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Scientific Article

Time-Related Outcome Following Palliative Spatially Fractionated Stereotactic Radiation Therapy (Lattice) of Large Tumors – A Case Series

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Purpose: Lattice radiation therapy (LRT), a form of spatially fractionated radiation therapy, holds promise for treating large tumors. Despite its introduction in clinical practice around 2010, there remains limited information on its time-related outcomes despite consistently high response rates and tolerability. We assessed the time-related outcome of our palliative LRT cohort.

Methods and Materials: We conducted an analysis of our LRT program, which involved 45 palliative patients with 56 lesions larger than 7 cm, treated between January 2022 and November 2023. Prospectively defined treatment protocols included delivering 20 to 25 Gy/5 fractions to the tumor with a stereotactic simultaneously integrated boost (SIB) of 60 to 65 Gy to lattice vertices (n = 45/56) or, mainly in preirradiated lesions, single fraction stereotaxy with 1 × 15 to 20 Gy to vertices only (n = 11/56). Follow-up (FU) intervals were determined based on clinical considerations, considering the mostly highly palliative situation of included patients. Outcome assessments focused on subjective benefit and objective radiologic FU response.

Results: The mean/median FU was 5.5/4.0 months (0.3-21 months). A total of 25/45 (56%) patients died after a mean/median of 3.9/2.0 months (0.3-14 months). Fourteen of 56 lesions (25%) were previously irradiated, with a mean/median of 18/13 months (4-72 months) prior to LRT. The mean/median gross tumor volume (GTV) measured 797/415 cc (54-4027 cc) and 14/13 cm (7-28 cm). Subjective statements at LRT completion were available from 37 symptomatic patients: 32/37 (87%) reported fast symptom relief, and 5/37 felt no change under LRT or at LRT completion. Early tolerance was excellent (G0-1). FU imaging was available from 40/56 lesions (71%): progression in 3/40 at first exam one at 1.5 and 4 months post-LRT, and stable disease (±10%) in 5/40 assessed at 2, 3, 3, and 4 months post-LRT. First measure shrinkage of 48%/30% (10%-100%) was found in 32/40 lesions (80%) after a mean/median of 2.8/3 months (0.3-7 months). Maximum shrinkage over time based on 21 cases with at least 1 FU imaging measured a mean/median of 62%/60% after 6.2/5.5 months. The duration of radiologic response was a mean/median of 7.4/7.0 months (1-21 months).

Conclusions: Short-course LRT emerged as an effective and well-tolerated palliative option for very large lesions, whether treatment-naïve or previously irradiated. Nearly 90% of symptomatic patients reported significant subjective benefit, and 80% of assessed lesions demonstrated tumor shrinkage ≥10%, with a mean response duration of >6 months.

Introduction

In recent years, there has been a significant increase in awareness and publications related to spatially fractionated radiation therapy (SFRT).[1-3] One promising form of SFRT, known as lattice radiation therapy (LRT), has

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Research data are stored in an institutional repository undergoing permanent updates; most recent data will be shared on request to the corresponding author.

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primarily been used to treat patients with large, inoperable, or metastatic tumors.[4] Initial clinical reports on LRT, dating back to around 2010, mostly in palliative care settings, consistently demonstrate unexpectedly high tumor responses and excellent treatment tolerance. Over the past 13 years, data from more than 250 patients with bulky tumors treated with LRT have been published. However, many questions about optimal dose volume, fractionation, and geometric solutions remain unanswered, and several experimental approaches are currently being explored.

A recent systematic review by Iori et al[5] in 2023 summarizes clinical results from 81 patients (84 lesions) across 12 selected articles published between September 2015 and September 2022, including case reports, case series, and clinical studies with image-based follow-up (FU) ranging from 1 to 10 months. The authors reported a median lesion reduction of approximately 50% or more when a complete response was not achieved within 3 to 6 months after LRT. An overview of phase 1 LRT trials and case reports (searched in PubMed and Google) is presented in Table 1.[6−27] Wu et al, in their 2020 paper[25], mentioned that since its introduction in 2010, over 150 patients with late-stage bulky tumors have received LRT, primarily at 2 centers: the Innovative Cancer Institute in Miami, Florida, and Fujian Union Hospital in Fuzhou, China.[6]

However, knowledge regarding the long-term outcomes of LRT, including the extent and duration of its effects, remains limited. Therefore, the aim of this analysis was to evaluate the time-related clinical outcomes of our prospective single-center cohort treated with palliative LRT.

Methods and Materials

We conducted an analysis of our LRT program, which involved 45 palliative patients with 56 lesions larger than 7 cm, treated between January 2022 and November 2023. Treatment concepts and data collected were prospectively defined.

