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Innovations in modern low-LET radiotherapy regimens for locally advanced non-small cell lung cancer: a meta-analysis and systematic review of high-dose-rate brachytherapy, stereotactic body radiotherapy, and hypofractionated proton therapy

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Abstract

Background This study assesses recent treatments for locally advanced non-small cell lung cancer (LA-NSCLC) ineligible for surgery, comparing high-dose-rate (HDR) brachytherapy with conventional low linear energy transfer (LET) hypofractionated radiotherapy methods.

Methods From 9435 papers, 8 meeting criteria were selected, covering 484 LA-NSCLC patients (2005–2019). Analysis focused on comparing outcomes, exploring biologically effective doses (BED), and examining toxicities.

Results HDR brachytherapy had better effectiveness. Specific data revealed that the median overall survival (OS) with HDR brachytherapy was 38 months, with a significant 2-year OS rate of 68.0% (95% CI, 58.2-79.4%). In comparison, stereotactic body radiation (SBRT) and proton treatment had 2-year OS rates of 54% (95% CI, 36-71%), and 56% (95% CI, 42-70%), respectively. In terms of local control (LC), the 2-year LC rate for HDR brachytherapy stood at 87.1% (95% CI, 79-95%), whereas the 2-year LC rates for SBRT and proton therapy were 75% (95% CI, 63-86%) and 84% (95% CI, 68 -100%), respectively. The 2-year OS for BED_{10} equal to or greater than 78 Gy was 62% (95% CI, 51-72%), compared to 38% (95% CI, 17-58%) for BED_{10} less than 78 Gy. Acute toxicity was lower with HDR brachytherapy (95% CI, 0-10%) versus SBRT (95% CI, 8-16%), with no grade 3 + events reported for proton therapy. Furthermore, the rate of late toxicity events above grade 3 was 3% (95% CI, 0-6%) for SBRT and 14% (95% CI, 4-24%) for proton therapy, while no late toxicities above grade 3 were observed with brachytherapy.

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Conclusions Hypofractionated low LET irradiation is efficacious and safe for LA-NSCLC, while HDR brachytherapy provides significant OS and LC advantages with few toxicities. Achieving $BED_{10} \geq 78$ Gy significantly impacts OS. These findings guide clinical practice and stimulate further LA-NSCLC treatment advancements.

Keywords Non-small cell lung cancer, Locally advanced, Non-surgical treatment, Hypofractionated, Low linear energy transfer radiotherapy

Background

Lung cancer is still one of the most common cancers worldwide, with an estimated 2.5 million new cases by 2022, according to the most recent cancer data report. With an estimated 1.8 million deaths predicted, or 18.7% of all cancer-related fatalities, lung cancer is the most common malignancy among males and the main cause of cancer-related mortality [1].About 90% of lung cancer cases are diagnosed as non-small cell lung cancer (NSCLC), which is highly dangerous for human life and poses a major challenge to cancer treatment [2]. Remarkably, approximately 30% of patients with NSCLC are at locally advanced stages (IIIA to IIIC), and most of them are not candidates for surgical surgery [3]. As such, the treatment of locally advanced non-small cell lung cancer (LA-NSCLC) that is incurable is a difficult but necessary task.

Over the past decade, concurrent chemoradiotherapy has emerged as the standard treatment for LA-NSCLC [4–5]. Conventional fractionated radiotherapy remains the primary radiotherapy modality for managing inoperable cases of LA-NSCLC. However, with the continuous advancements in science and technology, various radiotherapy modalities have gained prominence in the treatment landscape of NSCLC in recent years [6]. Stereotactic body radiotherapy (SBRT), characterized by delivering higher doses in a single session with fewer fractions, has primarily been indicated for early-stage patients [7–8]. Moreover, the influence of hypofractionated radiotherapy modalities extends to proton radiotherapy as well. A study conducted on patients with stage II or III NSCLC demonstrated that the side effects of hypofractionated proton therapy, when combined with concurrent chemotherapy, were deemed acceptable [9].

Brachytherapy represents a specialized form of radiotherapy involving the precise placement of a radiation source directly into or adjacent to a tumor. Its utilization in cancer therapy dates back to the advent of contact brachytherapy in the early 20th century [10]. In the context of lung cancer treatment, brachytherapy serves not only to administer targeted, high-dose radiation to the tumor but also to minimize radiation exposure to critical nearby organs [11].High-dose-rate brachytherapy (HDR brachytherapy) has garnered increasing attention in recent years. A study examining the outcomes of 26 patients with LA-NSCLC treated with HDR brachytherapy in conjunction with local positive lymph node radiation reported promising results. The 1- and 2-year overall survival (OS) rates were 90.9% and 67%, respectively, while the overall remission rates (including complete and partial responses) for both the primary tumor and positive lymph nodes were 100% and 92.3%, respectively. Moreover, the course of treatment showed acceptable side effects [12].

Indeed, questions have arisen regarding the efficacy of hypofractionated low linear energy transfer (LET) radiotherapy in the management of LA-NSCLC. Concerns have been raised regarding the therapeutic effectiveness of HDR brachytherapy compared to conventional non-invasive external irradiation, as well as the potential acceptability of associated toxic side effects. As a result, our study seeks to compare HDR brachytherapy to conventional hypofractionated radiotherapy, with the goal of thoroughly investigating both prognosis and side effects. By undertaking this comparative analysis, we aspire to catalyze advancements and enhance the efficacy of localized treatment strategies for LA-NSCLC.

Methods

Protocol registration

This study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring transparency and rigor in reporting. Furthermore, the review methodology and its protocols have been registered with PROSPERO (CRD42024532541), underscoring our commitment to methodological integrity and transparency in research practices [13].

Search strategy

Our retrieval methodology adheres closely to PRISMA guidelines and recommendations. We conducted an exhaustive search across five prominent databases, namely PubMed, Cochrane Library, Web of Science, Embase, and Medline. The search encompassed articles published from the inception of each database up to March 31, 2024. Detailed search strategies for each database are provided in the appendix for reference.

Inclusion and exclusion criteria

We included studies meeting the following criteria: (1) patients diagnosed with thoracic and bronchial NSCLC, encompassing squamous, adenocarcinoma, and adenosquamous subtypes; (2) patients classified as locally advanced (stage II-IIIC) who were deemed inoperable or

declined surgical intervention; (3) a median age at treatment falling within the range of 18–80 years; (4) absence of mutation-positive genes; (5) absence of prior thoracic radiation therapy; (6) treatment involving either hypofractionated proton radiotherapy, stereotactic body radiotherapy/stereotactic ablative radiotherapy (SBRT/SABR), or one of the HDR brachytherapy treatments; (7) reported outcomes related to tumor control, survival, and treatment-related complications; and (8) original research data, including randomized controlled trials, non-randomized clinical trials, case series, or observational studies.

We excluded studies meeting any of the following criteria: (1) those categorized as reviews, commentaries, or other non-original research articles; (2) studies with a sample size of fewer than 5 patients; (3) studies containing duplicated patient data; (4) studies from which it was not possible to extract survival data specifically related to NSCLC; (5) studies with a median follow-up time of less than 6 months; (6) studies involving systemic therapy that included targeted therapies; (7) patients with preexisting and/or co-morbid malignancies within the past 3 years; and (8) studies focusing on palliative radiotherapy.

