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Systematic Meta Analysis

Hypofractionated Versus Hyperfractionated Versus Conventionally Fractionated Thoracic Radiotherapy in Limited-Stage Small-Cell Lung Cancer: A Systematic Review and Meta-Analysis

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Abstract

Objectives: It remains unclear whether hypofractionated (Hypo) thoracic radiotherapy (TRT) is superior to hyperfractionated or conventionally fractionated (Con) TRT in limited-stage small-cell lung cancer.

Methods: PubMed, EMBASE, Web of Science, and the Cochrane Library were searched for eligible studies until April 30, 2023. The outcomes of interest were overall survival (OS), and grade ≥3 esophagitis and pneumonitis, reported as hazard ratios (HRs) or odds ratios (ORs) with their 95% confidence intervals (CIs).

Results: A total of 23 studies with 7987 patients were identified. Hypo-TRT showed similar OS compared to Hyper-TRT (HR = 1.22, 95% CI: 0.80-1.86 in randomized controlled trials [RCTs] and HR = 1.12, 95% CI: 0.99-1.28 in retrospective studies) and better OS compared to Con-TRT (HR =0.83, 95% CI: 0.70-0.97). Hyper-TRT achieved longer OS compared to Con-TRT in retrospective studies (HR = 0.91, 95% CI: 0.84-0.99), but not in RCTs (HR = 0.90, 95% CI: 0.80-1.01). There were no significant differences in incidence of grade ≥3 esophagitis or pneumonitis between the three schedules.

Conclusion: Hyper-TRT (45 Gy) or Con-TRT (60-70 Gy) remains a standard schedule. Hypo-TRT (40-45 Gy) is likely to be an alternative regimen. Nevertheless, these findings need to be validated in large phase 3 RCTs.

Keywords: Hypofractionated; hyperfractionated; meta-analysis; small cell lung cancer; thoracic radiotherapy

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Small-cell lung cancer (SCLC) accounts for approximately 15% of all lung tumors.[1] The standard treatment in patients with limited-stage disease remains thoracic radiotherapy (TRT) with concurrent chemotherapy. Prophylactic cranial irradiation (PCI) is recommended in patients who experienced good response to treatment. However, the optimal TRT schedule has not been established.

Currently, hyperfractionated (Hyper) (total 45Gy; 1.5Gy twice-daily) and conventionally fractionated (Con) (total 60-70Gy; 1.8-2Gy once-daily) TRT are two common schedules for limited-stage SCLC, and both recommended by the National Comprehensive Cancer Network (NCCN) guidelines. Nevertheless, the two schedules have their own advantages and disadvantages.[2,3] Compared to Con-

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TRT, Hyper-TRT has a shorter treatment duration which is important for the fast-growing SCLC, but the concern on tolerability and logistical challenges lead to the poor adoption in clinical practice. To date, except the Intergroup 0096 trial[4] which showed a superior 5-year overall survival (OS) in patients receiving Hyper-TRT (45Gy) vs Con-TRT (45Gy), none of the randomized controlled trials (RCTs)[5,6] demonstrated a significant difference in OS between the two schedules. For clinical experts, the selection of Hyper-TRT or Con-TRT is usually influenced by pragmatic factors such as availability of transportation and patients' performance status.[3]

In light of the limitations of the two TRT schedules mentioned above, there is increasing interest in examining the role of hypofractionated (Hypo) (fraction size >2Gy once-daily) TRT in limited-stage SCLC due to its shorter treatment duration and less logistical problems. In two phase 2 trials,[7,8] no significant difference in OS was observed between Hypo- and Hyper-TRT regimen, and toxicities were comparable. Nevertheless, it is still difficult to draw a conclusion on the superiority of Hypo-TRT due to lack of large head to head phase 3 trials.

In this meta-analysis, we compared the efficacy and safety among the three TRT schedules, aiming to add evidence for the clinical decision

Materials and Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[9] (Supplementary material: Table S1).

Literature Search Strategy

A systematic search was conducted in PubMed, Embase, Cochrane Library and Web of science for available studies published until April 30, 2023, using the search terms "small-cell lung cancer", "radiotherapy", "chemoradiotherapy", "once-daily", "twice-daily", "hyperfractionated", and "hypofractionated". The detailed search strategy was presented in Supplementary material: Table S2. Meeting abstracts of American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and World Conference on Lung Cancer (WCLC), were also inspected. The reference lists were checked for missing articles.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) RCTs or retrospective cohort studies assessing Hypo-TRT vs Hyper-TRT, or Hypo-TRT vs Con-TRT, or Hyper-TRT vs Con-TRT, in limited-stage SCLC; (2) reported OS and/or incidence of grade ≥3 esophagitis or pneumonitis; and (3) published in English. If multiple articles covered the same study population, the most comprehensive one was used.

Data Extraction

The following data were collected by two authors (SL and JC) independently: study characteristics, follow-up time, sample size, number of chemotherapy cycles at the start of TRT, TRT schedule, data of OS and grade ≥3 esophagitis and pneumonitis.