Patients

Inclusion criteria

All patients treated with LRT who were referred for palliative radiation therapy (RT) evaluation of large tumors ≥7 cm. In all cases, surgical intervention was either not feasible or not indicated, and systemic therapy was not indicated/not possible/not effective anymore.

Exclusion criteria

Patients who did not sign the Hospital General Informed Consent or the RT-specific information sheet were excluded (n = 0). Patients who were not willing (anymore) to undergo any RT or considered with terminal stage of disease with an expected life expectance of less than a few weeks were not treated. Cases with a histopathological diagnosis of Morbus Hodgkin disease (MH) or Non-Hodgkin lymphoma (NHL) were excluded.

Patient and tumor characteristics

For several of these patients with exceptionally large tumors, the omission of any palliative RT has been considered on the availability of LRT as an option. Prior to LRT, most patients had undergone one or more systemic treatments. Patient and tumor characteristics are summarized in Table 2. Clinical and radiological FU was conducted on an individualized basis, tailored to the needs of this palliative cohort. FU imaging was not performed solely for analytical purposes, resulting in incomplete radiographic FU for the cohort (40 out of 56 lesions were examined with at least 1 magnetic resonance imaging or computed tomography scan, accounting for 71% of cases), making precise time-related volumetric change analysis unfeasible.

LRT

Among the various dose-volume regimens reported in the specific SFRT literature,[1−27,29−32] our LRT schedule was prospectively decided based on the principles outlined by Duriseti et al[7] in 2020-2021 and applied in their LITE SABR M1 phase 1 trial published in 2022.[7,29] Our treatment protocols included delivering 20 to 25 Gy in 5 fractions to the tumor with a stereotactic simultaneously integrated boost (SIB) of 60 to 65 Gy to lattice vertices (n = 45/56) or, mainly in preirradiated lesions, a single fraction stereotactic LRT dose with 1 × 15 to 20 Gy to vertices only (non-SIB LRT, n = 11/56).

The lattice stereotactic body radiation therapy (SBRT) prescription was formulated with the goal of delivering a standard 5-fraction palliative dose of 2000 cGy to the tumor planning target volume (PTV) 2. Traditionally, spatially fractionated techniques create a peak-valley dose gradient ranging from approximately 100% to 30%. Consequently, a simultaneous integrated boost of 6670 cGy was selected as the lattice boost dose prescription.

Additionally, especially for LRT administered to previously irradiated lesions or regions deemed at high risk within normal tissues, we adopted the approach described by Jiang et al[13] and Dincer et al.[17] This involved delivering a single fraction of approximately 20 Gy to the vertices exclusively.[13,17]

Volumetric modulated arc therapy lattice SBRT plans were designed to provide a palliative PTV2 dose of 20 to 25 Gy in 5 fractions to the tumor mass (with or without margins). This was achieved while maintaining a peak-to-valley dose gradient of approximately 30% to 100%, resulting in a simultaneously integrated boost PTV1

Table 1 Selected phase 1 trials/case reports/cohort reports (PubMed, Google, July 2023)

Author<	Publication (Y)	Interval	Type	No. patients	No. lesions	Intention	Schedules	Diagnosis, inclusion	FU	Result	>1 FU imaging (CT, MRI, PET-CT)
Pollack et al[26,*] NCT01411319 LEAD	2020	December 2011 to December 2014	Phase 1 trial	25	25	Definitive	Sequential 1 × 12-14 + 76/38 fractions	Prostate	Mean, 66 mo	No G3	-
Duriseti et al [7] NCT04133415/ 04553471 LITE SABR M1	2022	October 2019 to August 2020	Phase 1 trial	20	22	12 palliative 5 palliative-progr 3 definitive	SIB 20/66.77 y in 5 fractions	4.5 cm, any (9 sar-coma, 7 NSCLC, 4 carcinoma	NR	47.4% shrinkage at 1 and 4.5 mo in 13 and 11 out of 22 patients, no G3	-
Larrea et al[8] Valencia protocol	2022	December 2019-? (abstract)	Phase 1 trial	21	21	Palliative	1 × 15-18 Gy + RT 2-3.5 Gy/ fractions	>45 cc, 1 sar-coma, 20 carcinoma	NR	>50% shrinkage in 9/9 patients 2 wk post LRT	-
Ferini et al[9] Lattice_01 multicenter	2022	June 2020 to December 2021	Phase 1 trial	30	31	Palliative	1 × >10 Gy-27 in 3 fractions, sequential 20/4 fractions-40/15 fractions homogeneous	>5 cm, stage IV bulky, 5 sar-coma, 3 melanoma, 18 carcinoma	Median, 11 mo (range, 6.8-20.5)	Clinical response 89%, 23% CR, symptomatic response in all	-
Amendola et al[10,*]	2010	-	Case report	1	1	curative	2 × 3 Gy + 20 × 1.8/2.4 Gy + CDDP + S	Cervical Ca	NR	70% shrinkage, histological. CR	-
Blanco Suarez et al[11,*]	2015	-	Case report	1	1	Palliative	SIB 9/27 Gy in 3 fractions + 20 fractions nRT	Mullerian ovarian tumor	4 mo	>70% shrinkage	-
Amendola et al[12,*]	2018	-	Case report	1	1	Curative	29 × 2 Gy + 1 × 18 Gy	SC lung	3 mo/6 y	7.5 to 2.8 cm shrinkage/ 2.8 cm	Yes (n = 1)
Jiang et al[13]	2021	-	Case report	1	1	Palliative	1 × 20 Gy	Chest wall	7 mo	CR at 2 mo	Yes (n = 1)
Schiff et al[14]	2022	-	Case report	1	1	Palliative	SIB 5 × 4/20 Gy	Endometrial M	4 d	Regression, lysis syndrome	-

