 Gy. The use of many (typically eight to 14) cross-firing beams directed at a small tumor produces a high dose in the middle of the tumor and a sharp decrease at the edge. In contrast to fractionated treatment, in which treatment has a small therapeutic index and cure is obtained by many applications, the concept of SBRT is to ablate the irradiated region without regard to the difference between tumor and normal tissues. This ablative approach (usually described as radiosurgery) has been used successfully since 1951[4] for the treatment of brain metastases and some nonmalignant conditions such as arterial venous malformation.

SBRT is an implementation of this technique for sites outside the cranium. Because SBRT delivers potentially ablative doses, it is of utmost importance to exclude normal adjacent tissue from the volume irradiated. Given that the thin rim of normal tissue that surrounds a tumor becomes larger with the cube of the radius, one must choose small tumors. Furthermore, the sharp decrease of dose becomes harder to achieve as tumor size exceeds 4 to 5 cm. Another important and related issue is the need to control target motion, given that the strategy of increasing the target volume is unacceptable. Modern SBRT accomplishes this by restriction of motion (such as with an abdominal compression device), target tracking or gating.

The use of SBRT is particularly appealing in the management of oligometastases,[5] that is, a limited number of metastases that may represent the only distant sites of disease. Effective local therapy for these oligometastases could result in cures; indeed, complete resection of pulmonary and hepatic metastases from colorectal cancer have been shown to result in long-term (10-year) survival in 20% to 35% of patients,[6-8] in settings in which systemic agents or conventionally fractionated radiotherapy are only palliative.

The systematic, prospective evaluation of SBRT as a treatment for liver and lung metastases is the subject of three articles published in this issue of *Journal of Clinical Oncology* that represent important contributions to this relatively new approach. Rusthoven et al[9] update the results of a multi-institutional phase I/II trial of SBRT for patients with one to three lung metastases, mostly smaller than 3 cm in diameter. After escalating the dose from 36 Gy to 60 Gy in three fractions, 29 patients were treated at the established phase II dose. In total, 63 lesions were treated. With a median follow-up time of 15.4 months, they report no grade 4 toxicity, low grade 3 toxicity (8%), and excellent 2-year local control (96%). Overall survival was poor (median of 19 months), most likely a reflection of the selection of patients with multiple features of unfavorable prognosis. A second article by Rusthoven et al[10] updates the results of a multi-institutional phase I/II trial of SBRT for patients with one to three liver metastases, mostly smaller than 3 cm in diameter. In this trial, too, the dose was escalated from 36 Gy to 60 Gy and 36 patients were treated at the established phase II dose. A total of 63 lesions were treated. With a median follow-up time of 16 months, they report low grade 3 to 4 toxicity (2%) and excellent 2-year local control (92%). For lesions smaller or equal to 3 cm, the 2-year local control was 100%. Median overall survival was only 20 months.

In a third article, Lee et al[11] report on a different approach to the use of SBRT for liver metastases. In this phase I trial, the investigators escalated the radiation dose in an individualized fashion, on the basis of each patient's expected risk of radiation-induced liver disease (5%, 10%, or 20%). The expected risk was calculated from a model developed at the University of Michigan, on the basis of an analysis of the relationship between the dose volume histograms of the normal liver (expressed in terms of the effective volume [V_{eff}]) and subsequent complications in more than 200 patients. The lesions treated in this trial were significantly larger that in the other trials, with 35 and 20 patients in the mid and high V_{eff} strata, respectively. Thus, the

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median prescribed dose was 41.4 Gy (range 27.7 to 60 Gy) in six fractions, and 42 patients were treated at the maximum tolerated dose for their V_{eff} cohort. The authors report excellent acute tolerance, with no dose-limiting toxicity, and only three patients had severe late adverse effects, potentially related to protocol therapy. These included one patient who experienced duodenal bleeding and two with intestinal obstruction. The median follow-up was 10.8 months and median survival was 17.6 months. The 1-year local control was 71%.

