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Effectiveness and Safety of Lattice Radiotherapy in Treating Large Volume Tumors: A Systematic Review and Meta-analysis Based on Single-arm Clinical Studies

Wei Li, Meina Piao, Lijun Zhai, Yinju Zhu, Fengjun Lou, Liang Chen, Huankun Wang

Department of Radiation Oncology, The Third People's Hospital of Dalian, Dalian Municipal Cancer Hospital, Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, China

Background: Lattice radiotherapy (LRT) is a novel spatially fractionated radiotherapy technique specifically designed to treat large tumors more effectively. By alternating high-dose and low-dose regions within the tumor, LRT generates a highly diverse dose distribution.

Aims: To review recent literature on LRT to determine its therapeutic efficacy, survival outcomes, and adverse event rates in treating large-volume tumors, thereby strengthening the evidence base for clinical application.

Study Design: Systematic review and meta-analysis.

Methods: We conducted a meta-analysis of all relevant LRT studies identified in four databases-PubMed, Embase, the Cochrane Library, and Web of Science-from their inception to September 2024. Only full-text articles were considered eligible. This study adhered to the 2020 PRISMA guidelines.

Results: The meta-analysis included seven single-arm studies comprising 187 patients. The pooled 3-month complete response rate and partial response rate were 36.67% and 42.49%, respectively, while the three-month progressive disease rate was 7.10%. The tumor volume was reduced by 48.95%. According to survival analysis, the pooled 6-month overall survival rate was 79.27%, with a median response time of 4.25 months. The pooled rates of mild and moderate-to-severe adverse events were 19.40% and 3.37%, respectively. LRT has demonstrated high local control rates and a favorable safety profile in managing large-volume tumors.

Conclusion: This is the first systematic meta-analysis examining the efficacy and safety of LRT in treating large-volume tumors. Although further high-quality studies are needed for validation, LRT exhibits encouraging efficiency and safety in patients with large solid tumors exceeding 5 cm in diameter.

INTRODUCTION

Lattice radiotherapy (LRT) is an emerging form of spatially fractionated radiotherapy (SFRT) technique that offers a promising approach for treating large tumors.[1,2] Its fundamental concept involves delivering a highly heterogeneous dose distribution in a three-dimensional space, where radiation is unevenly distributed within the tumor, strategically creating alternating high- and low-dose regions. This approach enables selective targeting, delivering higher doses of radiation to certain areas of the tumor while sparing the adjacent normal tissues through lower dose.[3] This deliberate dose heterogeneity within the tumor target may trigger the bystander effect and the abscopal effect[4], potentially augmenting inflammatory and immune responses.[5] Such mechanisms could boost immune cell infiltration into the tumor microenvironment, thereby improving overall tumor control.[6,7] Collectively, extensive clinical experience and theoretical studies have revealed that LRT offers remarkable tumor control in large tumors with minimal toxicity.[8]

Because LRT is primarily employed for providing palliative treatment to patients with large, unresectable tumors in advanced stages[9,10], conducting randomized clinical trials is challenging. Most available data are derived from real-world case reports and small case series with varying treatment approaches across different centers, leading to a lack of standardized measures for evaluating LRT's effectiveness and safety. To our knowledge, no published meta-analysis has

Corresponding author: Huankun Wang, Department of Radiation Oncology, The Third People's Hospital of Dalian, Dalian Municipal Cancer Hospital, Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, China

e-mail: 0411whk@163.com

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ORCID iDs of the authors: W.L. 0000-0001-7940-593X; M.P. 0009-0007-6629-5197; L.Z. 0009-0004-4505-750X; Y.Z. 0009-0006-2216-4403; F.L. 0009-0002-2723-3958; L.C. 0009-0008-9542-0329; H.W. 0009-0000-2396-349X.

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examined the efficacy and safety of LRT in treating large tumors. Our objective was to compile all available data on LRT for large tumors, discuss its objective response rates, survival outcomes, and adverse event rates, and provide more evidence for clinical practice.

MATERIALS AND METHODS

Search strategy

We systematically searched four databases (PubMed, Embase, Cochrane Library, and Web of Science) from their inception to September 2024 to identify clinical studies on LRT. Given that LRT is a subtype of SFRT, we included studies on SFRT to minimize the risk of selection bias. All identified records were imported into the reference management software EndNote. The search terms used were: "LRT" OR "LRT" OR "spatially fractionated radiation therapy" OR "SFRT." In addition to database searches, we manually screened conference abstracts and clinical trials to include relevant unpublished data. Given the limited number of LRT studies, we did not restrict the search by language; however, only full-text articles available in Chinese and English were considered.

Based on the predetermined LRT selection criteria[11], only studies that used LRT to treat tumors with a maximal diameter greater than 5 cm and reported post-radiotherapy tumor response, survival analysis, or adverse event rates were eligible for inclusion. Additionally, we looked through the listed research references to find more pertinent papers. Where there were multiple publications from the same population, only the largest study was included. Two researchers (L.W and P.MN) independently screened titles, abstracts, and full texts based on the predefined inclusion and exclusion criteria. Any disagreements were resolved through discussion with a third researcher (W.HK). Only peer-reviewed studies were included. Reviews, conference abstracts, case reports, preclinical studies, off-topic articles, comments, and feasibility studies were excluded. When necessary, we contacted the corresponding authors via email to obtain additional relevant data.