(*continued on next page*)

Table 1 (*Continued*)

Author<	Publication (Y)	Interval	Type	No. patients	No. lesions	Intention	Schedules	Diagnosis, inclusion	FU	Result	>1 FU imaging (CT, MRI, PET-CT)
Ferini et al[15,16]	2022	-	Case report	1	1	Palliative	1 × 15 Gy sequential 10 × 3 Gy	Skin SCC M	1/4 mo	Regress/absence of pathological metabolism	Yes (n = 1)
Dincer et al[17]	2022	July 8, 2021	Case report	2	2	palliative	SIB 50/30 Gy in 5 fractions	Rectal M/anal M	1/3 mo	Near CR/>50% shrinkage	-
Larrea et al[18]	2022	November 2019 to September 2020	Case report	2	2	Curative	1 × 15 Gy + EBRT/CDDP/ BT×	Cervical cancer > 45 cc	5 + 14 mo	CR	-
Borzov et al[19]	2022	NA	Case report	3	3	Preoperative	1 × 20 Gy + 50 Gy/25 fractions	Sarcoma	NR	CR in 2/3	-
Iori et al[20]	2022	-	Case report	1	1	Palliative	SIB 55/20 Gy in 5 fractions	Sarcomatoid lung cancer	3/6 mo	19 × 16 cm to 8 × 4 cm/stable	Yes (n = 1)
Montero et al[21]	2023	-	Case report	1	1	Palliative	1 × 20 Gy GRID + 50 Gy/25 fractions + pembrolizumab	Melanoma	2 and 5/ 12 mo	>75% shrinkage and CR	Yes (n = 1)
Hatoum et al[22]	2023	-	Case report	1	1	Preoperative	4 × 1 × >12 Gy/ wk + standard 50 Gy	Sarcoma	NR	>95% necrosis, wound complications	-
Price et al[23]	2023	-	Case report	2	2	Palliative	SIB 20/66.7 Gy in 5 fractions	Sarcoma and carcinoma	3 mo	88% and 15% shrinkage	-
Amendola et al[28,*]	2019	7 y	Cohort	10	10	Curative	1 × 18 plus 50 nRT/25-33 fractions	NSCLC	Mean, 10 mo (range, 1-73)	Mean shrinkage 42%	-

(*continued on next page*)

Table 1 (*Continued*)

Author<	Publication (Y)	Interval	Type	No. patients	No. lesions	Intention	Schedules	Diagnosis, inclusion	FU	Result	>1 FU imaging (CT, MRI, PET-CT)
Amendola et al[24]	2020	January 2013 to April 2019	Cohort	10	10	Curative	SIB 9/24 Gy/3 fractions + 45 Gy in 1,8 Gy + CDDP	Cervical carcinoma > 5.2 cm	2.2 mo (range, 0.2-4.5)	CR in 55%, 45 PR (mean, 63% shrinkage) All: mean, 54% shrinkage (range, 6-91)	-
Wu et al[25] -Innovative Cancer Institute* -Fujian Union Hospital	2020	April 2010 to July 2019 April 2017 to December 2020	Cohort Cohort	56 69	56 69	Mostly palliative	Vertex dose 2.4-18 Gy Vertex dose 8-20 Gy/fraction	All > 40 cc All > 17 cc	NR NR	NR NR	-
Larrea et al[6], abstract 2916]	2021	January 2020-2021	Cohort	11	11	Palliative	1 × 25 Gy + 55 Gy/20 fractions	NSCLC > 45 cc	NA	2 CR, 6 >50% shrinkage, 2 SD, 1 PD	-
This study	2024	January 2022 to November 2023	Cohort	45	56	Palliative	20-25/9-13 in 5 fractions (45) 1 × 20 Gy vertices only (11)	Sarcoma, melanoma, carcinoma, >7 cm	5.5/4.0 mo (range, 0.5-21)	In 40/56 imaged lesions, mean/median of 48%/30% shrinkage (range, 10%-100%)	Yes (n = 21): maximum shrinkage mean/median of 60%/62%
TOTAL	13 y			∼266	∼270	Mostly palliative					