Quality Assessment

Risk of bias of RCTs was assessed by two authors (SL and JC) independently using Cochrane Risk of Bias Tool.[10] The RCTs were finally classified as low (all domains indicated as low risk), high (one or more domains indicated as high risk), and unclear risk of bias (more than three domains indicated as unclear risk). The quality of retrospective studies were evaluated according to the Newcastle-Ottawa Scale (NOS),[11] and those scored with six stars or more were considered to be relatively high-quality studies.

Statistical Analysis

The outcomes of interest were OS and grade ≥3 esophagitis and pneumonitis. Statistical analysis was performed using the software Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). Hazard ratios (HRs) or odds ratios (ORs) with their 95% confidence intervals (CIs) were used as summary statistics. The heterogeneity among studies was evaluated via the Chi-square (χ^2) and I-square (I^2) test with significance set at $P<0.10$ or $I2 >50\%$. A random-effects analysis model was used when significant heterogeneity existed; otherwise, a fixed-effects model was used. Subgroup analyses according to RT dose (≥59.4Gy and <59.4Gy) were performed for Con-TRT. The stability of the results was assessed by sensitivity analysis. The funnel plot, Begg's test,[12] and the Egger's linear regression test[13] were performed to investigate publication bias.

Results

Search Results and Characteristics of Studies

A total of 15260 studies were identified from the initial search. After removing the duplicates, 6176 records were identified. After screening the abstracts and/or titles, 5980 studies were excluded (3946 with irrelevant topic, and 2034 of reviews, case reports, letters, or meta-analyses). The remaining 196 articles were screened through a full-text review for further eligibility, and 174 of them were excluded (94 with extensive disease, 71 without available data, and 9 covering the same study population). Finally, 23 stud-

ies (5 RCTs[4-8] and 18 retrospective studies[14-31]) with 7987 patients were eligible for inclusion. The detailed selection process are shown in Figure 1. Except the study by Turrisi et al (published in 1999),[4] all studies included were published after 2010. The median age was 63 years (interquartile range [IQR], 59-65), 62 years (IQR, 58-63), and 63 years (IQR, 60-65) for patients receiving Hypo-TRT, Hyper-TRT, and Con-TRT, respectively; the median sample size was 86 participants (IQR, 58-1117), 74 participants (IQR, 41-211), and 80 participants (IQR, 43-223), respectively; and the median follow up time was 24 months (IQR, 19-56), 30 months (IQR, 24-42), and 31 months (IQR, 26-45), respectively. The main characteristics and outcomes of included studies are presented in Table 1 and 2.

Assessment of Included Studies and Publication Bias

Among the five RCTs, one[6] was considered to be unclear risk of bias, and the others were rated with low risk of bias (Supplementary material: Figure S1). All retrospective studies demonstrated a score ≥6 (Supplementary material: Table S3). The Begg's and Egger's test results indicated no publication bias in OS (p>0.05 each result), except for Hypo-TRT vs Hyper-TRT in retrospective studies (Egger's test: p=0.021). The funnel plots are shown in Supplementary material: Figure S2.

OS for Hyper-TRT vs Con-TRT

There were 3 RCTs with 1602 patients[4-6] and 9 retrospective studies with 3149 patients.[14-21,31] There was no significant difference in OS between Hyper-TRT and Con-TRT in RCTs (HR = 0.90, 95% CI: 0.80-1.01, I^2 = 36%); similar result was observed when removing the old RCT by Turrisi et al (published in 1999)[4] (HR = 0.95, 95% CI: 0.76-1.18, I^2 = 50%) (Supplementary material: Figure S3). However, Hyper-TRT significantly improved OS compared to Con-TRT in retrospective studies (HR = 0.91, 95% CI: 0.84-0.99, I^2 = 0%) (Fig. 2).

In subgroup analysis according to RT dose of Con-TRT, Hyper-TRT achieved a longer OS compared to Con-TRT with dose <59.4Gy (HR = 0.77, 95% CI: 0.67-0.89, I^2 = 39%); similar result was also observed when removing the old study published in 1999[4] (HR = 0.70, 95% CI: 0.55-0.87, I^2 = 41%) (Supplementary material: Figure S3). However, Hyper-TRT showed a similar OS compared to Con-TRT with dose ≥59.4Gy (HR = 0.94, 95% CI: 0.87-1.01, I^2 = 0%) (Fig. 2).

OS for Hypo-TRT vs Con-TRT

There were 4 retrospective studies[22-25] with 683 patients. Hypo-TRT had significantly longer OS compared to Con-TRT (HR =0.83, 95% CI: 0.70-0.97, I^2 = 33%) (Fig. 3).

OS for Hypo-TRT vs Hyper-TRT

There were 2 RCTs with 339 patients[7,8] and 6 retrospective studies with 2259 patients.[26-31] No significant difference in OS was observed between the two schedules either in RCTs (HR = 1.22, 95% CI: 0.80-1.86, I^2 = 0%) or in retrospective studies (HR = 1.12, 95% CI: 0.99-1.28, I^2 = 21%) (Fig. 4).