This study was conducted in accordance with the PRISMA guidelines and was registered on the PROSPERO platform (CRD42024607993).

Data extraction

Two researchers (Z.LJ and Z.YJ) independently extracted data on the following variables: author, publication year, study type (prospective or retrospective cohort studies and case-control studies), number of patients, number of tumors, median age of patients, tumor type, median gross tumor volume (GTV), number of LRT vertices, diameter and spacing of vertices, radiation dose, treatment modality, tumor response, survival analysis, and adverse event data. Following data extraction, another researcher (W.HK) reviewed the data and full texts. Since all included studies were single-arm without control groups, two reviewers (L.FJ and C.L) independently evaluated the quality of the studies using the MINORS scale[12] and assessed the risk of bias employing the ROBINS-I-V2 tool.[13] Studies with a MINORS scale score of at least 13 and rated as having a "MODERATE" risk of bias according to the ROBINS-I-V2 tool were classified as high quality and included in the analysis. Disagreements were resolved through discussion, and if consensus was not reached, a third researcher (W.HK) was consulted.

Inclusion criteria

The inclusion criteria for the meta-analysis were as follows:

1) Study population: patients receiving LRT for tumors ≥ 5 cm in diameter.

2) Study type: prospective or retrospective cohort or case-control studies.

3) Outcome measures: these included three-month complete response (CR) rate, three-month partial response (PR) rate, three-month progressive disease (PD) rate, six-month overall survival (OS) rate, median duration of response times (DOR), and tumor volume reduction rate (RR), defined as the ratio of the maximum (max) tumor volume reduction after LRT to the baseline tumor volume, and rates of mild (G1-G2) and severe (G3-G4) adverse events, according to the Common Terminology Criteria for Adverse Events (CTCAE V5.0).

No minimum (min) patient number was required for study inclusion. For multiple articles based on comparable patient populations using identical detection methods, only the largest or most recent study was included.

Exclusion criteria

1) Original studies with flawed experimental design or statistical techniques (e.g., unreasonable design, incomplete data, or undefined outcome measures).

2) Case reports, reviews, and conference abstracts.

Statistical analysis

Statistical analysis was performed using the STATA software version 18.0 (StataCorp LP, College Station, TX, United States). A standard significance level of $\alpha = 0.05$ was applied. Heterogeneity was assessed using the chi-square test and I^2 statistic. If significant heterogeneity was detected ($p < 0.1$ and $I^2 > 50\%$), a random-effects model was used; otherwise, a fixed-effects model was applied. Given the limited number of included studies, the Hartung-Knapp adjustment was applied to the random-effects model to improve the robustness of our estimates. To explore the potential sources of heterogeneity, we performed meta-regression analyses. Covariates with p -value < 0.05 were considered significant contributors to heterogeneity and were further examined through subgroup analyses. We used the Begg's and Egger's tests to evaluate publication bias.

RESULTS

Literature screening

We retrieved 1049, 1146, 43, and 597 records from PubMed, Embase, Cochrane Library, and Web of Science databases, respectively. After eliminating duplicates and irrelevant records, 117 records remained for screening. Only full-text articles on LRT, including prospective or retrospective cohort and case-control studies, were deemed eligible. In total, 110 articles were excluded for the following reasons: case

reports (9), conference abstracts (19), dosimetry studies (17), basic research (15), clinical experience or feasibility articles (6), opinions or comments (23), preclinical studies (9), and off-topic studies or those with unavailable data (12). Figure 1 depicts the selection procedure.

Patient characteristics and quality assessment

As illustrated in Table 1, the meta-analysis eventually included seven eligible studies.[14-20] These studies were all single-arm studies involving 187 patients from various countries, with patient numbers ranging from 10 to 53 per study. The included cases involved large solid tumors with a max. diameter greater than 5 cm, totaling 209 lesions, with a median GTV volume of 146.5-36.0 cc. Palliative radiotherapy was administered via LRT, and vertex diameters ranged from 0.4 to 1.5 cm. The number of vertices was determined based on tumor size, with a center spacing of 2-6 cm and a min. distance of 1-2 cm from the organs at risk (OAR). The vertex doses ranged from 12 to 24 Gy. Two studies employed fractionated LRT, while five studies utilized single-fraction LRT followed by external beam radiotherapy (EBRT) (Table 1).

Given that all the included studies were single-arm, the MINORS scale and ROBINS-I-V2 tool were used to assess the study quality (Table 2 and Supplemental Table1). Five studies reported adverse event rates, seven studies reported three-month CR, PR, and PD rates, and four studies provided six-month OS and tumor volume RRs.