Abbreviations: BTx = Brachytherapy; CA = carcinoma; CDDP/5-FU = Cisplatin/5-Fluorouracil chemotherapy; CR = complete response; CT = computed tomography; EBRT< = External beam radiation therapy; FU = follow-up; G3 = grade 3; LRT = lattice radiation therapy; M = Metastasis; MRI = magnetic resonance imaging; NR = not reported; nRT = normofractionated radiation therapy; NSCLC = non-small cell lung cancer; PET = positron emission tomography; PR = partial remission; RT = radiation therapy; SC = small cell; SCC = squamous cell carcinoma; SD = stable disease; SIB = simultaneously integrated boost.

*: there may be some patient duplicates included.

Table 2 Patient and tumor characteristics

Parameter	N
No. patients	45
No. treated lesions	56
Age, mean/median (range), y	64.9/66 (18-93)
Localization of treated lesions	• 27 abdomino-pelvic/retroperitoneal • 8 pleuro-pulmonal • 6 lower extremity • 4 thoracic wall • 2 sternal • 5 axillary/breast • 1 skin • 1 upper extremity • 2 cervical/nodal
Histopathological diagnosis of lesions	• 24 carcinoma • 18 sarcoma • 14 melanoma
Lesion size, mean/median (range)	
• Diameter	• 14/13 cm (7-28)
• GTV	• 797/415 cc (54-4027)
Previous local RT	14/56 lesions (25%) after a mean/median of 18/13 mo (range, 2-72)
Systemic therapy	
• Previous ± post	• 39/56 lesions
• During LRT	• 3/56 lesions
• None	• 14/56 lesions
LRT schedule	
• 5 × 4-5 Gy/9-13 Gy, simultaneous integrated boost	• N = 45
• 1 × 20 Gy	• N = 11
LRT characteristics, mean/median (range)	
• PTV2 whole mass (0-5 mm margin to GTV)	• 1161/777 cc (87-4460)
• PTV1 vertices	• 5.4/3.3 cc (0.35-36.4)
• % PTV1 of PTV2	• 0.7/0.5% (0.05%-4%)
• No. vertices	• 8.6/5 (1-83)
FU, mean/median (range), mo	
• All patients	• 5.5/4.0 (0.3-21)
• Alive (n = 20/45)	• 7.5/7.5 (0.5-21)
• Dead (n = 25/45)	• 3.9/2.0 (0.5-14)

Abbreviations: FU = follow-up; GTV = gross tumor volume; LRT = lattice radiation therapy; PTV = planning target volume; RT = radiation therapy.

prescription dose of approximately 13 Gy per fraction to the vertices. The geometric arrangement of the lattice SBRT technique employed spherical vertices with a diameter of approximately 1 to 1.5 cm and a separation distance of roughly 3 cm between vertex centers. A minimum of 2 cm distance was prescribed from PTV1 (vertices) to surrounding normal tissues. Maximum distance between vertices measured 3.2 cm (anatomic reasons).

Besides the geometric constraints, the number of maximal vertices is limited by the tumor volume and shape, the potential mobility of the mass, and the surrounding normal tissue structures. In order to minimize any risks for normal tissue damage, the placement of especially lateral vertices was based on manual edition and individual decisions. Regarding the placement of vertices in different tumor zones, ie, well-oxygenated versus transitional zones versus necrotic areas, we did not take this too much into account (yet) considering the still limited knowledge on these aspects.[16]

All patients received treatment according to the 2 aforementioned regimens. Volumetric modulated arc

therapy was employed as the treatment technique using multiple coplanar and noncoplanar arcs to ensure an appropriate conformal dose gradient between the vertices. PTV1 vertice volumes were maintained at greater than 95% coverage with 95% of the prescribed dose, while the maximum dose remained below 120%.

Statistics

An Excel database was used for the collection and analysis of prospectively defined parameters. The VARIAN ARIA treatment planning system was used to assess tumor volumes using its automatic volume measure tool.

Ethical approval

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

The mean/median FU of the entire palliative cohort was 5.5/4.0 months (0.3-21 months). Twenty-five of 45 (56%) patients passed away after a mean/median of 4.4/2.0 months (0.3-14 months) (Table 2). The mean/median gross tumor volume (GTV) measured 797/415 cc (54-4027 cc), and the tumor diameter measured a mean/median of 14/13 cm (7-28 cm).