Grade ≥3 Pneumonitis and Esophagitis

No significant differences were observed in grade ≥3 pneumonitis and grade ≥3 esophagitis between Hyper-TRT and Con-TRT (HR =0.89, 95% CI: 0.49-1.48, I^2 = 27% and HR =1.65, 95% CI: 0.84-3.22, I^2 = 72%), Hypo-TRT and Con-TRT (HR = 0.64, 95% CI: 0.28-1.48, I^2 = 0% and HR =1.33, 95% CI: 0.74-2.38, I^2 = 0%), and Hypo-TRT and Hyper-TRT (HR =1.18, 95% CI: 0.52-2.67, I^2 = 0% and HR =0.95, 95% CI: 0.61-1.48, I^2 = 0%) (Fig. 5).

When removing the old study published in 1999[4] from analyses, there were also no significant differences in grade ≥3 pneumonitis and grade ≥3 esophagitis between Hyper-TRT and Con-TRT (HR =0.50, 95% CI: 0.23-1.06, I^2 = 0% and HR =1.35, 95% CI: 0.60-3.04, I^2 = 57%) (Supplementary material: Figure S3).

Sensitivity Analysis

Sensitivity analysis for OS were performed in retrospective studies. Except the study by Shidal et al.[21], when individual studies were removed one at a time from the analyses for OS, the results were not markedly altered by any single study (Supplementary material: Figure S4). However, when the study by Shidal et al was removed from the analysis, no significant difference in OS between Hyper-TRT and Con-TRT was observed (HR =0.86, 95% CI: 0.72-1.02).

Discussion

This is a comprehensive systematic review and meta-analysis to compare efficacy and safety between Hypo-TRT, Hyper-TRT and Con-TRT in limited-stage SCLC. It showed that Hyper-TRT had better OS compared to Con-TRT in retrospective studies, but not in RCTs; risk of grade ≥3 pneumonitis and esophagitis were similar. However, in sensitivity analysis for retrospective studies, no significant difference in OS was observed between the two schedules when removing the study by Shidal et al.[21] In fact, the study by Shidal et al.[21] involved 2261 patients from the National Cancer Database and showed a improved OS of Hyper-TRT vs Con-TRT. However, this study had some important limitations such as unbalanced characteristics between treatment groups (such as age, comorbidity score, and days to RT from diagnosis), unknown performance status, and unknown information on the use of PCI, which might lead to

Table 1. Characteristics of included studies

First author/year	Region	Study design	Sample size	TRT schedule (Total dose/ BED10, Gy)	RT technique	ENI	CT cycle	Use of PCI	Staging procedure
Turrisi/1999[4]	England	RCT	211	Hyper(45/52)	2D-RT	Yes	1	NR	CT/MRI
			206	Con(45/53)	2D-RT	Yes	1	NR	CT/MRI
Faivre-Finn/2017[5]	Multicountry	RCT	274	Hyper(45/52)	3D-CRT	No	NR	81%	CT/MRI/PET-CT
			273	Con(66/79)	3D-CRT	No	NR	81%	CT/MRI/PET-CT
Bogart/2021[6]	Multicountry	RCT	313	Hyper(45/52)	3D/IMRT	Yes	1-2	NR	CT/PET-CT
			325	Con(70/84)	3D/IMRT	Yes	1-2	NR	CT/PET-CT
Grønberg/2016[7]	Ethics	RCT	84	Hypo(42/54)	3D-CRT	Yes	NR	82%	CT/MRI
			73	Hyper(45/52)	3D-CRT	Yes	NR	84%	CT/MRI
Qiu/2021[8]	China	RCT	88	Hypo(65/81)	IMRT	No	1-3	72%	NR
			94	Hyper(45/52)	IMRT	No	1-3	71%	NR
Tomita/2010[14]	Japan	RS	37	Hyper(45/52)	2D-RT/3D-CRT	NR	1	65%	CT
			90	Con(40-66/47-79)	2D-RT/3D-CRT	NR	1	27%	CT
Watkins/2010[15]	USA	RS	54	Hyper(45/52)	3D-CRT	No	1-2	NR	NR
			17	Con(59/70)	3D-CRT	No	1-2	NR	NR
Gazula/2014[16]	USA	RS	26	Hyper(45/52)	3D/IMRT	No	NR	NR	CT/MRI
			19	Con(50-67/60-79)	3D/IMRT	No	NR	NR	CT/MRI
Winther-Larsen/2015[17]	Denmark	RS	130	Hyper(45/52)	3D/IMRT	No	NR	NR	CT/MRI/PET-CT
			17	Con(46-50/55-60)	3D/IMRT	No	NR	NR	CT/MRI/PET-CT
Han/2015[18]	China	RS	63	Hyper(45/52)	3D/IMRT	No	NR	59%	CT/MRI/PET-CT
			80	Con(60/72)	3D/IMRT	No	NR	50%	CT/MRI/PET-CT
Watkins/2020[19]	Poland	RS	52	Hyper(45/52)	3D/IMRT	No	1-2	83%	CT/MRI/PET-CT
			80	Con(59/70)	3D/IMRT	No	1-2	40%	CT/MRI/PET-CT
Tan/2021[20]	China	RS	74	Hyper(50/66)	3D-CRT	No	2	NR	CT
			74	Con(56/67)	3D-CRT	No	2	NR	CT
Shidal/2022[21]	USA	RS	876	Hyper(45/52)	NR	NR	NR	NR	NR
			1385	Con(60-70/72-84)	NR	NR	NR	NR	NR
Videtic/2003[22]	England	RS	122	Hypo(40/51)	2D-RT	No	2-3	17%	CT
			92	Con(50/60)	2D-RT	No	2-3	29%	CT
Socha/2015[23]	Poland	RS	100	Hypo(42/54)	3D-CRT	Yes	NR	52%	CT/MRI
			82	Con(44-60/53-72)	2D-RT/3D-CRT	Yes	NR	45%	CT/MRI
Zhang/2017[24]	China	RS	69	Hypo(55/69)	3D/IMRT	No	NR	67%	CT/MRI/PET-CT
			101	Con(56-66/67-79)	3D/IMRT	No	NR	48%	CT/MRI/PET-CT
Zayed/2020[25]	England	RS	36	Hypo(40-45/51-55)	3D/IMRT/VMAT	NR	NR	54%	NR
			36	Con(60-66/72-79)	3D/IMRT/VMAT	NR	NR	69%	NR
Bettington/2013[26]	Australia	RS	38	Hypo(40/51)	3D-CRT	No	2-3	50%	CT
			41	Hyper(45/52)	3D-CRT	No	2-3	68%	CT
Hu/2019[27]	China	RS	96	Hypo(55/69)	3D/IMRT	No	2-3	57%	CT/MRI
			92	Hyper(45/52)	3D/IMRT	No	2-3	65%	CT/MRI
Yan/2021[28]	Canada	RS	63	Hypo(40/51)	3D/IMRT/VMAT	NR	NR	NR	CT/MRI/PET-CT
			110	Hyper(45/52)	3D/IMRT/VMAT	NR	NR	NR	CT/MRI/PET-CT
Graabak/2021[29]	Norway	RS	792	Hypo(42/54)	NR	NR	NR	64%	NR
			313	Hyper(45/52)	NR	NR	NR	74%	NR
Zhou/2022[30]	China	RS	24	Hypo(45-60/59-78)	VMAT	No	3-4	67%	CT/MRI/PET-CT
			24	Hyper(45/52)	VMAT	No	3-4	71%	CT/MRI/PET-CT
Almahmudi/2020[31]	Canada	RS	638	Hypo(40/51)	NR	NR	NR	NR	NR
			28	Hyper(45/52)	NR	NR	NR	NR	NR
			47	Con(50/60)	NR	NR	NR	NR	NR

