



# Lattice radiotherapy: hype or hope?

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Symptomatic palliation is one of the most important treatment intents in radiation oncology (1,2). The development of radiotherapy enabled the delivery of very high doses on precisely delineated volumes that allowed for better local control and more rapid symptom relief. However, irradiation of large volumes with a uniform high dose may lead to significant toxicity from surrounding healthy tissues.

Spatially fractionated radiotherapy is a relatively old concept in radiation oncology that implements the delivery of non-homogeneous dose to treat tumors (3-5). As a result, alternating volumes of the tumor receive low and high doses. The main aim of such an approach is to increase the local efficacy of radiotherapy without causing significant toxicity. The original two-dimensional technique of delivery is known as GRID therapy. The special physical blocks with holes are used to shape beams in a form of pencils.

Nowadays, modern linear accelerators are equipped with multileaf collimators that enable the creation of 3D GRID-like treatment plans using dose modulation. This technique is called lattice radiotherapy (LRT) (6). The name originates from the shape of tumor volume seeded by high dose vertices separated by set distance to create peak-to-valley dose distribution.

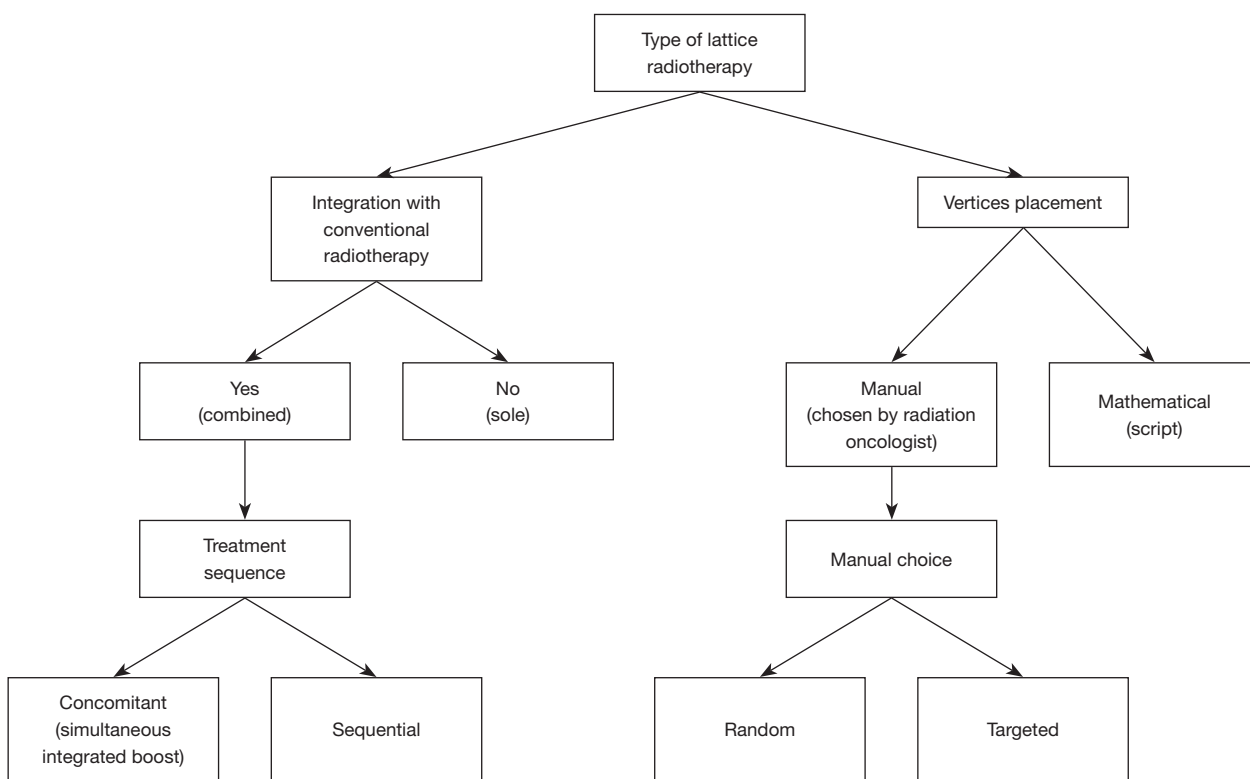
Both GRID and LRT techniques are mostly applied to unresectable, bulky, or symptomatic tumors where conventional radiotherapy may be not feasible due to the risk of unacceptable toxicity. Published case reports and retrospective studies reported unexpectedly good local

response after GRID/LRT with no or minimal treatment-related toxicity (7-11).