The studies published in this issue demonstrate that SBRT can produce impressive complete response rates and provides excellent local control for up to 2 years. However, how the long-term results of SBRT compare to resection or to other ablative modalities, such as radiofrequency ablation, is unknown. Is SBRT truly ablative? Can it cure certain subsets of patients with oligometastases? To answer these questions, new clinical trials will have to be designed, in which patients with more favorable disease characteristics will have to be enrolled and followed for many years. A clue to the long-term potential of SBRT is provided by the experience in early stage non–small-cell lung cancer. Fakiris et al[12] have recently reported the final results of the Indiana University phase II study. A total of 70 patients were treated to 60 to 66 Gy in three fractions during 1 to 2 weeks and followed for a median of 50 months. Cancer-specific survival was 82% at 3 years. Previously, Uematsu et al[13] reported on 50 patients, with similar stages, who were treated with SBRT to a total of 50 to 60 Gy in five to 10 fractions and followed for a median of 36 months (range, 22 to 66 months). The 3-year cause-specific survival was 88% and local control was 94%. Taken together, it appears that there is not a substantial decrease in disease control between 2 years and 3 to 5 years. Furthermore, these results are substantially better than what has been previously accomplished with conventionally fractionated radiotherapy and approximate outcomes of surgical resection.

If SBRT is more effective than conventional external-beam radiotherapy for small tumors, it would be important to understand the biologic differences between the two modalities so that SBRT can be optimized. It is not at all clear that the linear quadratic formalism that dominates conventionally fractionated biology applies to large doses per fraction.[14] Likely, this model overestimates tumor-cell kill by large dose per fraction. It is also not clear how the heterogeneity of dose, inherent to SBRT, affects the probability of local control. It is possible, for instance, that the higher dose (by as much as 30% in the center of the planning target volume) is more effective against hypoxic cells or tumor stem cells. It is becoming increasingly clear that tumor control probability is not wholly determined by the minimum dose[15,16]; en mass cell kill in the high-dose region of the target may deprive the rest of the tumor of pro-growth and pro-survival factors, or induce death through bystander effects. Finally, experimental models suggest that, in contrast to conventional fractionation, sphingomyelin-mediated endothelial apoptosis plays an important role in tumor-cell kill by high dose per fraction.[17] Today, SBRT fractionation schemes have been developed empirically, and we do not know what is the optimal fraction size or fraction number.

What can we learn from these three trials? First, we have learned once again that it is possible to conduct prospective trials of new technological approaches. This is an important lesson. This is how future technologies, such as proton therapy, should be tested. Second, although the poor overall survival of patients in these trials competes with the risk of local relapse, possibly leading to overestimation of the probability of local control at 2 years, it seems likely that SBRT is a good treatment for such patients. It would seem that a standardized dose/fractionation scheme, such as 60 Gy in three fractions, works well for tumors smaller than 3 cm; larger ones may benefit from an individualized approach, such as described by Lee et al.[11] However, we must continue to remember past experiences with hypofractionation of large volumes, which can produce severe late normal-tissue effects, especially fibrosis. Even if small volumes are irradiated, catastrophic complications can occur. In the case of lung cancer, severe unacceptable complications (bronchial fibrosis or hemorrhage) have been associated with treatment of lesions within 2 cm of major airways. A more protracted (five-fraction) regimen is about to be tested in a Radiation Therapy Oncology Group (RTOG) trial that will open in the coming months that will determine if these toxicities can be avoided. Lesions close to the chest wall may also benefit from a more protracted fractionation to avoid rib fractures. In the case of medial or central liver lesions, hypofractionation can cause intestinal obstruction or biliary fibrosis. Finally, we should recognize that the methodology used in these trials applies to patients with relatively normal liver and lung functions. At this time, it is not clear how to account for organ dysfunction in patients with lung cancer or primary liver tumors. Certainly, differences in tolerance to radiation between patients with liver metastases and those with primary liver tumors have been observed before.[18] Therefore, although SBRT seems to have given us a bigger hammer, we still have much to learn about how and when to strike the nails.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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