RCT: randomized controlled trial; RS: retrospective study; TRT: thoracic radiotherapy; CT: cycle, number of chemotherapy cycles at the start of TRT; Con: conventionally fractionated; Hyper: hyperfractionated; Hypo: hypofractionated; PCI: prophylactic cranial irradiation; ENI: elective node irradiation; 2D-RT: two-dimensional radiotherapy; 3D: three-dimensional conformal radiotherapy; IMRT: intensity-modulated radiotherapy; VMAT: volumetric intensity modulated arc therapy; NR: not report.

Table 2. Main outcomes of included studies

First author/year	Median OS (months)	Grade≥3 pulmonitis	Grade≥3 esophagitis	Follow up (months)
Turrisi/1999[4]	23	7%	33%	96
	19	4%	16%	96
Faivre-Finn/2017[5]	30	2%	18%	45
	25	2%	18%	45
Bogart/2021[6]	28.7	NR	NR	34.1
	30.5	NR	NR	34.1
Grønberg/2016[7]	18.8	6%	31%	59
	25.1	4%	33%	59
Qiu/2021[8]	39.3	2%	15%	24.3
	33.6	3%	17%	24.3
Tomita/2010[14]	24	NR	NR	33
	24	NR	NR	33
Watkins/2010[15]	21.4	4%	20%	26.2
	22.1	6%	24%	26.2
Gazula/2014[16]	23.8	0%	0%	30
	23	5%	0%	33.6
Winther-Larsen/2015[17]	NR	NR	NR	42.2
	NR	NR	NR	42.2
Han/2015[18]	31.4	6%	19%	27.1
	29.5	16%	6%	27.1
Watkins/2020[19]	21.2	NR	NR	18.5
	16.7	NR	NR	18.5
Tan/2021[20]	23.6	NR	NR	NR
	20.2	NR	NR	NR
Shidal/2022[21]	21.6	NR	NR	NR
	NR	NR	NR	NR
Videtic/2003[22]	14.7	NR	NR	14.8
	15.1	NR	NR	14.8
Socha/2015[23]	24	2%	24%	31
	18	6%	18%	31
Zhang/2017[24]	27.2	10%	12%	30
	25.3	12%	10%	30
Zayed/2020[25]	17	NR	NR	324
	20.2	NR	NR	120
Bettington/2013[26]	21	NR	NR	NR
	26	NR	NR	NR
Hu/2019[27]	22	NR	NR	17.8
	28.3	NR	NR	20.4
Yan/2021[28]	NR	8%	14%	20.4
	NR	6%	13%	20.4
Graabak/2021[29]	19.6	NR	NR	NR
	26.2	NR	NR	NR
Zhou/2022[30]	NR	0%	0%	23.9
	NR	0%	0%	23.9
Almahmudi/2020[31]	15.1	NR	NR	NR
	24.1	NR	NR	NR
	16.9	NR	NR	NR

OS: overall survival; NR: not report.