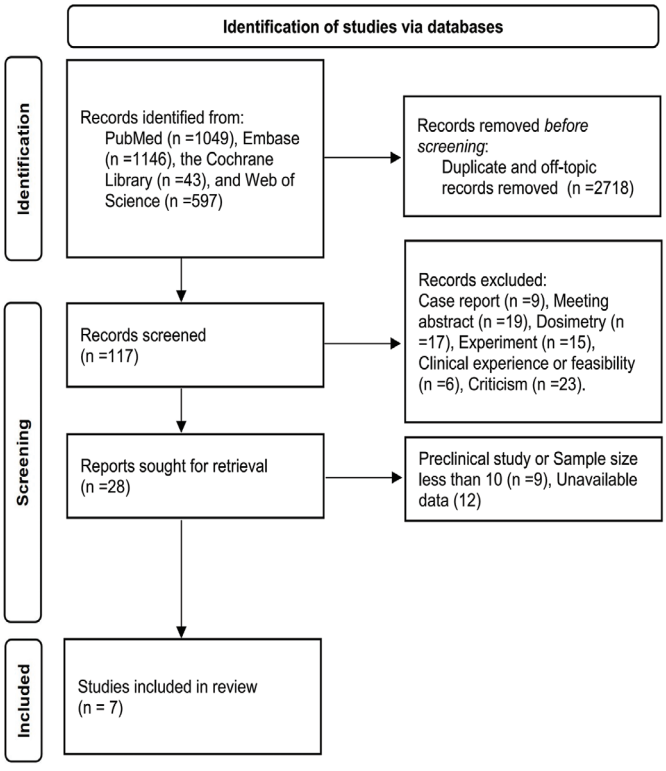

FIG. 1. Flow diagram illustrating the study selection process for inclusion/exclusion in the meta-analysis.

Objective response rates

Every study that was included reported that LRT was effective in treating large solid tumors. The 3-month CR rates across studies varied from 16.13% to 60.00%. Due to the significant heterogeneity (I^2 = 79.68%, $p < 0.001$), a random-effects model was employed. The pooled three-month CR rate, adjusted using the Hartung-Knapp method, was 36.67% [95% confidence interval (CI): 18.89%-54.45%] (Figure 2). Begg's test ($p = 0.282$) and Egger's test ($p = 0.151$) revealed no significant publication bias. The sensitivity analysis validated the stability of the results.

We conducted meta-regression analysis to explore potential sources of heterogeneity, examining the impact of patient age (65 years vs. ≥ 65 years), tumor volume (400 cc vs. ≥ 400 cc), peak dose (< 20 Gy vs. ≥ 20 Gy), and treatment modality (LRT alone vs. LRT + EBRT) on the clinical response. The overall model incorporating all four variables demonstrated $p > 0.05$, indicating that these covariates collectively did not significantly contribute to the heterogeneity in the pooled results. When analyzed individually using univariate meta-regression, neither advanced patient age ($p = 0.903$), greater tumor volume ($p = 0.837$), nor higher peak dose ($p = 0.684$) demonstrated statistically significant effects on clinical response. However, the treatment modality was identified as a potential source of heterogeneity ($p = 0.100$). Subsequent subgroup analysis revealed that the pooled CR rate for patients who received EBRT following LRT was 42.10% (95% CI: 23.52%-60.68%), compared to 23.18% (95% CI: 10.41%-35.94%) for those receiving fractionated LRT. With a p-value of 0.10, the difference was not statistically significant, indicating only a numerical trend between the subgroups.

Across all studies, the 3-month PR rates varied from 8.92% to 77.42%. Due to the significant heterogeneity (I^2 = 88.05%, $p < 0.001$), a random-effects model was used. The pooled PR rate, adjusted using the Hartung-Knapp method, was 42.49% (95% CI: 21.47%-63.51%) (Figure 3a). Begg's test ($p = 0.650$) and Egger's test ($p = 0.849$) demonstrated absence of significant publication bias. The sensitivity analysis confirmed the stability of the results. Meta-regression analysis revealed no significant differences in the three-month PR rates based on patient age ($p = 0.721$), tumor size ($p = 0.398$), treatment regimen ($p = 0.566$), or LRT peak dose ($p = 0.188$).

The three-month PD rates ranged from 4.55% to 30%. Due to the low heterogeneity ($I^2 = 0.00\%$, $p < 0.001$), a fixed-effects model was used. The pooled PD rate was 7.10% (95% CI: 3.65%-10.54%) (Figure 3b). There was no discernible publication bias, according to Egger's test ($p = 0.084$) and Begg's test ($p = 0.133$). Sensitivity analysis confirmed the stability of the results. According to the meta-regression analysis, three-month PD rates did not differ significantly based on patient age ($p = 0.496$), tumor size ($p = 0.347$), treatment regimen ($p = 0.982$), or LRT peak dose ($p = 0.610$).

Four studies reported RR, with the median volume RR ranging from 47.4% to 60%. Due to the high heterogeneity (I^2 = 72.48%, $p < 0.001$), a random-effects model was used. The pooled median volume reduction was 51.19% (95% CI: 38.46%-63.93%). Begg's test ($p = 1.000$) and Egger's test ($p = 0.841$) indicated no significant publication bias. The results' stability was validated by the sensitivity analysis (Figure 3c).

TABLE 1. Characteristics of Studies Included in the Meta-Analysis.