Thirty-four of 45 patients had undergone palliative systemic therapy prior to and/or after LRT, and 14/56 lesions (25%) in 14 patients had previously been irradiated at a mean/median of 18/13 months (range, 4-72 months) prior to LRT.

Treatment tolerance

All patients completed the prescribed short-course LRT. Early side effects were limited to G0 to 1, except for 2 patients who experienced G2 to 3 dermatitis because of lesions directly affecting the skin. No late radiation-associated side effects have been observed so far.

Patient-reported outcome

Regarding subjective benefits, 5/45 patients underwent LRT for asymptomatic masses. Three patients' post-LRT patient-reported outcome statements could not be adequately assessed, primarily because of poor general end-of-life conditions and/or simultaneous analgesic drug therapy; 5 patients did not experience early changes in symptoms at LRT completion. The remaining 32 out of 37 (87%) symptomatic patients able to provide subjective feedback reported rapid and significant symptom relief either during or immediately after LRT completion.

Objective response rate

Radiologic response

Radiologic treatment response data were available in 40 out of 56 lesions (71%). Among these, 21 lesions underwent second to fourth additional FU examinations, totaling 74 radiologic assessments. These assessments were conducted at mean/median intervals of 2.6/2.0 months, 5.1/5.0 months, 8.1/7.0 months, and 9.6/7.2 months from LRT to the first, second, third, and fourth FU, respectively. Stable disease was defined as <10% volumetric change compared with pre-LRT GTV. The following response patterns were identified:

- Progression occurred in 3/40 lesions (8%), as evidenced by the first FU exam at 1, 1.5, and 4 months post-LRT.
- Stable disease was found in 5/40 lesions (11%) assessed at 2, 3, 3, and 4 months post-LRT.
- First measure tumor shrinkage of a mean/median of 48%/30% (10%-100%) was found in 32/40 lesions (80%) after a mean/median of 2.8/3 months (0.3-7 months) post-LRT. Maximum shrinkage over time measured a mean/median of 62%/60% after 6.2/5.5 months.

Figure 1 provides volumetric changes in 21 lesions with >1 FU imaging. The graph suggests poorer outcomes when shrinkage was modest in the initial FU imaging (without a specific time reference).

Figure 2 illustrates individual volumetric responses over time in the 21 cases with multiple FU imaging sessions. In this subgroup, the mean/median duration of treatment response, defined as either stable disease or tumor size remaining smaller than before LRT, was 7.4/7.0 months (1-21 months). The following patterns were identified:

- Volumetric response appeared independent of pre-LRT tumor size; 20 lesions with smaller GTV (mean/median, 161/125 cc [54-310- cc]) versus 20 lesions with the largest GTV (mean/median, 1098/780 cc [337-2352 cc]).
- Notably, substantial LRT response was not solely reflected in shrinkage; 3 cases with former large lytic bony lesions exhibited significant recalcification as a morphological sign of response (Fig. 3A, B) despite no significant volumetric reduction.
- Volumetric response also appeared to vary with histopathologic diagnosis, with melanomatous lesions

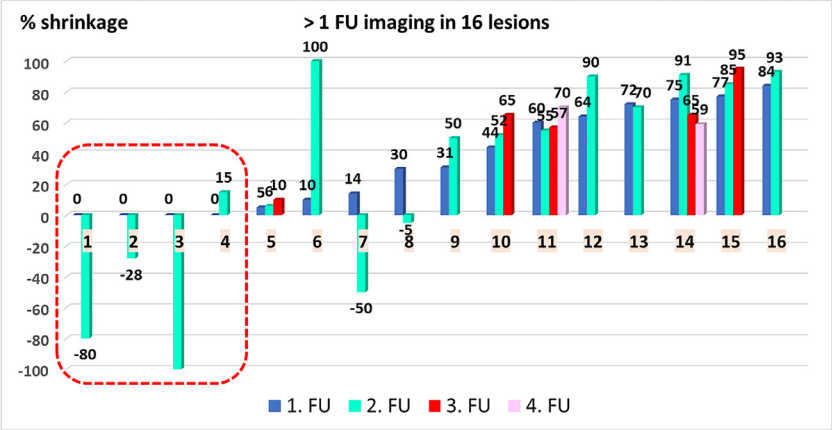

Figure 1 Development of tumor volumes over time in 16/36 imaged lesions that underwent >1 follow-up (FU) imaging (ranking according to percentage [%] shrinkage in the first radiologic FU exam, blue bars). The red dotted line indicates the lesions with no or limited shrinkage assessed in the first FU imaging exam that showed mostly progressive disease in a second FU exam (green bars).

being less responsive compared with carcinomatous and sarcomatous lesions:

- Melanoma (n = 14): mean/median GTV: 317/168 cc (66-4027 cc); mean/median shrinkage of 30%/28% (−10% to 90%) in 10/14 with radiologic FU.
- Sarcoma (n = 18): mean/median GTV: 653/420 cc (88-2105 cc); mean/median shrinkage of 46%/30% (0%-100%) in 11/16 with radiologic FU.
- Carcinoma (n = 24): mean/median GTV: 695/420 cc (141-2352 cc); mean/median shrinkage of 43%/60% (0%-93%) in 15/22 with radiologic FU.