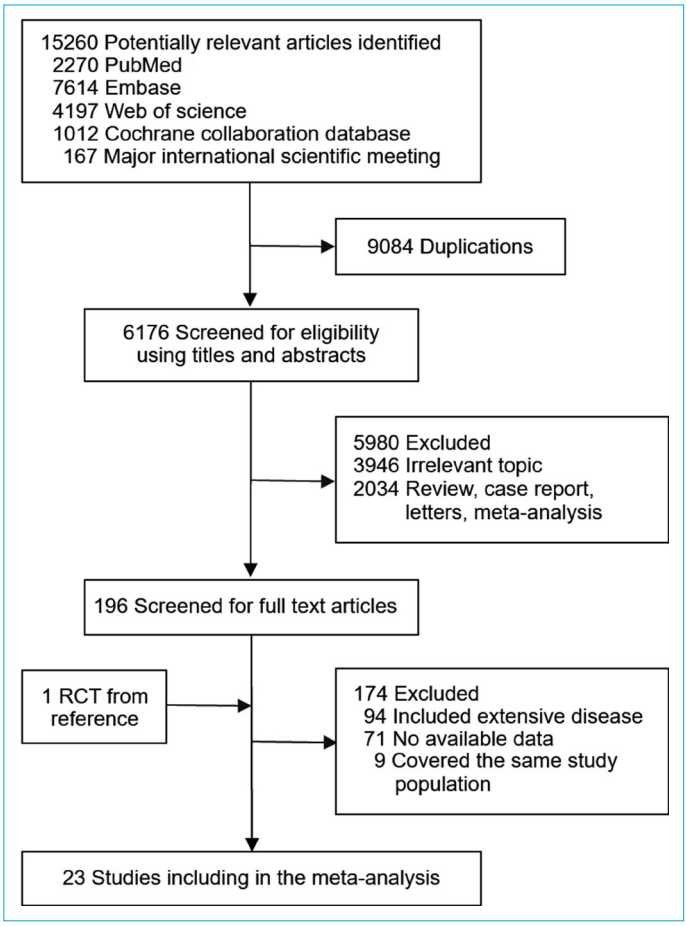

Figure 1. Literature search and selection.

RCT: randomized controlled trial.

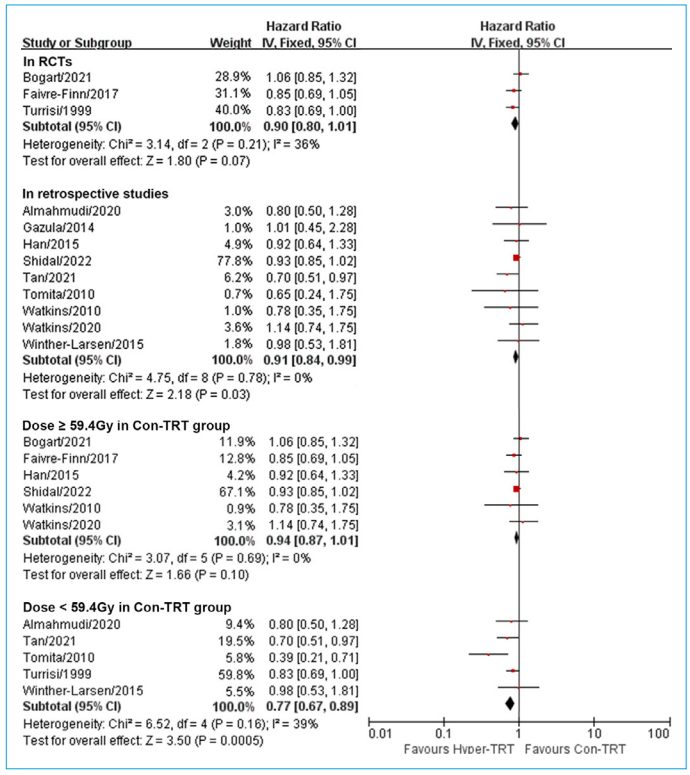

Figure 2. Overall survival of Hyper-TRT vs Con-TRT.

Hyper: hyperfractionated; Con: conventionally fractionated; TRT: thoracic radiotherapy; RCT: randomized controlled trial; CI: confidence interval.

less reliability of the results. In addition, TRT dose might be a confounding factor affecting the results. In our subgroup analysis, Con-TRT with a dose <59.4Gy was associated a worse OS compared to Hyper-TRT, but Con-TRT with a dose ≥59.4Gy was not. Thus, it is still hardly to draw a conclusion on the superiority of Hyper-TRT vs Con-TRT, and Con-TRT (dose ≥59.4Gy) remains an acceptable schedule, especially for patients unwilling or unable to receive twice-daily TRT.