Data extraction

Two reviewers, T.M.Y. and L.L., independently conducted the literature selection, data extraction, and assessment of potential bias in eligible studies. A third reviewer, T.B.X., independently validated the study findings. In case of any discrepancies, the three investigators resolved them through discussion until a consensus was reached. Data extraction encompassed the following details: (1) first author, journal information, year of publication, research institution, study design, and duration; (2) follow-up duration, patient count, gender distribution, age distribution, tumor site, tumor size, tumor stage, radiation dose, and treatment regimen; (3) primary endpoints, namely OS and local control (LC), and secondary outcomes involving treatment-related toxicity; and (4) evaluation indicators for quality assessment and bias evaluation.

Quality and risk of bias assessment

Two reviewers, T.M.Y. and L.L., independently evaluated the quality of each included study. In instances of disagreement, a third author, T.B.X., made the final determination. The risk of bias for all selected studies was assessed following Cochrane's "Risk of Bias in Non-randomized Intervention Studies" methodology [14]. Bias risk was categorized as low, moderate, severe, or serious.

Statistical analysis

Descriptive statistics were employed to summarize baseline parameters and the incidence of toxicity. Frequencies and percentages were utilized to present dichotomous data, while continuous data were described using ranges between mean and standard deviation or median and interquartile range. Given the diversity of settings in the case series studies, random effects (RE) models were employed to generate comprehensive summary estimates. Effect sizes for continuous outcomes were determined by calculating proportions with 95% confidence intervals (CIs).

All analyses were conducted using STATA version 17.0 (StataCorp, College Station, Texas).

Results

Search results and selection

A total of 9,435 papers were initially retrieved from the 5 databases. Following the removal of 4,157 duplicates, 5,278 articles remained. Subsequently, 4,983 articles were excluded based on title and abstract screening. Of the remaining 295 studies, 287 were excluded for various reasons: (1) studies focusing on early-stage NSCLC (pre-stage II and earlier tumors) ($n = 237$); (2) studies involving treatment modalities including complete surgical resection or targeted therapy; (3) studies investigating conventional dose-divided radiotherapy ($n = 17$); (4) studies involving patients aged 80 years and above ($n = 6$); and (5) studies with duplicate data ($n = 1$). Ultimately, eight studies met the inclusion criteria. The selection process is depicted in Fig. 1.

Features of the included research

The seven studies included in the analysis were conducted between 2005 and 2019. Among them, three studies originated from the USA [15–17], three from China [18–20], one from Japan [21], and one from Ireland [22]. Table 1 provides a summary of the characteristics of the eight included studies.

Participants

The eight studies collectively enrolled 484 patients diagnosed with NSCLC, with central lung cancer being the most prevalent subtype. Patients' median age ranged from 64 to 79 years, and the median follow-up duration varied from 18.2 to 53.7 months. Among the patients, 224 (46.3%) had squamous carcinomas, 219 (45.2%) had adenocarcinomas, and the remainder had other histological types. Additionally, 95 (19.6%) patients were categorized as stage II, including eight (1.7%) with stage IIA, 87 (18%) with stage IIB, and the remaining with stage III disease. Among the five studies reporting tumor volume, the median pre-treatment tumor size ranged from 3.8 cm to over 7 cm. The BED for brachytherapy was consistent at 120 Gy, with regional lymph node irradiation extending up to 70 Gy. In contrast, the BED for SBRT ranged from 58.3 Gy to 120 Gy, with doses exceeding 100 Gy in all but

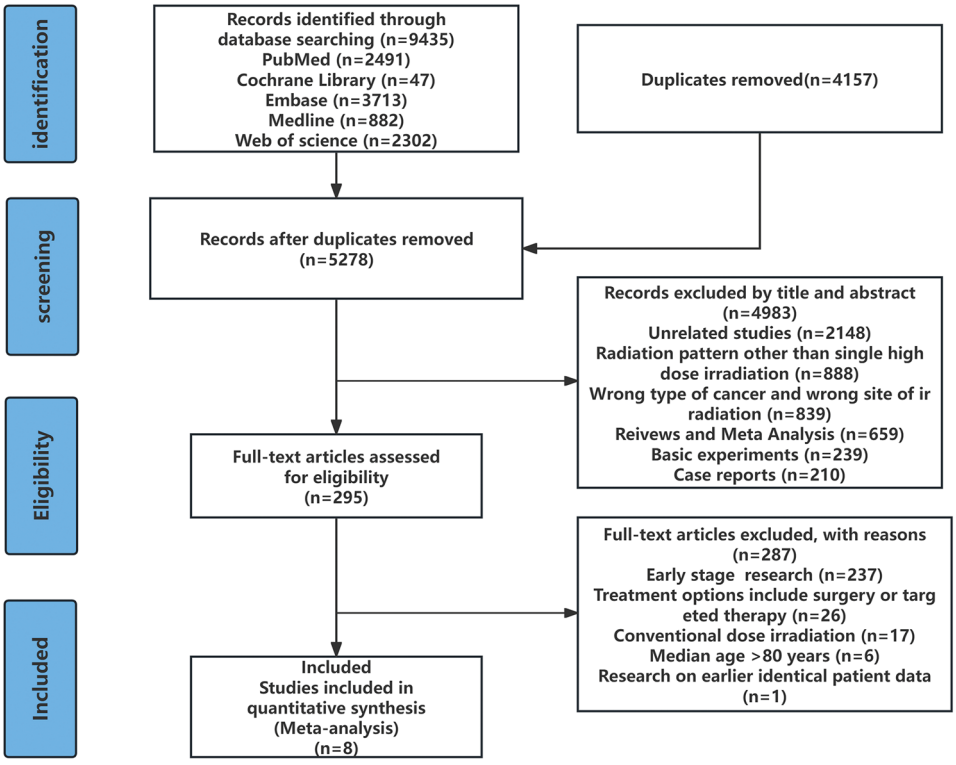

Fig. 1 Flow chart of study selection

two studies. The BED doses for the two proton therapy studies were 71 Gy and 78 Gy, respectively. Regarding systemic treatment, simultaneous radiotherapy based on platinum-based chemotherapy predominated in four out of the five studies reporting systemic therapy.

Interventions and controls

One of the studies exclusively utilized HDR brachytherapy as the primary radiotherapy intervention, while five studies employed SBRT. Additionally, two studies employed hypofractionated proton treatment as part of their intervention.

Outcomes

Survival outcomes including OS and LC were reported in all studies. Additionally, toxic adverse effects were documented. Table 2 provides a summary of the treatment characteristics and outcomes observed in the eight included studies.

Risk of bias assessment

Among the eight studies, seven were categorized as being at moderate risk of bias, while the remaining one [19] was deemed to be at low risk. The majority of studies were classified as moderate risk of bias due to "Bias due to deviations from intended interventions." This classification was influenced by the uneven distribution of radiological patients and variations in treatment doses across the studies.

Results of meta-analyses

Efficacy

OS rate per study

The median OS for patients treated with brachytherapy was 38 months. The 2-year OS rate was 68.0% (95% CI, 58.2-79.4%), and the 5-year OS rate was 44.5% (95% CI, 33.8-58.6%). For patients treated with SBRT, the 2-year OS rates varied across the five studies: 61% (95% CI, 38-84%), 27% (95% CI, 5-49%), 48% (95% CI, 38-59%), 73.7% (95% CI, 73.4-74%), and 53% (95% CI, 34-71%). In the proton therapy group, the 2-year OS rates were reported as 48% (95% CI, 26-70%) and 61% (95% CI, 42-77%), respectively.