Furthermore, the volumetric response appeared comparable in previously irradiated and radiation-naïve lesions. Among the 9 out of 14 reirradiated lesions with available FU imaging, 1 displayed progression, 2 showed no change, and 6 (66%) exhibited a mean/median shrinkage of 39% (20%-72%). Forty-five of 56 lesions were treated with the 5-fraction SIB-LRT, and 11/56 with single fraction non-SIB LRT (dose to vertices only); the comparison between the 36/45 SIB-LRT lesions with available FU imaging and 4/11 lesions with FU imaging treated with a single fraction non-SIB LRT is challenging because of the imbalanced sample sizes.

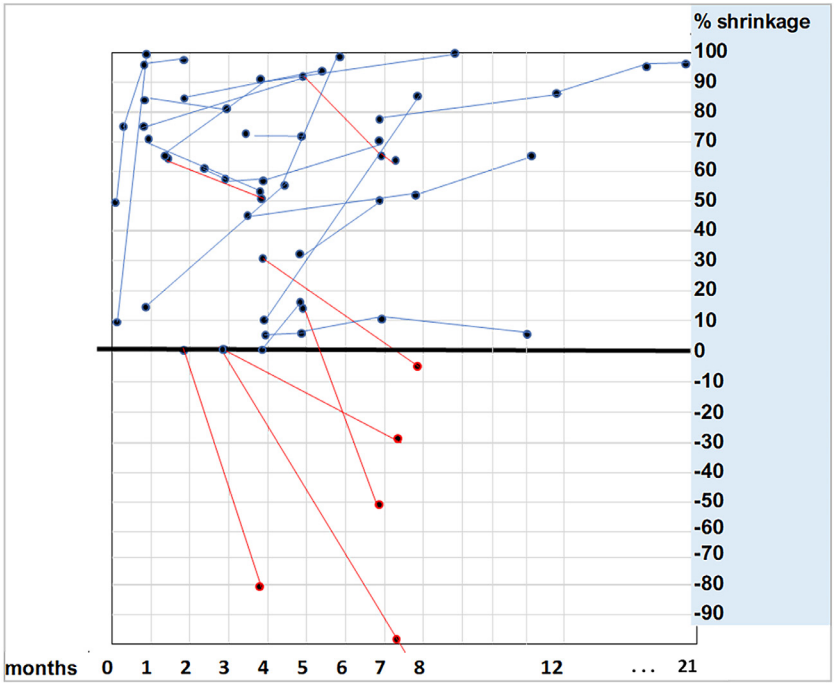

Figure 2 Development of individual tumor volume response over time in 21 lesions with >1 follow-up imaging. The red lines indicate "negative shrinkage," ie, progression following stable disease or following initial tumor shrinkage dots, and each dot indicates one radiologic imaging.

