Editorial

Lattice radiotherapy: where less is more?

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We read with great interest the case report by Iori et al. who treated a large sarcomatoid lung cancer with lattice radiotherapy (LRT) (1). The authors reported good radiological response and patient reported symptom relief. We commend their efforts in implementing this emerging radiotherapy technique at their centre. We hope that this case report raises awareness and interest in the implementation of LRT in other institutions.

LRT derived its basis from grid radiotherapy (GRID RT), where a wide radiation beam is passively filtered through a heavy metal block to deliver radiation in beamlets. This technique was popularized in the 1990s by Mohiuddin *et al.*, with patients experiencing good clinical response despite partial irradiation of tumours, albeit at high doses (2). There were subsequently many pre-clinical and clinical studies exploring different aspects of GRID RT (3-5). However, the use of GRID RT remains limited to few centres worldwide. Possible reasons include difficulties with commissioning and delivering treatment with a GRID block or multileaf-collimator. As GRID RT is delivered as a static field, treating deep seated tumours may be difficult without unnecessary risk to adjacent organs at risk.

Since the initial reports from Mohiuddin et al, we have seen technological advances in radiotherapy equipment and techniques over the past few decades. The early 2000s have seen the advent of intensity modulated radiotherapy that enabled us to deliver radiation via dose painting. Radiation techniques have also evolved with time and ablative doses can now be delivered via stereotactic body radiotherapy (SBRT). However, the lesions treatable with SBRT is often limited by size.

So how do we marry the learnings of GRID RT and SBRT in the treatment of large tumours? LRT may be a potential solution. In essence, LRT takes dose painting to the extreme by delivering precise SBRT-like doses to spherical sub-volumes termed vertices, spread out within the tumour whilst simultaneously covering the entire tumour to a lower dose. In two recently reported studies, namely the LITE-SABR-M1 trial (6) as well as the LATTICE_01 study (7), we now have good clinical evidence supporting the use of this emerging radiotherapy technique.

The LITE-SABR-M1 trial was a single-arm phase I trial conducted between October 2019 and August 2020 on 22 patients with tumours >4.5 cm. LRT technique was as described in the accompanying case report, except that the vertices received 66.7 Gy instead of 50 Gy. Importantly, concurrent systemic therapy was not allowed and a 2 week washout period was recommended before and after LRT. The authors reported a good safety profile with no treatment related grade 3 or more toxicity noted in the acute period. Patients also reported improvements in anxiety, depression, pain interferences, physical global health and physical function. Whilst not the primary endpoint, good radiological tumour responses were also

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noted. The authors reported a median 24.4% decrease in tumour size at a median of 1 month post LRT. At a median of 4.5 months post LRT, all but one tumour continued to shrink with a median 47.4% decrease in volume. However the caveat is that only 13 and 11 (out of 22) patients had diagnostic imaging at a median of 1 and 4.5 months post LRT respectively.

The LATTICE_01 multicentre study, on the other hand, explored adding another dimension to LRT: by using tumour metabolic activity as seen on positron emission tomography (PET) to determine the placement of vertices. The vertices were placed at the interfaces of high (>75% of maximum standardized uptake value) and low metabolic activity within the tumour. The authors recruited 30 patients and treated 31 lesions in total. The tumours were at least 5cm. The authors reported 100% symptomatic relief after irradiation. There was similarly no grade 3 or more toxicity reported. In terms of radiological response, all except 1 showed complete or partial response.

On the basis of the results from these 2 studies, one could conclude that LRT is safe and potentially efficacious despite the myriad of histologies and clinical histories that these patients presented with. However one might ask which technique is preferable?

In contrast to LITE-SABR-M1, the LATTICE_01 study delivered single fraction LRT 15 Gy followed by hypofractionated radiotherapy with a median prescribed dose of 20 Gy in 4 fractions. Thus, two radiotherapy plans are needed for each patient. A PET scan is also a pre-requisite for planning. Overall treatment duration is longer given the 1 week break in between LRT and hypofractionated treatment.

