



Lattice radiotherapy: many reasons for hope

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Comment on: Spalek MJ. Lattice radiotherapy: hype or hope? *Ann Palliat Med* 2022;11:3378-81.

Submitted Feb 08, 2023. Accepted for publication Jun 25, 2023. Published online Jul 31, 2023.

doi: 10.21037/apm-23-146

View this article at: <https://dx.doi.org/10.21037/apm-23-146>

We commend Dr. Spalek for his editorial regarding the techniques of spatially fractionated radiation therapy (SFRT) and its applicability to palliation of advanced cancers (1). We are particularly thankful that Dr. Spalek has used the occasion of a first-case report of Lattice radiation therapy to comment on the role of SFRT in palliative care (2). We agree wholeheartedly that these approaches require concerted, prospective study to better define their roles and possible advantages. However, we do not agree with the author's conclusions about the current role of SFRT techniques and the suggestion that SFRT "should be limited to carefully selected cases where conventional palliative radiotherapy is not feasible" and that "we must be skeptical until we receive satisfactory scientific evidence to justify the routine use of SFRT in daily clinical practice" (1).

While scientific evidence of SFRT's biological underpinnings is to date incomplete, we believe that there is already ample clinical evidence of the ability of this modality to achieve high tumoral response rates with low rates of toxicity. Treatments with SFRT have consistently shown promising clinical, radiographic, and pathologic response results in multiple retrospective and prospective series (3-8). This includes the original 2-D techniques [with a physical block or multileaf collimator (GRID)], which have been widely employed in clinical practice for decades; and the more recent 3-D techniques utilizing intensity modulation (Lattice therapy), which have been practiced for over a decade (3). Further evidence that SFRT is increasingly becoming established clinically is the expansion of SFRT use from palliative indications to the definitive treatment of bulky, advanced, non-metastatic cancers, including sarcomatous, head and neck, cervical, and lung cancers.

SFRT offers unique radiobiologic properties to aid radiation oncologists in treating the notoriously challenging bulky/advanced and therapy-refractory tumors. Current high-dose per fraction and stereotactic radiotherapy techniques are generally limited to relatively small-volume cancers. GRID and Lattice therapy, however, depart from the uniform dose paradigm by intentionally utilizing highly heterogeneous dose distributions. This heterogeneous dosing allows high-dose vertices (peaks) to be distributed deeply within the gross tumor volume, while exposing nearby intratumoral low-dose regions (valleys) and surrounding organs-at-risk to relative normo-fractionation or at most standard palliative mild hypofractionation (3-5 Gy per fraction). These are dose levels that are generally well tolerated by normal tissues. Consequently, the well-characterized radiobiologic advantages of stereotactic body radiation therapy (SBRT) can be brought to bear on tumors that are too large for pure SBRT approaches.

In addition, and perhaps more importantly, the inherent dose heterogeneity of SFRT is postulated—based on an increasing body of preclinical data—to generate bystander, vascular, and immunostimulatory effects that lend SFRT biologic advantages over homogeneous dose distributions. Further study is needed to elucidate the true mechanisms, but there is promise in further synergisms in this era of increased utilization of immune checkpoint inhibitors. Large clinical trials in SFRT, especially ones with homogeneous patient and tumoral populations, will be challenging to complete, but more data are emerging and the SFRT community is committed to generating prospective evidence evaluating the utility of this modality.

While institutions with training and experience in

SFRT (particularly Lattice therapy) are still relatively few in number at this time, it is encouraging to see that Iori *et al.* have successfully treated their first case with SFRT, and we again thank Dr. Spalek for raising awareness for the modality through this editorial (2). Recent technological advances in radiation therapy are poised to further broaden SFRT applicability in the clinic. Multi-leaf collimator and pencil beam scanning proton therapy approaches to GRID already obviate the necessity of a hardware addition (GRID collimator), and the wide availability of arc therapy for delivery of Lattice therapy can further facilitate adoption of this technology into many radiation oncology facilities. It is our hope that institutions with active programs will become resources to support and advise new centers in starting SFRT programs.

Efforts are underway, spearheaded by the Radiosurgery Society (RSS), NRG Oncology, and the American Association of Physicists in Medicine (AAPM) to improve awareness, education, and training for SFRT techniques. Working groups within each society aim to help expand the safe and effective use of SFRT through knowledge sharing, hands-on training, and expert proctoring. Multiple workshops have been held, especially in conjunction with the RSS, to educate the radiation oncology community about this emerging therapy option. Additionally, numerous publications, including a special issue in the journal *Radiation Research*, and consensus statements from SFRT experts have lent guidance towards best practices in treatment planning and methods for future clinical trial development (9,10). Cooperative and consortium trials are needed, and multi-institutional efforts will be critical in generating meaningful data with sufficient power to detect potential improvements in outcomes from SFRT. Such trials may also help refine techniques and advance our understanding of the biological underpinnings of SFRT through incorporated translational efforts.

In summary, we commend Dr. Spalek for this thought-provoking editorial, as well as Iori *et al.* for their first-case report (1,2). We believe there is a great deal more hope than hype in SFRT as a modality for addressing challenging, bulky, and refractory tumors. Supported by a growing body of literature, SFRT can and has been safely utilized in regular radiation oncology practice in clinics worldwide. Instead of being “skeptical” at this stage of current clinical SFRT use, we recommend focusing on ensuring its thoughtful, careful, and trained activation in new centers, while conducting additional prospective research with SFRT in both the palliative and definitive settings.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was a standard submission to the journal. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://apm.amegroupp.com/article/view/10.21037/apm-23-146/coif>). CBS serves as the Editor-in-Chief of *Annals of Palliative Medicine*. JWS receives honoraria/travel fees from Varian Medical Systems. JWS serves as consultant for Siemens Healthineers and Proton International LLC. JWS holds patent for novel spatially fractionated proton therapy technique. NAM declares consulting in a medical legal case. All authors serve as Co-Chairs of the Radiosurgery Society Working Group on GRID/LATTICE/FLASH/Microbeam therapies.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Snider JW, Mayr NA, Simone CB 2nd. Lattice radiotherapy: many reasons for hope. *Ann Palliat Med* 2023;12(5):1109-1111. doi: 10.21037/apm-23-146