Study	Patient number	Lesion number	Age (years)	GTV volume (cc)	Peak dose (Gy)	EBRT dose (Gy/Fx)	RT plan	Peak diameter (cm)	CCD (cm)	Peak number	CDO (cm)	Histology (number)
Ferini et al.[14]	30	31	74.5 (42-91)	146.48 (50.9-2039.7)	15	20/4	LRT + EBRT	1	2	4 (1-6)	NR	ADC (8); SCC (7); UC (5); SARC (5); CHOL (2);MM (3)
Duriseti et al.[15]	20	22	67 (31-86)	579.2 (54.2-3713.5)	20	-	LRT*[5]	1.5	6	NR	1.5	SARC (9); NSCLC (7); THYM (1); MM (1); ADC (1); COAD (1)
Amendola et al.[16]	10	10	73 (49-87)	195 (46-487)	18	66/33	LRT + EBRT	1	3.6	3 (2-7)	NR	NSCLC (10)
Ahmed et al.[18]	53	61	60 (15-90)	636 (47-13373)	20	40/10	LRT + EBRT	1-1.5	2-3	NR	1	SARC (46); OS (15)
Amendola et al.[17]	10	10	60.5 (5-90)	200.35 (74.1-412.4)	24	45/25	LRT + EBRT	NR	NR	5 (2-11)	NR	SCC (7); ADC (3)
Xu et al.[19]	19	19	62 (39-79)	208 (48-701)	12	-	LRT*[2-3]	0.4	2	NR	1	SCC (17); AS (1); ASC (1)
Studer et al.[20]	45	56	66 (18-93)	415 (54-4027)	15-25	60/30	LRT + EBRT	1-1.5	3	NR	2	Carcinoma (24); SARC (18); MM (14)

NR, not reported; GTV, gross tumor volume; RT, Radiotherapy; EBRT, external beam radiotherapy; LRT, lattice radiation therapy; CCD, center-to-center distance; CDO, closest distance to organs at risk (OAR); SCC, squamous cell carcinoma; ADC, adenocarcinoma; UC, urothelial carcinoma; SARC, sarcoma; CHOL, ductal carcinoma; MM, malignant melanoma; NCSLC, non-small-cell lung cancer; THYM, thymic carcinoma; COAD, colonic adenocarcinoma; OS, osteosarcoma; AS, angiosarcoma; ASC, adenosquamous carcinoma.
Peak numbers may vary according to tumor size and treatment plan.

TABLE 2. Quality Assessment of Included Studies Using the MINORS Scale.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total
Ferini et al.[14]	2	2	2	2	2	2	2	1	15
Duriseti et al.[15]	2	2	2	2	2	1	2	1	14
Amendola et al.[16]	2	2	2	1	2	1	2	1	13
Ahmed et al.[18]	2	2	2	2	2	1	2	2	15
Amendola et al.[17]	2	2	2	2	2	2	2	1	15
Xu et al.[19]	2	2	2	2	2	1	2	1	14
Studer et al.[20]	2	2	2	2	2	1	2	1	14

Numbers Q1-Q8 in heading signified: Q1, well-defined question; Q2, inclusion of consecutive patients; Q3, prospective data collection; Q4, endpoints appropriate to the study question; Q5, unbiased assessment of the endpoints; Q6, follow-up period appropriate to the aims of the study; Q7, less than 5% loss to follow-up; Q8, prospective calculation of the study size.

Survival analysis

The median response time following radiotherapy was published in two studies, while the 6-month OS rate following LRT was reported in four studies. Using a random-effects model ($I^2 = 52.97\%$, $p < 0.001$), the pooled 6-month OS rate was 79.27% (95% CI: 62.56%-95.97%). Begg's test ($p = 1.000$) and Egger's test ($p = 0.776$) indicated no significant publication bias.

Due to the small number of studies reporting the median DOR and substantial heterogeneity ($I^2 = 94.73\%$, $p = 0.020$), publication bias could not be evaluated. A random-effects model was used, and the pooled median DOR was 4.25 months (95% CI: 0.73-7.77 months), as depicted in Figure 4. The stability of these results was verified using sensitivity analysis.

Adverse events

Based on the (CTCAE V5.0), five studies documented and analyzed the most common adverse events linked to LRT for large tumors (Table 3). The pooled incidence rate for mild adverse events (G1-G2) was 19.40% (95% CI: 6.27%-32.52%) (Figure 5a). Begg's test ($p = 1.000$) and Egger's test ($p = 0.262$) indicated no significant publication bias. The most common adverse events were skin injury, mucositis, and gastrointestinal reactions, with incidence rates of