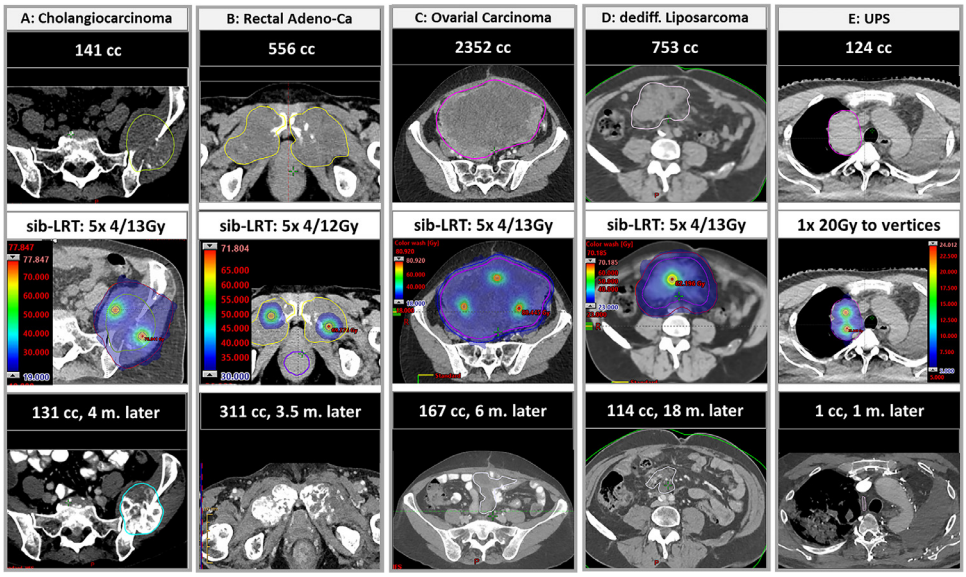

Figure 3 Six examples of morphologic responders out of 40 lesions with available follow-up imaging. (A, B) Substantial recalcification indicating treatment response despite limited volumetric shrinkage. (C-E) Substantial volumetric response.
Abbreviations: LRT = lattice radiation therapy; SIB = simultaneously-integrated boost; UPS = undifferentiated pleomorphic sarcoma;

Among the 4 lesions irradiated with the 1-fraction schedule and having radiologic FU data so far, 1 exhibited no change, while 3 displayed shrinkage of 28%, 100%, and 100%, respectively.

Discussion

The aim of this study was to evaluate the subjective and objective tumor response over time following short-course LRT. Our findings indicate that ~90% of symptomatic patients experienced a rapid and substantial benefit. This observation, combined with excellent treatment tolerance, suggests that LRT fits the profile of an ideal palliative therapy, especially for patients with a limited life expectancy. Objective treatment response, averaging approximately 50%, was observed in 80% of lesions as determined by FU imaging, regardless of their initial size. Notably, lesions that shrank quickly and those of sarcomatous and carcinomatous origin responded more favorably compared with melanoma lesions. The interim analysis showed a response duration of approximately 6 months in cases with multiple radiologic assessments.

However, this analysis has limitations, including a small sample size, a relatively short FU period, and a lack of direct comparisons with other LRT data or conventional palliative radiation schedules for very large lesions.

Comparisons with time-related LRT data

Existing time-related LRT data are scarce, primarily limited to a few case reports (Table 2), which, being selected cases, may not represent general response patterns. Cohort reports providing response-over-time data were not found. The observation of a rapid subjective benefit following LRT aligns with reports from other authors. With an average morphologic response duration of approximately 6 months, LRT may be suitable for patients with both short and longer life expectancies. It may also serve as an effective and safe reirradiation option, resulting in a shrinkage of approximately 40% in about two-thirds of cases. However, there is no available LRT data for preirradiated lesions. The lower responsiveness of melanomatous lesions compared with carcinoma or sarcoma may be suggestive but requires larger sample sizes for reliable conclusions. We found one case report[22] and 3 melanoma cases out of 30 cases in a phase 1 trial[8] with no separate diagnosis-related outcome analysis.

Comparison of shrinkage following LRT

Comparing shrinkage with the existing literature presents some challenges because of variations in the timing of assessments and imprecise reporting of methods (eg, the inclusion of all cases vs responders only, assessments at the first FU imaging, or assessments at the point of maximum response across multiple images). However, on the whole, most authors consistently report approximately a 50% shrinkage, irrespective of the cases included or treatment schedules, a trend similarly observed in our own cohort.

Regarding the available phase 1 trial (as listed in Table 1), our data align with the findings of Pollack et al[6] and Duriseti et al[7], indicating the absence of grade 3 side effects following LRT. Notably, Pollack et al[6] reported

Table 3 Selected reports on palliative hypofractionated nonlattice radiation therapy over the past 15 years (no stereotactic techniques)

