Editorial Commentary

The evolving landscape of stereotactic radiosurgery for localized vertebral metastases of the spine

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"*The greatest ideas are the simplest*."—William Golding, *Lord of the Flies*

When important work published in other journals may provide insight for our readers, *Annals of Palliative Medicine* has been open to its review and discussion. Such is the case with the recently published results of NRG Oncology/RTOG 0631 (1). Spurred by new technologies that allow for the treatment of more complex tumors and more conformal radiation dose distribution, the trial was designed for patients with 1 to 3 sites of vertebral metastases, determining whether their pain relief was improved with single-fraction stereotactic radiosurgery (SRS) over an older conventional technique.

To its credit, the RTOG has been on the forefront of clinical trial research in pain from bone metastases for nearly 50 years, initially with the RTOG 7402 trial beginning accruing patients in August 1974 (2). Patients with either single or multiple bony metastases were randomized between several dose distribution schedules. Conclusions included that local radiation therapy was an effective palliative treatment of symptomatic bony metastases, and that low-dose shorter schedules were as effective as more protracted regimens.

The conventional technique from RTOG 0631 (8 Gy delivered in a single fraction using an anteroposterior set of fields) was first compared with 30 Gy in 10 fractions in a seminal work reported by investigators at the Royal Marsden Hospital in 1986 (3). In that study, and in many studies and meta-analyses since (4,5), no difference was noted in the speed of onset or duration of pain relief between the two techniques. It has been a source of frustration for some that single fraction conventional radiotherapy (RT) in the United States is not used as often as it should be for symptom palliation based on the preponderance of evidence supporting its use (6). For instance, a study by Bekelman and associates examined national patterns of care in the Surveillance, Epidemiology, and End Results-Medicare database. In their data, only 3.3% of 3,050 patients received single-fraction radiotherapy for palliation of prostate cancer bone metastases; over half received 11 or more fractions (7). It must be kept in mind that for complicated bone lesions (such as those causing spinal cord compression), or for radioresistant lesions, fractionation is an even more contentious point (8).

Given the newer technology available, the RTOG opted for a trial design that tested 1970's-era single dose technique *vs.* 2020's-era single dose technique. The results: the former is cheaper and simpler and is no less effective. This is terrific news for several reasons. First, use of 8 Gy in 1 fraction is far more frequent and available globally than SRS. Secondly, using 8 Gy ×1 is a cheaper alternative than SRS. Third, SRS is more labor-intensive to deliver and requires more time to plan for treatment facilities. Furthermore, in the USA, where up to 15% of patients receive radiotherapy in the last 30 days of life (9), a single

fraction of treatment—either in a conventional 8 Gy fraction or a single SRS fraction—minimizes the disruption of the procedure and may allow some pain relief prior to death. This is an important consideration, as several prior SRS trials have investigated multi-fraction regimens (10).

There are interesting data available in the piece. Given similar patient populations and a 2:1 randomization towards SRS, statistically better pain relief at 3 months was noted in the conventionally-treated cohort: 60.5% *vs.* 41.3% (P=0.01). Two-year crude risk of compression fracture was 19.5% for SRS and 21.6% for conventional technique (P=0.59). No spinal cord complications had been reported at 2 years, which is an appropriate follow-up period for that toxicity.

Does this sound the death knell for spine SRS? Certainly not. Interestingly, the authors note: "*This finding may inform further investigation of using spine radiosurgery in the setting of oligometastases, where durability of cancer control is essential.*" It is noteworthy that the biologically effective dose of the experimental arm in RTOG 0631 of 16–18 Gy in a single fraction was notably lower than that delivered in two prior randomized trials showing a benefit in complete pain response to SRS over conventional radiotherapy for bone metastases, such as 24 Gy in a single fraction (11) or 24 Gy in two fractions (10). There are other major differences between the RTOG study and the CCTG SC.24/TROG 17.06 (11) and Heidelberg studies (10), beyond the scope of this editorial. Thus, one may anticipate further dose escalation trials on the horizon even though durability of pain control was similar and both RTOG 0631 patient cohorts had nearly a third of patients alive at 24 months on actuarial analysis. Pain control at 12 months was apparently similar but hampered by insufficient data reporting.

We expect that readers will be of two minds about the results from RTOG 0631 since clinical equipoise is rare under these circumstances. Some oncologists may applaud the persistent value of a technique from the Stone Age. Some oncologists, who know that SRS is better, will design new trials until we find the appropriate population for this technique. Thus, the real message of the trial may be lost in our First World sensibilities: for patients worldwide, who likely will have a short survival after diagnosis of metastasis, a single fraction of 8 Gy remains appropriate, durable, merciful, and inexpensive.

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