Spatially fractionated radiation therapy with photon beams-literature review

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Introduction

Spatially fractionated radiation therapy (SFRT) is a promising approach for treatment of bulky tumours (>5-6cm diameter) which usually have a poor blood supply and hypoxia, leading to protection against apoptosis. In addition, an unacceptable RT related toxicity is predicted with a high dose RT or SBRT which limits their use. Using advanced IMRT/VMAT, IGRT and inverse planning, intentionally high heterogeneous dose distributions are created in the pattern of lattice of multiple spherical vertices of high dose (peaks) and regions of low doses (valleys) with a typical dose ratio 100%/30%, a technique known as Lattice RT (LRT), a subcategory of SFRT (Figure 2, 3).

These highly heterogeneous dose distributions are the basis for the SFRT radiobiological rationale and effects [1]:

◊ **Cell signalling effects**:

- **bystander-like effect**-invoked on the tumor cells located in the dose valley regions. Some positive bystander-like effects on normal tissues has been hypothesised,

- **abscopal effect**- deceleration of distant tumour growth- regulated by immune system.

◊ **Microvascular changes** and preferential vascular damage on the immature tumour vessels.

◊ **Immunomodulation** - SFRT might prime an effective immune response against cancer cells both in irradiated and not irradiated lesions.

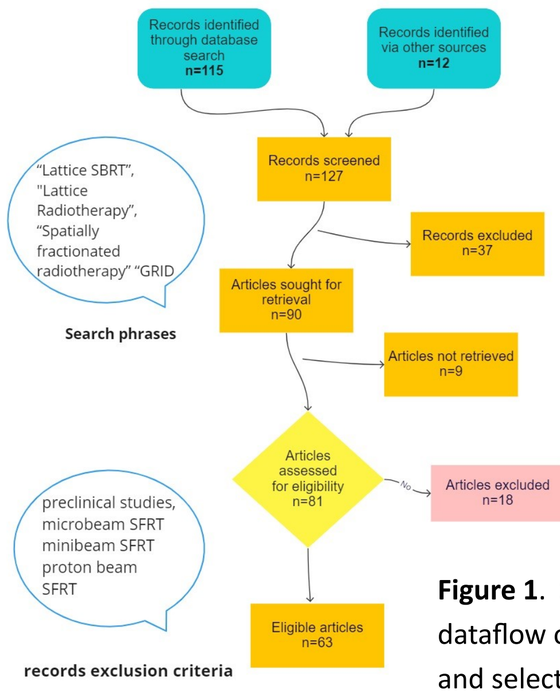

Figure 1. Search phrases, dataflow of the screening and selection processes

Purpose

To review SFRT/LRT clinical results and various planning & plan evaluation SFRT/LRT methodologies with photon beams from clinical radiotherapy systems.

Methods

A search in the Medline database (PubMed search tool) was performed on the 2nd of January 2023. The search phrases, dataflow of the screening and selection processes are shown in Figure 1.

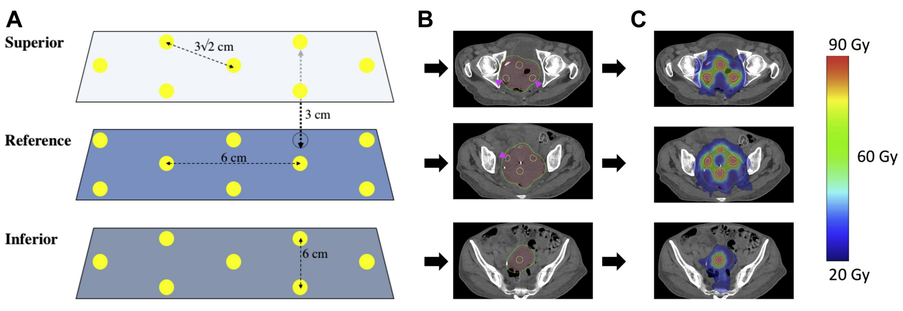

Figure 2. A regular diamond- shaped geometric lattice pattern. From *Duriseti, S., et al., 2021 p.2* [5].