Author [ref]	Year	Type	Diagnosis	No. patients	Schedule	TTT	Palliative response/PROM	Objective outcome	G3, %	Median survival (mo)
Chen et al[32]	2008	Retrospective	H&N	23	Quad shot	2 d to ~4-6 wk	Palliative response 83%	NA	9 G3+	4
				12	30 Gy/10 fractions	2 wk	67%	NA	37 G3+	8
				7	37.5 Gy/15 fractions	3 wk	68%	NA	37 G3+	5
				5	20 Gy/5 fractions	1 wk	60%	NA	37 G3+	3
Ghoshal et al[33]	2009	Pilot	H&N	15	Quad shot	2 d to ~4-6 wk	13/15 > 50% response	NA	0	Mean 6
Lok et al[34]	2015	Retrospective	H&N	75	Quad shot	2 d to ~4-6 wk	65%	NA	7	5.7
			(SCC 55%)							
Fortin et al[35]	2016	Phase 2	H&N	32	25 Gy/5 fractions	1 wk	~60% same or better at 1-6 mo	NA	13	6.5
							~30% worse at 1-6 mo			
Finnegan et al[36]	2016	Retrospective	H&N	70	Quad shot	2 d to ~4-6 wk	61% pain response	NA	9	3.8
			(SCC 100%)							
Veluthattil et al[37]	2009	Prospective trial	H&N	25	52.5 Gy/15 fractions	3 wk	Overall response rate 47%:	NA	73	5.1
			OCC				CR/PR 12%/35%			
Hartsell et al[38]	2003	Phase 3	Bone M	454	8 Gy/1 fraction	1 d	CR/PR 15%/50% at 3 mo	NA	24 (all)	9
				443	30 Gy/10 fractions	2 wk	CR/PR 18%/48% at 3 mo	NA		9
Roos et al[39]	2005	TROG 96.05	Bone M	137	8 Gy/1 fraction	1 s	53%, CR 26%, TTF 2.4 mo	NA	NA	4.8 (all)
		Phase 3		135	20 Gy/5 fraction	1 wk	61%, CR 27%, TTF 3.7 mo			
Strøm et al[40]	2014	Phase 3 subset analysis	NSCLC	94	42 Gy/15 fractions	3 wk	HRQOL maintained	NA	30	13.4
Soyfer et al[41]	2010	Retrospective	Sarcoma	15	39 Gy/13 fractions	2.5 wk	12/15 durable pain control	NA	NA	NA
Jacbson et al[42]	2021	Retrospective	Breast CA	9	8 Gy/1 fraction	1 d	Durable response in all 53 parts	NA	~5	NA
				44	39 Gy/13 fractions, 45 Gy/15 fractions, 50 Gy/25 fractions	2.5-5 wk				
Maity et al[43]	2021	Phase 1	Melanoma	22	2-3 × 6 or 8 Gy	1 wk	PR/SD 22.7%/13.6%	NA	50	10.7
					4 cycles ipilimumab post					
Funk-Brentano et al[44]	2020	Retrospective	Melanoma	26	20-26 Gy/3-5 fractions	NA	CR/PR 46%/12%	NA	0	NA

Abbreviations: CA = carcinoma; G3 = grade 3; CR = complete response; H&N = head and neck cancer; HRQOL = health-related quality of life; NA = not assessed; NSCLC = non-small cell lung cancer; PR = partial remission; PROM = patient-reported outcome; Quad shot = 14 Gy in 2 × /d 3.8 Gy over 2 days, 1 to 3 × at 2- to 3-week intervals (RTOG 85-02); SCC = squamous cell carcinoma; TTF = time to failure; TTT = total treatment time.

early shrinkage of 47% in their cohort of 20 patients (excluding melanomas) with lesions measuring ≥4.5 cm, which is comparable to the ∼48% (first imaging) and ∼60% (further FU images) shrinkage observed in our cohort, where larger tumors (≥7 cm) and 1/3 melanomas were included. Furthermore, Larrea et al[8] observed an early shrinkage of approximately 50% in all 9 out of 20 mainly carcinoma patients with lesions measuring ≥45 cc. Similarly, Ferini et al[9] reported on 31 lesions (including 3 melanomas) larger than 5 cm with a clinical response rate of 89%, including a 23% complete response rate, and a symptomatic response observed in all cases. These findings collectively contribute to the growing body of evidence supporting the effectiveness and safety of LRT in various patient populations.

Comparison attempts with time-related non-LRT data

Comparing LRT data with palliative hypofractionated non-lattice RT schedules is challenging, as subjective responses are mostly reported and specific attention to large tumors is lacking. Different approaches to describe subjective outcomes have been reported in Table 3.[32−44] In general, the listed non-LRT data suggest longer treatment duration, higher doses, and, consequently, higher rates of side effects.

Lesions treated with LRT seem to shrink more quickly, and retrospective comparison with historical data remains difficult.

Outlook

Further clinical evaluations are needed to refine optimal dose-volume schedules in LRT. Future comparative analyses, including a comparison between the 5-fraction SIB schedule and the 1-fraction high dose to vertices-only schedules, are planned in order to optimize treatment efficacy for patients and address institutional economics.

Conclusions

In summary, short-course LRT emerges as an effective and well-tolerated palliative treatment for both large, untreated lesions and previously irradiated ones. Approximately 90% of symptomatic patients reported a rapid onset of subjective benefit, and objective radiologic response was observed in 80% of assessed lesions with an average response duration of around 6 months.

Disclosures

None.

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Declaration of AI and AI-Assisted Technologies in the Writing Process

Declaration of generative AI and AI-assisted technologies in the writing process:

During the preparation of this work, the first author used Chat GPT exquisitely to improve language and readability. After using this tool/service, the author reviewed and edited the content as needed and take full responsibility for the content of the publication.

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