Hypo-TRT is another once-daily regimen for limited-stage SCLC. This regimen has unique advantages such as having shorter treatment time compared to Con-TRT and with less logistical problems compared to Hyper-TRT. However, the schedule has not been routinely recommended due to the limited evidence for its efficacy and safety. In our meta-analysis, we assessed OS of Hypo-TRT vs Hyper-TRT

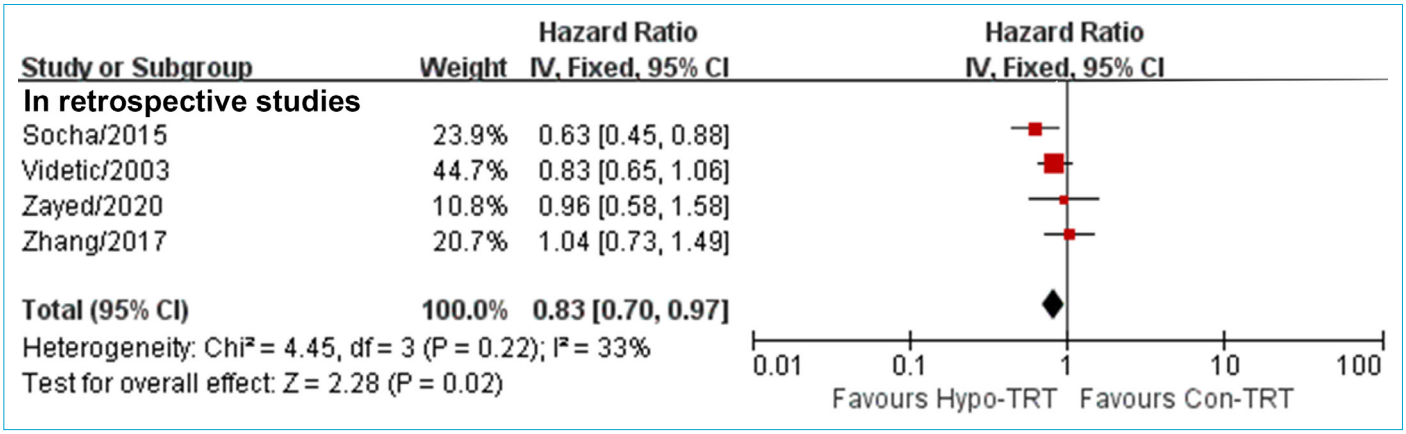

Figure 3. Overall survival of Hypo-TRT vs Con-TRT.

Hypo: hypofractionated; Con: conventionally fractionated; TRT: thoracic radiotherapy; CI: confidence interval.