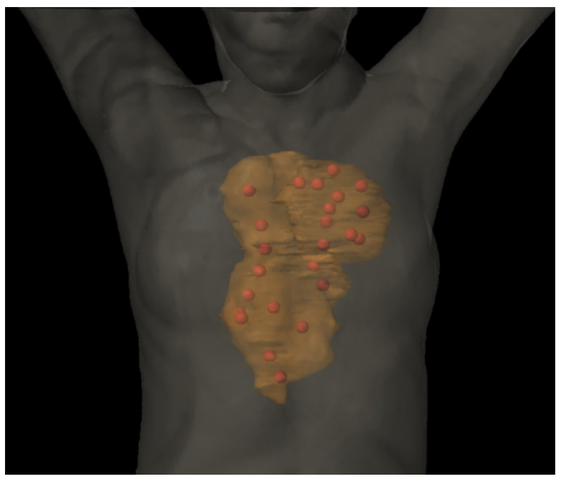

Figure 3. Irregular placement of 1.5-cm diameter spherical contours throughout the GTV. From *Grams et al., 2021, p. e341* [6].

Results

The search returned 115 records, 12 were identified via other sources and 63 eligible articles were reviewed. There is intensive growth of ~30% in the number of SFRT publications in the last 12 months. Hundreds of patients, mainly in three centres in the USA with H&N, sarcoma, gynaecological and lung disease sites, were treated with Lattice SBRT. The majority of clinical publications on SFRT are case reports and retrospective studies [2, 3], however the initial results from a phase I prospective study with 20 patients (22 tumours) demonstrated no likely treatment-associated grade 3 + toxicity (90-day period) and one case of grade 4 toxicity (possibly associated with LTR) [4]. An ongoing phase II clinical trial will evaluate late safety and efficacy of Lattice SBRT. The details of a selection of the reviewed clinical studies are listed in Table. 1

The vertices' diameter and separation, Dose in vertices and Dose in valleys are the main LRT plan parameters (Figure 2). Two main geometrical lattice patterns & creation approaches were identified [5, 6]:

- regular diamond- shaped lattice pattern (1.5cm spherical vertices, 6cm separation (Figure 2),
- irregular placement of the high dose vertices to fit induvial GTV in terms of shape, volume, location (Figure 3).

More details of the lattice parameters, example of non-geometrical biological-guided vertices placement, and QA delivery methods used in some reviewed articles, are listed in Table 2. Dose heterogeneity is the most important dosimetric characteristic to be defined and reported for plan evaluation. No consensus on the LRT quantities describing high heterogeneity, as well as LRT dose prescribing & reporting approach, has been reached.