OS rates for hypofractionated radiotherapy regimens

The overall 2-year OS rate for all studies combined was 56% (95% CI, 45-68%). Specifically, the combined 2-year OS rate for SBRT was 54% (95% CI, 36-71%), and for proton therapy, it was 56% (95% CI, 42-70%). These results are depicted in Fig. 2.

The impact of BED_{10} on 2-year OS

Among the included studies, six studies utilized a BED_{10} greater than or equal to 78 Gy, while two studies [15, 18] employed a BED_{10} less than 78 Gy. The 2-year OS rates

Table 1 Baseline characteristics of included studies

Study	Experiment period	Country	Study type	Sample size	Median age (year)	Male/female	Median follow-up (month)	ECOG performance status	KPS score	Location	Path subtypes	Pre-treatment tumour size, median (range), cm	Stage	Tumor status *P/R/M*
Xiang2022	2011-2019	China	Prospecttive	75	64 (44–80)	56 / 19	53.7 (range:4.3–120.4)	0 28(37.3%);1 47(62.7%)	NR	Peripheral	Squamous cell carcinoma 38 (50.7%);Adenocarcinoma 35 (46.6%); Other 2 (2.7%)	4.3 (1.5–8.3)	IIIA 34 (45.3%); IIIB 41 (54.7%)	p
Eriguchi2016	2005-2013	Japan	Retrospective	25(19 SBRT alone)	79(60 - 86)	17/8	25 (range: 5–100)	NR	NR	Central 19(76%); Peripheral 6 (24%)	Squamous cell carcinoma 12(48%); Adenocarcinoma 7(28%);Non–small cell carcinoma 4(16%);Pathologically unproven 2(8%)	4.0 (2.3–8.5)	IIB 15 (60%); IIIA 10 (30%)	p
Cong2019	2014-2017	China	Retrospective	15	66 (52–78)	12/3	16.5 (range: 3–50)	0 4(9.1%);1 39(88.6%);2 1(2.3%)	NR	Central	Squamous cell carcinoma 100%	>5,<7 2 (13.3%);>7 13 (86.7%)	III	p
McDermott2020	2009-2018	Ireland	Retrospective	86	77(58 - 91)	46/34	19.6 (range 2.5-98.7)	0 3(3.8%);1 48(60%);2 16(20%);unknow 13(13.2%)	NR	Central 57 (71.3%);Peripheral 23 (28.8%)	Squamous cell carcinoma 30 (37.5%);Adenocarcinoma 31 (38.8%);NSCLC eNOS 3 (3.8%);Sarcomatoid 1 (1.2%); Anaplastic large cell 1 (1.2%); Not biopsied 14 (17.5%)	5.8 (5.0-9.3)	IIB 67 (83.8%);IIIA 13 (16.3%)	p
Jia2023	2013-2018	China	Retrospective	213	72(38–89)	175/38	40 (range 5.28–100.70)	NR	90 71(33.3%);80 125(58.7%);70 17(8%)	Central 86 (40.4%);Peripheral 127 (59.6%)	Squamous cell carcinoma 93 (43.7%);Adenocarcinoma 109 (51.2%);NOS 11(5.2%)	3.8(1.2–11.5)	IIIa 108(50.7%);IIIb 61%(28.6);IIIc 44 (20.7%)	p 85(39.9%)
Wu2024	2011-2018	USA	Retrospective	28	70(51-88)	16/12	18.2 (range 1.8–99.7)	NR	median (range):80(70-100)	NR	Squamous cell carcinoma 10 (36%);Adenocarcinoma 18 (64%)	NR	IIA 3(11%);IIB 1 (4%); IIIA 14 (50.0%);IIIB 10 (36.0%)	p
Contreras2021	2015-2016	USA	Retrospective	20	66.5(54-89)	12/8	20.3 (range 1-38)	0 13(65%);1 6(30%);2 1(5%)	NR	NR	Squamous cell carcinoma 13 (65%);Adenocarcinoma 5 (25%); Other 2 (10%)	NR	IIA 2 (10.0%);IIB 1 (5.0%); IIIA 15 (75.0%);IIIB 2 (10.0%)	p 18(90%)
Hoppe2022	2013-2018	USA	Prospecttive	28	70(50-86)	20/8	31 (range 1-82)	0 12(43%);1 16(57%)	NR	NR	Squamous cell carcinoma 13 (46%);Adenocarcinoma 14 (50%);Mixed adeno-squamous carcinoma 1 (4%)	NR	IIA 3 (11%);IIB 3 (11%);IIIA 15 (54%);IIIB 7 (25%)	p

NR, not reported; P/R/M, Primary/Recurrent/Metastasis

for these two groups were 62% (95% CI, 51-72%) and 38% (95% CI, 17-58%), respectively. There was observed high heterogeneity between the groups. Please refer to Fig. 3 for specific results.

LC rate per study

Among the included studies, six reported 2-year LC rates. In the study utilizing brachytherapy as the treatment modality, the 2-year LC rate was 87.1% (95% CI, 79.6-95.4%).For the four studies employing SBRT, the 2-year LC rates were as follows: 85% (95% CI, 59-100%), 71% (95% CI, 58-84%), 64.3% (95% CI, 57.9-70.7%), and 86% (95% CI, 73-99%).In one study using proton therapy, the 2-year LC rate was reported as 84% (95% CI, 68-100%).

LC rates for hypofractionated radiotherapy regimens

The overall 2-year LC rate for the combined six studies was 79% (95% CI, 69-89%). Additionally, the overall 2-year LC rate for combined SBRT was 75% (95% CI, 63-86%). These results are depicted in Fig. 4.

The impact of BED_{10} on 2-year LC

Among the six studies reporting 2-year LC rates, three (references 17, 18, and 22) utilized a biologically effective dose at 10 Gy (BED_{10}) greater than or equal to 104 Gy, while the remaining three employed a BED_{10} less than 104 Gy. In these studies, the 2-year LC rates in the two groups were 83% (95% CI, 77-89%) and 76% (95% CI, 60-92%), respectively. Importantly, there was no significant heterogeneity observed between the groups. For detailed results, please refer to Fig. 5.

Safety

Among the five studies reporting grade 3 and higher acute toxicities, including radiation pneumonitis, esophagitis, and hematological side effects during concurrent radiotherapy, the rate of grade 3 or higher acute toxicity events was 5% (95% CI, 0-10%) for brachytherapy compared with 12% (95% CI, 8-16%) for SBRT, and no grade 3 or higher acute toxicities were observed for proton therapy. The combined rate of grade 3 + acute toxicity was 9% (95% CI, 5-14%). Additionally, four studies reported grade 3 and higher late toxicities, including cough and pulmonary toxicity. Of these, the rate of grade 3 or higher late toxicity events was 3% (95% CI, 0-6%) for SBRT compared with 14% (95% CI, 4-24%) for proton therapy, while no grade 3 or higher late toxicities were reported for brachytherapy. The rate of grade 3 + late toxicity after combination was 7% (95% CI, 1-13%). For more detailed results, please refer to Figs. 6.