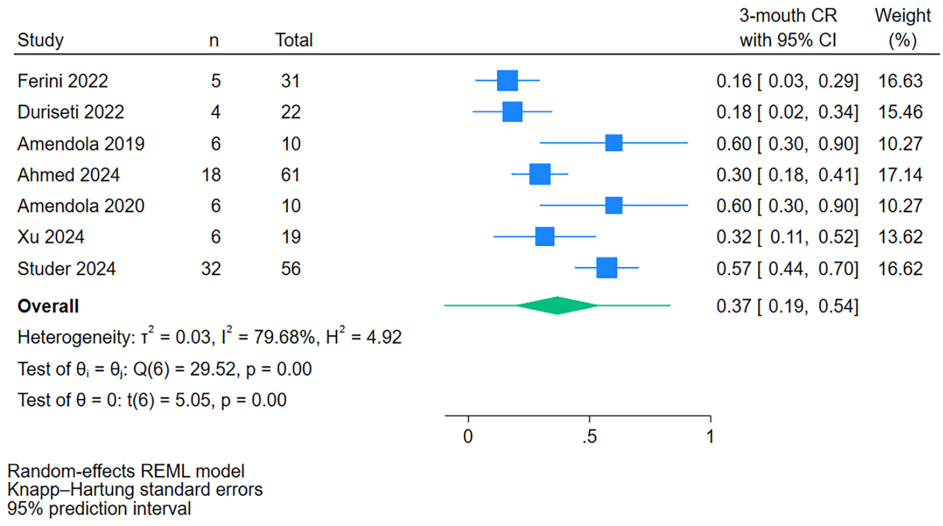

FIG. 2. Three-month CR rate.
CI, confidence interval; CR, complete remission.

7.82% (95% CI: -1.53%-17.16%), 5.73% (95% CI: 1.28%-10.19%), and 6.49% (95% CI: 1.54%-11.44%), respectively. Meta-regression analysis demonstrated no significant association between the incidence of G1-G2 adverse events and patient age (p = 0.620), tumor size (p = 0.226), or treatment regimen (p = 0.331). However, higher peak doses exhibited a tendency toward increased mild toxicity (p = 0.130), indicating a potential dose-dependent relationship that was not statistically significant in this analysis.

The pooled incidence rate for moderate-to-severe adverse events (G3-G4) was 3.37% (95% CI: 0.35%-6.39%) (Figure 5b). There were no significant differences in the incidence of G3-G4 adverse events based on patient age (p = 0.392), tumor size (p = 0.186), LRT peak dose (p = 0.177), or treatment regimen (p = 0.968). The stability of these results was confirmed by employing sensitivity analysis.

DISCUSSION

LRT, as a novel SFRT technique, presents notable advantages in treating large tumors through its distinctive heterogeneous dose distribution. Such a dose distribution can significantly improve local tumor control rates while mitigating radiotherapy toxicity. As a three-dimensional modulation method, LRT outperforms conventional 2D-GRID techniques, improving peak-to-valley ratios within the tumor while minimizing radiation exposure to adjacent normal tissues.[21-23] This technique is particularly effective for deep-seated tumors and those surrounded by radiation-sensitive critical organs, such as large soft tissue tumors in the abdomen and pelvis as well as gynecological malignancies.[24,25] LRT can be easily administered using the most modern radiotherapy delivery systems and enables adjustable tumor-specific dose distributions.[26,27] Notably, clinical research standards for SFRT were established several years ago[28,29], and numerous clinical studies have been conducted. As these studies yield results, the consensus on LRT treatment planning standards will be reached within the medical community. Although several dosimetry studies have theoretically demonstrated the feasibility and safety of LRT[3,30-32], no systematic review to date has evaluated its clinical effectiveness and safety.

This meta-analysis incorporates all available clinical data on LRT for large tumors and is the first systematic review to document its effectiveness and safety in treating large solid tumors. We calculated the pooled three-month CR and PR rates to be 36.67% and 42.49%, respectively, with a three-month PD rate of 7.10% and a tumor volume reduction of 48.95%. The pooled 6-month OS rate, according to survival analysis, was 79.27%, and the median response time was 4.25 months. These results are consistent with general clinical observations, indicating that LRT is effective in treating large tumors and could be an effective palliative treatment alternative for patients with inoperable large tumors.

The pooled rate of mild adverse events (G1-G2) was 19.40%. The most prevalent adverse events included cutaneous, mucosal, and gastrointestinal injuries, with incidence rates of 7.82%, 5.73%, and 6.49%, respectively. While an increase in the peak dose exhibited a numerical trend toward increased incidences of mild toxicity, consistent with radiobiological assumptions, this difference was not statistically significant (p = 0.013). The incidence of moderate-to-severe (G3-G4) adverse events was 3.37%, with the most severe case involving uremia causing fatal renal failure. Given the heterogeneity of the included studies, which incorporated LRT applications across diverse tumor sites and histologies, the spectrum of reported toxicities differed substantially across organ systems. Therefore, caution should be exercised when interpreting the site-specific toxicity rates. When benchmarked against standard palliative radiotherapy regimens, LRT demonstrated a favorable safety profile.