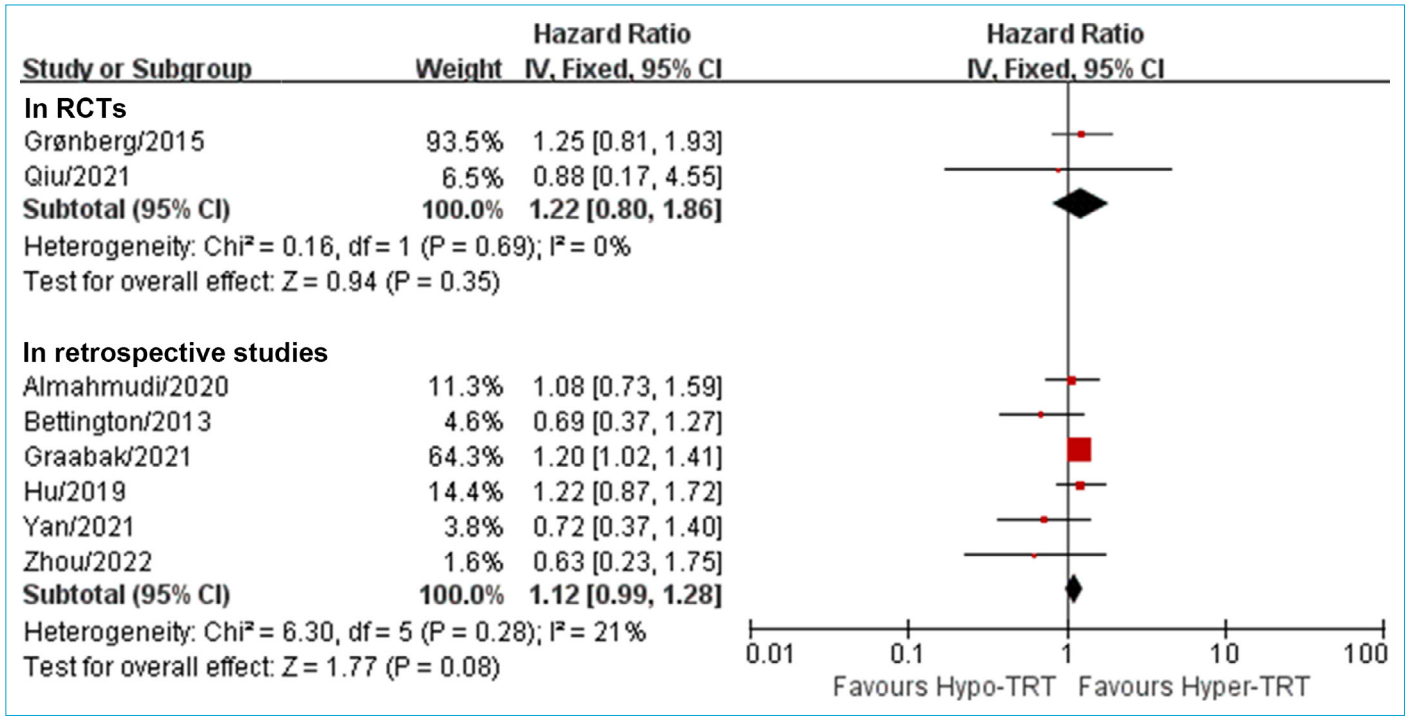

Figure 4. Overall survival of Hypo-TRT vs Hyper-TRT.

Hypo: hypofractionated; Hyper: hyperfractionated; TRT: thoracic radiotherapy; RCT: randomized controlled trial; CI: confidence interval

and Hypo-TRT vs Con-TRT, respectively. We found that OS was comparable between Hypo-TRT and Hyper-TRT either in RCTs or in retrospective studies. As for Hypo-TRT vs Con-TRT, there is still no RCTs to date. Hypo-TRT was found to be associated with a significantly improved OS compared to Con-TRT in retrospective studies. There were no significant differences in incidence of grade ≥3 esophagitis or pneumonitis between Hypo-TRT and Hyper-TRT, and between Hypo-TRT and Con-TRT. Based on current evidences, Hypo-TRT is likely to be an alternative schedule for limited-stage SCLC.

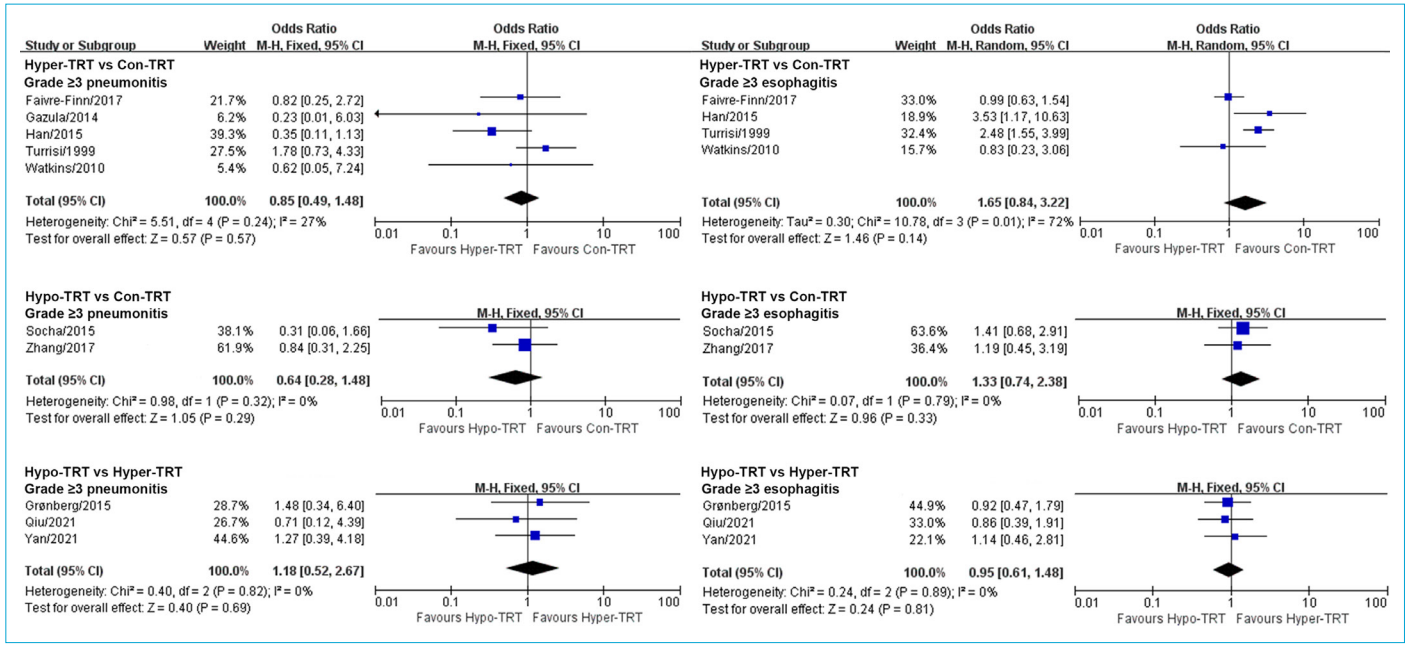

Figure 5. Incidence of grade ≥3 pneumonitis and esophagitis.