Treatment-related death

Three studies documented treatment-related deaths, all of which were associated with SBRT treatments. One study reported the deaths of two patients, potentially due to treatment-related grade V toxicity [18]. Another study documented the death of one patient attributed to acute radiation pneumonitis [20]. The third study reported the deaths of two patients as a consequence of treatment [17].

Discussion

This systematic review, covering the period from 2016 to 2024, focuses on the efficacy and safety of hypofractionated radiotherapy as a primary treatment approach for LA-NSCLC. Based on our analysis, we derived the following conclusions: (1)The 2-year OS rate for LA-NSCLC treated with hypofractionated radiotherapy was determined to be 57%; (2)The 2-year LC rate for LA-NSCLC treated with hypofractionated radiotherapy was found to be 77%; (3)For patients with LA-NSCLC, the 2-year overall survival (OS) rates were 62% (95% CI, 51-72%) for a biologically effective dose at 10 Gy (BED_{10}) greater than or equal to 78 Gy, and 38% (95% CI, 17-58%) for a BED_{10} less than 78 Gy. The heterogeneity between the two groups may be attributed to the unequal number of studies included in each subgroup. The 2-year LC rates were 83% (95% CI, 77-89%) for BED_{10} greater than or equal to 104 Gy and 76%(95% CI, 60–92%) for BED_{10} less than 104 Gy. No significant heterogeneity was observed between the groups; (4) The acute toxicity rate for grade 3 and above was 9%, while the late toxicity rate was 8%; All things considered, our results imply that hypofractionated radiotherapy demonstrates significant LC and relatively good OS outcomes for the treatment of patients with LA-NSCLC. Moreover, it exhibits a favorable safety profile. These results provide robust evidence supporting the use of hypofractionated radiotherapy in the management of LA-NSCLC and offer valuable insights for guiding future clinical practice.

This study focused on evaluating the impact of hypofractionated radiotherapy on the survival and toxicity profiles of patients with LA-NSCLC. Despite the considerable heterogeneity among the study populations, no significant differences were observed in terms of survival and toxic side effects. This indicates that hypofractionated radiotherapy does indeed have a role to play in the treatment of LA-NSCLC. Conventional fractionated radiotherapy remains the standard modality for LA-NSCLC due to the challenges associated with implementing SBRT, which requires high-quality equipment and technical expertise not readily available in all healthcare settings. However, emerging evidence from numerous studies comparing SBRT with conventional fractionated radiotherapy has demonstrated the superiority of SBRT

Table 2 Treatment regimens main results of all included studies

Study	Type of radiation	Single dose and fractions	Median BED10	Systermatic therapy mode	Systermatic therapy detail	Survival	Failure	Grade 3 and above acute adverse events	Grade 3 and above late adverse events	Late severe adverse events
Xiang2022	high-dose-rate brachytherapy	Primary site: 30 Gy/1f	120 Gy	Concurrent 72(96.0%);Sequential 71(94.7%);No chemotherpy 3(4.0%)	Concurrent cisplatin+etoposide;2 cycles sequential cisplatin+paclitaxel	The median OS was 38.0 months, and the 2- and 5-year OS rates were 68.0%and 44.5%. The local recurrence-free survival (LRFS) rates at 2 and 5 years were 87.1% and 79.2%. The regional recurrence-free survival (RRFS), distant metastasis-free survival (DMFS), and PFS at 5 years were 73.6%, 50.3%, and 29.3%, respectively.	Distant metastases 30(65.2%);Local and regional relapse 14 (18.7%)	Grade3 leukopenia, thrombocytopenia, haemoglobin decreased, neutropenia, nausea, vomiting events were 6(8%),3(4%),1(1.3%),7(9.3%),8(10.6%),6(8%).Grade 2 and 3 acute esophagitis occurred in 11 (14.7%) and 4(5.3%)patients.	None	None
Eriguchi2016	SBRT	8 Gy×5f 9(36%);10 Gy×5f 10(40%)	100.2 Gy	None	None	The 2-year OS, CSS and LC rates were 61%, 80% and 85%, respectively.	11(44%) had local, mediastinal or intrapulmonary progression at 1 year after SBRT.	Grade 0–1, Grade 2 and Grade 3 radiation pneumonitis occurred in 23, 1 and 1 patient, respectively.	None	None
Cong2019	SBRT	7 Gy×5f;7.5 Gy×5f	58.3 Gy	Concurrent 2 (13.3%); Sequential 4 (26.7%); No chemotherpy 9 (60.0%)	None	The 1-year OS, LC and PFS rates were 66.7%, 60.8% and 33.3%, respectively.The 2-year OS rates was 27%, respectively.	NR	Grade ≥3 toxicity 3 (20.0%)	None	2 possibly treatment-related deaths were recorded as grade 5 toxicity

Table 2 (continued)

Study	Type of radiation	Single dose and fractions	Median BED10	Systermatic therapy mode	Systermatic therapy detail	Survival	Failure	Grade 3 and above acute adverse events	Grade 3 and above late adverse events	Late severe adverse events
McDermott2020	SBRT	7.5 Gy×8f 62 (77.5%);12 Gy×5f 13 (16.3%);12 Gy×4f 3 (3.8%); 5 Gy×10f 2 (2.5%)	105 Gy	None	None	The median OS was 20.9 months.The OS rates at 1, 2 and 3 years was 71%, 48% and 32%, respectively. The median local failure-free survival was 19.5 months. The median DFS was 15.1 months. The LC rates at 1, 2 and 3 years was 85%, 71% and 57%, respectively.	Distant metastases 20 (25%). Local failure 19 patients alone or in combination with other progression.	None	Grade 3 late dyspnoea 2	NR
Jia2023	SBRT	6–7 Gy×5–10 f	85.8 Gy	Induction; Consolidation	Platinum-based doublet chemotherapy	The median OS was 36.5 months; The estimated 1-, 2-and 3-year OS rates were 90.6%±2.0%, 73.7%±3.0% and 52.0%±3.4%, respectively.The 1-, 2- and 3-year PFS rates were 69.5%±3.2%, 25.4%±3.1% and 15.0%±2.5%, respectively.The 1-, 2- and 3-year LC was 87.8%, 64.3% and 57.2%, respectively.	Distant metastases 151(70.9%);Local and regional relapse 71 (34.74%)	Grade ≥3 toxicity 28 (13.1%)	None	1 patient (0.5%) died of acute radiation pneumonitis without evident disease progression.He was diagnosed with radiation pneumonia by CT and died 75 days after SBRT.