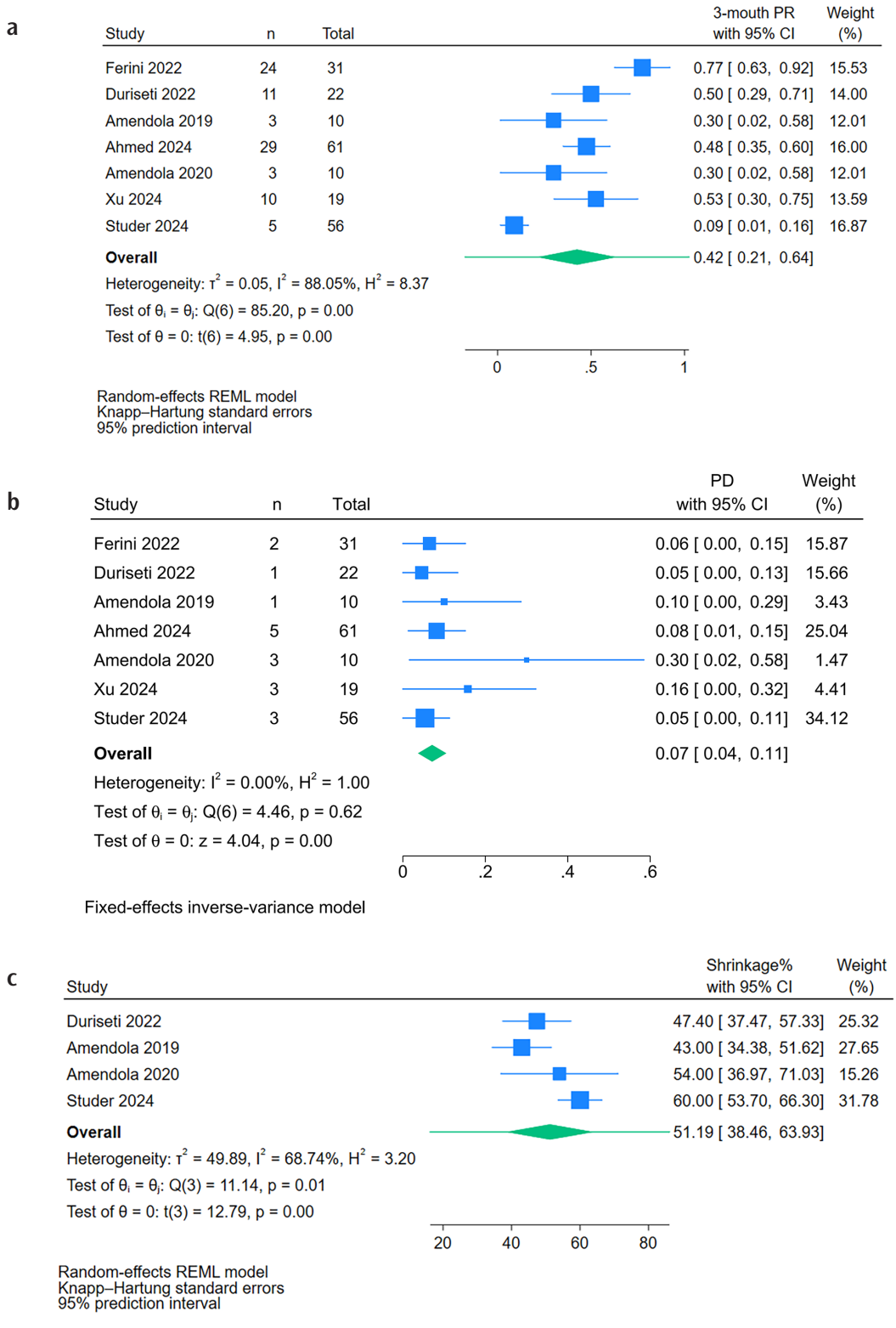

FIG. 3.(a-c) Objective response rates. Three-month partial response (PR) rate (a); three-month progression disease (PD) rate (b); maximum tumor reduction rate (c).

CI, confidence interval.

