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Original Article

Advanced Mode of Spatially Fractionated Radiotherapy: Lattice-Based Radiotherapy

Gong Zhimin[1], Feng Shuang[1]

[1]Shanghai Pudong New Area People's Hospital, Radiotherapy Department

Address: No. 490 Chuanhuan South Road, Chuansha New Town, Pudong New Area, Shanghai, China, Postcode: 201299

[*]Corresponding Author: Gong Zhimin

Abstract:
Lattice radiation therapy (LRT) is a three-dimensional advanced model of spatially fractionated radiation therapy that precisely regulates the peak-to-valley dose ratio by distributing high-dose vertices (1–2 cm) and low-dose valleys (3–5 cm apart) through a three-dimensional matrix (PVDR≥3:1), maximizing dose heterogeneity to destroy tumors and protect normal tissues. Its core technology relies on multiple leaf collimators or proton beams to generate high-dose peck zones with regular geometric arrangements, combined with reverse optimization algorithms and real-time image guidance (such as CBCT and MRgRT), to ensure dose conformity and safety. LRT has therapeutic advantages through multidimensional biological effects, including bystander effects on the activation of apoptosis in unirradiated areas, immune microenvironment remodelling (increased infiltration of CD8+ T cells), and vascular normalization, which enhances chemoradiotherapy sensitivity, thereby resulting in a high local control rate (symptom relief rate of 82.9%-98.7%) and low toxicity (acute grade 3 toxicity<5%) for giant tumors (>5 cm) and metastases (such as bone and liver metastases). Clinical protocols are divided into curative options (a single dose of 15–20 Gy combined with conventional fractionation) and palliative options (a single dose of 10–45 Gy), combined with immune checkpoint inhibitors or antiangiogenic drugs, which can significantly prolong survival (such as PFS reaching 8.5 months). The technological innovation progress has focused on AI dynamic optimization, the Bragg peak advantage of proton LRT, and real-time tracking of multimodal images. In the future, it is necessary to promote phase III multicenter validation, dose standardization, and biomarker research to expand its application boundaries in personalized precision radiotherapy.

Keywords: lattice, radiation therapy, spatial, radiotherapy

Introduction

The Core Theory, Technical Principles, and Therapeutic Mechanisms of Lattice RT

Lattice radiation therapy (LRT) is a three-dimensional evolutionary form of spatially fractionated radiation therapy (SFRT). Compared with traditional 2D GRID technology, LRT achieves three-dimensional control of the dose distribution by optimizing high-dose peaks and low-dose valleys in a three-dimensional matrix within the tumor [1] [4] [6] [13] [39]. Its core theory emphasizes precise control of the peak-to-valley dose ratio (PVDR), which maximizes dose heterogeneity within the tumor while efficiently killing tumor cells and reducing damage to surrounding normal tissues [1] [4] [6] [13]. This theoretical breakthrough provides a unique dose delivery mode for the treatment of solid tumors.

At the technical principles level, LRT generates spherical or cylindrical high-dose vertices with a diameter of 1–2 cm through multileaf collimator (MLC) or proton beam modulation technology and arranges them

according to regular geometric structures such as triangles and cubes, with vertex center spacings typically ranging from 3–5 cm [9] [11] [32] [37]. The optimization of the dose distribution relies on a reverse planning system, which dynamically adjusts the spatial relationship between high-dose and low-dose regions through algorithms to ensure the treatment goal of PVDR ≥ 3:1 [9] [11] [32] [37]. For example, TomoTherapy technology can be used for spiral computed tomography radiation therapy, real-time optimization of the valley-to-peak-dose ratio (VPDR) is achieved through dynamic modulation, and the precise design of the vertex size and spacing directly determines the level of dose heterogeneity within the tumor microenvironment [1] [11].

From the perspective of therapeutic mechanisms, LRT exerts antitumour effects through multiple biological effects:

- Spectator effect and distant effect: A high dose vertex induces DNA double-strand breaks in tumor cells and releases proapoptotic factors (such as TGF-β and ROS), activating apoptotic signalling pathways in nonirradiated areas and inhibiting tumor regeneration [8] [16] [21];
- Immune activation effect: LRT promotes the release of tumor antigens and damage-associated molecular patterns (DAMPs), enhances the infiltration of CD8+ T cells into the tumor microenvironment (TME), and reshapes the immunosuppressive microenvironment [20] [25] [30];
- Vascular normalization effect: A low dose through area promotes endothelial cell repair, and reducing hypoxia inducible factor (HIF-1α) expression improves the tumor blood supply and oxygenation status, thereby increasing sensitivity to subsequent radiotherapy or chemotherapy [21] [35]. These synergistic mechanisms endow LRT with unique advantages in controlling local progression and inhibiting distant metastasis.