Table 2 (continued)

Study	Type of radiation	Single dose and fractions	Median BED10	Systermatic therapy mode	Systermatic therapy detail	Survival	Failure	Grade 3 and above acute adverse events	Grade 3 and above late adverse events	Late severe adverse events
Wu2024	SBRT	4 Gy×10f+5 Gy×5f(36%);4 Gy×10f+6 Gy×5f(32%);4 G y×10f+7 Gy×5f(32%)	104 Gy	Consolidation	Carboplatin/paclitaxel 6 (21%);Durvalumab 1 (4%)	All patients 1-year OS, LC and PFS were 78.6%,90.8% and 35.1%0.2-year OS, LC and PFS were 52.5%,85.7% and 22%, respectively.	NR	Grade ≥3 toxicity 11%	Grade ≥3 toxicity 7%	The cumulative treatment-related mortality was 7% (n = 2), with both deaths occurring in the high-dose cohort.
Contreras2021	Proton	26.25 Gy×2f;13.125 Gy×4f; 4.29 Gy×14f	71 Gy	Concurrent 19 (95%); Consolidation 16 (80%)	NR	Estimates 2-year OS, LC, RC, DC and cancer specific survival rates were 48%,84%, 77%, 79% and 60%, respectively.	Distant failures 4;Isolated regional failures 3;Isolated local failures 2;Synchronous local and regional failure 1	Acute, nonserious AEs included grade 2 esophagitis in 7 patients (35%) and grade 2 pneumonitis in 1 patient (5%).	All 3 patients with grade 3 toxicity at follow-up were in the 4 Gy per fraction dose level.	NR
Hoppe2022	Proton	2.5 Gy×24f 14(50%);3 Gy×20f 6(21%);3.53 Gy×17f 7(25%);4 Gy×15f 1(4%)	78 Gy	Concurrent	Carboplatin/Paclitaxel 20 (71%);Paraplatin/Paclitaxel 5 (18%) Carboplatin/Pemetrexed 1 (4%);Cisplatin/Pemetrexed 1 (4%) Cisplatin/Etoposide 1 (4%)	The 1, 2 and 3-year OS rates were 89%,61%and 49%, and PFS rates were 58%, 41% and 32%, respectively.	Distant metastases 16 (57%). Local failure 18(64%)	No acute grade 3 or higher esophagitis occurred.	14% developed a grade 3 or higher radiation-related pulmonary toxicity.	NR

SBRT, Stereotactic body radiationtherapy; LRFS, local recurrence-free survival; RRFS, regional recurrence-free survival; LC, Local control; OS, Overall survival; DMFS, Distant metastasis-free survival; LRRFS, Local-regional recurrence-free survival; PFS, progression-free survival; CSS, Cancer-specific survival; NR, not reported

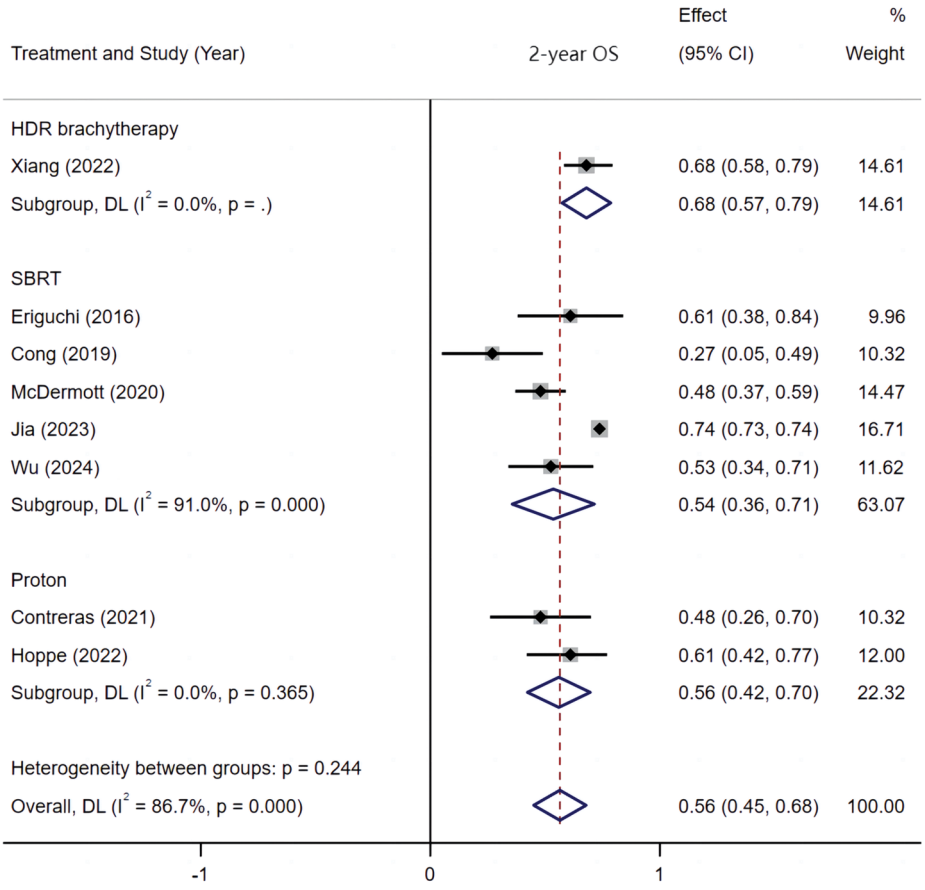

Fig. 2 Random-effects meta-analysis of 2-year OS among LA-NSCLC patients.OS Overall Survival

or hypofractionated radiotherapy. Two important studies focused on patients with early-stage NSCLC examined the efficacy of SBRT. The first, a randomized phase II trial named SPACE, compared SBRT with conventionally fractionated radiotherapy (3DCRT) and found that SBRT provided comparable survival and progression-free survival to 3DCRT in patients with inoperable stage I NSCLC, with better disease control and fewer toxicities [23]. The efficacy and safety of SBRT as a treatment option for early, inoperable peripheral-stage 1 NSCLC were demonstrated in the second study, a multicenter phase 3 randomized controlled trial, which compared SBRT with standard radiotherapy for peripheral stage I NSCLC. No increase in major toxicities was observed, and a lower rate of local treatment failure was observed [24]. There may also be advantages of SBRT over intensity-modulated radiation therapy (IMRT) in the treatment of LA-NSCLC. A retrospective analysis of stage III patients with super central squamous NSCLC found no significant difference between SBRT and IMRT in terms of 1-year LC rate and incidence of grade ≥ 3 toxicity [18].The effectiveness and safety of hypofractionated HDR radiation have been further proven with the development of radiotherapy techniques. According to a Brazilian cost-effectiveness research, SBRT was a more cost-effective option than traditional fractionated radiation for inoperable stage I NSCLC, which is a favorable finding given its financial consequences [25].In summary, the results of these studies collectively suggest that SBRT represents a viable localized treatment option providing improved efficacy and safety for lung cancer patients. Cost-effectiveness analyses also support the advantages of SBRT in the treatment of inoperable NSCLC, making hypofractionated radiotherapy the preferred choice from an economic standpoint.

The research highlights the exceptional survival outcomes and favorable toxicity profiles associated with brachytherapy, specifically in the treatment of lung cancer. Mainstream brachytherapy options for lung cancer encompass bronchial brachytherapy and particle implantation, traditionally reserved for palliative purposes following treatment failures. However, recent advancements in radioactive particles like iodine 125 and cesium 103, coupled with progress in image-guided technology, have pushed particle implantation as a new treatment option [26]. An evaluation of iodine 125 particle implantation