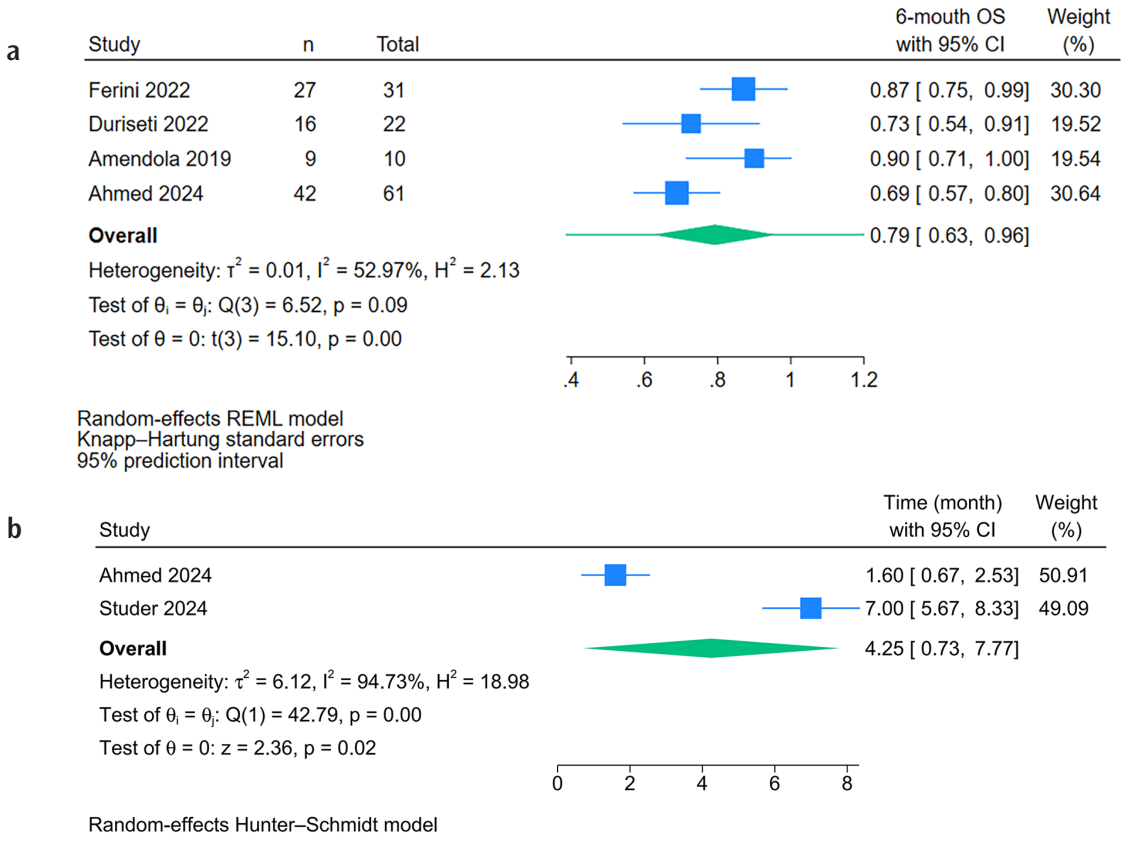

FIG. 4. (a, b) Survival analysis. Six-month overall survival (OS) rate (a); median duration time of tumor response (b).
CI, confidence interval.

TABLE 3. Adverse Events Included in the Meta-Analysis.

Study		Ferini et al.[14]	Duriseti et al.[15]	Ahmed et al.[18]	Amendola et al.[17]	Xuet al.[19]
Patient number		30	20	53	10	19
Mild adverse events	Mucositis	3		2		3
	Skin	5		1		2
	Gastrointestinal	1		6	1	
	Fatigue			6		
	Pneumonitis		1	3		
	Pain			2		
	Cystitis			1	1	
	Bone fracture			2		
Severe adverse events	Skin			1		
	Gastrointestinal			2		
	Pneumonitis			1		
	Uremia		1			

For instance, Wang et al.[33] reported G1-G2 gastrointestinal toxicity rates exceeding 50% and G3-G4 events exceeding 10% in patients with bulky cervical cancer treated with intensity-modulated radiation therapy. Conversely, LRT achieved substantially lower toxicity rates, especially in large-volume tumors. These findings suggest that LRT demonstrates an acceptable safety profile in the palliative management of large-volume tumors, supporting its potential as a viable and safe therapeutic alternative in clinical decision-making.

According to the subgroup analysis, patients who received LRT followed by EBRT had a pooled CR rate of 42.10%, while those who