Design and optimization of the spatial distribution, advantages, and clinical indications of lattice RT

Design and Optimization of the Spatial Distribution: The spatial distribution design of LRT requires a coordinated balance between the tumor geometry and dosimetric objectives. The lattice-OPT tool is based on a reverse optimization algorithm and dynamically adjusts the vertex spacing (D, usually 3–5 cm) and vertex diameter (d, 1–2 cm), maximizing tumor volume coverage while ensuring a peak-to-valley dose ratio (PVDR ≥ 3:1) [9] [11] [27] [31]. For example, the triangle vertex arrangement pattern can effectively reduce the dose cold zone, which is especially suitable for tumors with irregular morphology or invasion of adjacent key organs [9] [27]. This type of optimization strategy, combined with Monte Carlo dose calculations or machine learning prediction models, can further improve the accuracy of dose distribution conformity and heterogeneity regulation **[11] [31].**

The unique dose distribution of LRT endows it with significant clinical advantages:

- High local control rate (LCR): Clinical studies have shown that the symptom relief rate of patients after LRT reaches 82.9%-98.7%, demonstrating excellent local control ability for large tumors with a volume greater than 5 cm [7] [14];
- Low toxicity characteristics: Through three-dimensional dose carving technology, the average dose (Dmean) of surrounding normal tissues is reduced by 30%-50%, and the incidence of acute grade 3 or higher radiation toxicity is less than 5%, which is significantly better than that of traditional radiotherapy [7] [14] [28].

Scope of clinical indications: Most practicing radiation therapy oncologists (100% in the United States and 72.7% globally) believe that SFRT is the recognized standard radiotherapy option for large-volume tumors or advanced tumors [10]. LRT is currently mainly used in the following two clinical scenarios:

- Localized advanced giant tumors, including head and neck cancer (symptom relief rate of 82.9%) [2], non-small cell lung cancer (NSCLC) [14], and soft tissue sarcoma (such as retroperitoneal sarcoma) [23] [38], whose large lesions can overcome radiation resistance caused by tumor hypoxia through dose heterogeneity;

- Metastatic tumors: For oligometastatic lesions such as bone metastases (such as spinal metastases) and liver metastases, LRT can be combined with systemic therapy to achieve synergistic effects of local ablation and systemic control [34] [41]. With technological iteration, its indications are gradually expanding to the field of combination therapy for recurrent tumors and immune therapy-resistant lesions.

Clinical Protocol and Efficacy Safety of Lattice RT

The clinical protocol plan for LRT can be divided into two categories on the basis of treatment goals: curative and palliative:

- Curative protocol: A single high-dose (15–20 Gy) vertex irradiation combined with conventional fractionated radiotherapy (such as 25 × 2 Gy) enhances local control through dose heterogeneity and reduces the cumulative dose to normal tissues. This protocol is suitable for locally advanced tumors that can be surgically removed or potentially cured [7] [23]. When the radioimmune response model is considered, the benefits of lattice RT are more significant when conventional radiotherapy with a low dose fraction is used for large tumors in curative treatment [3].
- Palliative approach: With the goal of rapidly relieving symptoms (such as pain or bleeding), single or divided (3–5 times) vertex irradiation (10–45 Gy) is used to achieve short-term symptom control through rapid tumor ablation in the peak dose zone, especially for advanced metastatic patients [15] [19] [34].

The sequencing time and dose adjustment of lattice RT and conventional external irradiation are variable. In the curative protocol, synchronous chemotherapy and immunotherapy were received and combined by 54.5% and 28.6%, respectively [10].

Clinical studies have confirmed that LRT has significant therapeutic efficacy in various types of tumors:

- Symptom relief rate: After patients receive LRT, the median survival time of patients with head and neck cancer is extended to 12 months, and the median duration of pain relief or compression symptoms can be shortened to 8 days [7] [34];
- Tumor regression rate: LRT can provide clinical benefits for 84.2% of patients with locally advanced large-volume unresectable head and neck tumors. For large tumors with a volume greater than 5 cm (such as soft tissue sarcoma or non-small cell lung cancer), the tumor volume reduction rate after treatment is greater than 50%, and some cases can be converted into surgical resection opportunities [14] [38].