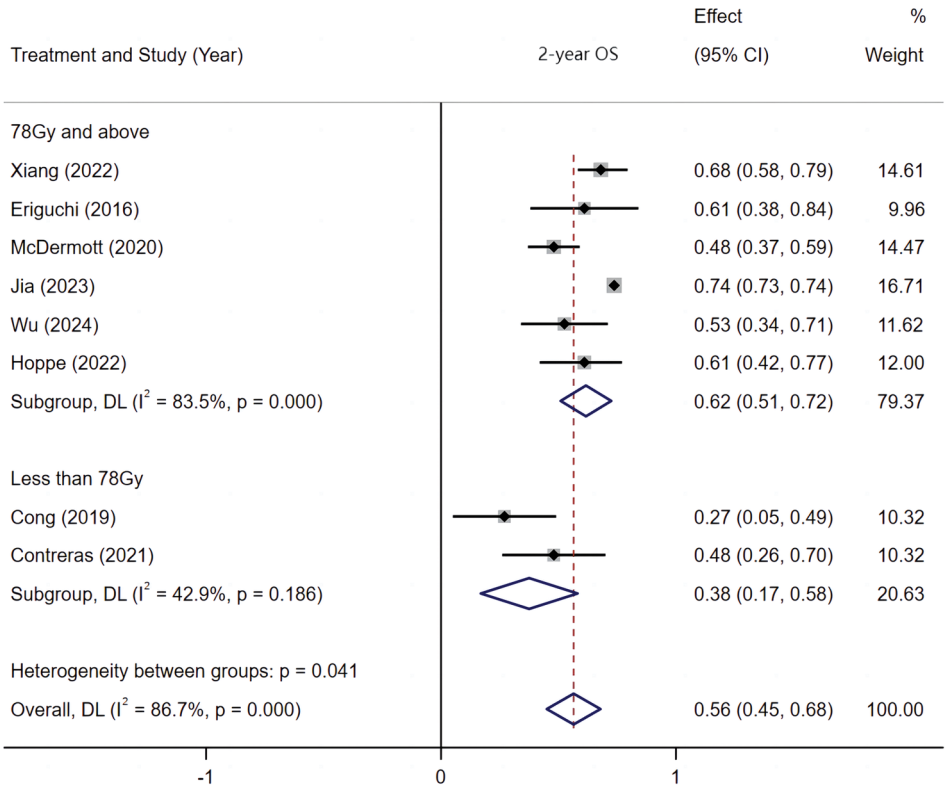

Fig. 3 Random-effects meta-analysis of 2-year OS among LA-NSCLC patients with BED78Gy subgroups.OS Overall Survival

combined with systemic therapy in NSCLC showcased promising results. Conducted through meta-analysis and comprehensive database searches including PubMed and EBSCO, the study encompassed 17 randomized controlled trials involving 1,315 NSCLC patients. The findings indicated that combination therapy significantly enhanced remission rates and OS, albeit with a heightened incidence of pneumothorax [27]. Nevertheless, widespread adoption of particle implantation remains challenging due to its demanding requirements in handling and post-implantation care. Moreover, a critical component affecting survival is the bioequivalent dose of total radiation dose (BED_{10}). A retrospective analysis [28] utilizing the National Cancer Database compared different SBRT regimens based on BED_{10} effects on OS in stage I NSCLC patients. High BED_{10} (≥ 130 Gy) SBRT treatments correlated with improved 5-year OS, while lower BED_{10} (100–129 Gy) regimens exhibited reduced survival rates. For inoperable LA-NSCLC, irradiation doses targeting BED_{10} ≥ 78 Gy are recommended for enhanced OS, providing a dosimetric rationale for treatment planning [29]. Despite brachytherapy's demonstrated advantages, its utilization has significantly declined over the past two decades, attributed to logistical constraints, reduced reimbursement, and inadequate training [30]. However, with improved operative radiotherapy accuracy supported by medical imaging and future high-dose-rate single-treatment technologies, HDR brachytherapy appears to be a potential radiotherapy modality for advanced tumors such as LA-NSCLC, if standardized training guidelines are followed.

Over several decades, stereotactic body radiation therapy (SBRT) has evolved as a lung cancer treatment. Its effectiveness in the early and advanced phases of inoperable disease is examined in two thorough meta-analyses. Firstly, an analysis revealed significant benefits in LC and OS of SBRT for inoperable early-stage lymph node-negative small cell lung cancer (SCLC) with minimal toxicity. The study revealed a 1-year LC rate of 97.3% (95% CI, 92.3–99.8%) and a 2-year LC rate of 95.7% (95% CI, 74.2–100.0%) by methodically analyzing the literature on SBRT for T1-2N0M0 SCLC [31]. On the other hand, for unresectable stage III NSCLC, an analysis incorporating 18 studies and 447 patients, predominantly prospective ($n = 10$, including five phase 2 trials), showcased varied median survival durations ranging from 10 to 52 months. The incidence of severe side effects remained low, with grade 5 toxicities < 5%, predominantly observed in mediastinal SBRT with no dose limitation to the proximal broncho vascular. It was suggested that biologically effective doses exceeding 112.3 Gy might augment local-regional control [32].It is clear that SBRT is a feasible local therapy option for all non-operable NSCLC,

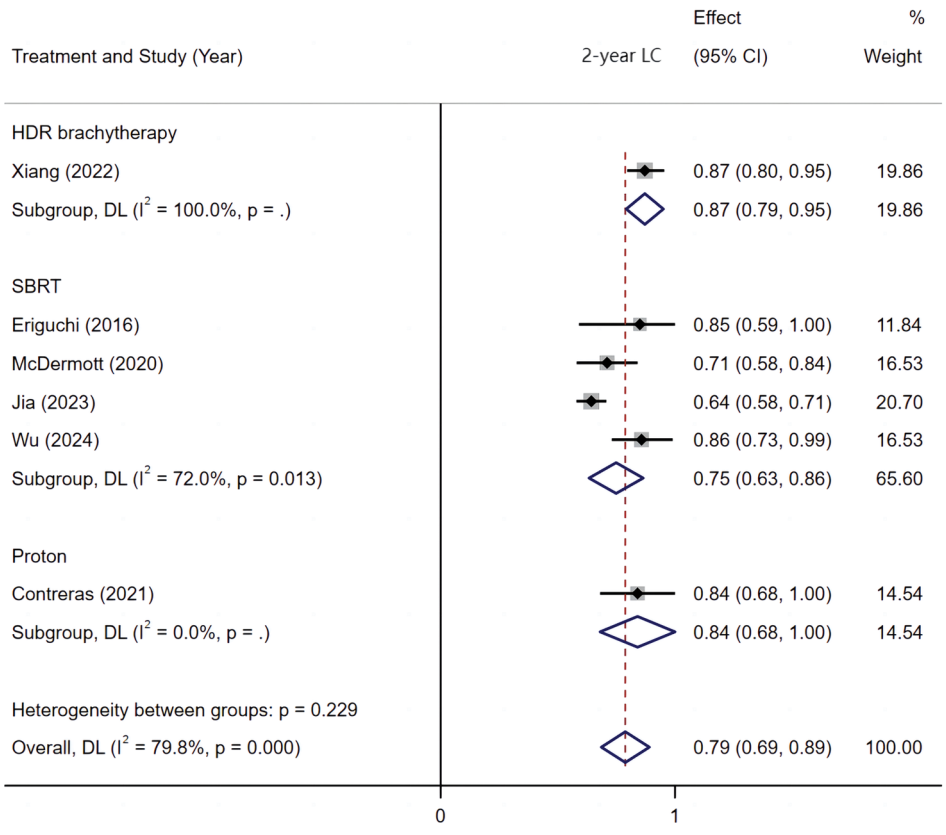

Fig. 4 Random-effects meta-analysis of 2-year LC among LA-NSCLC patients. LC Local control