Thus for pragmatic reasons, LRT as per LITE-SABR-M1 may be more preferable. Though the median follow-up for patients in LITE-SABR-M1 was shorter, this may be attributed to a heavier disease burden as evidenced by larger tumour volumes (median tumour volume: LITE-SABR-M1=579.2 cc, LATTICE_01=146.48 cc). Furthermore, if PET imaging is available, it would not be unreasonable to apply the concept of LATTICE_01 in the placement of vertices.

Beyond using LRT as a single site treatment, it may also complement multisite SBRT in the treatment of the oligometastatic patient. In the seminal SABR-COMET trial, SBRT to all metastatic lesions (up to 5) have shown to improve survival outcomes (8). However, the cases recruited in the trial do not have large lesions. Having LRT in the armamentarium to control a bulky primary (as seen in the case report) or a large dominant metastasis may enable more cases to be considered for multisite SBRT in a concurrent or sequential manner. This may have implications when one is considering combining radiotherapy with immunotherapy.

Luke *et al.* studied the potential of combining pembrolizumab and multisite SBRT in treating patients with advanced solid tumours (9). The patients who were enrolled had disease progressing on standard treatment. Most patients received at least one cycle of pembrolizumab with SBRT to at least 2 lesions. The objective overall response rate was modest at 13.2%. What was interesting in their protocol was their approach to large lesions: metastatic lesions >65 cc were partially irradiated by creating a target volume <65 cc. The median volume of lesions treated with this approach was 116.6 cc. However, considering both methods of partial irradiation, why should LRT be favoured for combination with immunotherapy given its inherent complexities?

There exists in the literature case reports that suggest potential synergies between immunotherapy and GRID RT/LRT (10,11). Jiang *et al.* reported a case of metastatic non-small cell lung cancer who was treated with pembrolizumab after having disease progression despite various chemotherapy and radiotherapy regimens. However, a chest wall lesion progressed from 2 to 63.2 cc within 1 month of starting pembrolizumab. The lesion was treated with single fraction LRT 20 Gy alone. The patient continued receiving pembrolizumab, complemented by SBRT or conventional RT to other lesions in the body. However, only the lesion treated with LRT achieved complete clinical and radiological response. This was despite only 6.5% of the lesion receiving a dose of 20 Gy and higher. The low effective uniform dose (EUD) of 1.2 Gy was also not expected to cause any tumour response. Thus, the authors postulated that there was synergy between LRT and immunotherapy. What was also intriguing was that fact that none of the other lesions treated with SBRT or conventional RT achieved complete response. Against conventional radiotherapy dogma, does deliberate underdosing and extreme dose inhomogeneity confer an advantage with immunotherapy?

Along this line of thought, we refer to a recently reported clinical trial on the Radscopal technique, where patients with metastatic disease that progressed on immunotherapy were given a combination of high dose (SBRT doses where possible) and low dose radiation (typically 7 Gy in 5 fractions at 1.4 Gy per fraction) directed to separate lesions (12). The authors found that low dose irradiated