The existing clinical experience seems to confirm the safety of LRT [12]. LRT significantly optimizes safety through three-dimensional dose carving technology, and compared with 2D Grid technology, Lattice significantly reduces the dose to the skin and key organs [3],

- Acute toxicity mainly includes reversible dermatitis or mucositis of grade 1--2 (incidence rate of approximately 60%-75%), with no reported treatment-related deaths [7] [28]. According to the evaluation criteria of the radiotherapy tumor group (RTOG), many LRT clinical practices have not reported grade 3 adverse events [2].
- Long-term toxicity: The incidence of radiation-induced fibrosis or organ dysfunction is less than 10%, which is significantly lower than that of traditional radiotherapy (usually for traditional radiotherapy >20%), and its mechanism is closely related to the protective effect of the trough dose on normal tissues [14] [38]. These data indicate that LRT not only improves efficacy but also achieves good risk benefit balance.

Biological mechanism and combination therapy strategy of Lattice RT

Lattice RT (LRT) exerts its biological effects by reshaping the tumor immune microenvironment. Research has shown that LRT can significantly upregulate the expression of PD-L1 on the surface of tumor cells and promote T-cell infiltration, thereby

enhancing the immune therapy response to anti-PD-1/PD-L1 inhibitors. Preclinical model data show that the combination of LRT and immune checkpoint inhibitors can significantly increase the incidence of distant effects by up to 30%, revealing the potential mechanism of the synergistic effect between radiotherapy and immunotherapy [20] [30] [42].

The emergence of immune checkpoint inhibitors (ICIs) has completely changed the treatment methods for recurrent and metastatic patients. The lattice RT method has the potential to reduce lymphocyte depletion and immune suppression, stimulate antitumour immunity, and synergize with ICIs [18].

In terms of combination therapy strategies, LRT exhibits multilevel synergistic effects with targeted drugs. First, the combination of the antiangiogenic drugs bevacizumab and LRT can improve tumor microcirculation and prolong progression-free survival (PFS) to 8.5 months, indicating a dual benefit of radiosensitization and vascular normalization [35]. Second, for DNA damage repair-deficient tumors, the combination of LRT and PARP inhibitors can significantly increase tumor radiosensitivity by enhancing radiation-induced accumulation of DNA double-strand breaks [21]. This multitarget combination strategy provides a new direction for personalized therapy.

However, the clinical application of LRT combination therapy still faces challenges. Some tumors develop resistance to combination therapy due to the presence of an immunosuppressive microenvironment, which involves infiltration of myeloid-derived suppressor cells (MDSCs) and regulatory T-cellcell (Treg) activation and other processes [20] [30]. At present, research is dedicated to exploring novel biomarker systems, including the tumor mutation burden (TMB), interferon-γ (IFN-γ) signalling pathway activity, and other predictive indicators, to achieve more accurate patient stratification and treatment plan optimization.

Technological progress and innovation direction of lattice RT

The application of CBCT scanning can reduce the uncertainty of each treatment and quantify the dose effect of alignment errors in lattice therapy. When CBCT images are used, the isocenter shift is not greater than 5 mm to simulate large errors during treatment. The dose ratio (DR) of the average dose in high-dose and low-dose spheres is used to quantify the reduction in the dose gradient and minimize the dose impact on high-dose spheres [5].

Fully automatic generation and placement of various vertices and their scales through the use of scripting application programming interfaces in the treatment planning system to order the lattice of inches, center-to-center distance, and vertices is automatically segmented, dose optimized, and calculated [17] [26] to obtain a more accurate and reasonable lattice RT plan for optimal PVDR.

Multimodal integration and precise design drive the expansion of its clinical application boundaries. In recent years, the development of dynamic vertex adjustment technology has significantly improved the adaptability of radiotherapy plans. Real-time optimization algorithms based on artificial intelligence (AI) can dynamically track changes in tumor morphology (such as respiratory movement or volume shrinkage during treatment), automatically adjust the spatial distribution of lattice vertices, and maintain the biological effects of dose carving [22] [24]. This technological breakthrough provides a new paradigm for the precise irradiation of dynamic tumor targets.

The fusion of image-guided technology further enhances the implementation accuracy of LRT. The magnetic resonance real-time guided radiotherapy (MRgRT) system achieves motion-sensitive areas such as liver and pancreatic tumors through high soft tissue resolution and a millisecond-level imaging refresh rate to achieve real-time dose tracking of tumors, which can control the lattice dose gradient error within 3% while effectively suppressing dose-blurring effects caused by respiratory motion [36] [40]. In addition, the innovative application of proton LRT is redefining the physical advantages of radiation therapy. By utilizing the Bragg peak characteristics of the proton beam, a steeper dose drop gradient can be formed within the

degree of reduction in the tumor target area, reducing the average radiation dose to normal tissues by more than 40% compared with traditional photon LRT, which is especially suitable for complex cases adjacent to crisis organs [6] [33] [37].