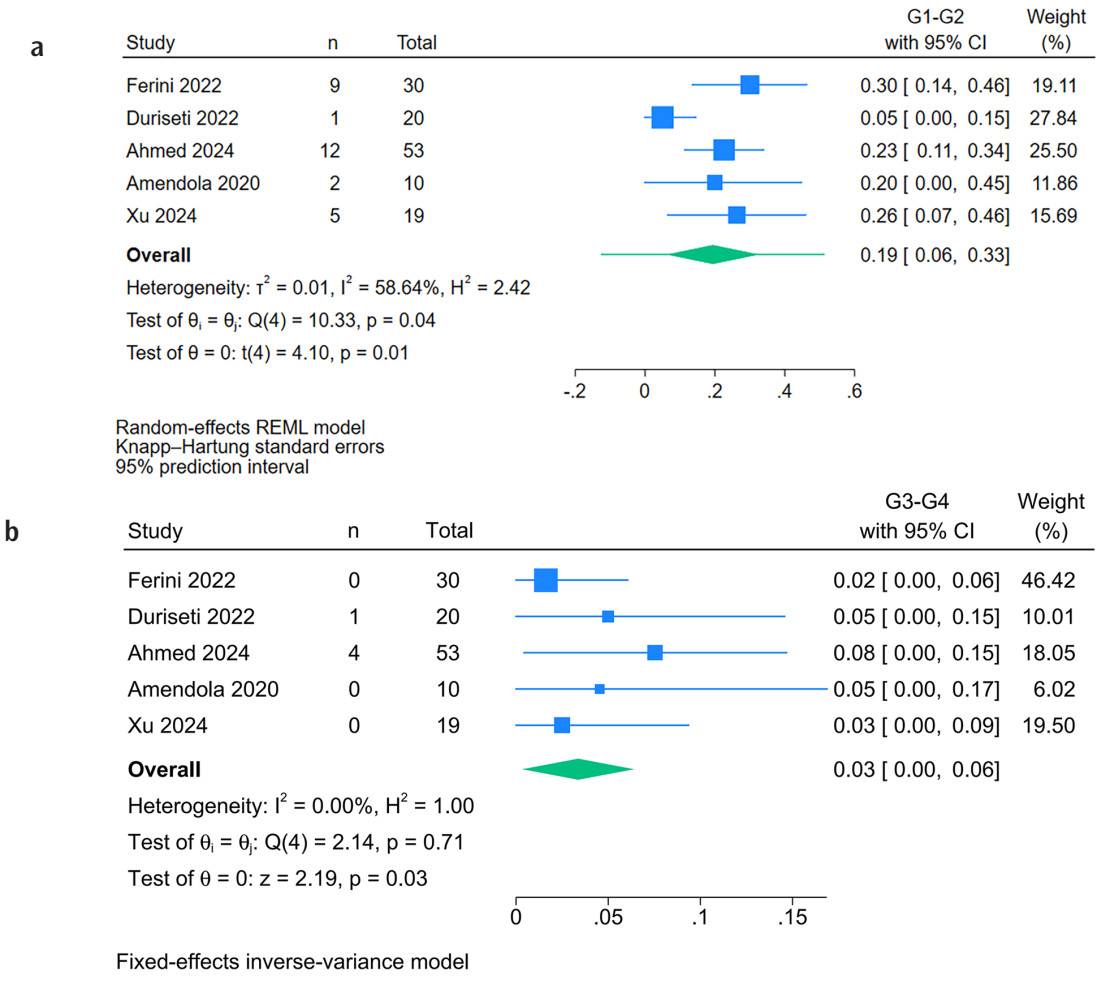

FIG. 5. (a, b) Adverse events. Incidence of mild (G1-G2) adverse reactions (a); incidence of severe (G3-G4) adverse reactions (b).
CI, confidence interval.

received fractionated LRT alone had a rate of 23.18%. Although the CR rate was numerically greater in the LRT + EBRT group, the difference was not statistically significant ($p = 0.10$), possibly due to the small sample size. Additional research is needed to corroborate this finding. In clinical practice during the GRID era, GRID radiotherapy was frequently paired with EBRT because GRID radiotherapy reduced tumor volume, allowing EBRT to effectively treat the residual cancer tissue.[1,34-36] Since this approach has been demonstrated to be reliable in clinical practice, the combination of GRID and EBRT is recommended in relevant clinical practice guidelines.[9] However, even the widely used GRID technique lacks rigorous clinical trials and meta-analyses to validate the rationale for using it in conjunction with EBRT. There is even less reliable data for the still-emerging LRT technique, implying that the experience from the GRID era may not necessarily be applicable to LRT. We must exercise caution when interpreting the findings of this study because there are very few studies, all of which are single-arm, have small sample numbers, and have brief follow-up periods, which may result in inappropriate statistical analysis and limitations in the results. Recently, several clinical trials related to LRT have been initiated[37-39], and we look forward to these studies addressing these questions.

This meta-analysis had several limitations. First, all included studies were single-arm, which inherently cannot adequately control for reporting bias, confounding variables, or selection bias (such as patient baseline characteristics and the impact of combination therapies), resulting in substantial heterogeneity in the data. Second, we observed notably wide confidence intervals for several outcome measures. This can be attributed, on one hand, to the limited number of eligible studies with small sample sizes, compounded by their exclusive use of single-arm designs; and on the other hand, to the developmental nature of LRT as a novel radiotherapy modality, with key parameters-including dose prescription, treatment protocols, delivery techniques, and response assessment methods-still in the exploratory phase. These technical uncertainties invariably introduce unrecorded confounding variables that may undermine the reliability of our findings. Therefore, we only evaluated the efficacy and safety of LRT and interpreted the conclusions with caution. Fourth, we performed comprehensive subgroup analyses to evaluate the possible influences of variations in the study design

and patient characteristics. Our findings revealed that, except for LRT treatment protocols, none of the examined characteristics (including patient age and tumor size) demonstrated statistically significant differences or notable numerical trends. However, due to limitations in the available data, we were unable to conduct subgroup analyses based on tumor histopathological characteristics. Although histopathological differences may not be the primary focus in current LRT palliative therapy research, we acknowledge that variations in tumor biology could potentially contribute to unmeasured heterogeneity. We anticipate that future well-designed randomized controlled trials with rigorous pathological stratification will help bridge this knowledge gap.

We believe that future research should combine molecular imaging experiments to establish the relationship between LRT dose distribution and biological effects. Furthermore, additional large-scale randomized controlled trials should be performed to determine radiotherapy target areas, dose settings, peak-valley dose patterns, and OAR dose limits, with the goal of establishing LRT target delineation and radiotherapy planning guidelines.

This study suggests that LRT may serve as an effective palliative treatment option for patients with inoperable large tumors. However, its efficacy and safety need to be further confirmed through multicenter randomized controlled trials, particularly for standardizing target design and dose fractionation protocols.

Ethics Committee Approval: Not applicable.

Informed Consent: Not applicable.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authorship Contributions: Concept- W.L., H.W.; Design- W.L., M.P.; Supervision- H.W.; Materials- Y.Z., F.L., L.C.; Data Collection or Processing- M.P., L.Z., Y.Z., F.L., L.C.; Analysis and/or Interpretation- M.P., L.Z., Y.Z., F.L., L.C.; Literature Review- W.L., M.P.; Writing- W.L.; Critical Review- H.W.

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Supplementary Tables 1-7: https://www.balkanmedicaljournal.org/img/files/supplement%20table%202025-2-129.pdf

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