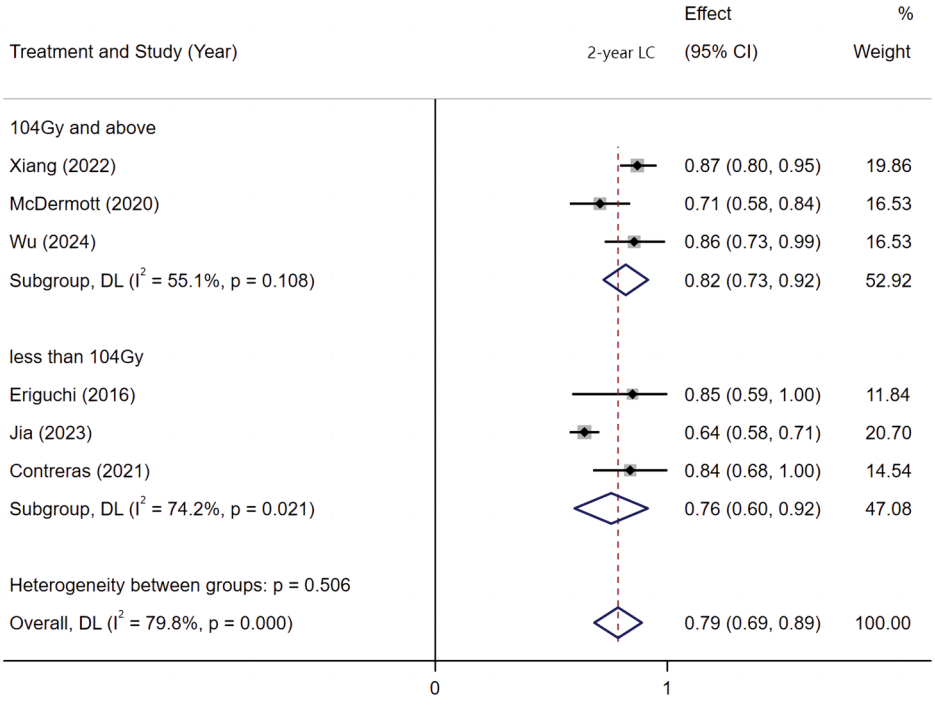

Fig. 5 Random-effects meta-analysis of 2-year LC among LA-NSCLC patients with BED104Gy subgroups. LC Local control

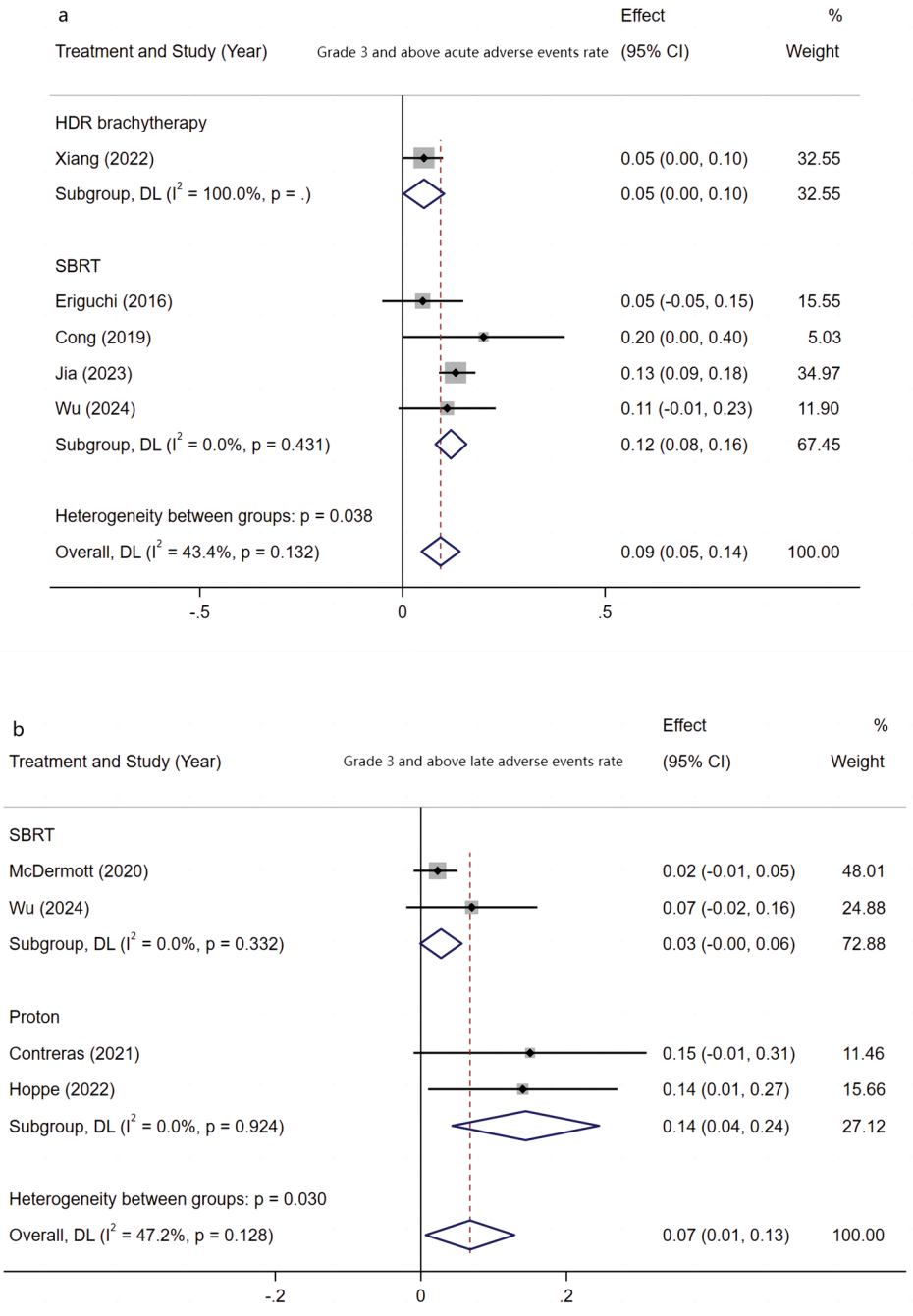

Fig. 6 (**a**) Grade 3 and above acute toxicity; (**b**) Grade 3 and above late toxicity

highlighting its wide range of applications and requiring further extensive research and promotion.