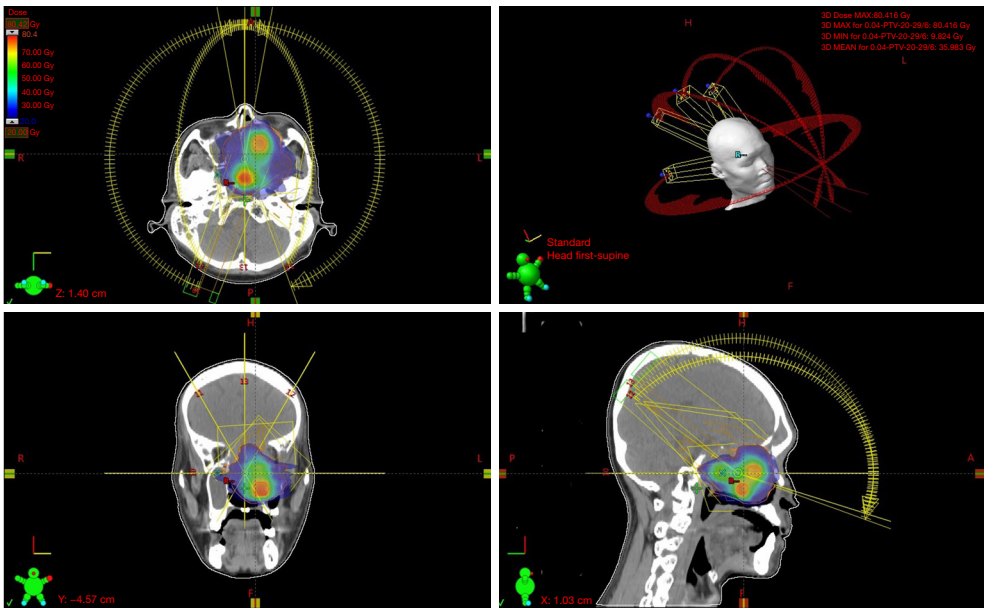

Figure 1 A screenshot of the Eclipse treatment planning system showing the LRT plan used to re-irradiate a solitary fibrous tumour of the sphenoid sinus. LRT, lattice radiotherapy.

lesions had a 53% response rate as compared to 23% in nonirradiated lesions. T and NK cell infiltration was enhanced in lesions treated with low dose RT. We see parallels between LRT and Radscopal where radiation dose inhomogeneity, directed intra- or inter-tumour, may have a role to play in enhancing treatment outcomes with immunotherapy.

On the horizon, Moore *et al.* reported interesting pre-clinical results of Personalised Ultrafractionated Stereotactic Adaptive Radiotherapy (PULSAR) in combination with single agent immune checkpoint blockade (13). They have found that SBRT given in "pulses" separated by 7 or more days was able to enhance the effect of immunotherapy in mice models. It is unknown if this treatment schedule can be directly translated into clinical practice. However, drawing on the experience of Jiang *et al.* (11), perhaps a pragmatic method would be to administer single fractions of LRT in tandem with immunotherapy dosing schedules. This could be repeated to the same or multiple lesions, thereby achieving a form of spatio-temporally fractionated immuno-radiotherapy.

At our centre, we have been able to offer both GRID RT (via a commercially available GRID applicator from .decimal) and LRT. Our first patient who was treated with LRT had a solitary fibrous tumour of the sphenoid sinus that received 2 previous courses of conventional radiotherapy. As the disease was encroaching on the left optic nerve and orbit, the patient suffered from diplopia, blurring of vision and proptosis. As there was a lack of viable treatment options, a third course of palliative RT was offered.

Due to the complexity of the case, we discussed about alternative methods to deliver RT. GRID RT was not possible given the multiple organs at risk in the small confines of the craniofacial region. We turned to LRT as expounded by Duriseti *et al.* as there was a clear step by step approach to generating and delivering LRT plans (14). Their approach was further backed by the publication of the clinical and dosimetric outcomes of their LITE-SABR-M1 trial (6,15). This was also pragmatic as we had originally planned to re-irradiate at a dose of 20 Gy in 5 daily fractions. Thus by delivering LRT, we aimed to achieve an iso-toxic treatment with potentially better tumour response.

RT planning was done on Eclipse Treatment Planning System version 13.6 (Varian Medical Systems, Palo Alto, CA). We employed four non-coplanar treatment arcs with 6 MV flattening filter free beam at a dose rate of 1,400 MU per min using dose painting technique (*Figure 1*). Treatment was delivered on a Varian Truebeam Linear Accelerator. The patient tolerated treatment well and reported less proptosis at two months post LRT. Reimaging of the tumour was pending at the point of writing this editorial.

In 2018, the Radiosurgery Society (RSS), in conjunction with the National Institute of Health, hosted the inaugural workshop on understanding spatially fractionated radiotherapy. This has been followed by the establishment of GRID, Lattice, Microbeam and FLASH Radiation Therapy Working Groups. As a group, they have published a white paper on GRID RT (16) and developed consensus on the design of clinical trials in spatially fractionated radiotherapy (17,18). More recently, the RSS has also opened a patient registry to incorporate GRID RT and LRT data to better understand the delivery techniques and outcomes. We look forward to seeing more developments in this field of radiotherapy in the near future.

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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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