The mechanism of action is not fully known and exceeds the “conventional” radiobiology. Inhomogeneous dose distribution might cause so-called bystander and abscopal effects within the tumor (12-14). Furthermore, higher doses per fraction induce an immunomodulatory effect (14,15). That may result in significant tumor shrinkage and palliation of disease-related symptoms.

LRT may be divided based on various factors. I have chosen and proposed two factors that should be considered during LRT planning. My proposal is presented in *Figure 1*. The first division is based on integration with conventional radiotherapy. LRT could be given as a sole treatment or combined with another form of irradiation, usually conventionally fractionated. Then, concomitant irradiation may be delivered in a form of an integrated boost, for example, 20 Gy to the whole tumor and 60 Gy to vertices in five fractions, or sequentially, for example, a single fraction of 20 Gy to vertices followed by 2 to 50 Gy to gross tumor volume. The other division is related to the positioning of vertices. It could be done automatically using a dedicated script or contoured manually by a radiation oncologist. In the second case, the exact position of vertices may be selected randomly, as per the assessment of the planning physician, or based on previously specified assumptions associated with biological properties, for example, hypoxia/hyperoxia in positron emission tomography (PET) or diffusion restriction in magnetic resonance.

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**Figure 1** Types of lattice radiotherapy.

I had the honor to review the article presenting a case report of a patient who underwent LRT for bulky sarcomatoid lung cancer (16). This kind of case report provides valuable insight into the clinical application of LRT, i.e., optimal fractionation regimens, response, and toxicity. The three lines of systemic treatment were found ineffective in achieving any tumor response that resulted in symptomatic progression of the primary lesion up to 19 cm in the longest dimension. Then, the patient received five fractions of LRT, namely total doses of 55 Gy on the vertices and 20 Gy on the periphery of the gross tumor volume, using volumetric modulated arc therapy. Vinorelbine-based chemotherapy was temporarily withdrawn during the radiotherapy.

The authors reported a dramatic response to irradiation with tumor shrinkage up to 8 cm × 4 cm and relief of the dyspnea. After six months of follow-up, the disease remained stable. No late toxicity was observed.

LRT seems to be an attractive direction for further development of radiotherapy, especially for patients with locally advanced unresectable tumors. It could be easily incorporated into modern biologically guided radiotherapy

that adapts dose distribution to tumor heterogeneity and its microenvironment (17). The application of PET to image tumor hypoxia and an interfraction shift of actively proliferating cells is another exciting solution to enter the era of “precision LRT” (18). Furthermore, the appropriate use of different fractionation regimens with known immunomodulatory effects may enhance the efficacy of immunotherapy used in various cancers (19).

However, we must be skeptical until we receive satisfactory scientific evidence to justify the routine use of LRT in daily clinical practice. The first concern is related to the choice of the optimal method of LRT. There are still too many unknowns about the type of LRT, fractionation regimen, contouring process, organs at risk, motion management, or interfraction changes within the tumor.

Another issue is potential toxicity. Although first reports showed good tolerance of such an approach, mature data regarding toxicity are still missing. There is no guideline on how to safely apply LRT in combination with systemic therapy. Moreover, ablative doses used in LRT may be suppressed by sequential conventionally fractionated radiotherapy (20). Thus, the choice of the optimal type of

LRT remains a challenge.

Future controlled trials may give answers about indications and safety of LRT (21,22). Based on the published case report and other available data, the application of spatially fractionated radiotherapy should be limited to carefully selected cases where conventional palliative radiotherapy is not feasible.

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