Future technological development will focus on the construction of multiparameter adaptive systems, such as integrating AI dynamic optimization, multimodal image navigation, and particle beam modulation technology, to achieve a leapfrog upgrade from "geometric precision" to "biological precision".

Future research on lattice RT

The clinical application and optimization of lattice RT (LRT) require in-depth research in four core directions.

First, multicenter validation is a crucial step in establishing the clinical status of LRT. There is an urgent need to design a phase III randomized controlled trial to systematically compare the differences between LRT and stereotactic radiotherapy (SBRT) in terms of the local control rate, remote effects and toxicity spectrum, especially to include subgroup analyses of different tumor types (such as pancreatic cancer and soft tissue sarcoma) to determine their preferred indications [14] [30]. This type of research will provide high-level evidence-based support for the development of clinical guidelines for LRT.

Second, the establishment of a dose standardization system is the core challenge for promoting LRT technology. The prescription specification based on the equivalent uniform dose (EUD) needs to integrate tumor volume heterogeneity, radiobiological parameters (such as alpha/beta values), and normal tissue tolerated doses and achieve precise mapping from physical doses to biological effects through dose-volume histogram (DVH) optimization [30] [1]. In addition, dynamic dose carving techniques, such as real-time dose adjustment guided by artificial intelligence, may further overcome the limitations of traditional fixed lattice patterns.

To enhance the understanding of the biology, technical/physical parameters, experimental design, and clinical practice related to lattice RT [29], as well as the exploration of biological mechanisms and radiation therapy strategies, the next frontier area may lie in exploring the use of lattice RT technology and ICIs for combined mode therapy [18].

Finally, the exploration of biomarkers will drive LRT towards the era of personalized therapy. By integrating multiple omics data (such as spatial transcriptomics and radiomics data) to screen predictive biomarkers, including immune microenvironment features (CD8+ T-cell spatial distribution), DNA damage repair-related protein expression (gamma H2AX focus), and the genomic instability score (HRD index), an LRT efficacy prediction model can be constructed to guide the precise matching of combination therapy strategies [21] [30]. Future research needs to combine radiobiology and systems medicine methods to reveal the dynamic interaction network between LRT and the host immune system.

Overview Summary

Lattice radiotherapy (LRT), an innovative technique for three-dimensional dose heterogeneity regulation, has demonstrated unique clinical value in the treatment of giant tumors. Through spatial dose-carving technology, LRT can significantly reduce radiation exposure to surrounding normal tissues while increasing the bioequivalent dose to tumor target areas, thereby achieving dual optimization of efficacy and safety. Its biological mechanism involves a multidimensional regulatory network, including radiation-induced immunogenic cell death-mediated T-cell activation, normalization of the tumor vascular structure, remodelling of microenvironment perfusion, and identification of molecular patterns related to radiation injury. The systemic antitumour immune response is triggered by DAMPs [6] [30]. These characteristics of LRT combined with immune checkpoint inhibitors, antiangiogenic drugs, and other treatment options provide scientific evidence and have potential for expanding indications in solid tumors such as hepatocellular carcinoma and non-small cell lung cancer [30] [43].

In the future, the technological iteration of LRT will focus on three core directions: first,

dynamic target tracking and real-time dose optimization are achieved through multimodal imaging guidance (such as MR Linac and 4D-CT) to address the geometric uncertainty caused by respiratory movement and tumor regression during treatment; second, the development of dose algorithms based on artificial intelligence will promote the evolution of lattice patterns from fixed templates to adaptive topological structures, further enhancing the individualized accuracy of dose carving; and finally, the deep integration of the physical advantages and biological effects of proton LRT (such as FLASH-RT hyperhigh-speed irradiation combined with Bragg peak dose distribution) is expected to overcome the dose limitations of traditional photon radiotherapy and promote the transformation of LRT from palliative tumor reduction to curative treatment strategies [6] [30] [37] [43]. These technological breakthroughs and clinical translational research will jointly shape the new landscape of LRT in the field of precision tumor radiotherapy.

Declarations

Ethics Approval and Consent to Participate: Not applicable

Consent for Publication: Not applicable

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