The linear energy transfer (LET) associated with proton beams positions them as low LET radiation, bridging the gap between photon and heavy ion beams. Despite their relative biological effect (RBE) being typically set at 1.1 for clinical use, akin to photons, the primary advantage of proton beams lies in their precise dosing and the Bragg peak phenomenon [33–34].Proton radiation therapy is currently becoming more and more popular as a treatment for NSCLC. Two studies compare intensity-modulated proton therapy (IMPT) with passive scattering proton therapy (PSPT) and examine the possibility of proton beam radiation (PBT) in treating LA-NSCLC. The first study [35] conducted an open-label, single-component matched study involving 64 patients with unresectable stage III NSCLC treated with concurrent chemotherapy and high-dose PBT. Results showcased a

median OS of 26.5 months, 5-year OS of 29%, and 5-year progression-free survival (PFS) of 22%. Predominant modes of treatment failure included distant metastasis (54%), local recurrence (28%), and local/regional recurrence (16%). Notably, acute and late toxic effects, primarily oesophagitis and pneumonitis, were infrequent. Even though PBT and concurrent chemotherapy showed better toxicity profiles and clinical results than previous photon therapy studies, more tuning is still necessary. In a subsequent study, a comparison between IMPT and PSPT for LA-NSCLC post-proton radiotherapy optimization revealed that the IMPT group exhibited lower mean radiation doses to the lungs, heart, and esophagus, with a decreased incidence of grade 3 or higher pulmonary and cardiac toxicity. Despite baseline imbalances, the IMPT group demonstrated a reduced occurrence of pulmonary and cardiac toxicity and a trend toward prolonged median OS [36]. Hypofractionated irradiation patterns impact proton radiotherapy outcomes. In early-stage NSCLC treatment, a meta-analysis examining the impact of low fractionated PBT found that high BED (≥ 105.6 Gy (RBE)) proton therapy increased OS, DFS, OS-specific survival (CSS), and LC rates. However, a heightened risk of late toxic events, particularly rib fractures, was observed in the high BED group [37].Proton radiotherapy exhibits promise in LA-NSCLC treatment, leveraging its precision and relatively low toxicity. However, ongoing optimization and research are crucial for maximizing treatment efficacy and patient survival. Future studies exploring high-dose proton therapy and its unique Bragg peaks, alongside the proliferation of proton centers, will further advance low LET radiation applications in refined proton radiotherapy protocols.

In recent years, the emergence of FLASH technology has garnered significant attention. This innovative technique utilizes electron pulses at higher dose rates (> 40 Gy/sec), a stark departure from conventional rates (around 0.05 Gy/sec) [38]. FLASH demonstrates the potential to better safeguard normal tissues while maintaining comparable efficacy in tumor eradication compared to conventional radiotherapy. In studies focusing on lung cancer treatment, photonic FLASH technology has shown promise in minimizing irreversible damage to healthy tissues. Investigations into the response of C57BL/6J wild-type and Terc/mice, along with in vitro cultured human lung cells, to FLASH irradiation have employed various methods including qPCR, single-cell RNA sequencing, and histological analyses. Results indicate that FLASH irradiation significantly reduces DNA damage levels and exhibits beneficial effects on cells in vitro. In mouse lung experiments, FLASH irradiation attenuated the induction of pro-inflammatory genes and decreased cell proliferation post-injury, as observed through single-cell RNA sequencing and proliferating cell monitoring. Pathological analysis of lung tissue further revealed that FLASH irradiation promoted higher regenerative potential in lung tissue [39]. Furthermore, research suggests that 2 Gy may be the minimum dose required to achieve FLASH effects. Compared to conventional irradiation, FLASH-induced acute radiation pneumonitis was less severe, while the degree of tumor cytolytic damage and inflammation remained similar to conventional radiation [40]. Studies exploring FLASH's potential in proton radiotherapy have yielded promising results. A study was conducted that highlighted the superiority of Bragg peak beams over conventional radiation in maintaining normal tissue and boosting flash dose rates. The study also introduced a revolutionary hardware design and inverse planning method [41]. Lung cancer treatment outcomes were improved by another study's optimization of the proton pencil beam scanning approach, which allowed for appropriate dose coverage while preserving treatment quality [42]. These findings underscore the potential of FLASH irradiation as a strategy to reduce radiotherapy toxicity and enhance treatment efficacy, offering valuable insights for its clinical application.

Among the included studies, only Wu [17] reported on gene mutations, with clear mutation status identified in just 14% of patients. Since our meta-analysis excluded patients who received targeted therapy, and no additional data were provided regarding mutation status, it is likely that most patients were either mutation-negative or had unknown genetic profiles. In cases where patients harbor actionable mutations and are receiving effective targeted therapy, the role of novel radiation strategies may become less significant. Based on the pivotal PACIFIC study, the current standard of care for inoperable LA-NSCLC involves concurrent chemoradiotherapy followed by immunotherapy as consolidation therapy, aimed at enhancing OS and progression-free survival [43]. Immuno-maintenance therapy has become increasingly prevalent. However, due to the early and retrospective nature of our study, the majority of cases did not receive immuno-maintenance therapy. Concurrent chemoradiotherapy is principally responsible for the current OS rate. For patients with inoperable LA-NSCLC, recent studies have examined the use of immunotherapy in addition to proton beam radiation and stereotactic ablative radiation (SABR). In one trial, immunotherapy (I-SABR) and SABR alone (SABR) were compared. Compared to SABR alone, I-SABR significantly improved patients' 4-year event-free survival (from 53 to 77%) at a mean follow-up of 33 months in this randomized phase 2 trial, which included 156 patients. This suggests that I-SABR is a viable therapeutic option for early-stage NSCLC with manageable toxicity [44]. Another study analyzed data from 377 patients to assess the effects of proton beam radiotherapy

(CPBT) combined with immunotherapy (IO) versus CPBT alone. After propensity score matching, patients receiving adjuvant IO demonstrated significantly better three-year survival rates (67% versus 30%, respectively). Multivariate analysis identified adjuvant IO as a robust predictor of overall and progression-free survival. However, the CPBT + IO group exhibited a slight increase in the incidence of grade ≥ 3 esophagitis, raising concerns about toxicity [45].It's worth noting that immunotherapy may elevate the risk of radiation pneumonitis, and the affordability of maintenance therapy, particularly in remote areas of China, remains a challenge [46]. In conclusion, while immunotherapy as consolidation therapy for NSCLC patients holds promise for improved survival, clinicians should be mindful of potential adverse effects and consider the economic implications of treatment.

It must be acknowledged that this meta-analysis has some limitations: (1) there were no randomized controlled trials among the included studies; (2) the median follow-up time was short, and there were no studies with a median follow-up time of more than five years; (3) there was a limited number of patients, especially in the back-loaded treatment group, has contributed to intergroup heterogeneity in certain subgroups; (4) patients were included, and there were also a very small number of patients with stage II; (5) balancing key variables such as performance status, age, gender, and tumor histology across treatment groups proved challenging.(6) systemic treatments were more heterogeneous, which made it difficult to make comparative analyses; and (7) publication bias was inevitable because unpublished data were not evaluated.

Conclusions

Hypofractionated low LET irradiation has become a viable, safe, and successful therapy option for LA-NSCLC management.Specifically, HDR brachytherapy has demonstrated remarkable outcomes in terms of OS and LC while exhibiting relatively few toxic side effects. Our study suggests that primary focus irradiation doses of BED_{10} ≥ 78 Gy and BED_{10} ≥ 104 Gy may exert a significant impact on OS and LC. These findings serve as crucial guidance for clinical practice, offering valuable insights for optimizing LA-NSCLC treatment strategies. Furthermore, they have the potential to spur additional developments and improvements in the field, which will ultimately improve patient outcomes and care quality.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14328-0.

Supplementary Material 1: Risk-of-bias summary for the studies included in the meta-analysis, using Cochrane risk-of-bias tool ROBINS-I

Supplementary Material 2: Search strategy

Supplementary Material 3: PRISMA 2020 Checklist

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Methodology, Mingyu Tan and Lu Li; Conceptualization, Mingyu Tan and Lu Li; Writing - Original Draft, Mingyu Tan; Data curation Mingyu Tan and Lu Li; Investigation, Bangxian Tan; Project administration, Bangxian Tan; Writing - Review & Editing, Jinxin Yang; Validation, Lu Li; Supervision, Jinxin Yang.

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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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