Song and colleagues deliver a thorough and fair review of the initial clinical investigations of a new paradigm in radiotherapy most recently called stereotactic body radiation therapy (SBRT).[1] Oncology observers may take exception with the use of the designation "new paradigm." After all, from a tumor control point of view, skeptics might say, "radiotherapy is radiotherapy." Recent advances in radiotherapeutic technology such as three-dimensional (3D) conformal therapy and intensity-modulated radiotherapy (IMRT) have made treatments less toxic, but not particularly more effective in curing cancer.

In contrast, the review by Song and colleagues describes promising results after treatment of "radioresistant" solid tumor deposits, with rates of local control (an established efficacy end point) ranging from 80% to more than 90%. Although the followup for most of these reports is short, the results strongly contrast with the customary 30% to 50% local control rates achieved for the same tumor presentations treated with conventional radiotherapy.[2]

**Unique Radiobiology**

SBRT utilizes almost every "high tech" advancement in radiation oncology, including improved immobilization techniques, careful accounting of patient positioning and target/organ motion, 3D beam arrangements and dosimetry, advanced treatment planning, IMRT methods, stereotactic treatment setup and delivery, and more formal evaluation of treatment accuracy and reproducibility. Students of this new form of treatment might justifiably be enamored with the physics and technology of the process. In reality, however, what is truly "special" about SBRT is not the technology, but rather, the unique radiobiology. In fact, the use of SBRT methods to deliver conventional dose/fractionation radiotherapy schedules (eg, a dose per fraction of < 6 Gy) would be best characterized as a missed opportunity. The biology of both tumor and normal tissue response outside of the central nervous system to very large doses of radiation is poorly understood.

Treatment strategies using few very large fractions per treatment were conducted during the infancy of radiation therapy at the turn of the last century. Although much of that experience is forgotten, memory of the late toxicities encountered, including severe fibrosis, vascular injury, and ulceration, is stressed to students in every radiation oncology residency program. In those early days, the technology available resulted in dramatically higher doses within normal tissues than in tumor targets. With the help of our colleagues in physics, large-dose-perfraction treatments can now be delivered to tumors with dramatically lower doses to normal tissues. As a result, tumors receive dose levels that affect mitosis by "exponential" killing with little chance of repair. Moreover, it is possible that other mechanisms of tumor cell injury come into play, further increasing the potency of these treatments.[3-5] For whatever the reason, it is already clear that SBRT is different and defies the notion that "radiotherapy is radiotherapy."** A Not So Perfect Therapy**

The article by Song and colleagues correctly represents what is conveyed in the published results using SBRT. Most clinical articles relate high rates of local control with practically no side effects, implying a nearly perfect therapeutic outcome. However, with longer follow-up and larger numbers of patients treated will come the realities associated with a not so perfect therapy. Indeed, at Indiana University, we initially observed impressive tumor responses with minimal side effects. Our phase I early-stage lung cancer protocol enjoyed dose escalation to extremely high doses without many toxic events, probably owing to the selection of patients with mostly peripheral lesions.[6] However, in our larger experience accumulated since 1994, we have seen local failures occurring most often more than 1 year and frequently more than 2 years after treatment. Furthermore, we have treated patients who subsequently experienced very severe toxicity, including total lung collapse due to
bronchial injury, biliary stenosis with jaundice, bowel obstruction, and severe skin reactions. In the end, SBRT will be limited by its toxicity. It is fairly clear already that SBRT using very potent large-dose-per-fraction treatments will "ablate" small tumors and cause minimal side effects in the classic parallel functioning tissues, including the peripheral portions of the lungs, liver, and kidneys. However, each of these organs contain significant amounts of serially functioning tissue (eg, the bronchi/bronchioles, biliary drainage ducts, renal collecting ducts) that will be severely damaged by the same doses of SBRT. With conventionally fractionated radiation, it has always been difficult to justify aggressive and potentially toxic treatments, given the relatively low likelihood of tumor control. Even grade 2 pneumonitis, a reversible condition managed on an outpatient basis with oral medicines, has been used as a criteria for holding back on treatment with conventionally fractionated radiotherapy. With higher tumor control rates using SBRT, it may be appropriate to reconsider exactly what is "too toxic." If the rate of tumor control achieved with SBRT is 90%, would it be reasonable to accept the possibility of permanently losing a lobe of the lung or even an entire lung? As a point of comparison, surgeons explain to their patients that removal of significant portions of lung is justified because surgery constitutes the best chance of cure. **Future Directions**

The future of SBRT and similar minimally invasive treatments for gross disease will follow two important realms. First, it is understood that SBRT offers a tool to achieve very high rates of local control. While local control is an essential component of effective cancer management, it is not by itself a surrogate of cure except for limited cancer presentations (eg, early-stage lung cancer). Currently, many cancers present in advanced stages, when they are not well suited for approaches like SBRT. If planned and ongoing screening and early access to care campaigns are successful, it is conceivable that cancer patient populations will undergo stage migration toward earlier stages more suitable for cure by local therapies alone. The second future realm of SBRT relates to what appears to be an ongoing shift in strategy from eradication of cancer to control of cancer, especially in advanced stages. In all likelihood, new-generation systemic therapies used to control cancer, including the targeted tumor receptor therapies, immunotherapies, and less toxic chemotherapies, will continue to have problems stabilizing gross disease. Historically, radical surgery and radical radiotherapy have been used to try to control gross disease at the cost of significant toxicity. By managing cancer as a chronic disease, using effective systemic agents akin to the management of diabetes or acquired immunodeficiency syndrome, SBRT will be useful for the likely "flare-ups" of gross, symptomatic disease. **Conclusions**

Song and colleagues should be congratulated for providing a clear review of the experience published for SBRT thus far. To date, most major centers that use this treatment are prospectively collecting treatment outcome data while treating patients in clinical trials. Hopefully, prospective testing will evolve toward multi-institutional trials. Meanwhile, we urge our radiobiology colleagues to investigate the effects of limited fractions of very large doses to tumors and normal tissues. In this manner, SBRT will most quickly find its proper place in the modern cancer treatment arsenal.

**Disclosures:** The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

**References:**

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