Reference LATTICE SBRT/LRT	Treatment site/tumour	LRT Dose & fractionation	Patients treated	LRT type	End point, aim	Follow up	Consolidating RT / chemotherapy	Results
Tubin S, Helmut P, Brcic I, 2019 doi.org/10.1186/s13014-019-1227-y **(SBRT-PATHY)**	bulky tumors >6cm on CT; chest, abdomen, H&N, with limited treatment options; diameter was 8.8 cm (range 6–17 cm); hypoxic tumor segment, bystander tumor volume (BTV), mean 57.1 mL (range 5–137 mL);	1–3 fractions each of 10–12 Gy to the 70% isodose-line to BTV (neoadjuvant, palliative, salvage)	23 patients, retrospectively, treated 03/2016 to 02/2018	VMAT SBRT by VERSA HD (Elekta AB	Overall and progression-free survival rates - 70% (16/23) and 87% (20/23), respectively (95% confidence interval)	median follow-up 9.4 months (range 4–20 months)	No systemic therapy	mean time of 4 weeks, the median bulky shrinkage was 70% (range 30–100%) with four (17%) complete responses, and 50% (range 30–100%) for unirradiated metastases
Amendola et al., 2020 doi.org/10.1667/RADE-20-00038.1	patients with **bulky NSCLC** unresectable tumours; PET-CT baseline assessment	18Gy/1fr 3Gy/1fr in the periphery; no previous lung irradiation	10 (over 7 years), clinical study	VMAT RapidArc	evaluation of tumor response and the overall safety	median follow-up of 6 months (range: 1-71 months)	After LRT - conventional RT of 25-33 fr in 1.8-2.0 Gy +boost up to 90 days for 7 pts	mean decrease in tumor volume was 42% (statistically significant); no mortality related to LRT. No significant acute or chronic toxicity was noted; grade 1 radiation pneumonitis
Ferini et al., 2022a, doi.org/10.3390/cancers14163909 **(LATTICE_01 multicenter study)**	solid cancers (bulky disease>5cm) in clinical stage IV; Intrathoracic 5, Abdomen–pelvis 15, Breast 2, Soft tissue 4, H&N 4	10–27 Gy in 1/3 fr; then followed by conventional palliative RT, within 7 days	30 (prospective observational study(	VMAT/IMRT on Linac or Cyberknife	feasibility, toxicities, and clinical response in Stage IV patients treated with palliative "metabolism-guided" lattice technique	8, 30, and 60 days from the end of irradiation	with or without chemotherapy, or immunotherapy, hormone therapy, or targeted therapy	(CTCAE and RTOG criteria); rate of symptomatic response - 100%; Radiation-related acute grade ³1 toxicities - observed in 6/30 (20%) patients. The rate of overall clinical response was 89%, 23% of complete remission. The 1-year overall survival rate was 86.4%
Dincer et al, 2022 doi.org/10.7759/cureus.23980	two cases of bulky liver metastases	50Gy-vertices; 30Gy- valley;in 5 fractions	2 cases	MRgRT online adaptive LRT (OALRT); step and shoot IMRT			-	Both patients had good treatment compliance without any Grade 3+ side effects
Duriseti et al., 2022 doi.org/10.1016/j.radonc.2021.11.023	20 patients (22 tumours); GTV range: 54.2–3713.5 cc; 11.1 cm median (range: 5.6–21.4 cm)-greatest axial diameter; soft tissue sarcoma, NSCLC, 1 thymic and 1 mesothelioma, endometrial and colonic adenocarcinoma	5 fraction Lattice SBRT, 20 Gy in 5 fractions with a SIB to 66.7 Gy in a defined geometric arrangement (Lattice boost	20 (22 tumours)	VMAT RapidArc	the rate of 90-day treatment-associated grade 3 + acute toxicity by CTCAE; changes in GTV and peripheral blood cytokines	3 months	no concurrent systemic therapy; 2 week washout period before and after LRT; other conventional palliative RT courses to other lesions	no likely treatment-associated grade 3 + toxicity in the 90-day period (acute and sub-acute); one case of grade 4 toxicity (possibly associated with Lattice SBRT)
Borzov , Bar-Deroma and Lutsyk, 2022 doi.org/10.1016/j.phro.2022.04.010	non-metastatic patients with large soft tissue sarcoma, hip region 5 cm or more in size	Pre-op, single fraction of 20 Gy	3 patient to date (2022)	LRT, VMAT	Reported elsewhere	Reported elsewhere	Sequentially to LRT 50 Gy in 25 fr; delivered over 5 weeks	Only Grade 1 (accordingly to CTCAEv4); all 3 pts underwent surgery, one had skin healing problems after surgery.

Table 1. LRT clinical studies and clinical results

Study (clinical or planning dosimetric)	LRT Lattice patterns of vertices placement	vertex diameter	vertices (peaks) separation, (center-to-center)	GVT volume; greatest dimension	vertices volume to GTV ratio, V_v /V_{GTV} (volume ratio), %	Dose $_{vertices}$ & Dose $_{valeys:}$ (PVDR or VPDR, peak-to-valley dose ratio)	Sequential RT	Lattice Inward margin and dose	Delivery techniques and platform	QA, plan integrity and deliverability, motion management; Lattice and other comments
Jin et al., 2015 doi.org/10.1016/j.radonc.2015.07.047 **(dosimetric study)**	Geometrical-regular	0.5 cm	1.5 cm	112.9cc	Large number of spheres, orderly positioned to form a lattice	N/A	N/A	N/A	IMRT plan with 9 non-coplanar beams at special tunneling directions	Gafchromic film EBT3 film, coronal plane; criteria 3%/ 1 mm showed a passing rate of >95%
Amendola et al., 2019 doi.org/10.7759/cureus.4263	Geometrical-irregular	0.8 to 1.5cm	3.6 cm (average); varies within lattice	46 - 487 cc (mean 195 cc) max diameter: 5 - 14 cm (mean 8 cm);	from 0.8% to 2.2%. number of vertices 2-7	Dvertices =18Gy; GTV - 3 Gy; 6 MV photons; 1#	45–58 Gy (1.8–2 Gy/fr)	N/A	VMAT- 6MV RapidArc, Varian Trilogy or Edge	NSCLC
Wu et al., 2020 doi.org/10.1667/RADE-20-00066.1	Geometrical-irregular	0.5-1.5cm	2.0-5.0cm	GTV ³ 50 cc	V_v / V_{GTV} = 1.0-10.0%	$D_{vertices}$=10-25Gy/fr; D_{valeys}<5Gy/fr	Yes	1-2cm; $D_{GTVmargin}$ =2-5Gy	IMRT/VMAT; Cyberknife	Intra-fractional motion considered in tuning vertices sizes
Kopchick et al., 2020 doi.org/10.1002/mp.14379	Geometrical-regular	5 mm; non-coplanar beams	2 cm apart - transverse& sagittal planes; 2.5 cm - coronal plane,	hemispherical digital phantoms of 10, 15, and 20 cm in diameter	N/A	N/A	N/A	N/A	N/A	Simulation of small collimator on GammaPod
Duriseti et al., 2021 doi.org/10.1016/j.adro.2020.100639 **Kavanaugh et al., 2021**	Geometrical-regular diamond--shaped lattice	1.5 cm	6 cm in orthogonal axes, and 3√2 cm along the diagonal	GTV = 350-4475 cc; range, 10-18.5 cm; GTV range: 54.2–3713.5 cc; Median diam 11.1 cm (range: 5.6–21.4 cm)	Lattice composite, PTV6670/ GTV2000 x 100) 1.9-4.3% range	66.7Gy & 20Gy/5fr SIB; Peak-valley dose gradient 100% to 30%	No	0.5 cm contraction of the GTV_2000,	VMAT Varian Truebeam Linac	As per the standard SBRT QA: (EPID) portal dosimetry 3%/3 mm and 2%/2 mm; 1D ion chamber absolute dose measurements within 3% of expected dose; in PTV_Avoid structure-larger deviation of 5% local dose; Dyna QA-Dynalog files-Varian; vertices outside lattice volume -removed
Grams et al., 2022 doi.org/10.1016/j.radonc.2021.12.003	Geometrical-irregular	1.5-cm diam. spherical contours throughout GTV	Placement of spheres is variable; center-to-center ³3cm-any direction	Two GTVs -1703cc and 3680cc	N/A	20Gy/1fr; valley doses 30-40% of Px	Yes, 20Gy/5fr	0.5cm inward; edge of any sphere must be >1 cm from any OAR.	VMAT RapidArc; 3 to 4 arcs, or more if >"5 spheres; couch up to 10 deg;	only D50% of each vertex = prescription dose
Borzov , Bar-Deroma and Lutsyk, 2022 doi.org/10.1016/j.phro.2022.04.010	Geometrical-irregular high dose nuclei (HDNs)	cylinders 1 cm diam and 1 cm height	distance between HDNs was 1–2 cm	202, 181 and 132 cm3 leg sarcomas masses	~3%	20Gy and 5-7Gy in 1 fr.; PVDR as D10/D90 ratio is 3.5-4.7	Yes, 50Gy/25fr	Not specified	VMAT, 6FFF; Elekta VersaHD; Agility HD MLC, Monaco TPS	Delta4 + phantom (ScandiDos, Sweden); higher than 95% pass rate for a 3%/2 mm criterion; 5 to 8 HDNs, position of each HDN –by rad oncologist with regards GTVcomplexity, OARs proximity,
Ferini et al., 2022a doi.org/10.3390/cancers14163909 **LATTICE_01**	Non-geometrical; arbitrarily by each radiation oncologist	1.0 cm	at least a 2.0 cm separation	Range 50.9–2039.7cc; 5 – 10cm in 25 patients; >10cm in 6 patients;	number of spheres: median 4, range 1–6; Vv /GTV not reported	Dose vertices-15 Gy/1 fr. (range 10–27 Gy in 1/3 fr); dose to the valley not reported.	conventional palliative RT, within 7 days	Not reported	IMRT or VMAT on TrueBeam, Agility, Synergy, Cyberknife, 6D-Robotic-Couch	≥98% dose coverage of the vertices volume; spherical "Vertex" interface is the SuperAvid PET Area (SAPA) and the remaining part of the AvidPETArea (APA); or between APA and photopenic PETArea (PPA);

Table 2. Lattice parameters , planning parameters and QA of LRT

Conclusions

SFRT and LRT planning & plan evaluation methodologies and clinical studies for LRT efficacy are very dynamic and developing areas in modern radiotherapy. SFRT and LRT have the potential to become a main stream RT approach in the near future.

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