Hypo: hypofractionated; Hyper: hyperfractionated; Con: conventionally fractionated; TRT: thoracic radiotherapy

In addition to TRT schedule, the optimal dose of TRT is also being explored. In a recent phase II trial examining high dose Hyper-TRT (60Gy, BED10 = 78Gy) vs the standard Hyper-TRT (45Gy, BED10 = 52Gy), a significant improvement in OS (42 months vs 23 months) was observed and without adding toxicity.[32] However, there is query that the comparable toxicity might be caused by some unreported biases such as differences in tumour burden or patient selection between arms. There are also trials assessing efficacy of high dose Con-TRT (70Gy, BED10 = 84Gy) [6] or Hypo-TRT (65Gy, BED10 = 81Gy).[8] Unfortunately, both the two high dose regimens failed to significantly improved OS compared to the standard Hyper-TRT. Thus, 60-70Gy, 45Gy, and 40-45Gy remain the standard dose for Con-TRT, Hyper-TRT, and Hypo-TRT, respectively. Whether increased TRT dose is associated with improved survival needs further investigation in more trials.

Several previous meta-analyses[33-37] have also evaluated the schedules of TRT in SCLC, but with some limitations. For example, meta-analyses performed by Yang et al.[33] and Wu, et al.[34] included only five studies, and without examining the schedule of Hypo-TRT. Another network meta-analysis conducted by Zhou et al.[35] included a number of retrospective studies, which was statistically unreasonable for this type of meta-analysis. A more recent meta-analysis by Viani et al.[36] included five RCTs. Inconsistent with our results, they found that Hypo-TRT was associated with a better OS than Hyper-TRT. Of note, in their study, the HRs of OS were extracted from survival curves at 1, 2, and 3 year instead of using the HRs directly reported in individual studies. However, this is not a common used statistical method in meta-analysis and with controversy. Moreover, HRs manually extracted from survival curves may result in bias and error. Another recent meta-analysis by Zhao et al.[37] included 53 studies and with similar conclusions to our study. However, the majority of the studies included were single-arm studies (n=37), and the cross-study comparisons have inherent methodological limitation. In addition, their meta-analysis included more RCTs (n=7) compared to our study. However, 2 of them (published 1999 and 2005, respectively)[38,39] appeared to be ineligible because split-course irradiation was adopted in their experimental arms, which is not a standard TRT regimen and is no longer used now. Moreover, there were additional 9 eligible cohort studies[15,17,19,21,22,27,29-31] which were not included in their meta-analysis. To our knowledge, our meta-analysis included all eligible head to head comparison studies on the current subject until now. In addition, our study compared the three schedules in RCTs and real-world studies, respectively, and with similar findings. Moreover, we performed subgroup analysis according to RT dose, and found that Hyper-TRT had superior OS compared to Con-TRT with dose <59.4Gy but dose ≥59.4Gy. Our findings would be helpful for the clinical selection of TRT schedules.

Nevertheless, there are also limitations in our meta-analysis. First, the number of studies included in this meta-analysis was still relatively small, and the data extracted from retrospective studies might have selection bias. Second, although most of studies adopted modern techniques, the use of three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), and volumetric intensity modulated arc therapy (VMAT) were not balanced between treatment groups in several studies. For example, in study of Zayed et al.,[25] the use of IMRT/VMAT was 89% in Con-TRT group, while was only 9% in Hypro-TRT group. In addition, many studies did not report the proportion of techniques used, which might also be unbalanced due to the nature of retrospective studies. This imbalance may have an impact on the outcomes, especially toxicities. Third, the target volume strategy adopted in individual studies was inconsistent, which might also have an influence on the amount of side effects. For example, incidence of grade ≥3 esophagitis for patients receiving Hyper-TRT was 31% in trial of Grønberg et al.[7] adopting elective nodal irradiation, which was obviously higher than that in trial of Faivre-Finn et al.[5] (18%) using involved-field irradiation. Fourth, staging procedures were various among studies. Many studies did not use PET-CT and/or brain MRI, which might result in inaccurate clinical staging and diminish the differences in oncological outcome. Finally, different TRT doses used in individual studies may also be confounding factor. In addition, some studies did not provide information of patients performance status, clinical stage, number of chemotherapy cycles at the start of TRT, and/or the use of PCI. These characteristics might be unbalanced between treatment groups, leading to the results unstable.

Conclusion

Hyper-TRT with a total dose of 45 Gy or Con-TRT with a total dose of 60-70 Gy remains a standard schedule, excluding any elective node irradiation and using IMRT/VMAT. Hypo-TRT appears to have comparable efficacy and safety with Hyper-TRT. Together with its additional advantages of short treatment duration and less logistical issues, Hypo-TRT with a total dose of 40-45 Gy is likely to be an alternative TRT schedule in limited-stage SCLC. Nevertheless, these findings need to be validated in large phase 3 RCTs.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – D.J.; Design – D.J.; Supervision – D.J.; Materials – L.S., R.C, C.J., L.T.; Data collection &/or processing – L.S., R.C.; Analysis and/or interpretation – All authors; Literature search – L.S., R.C.; Writing – All authors; Critical review – D.J.

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Table S1. PRISMA Checklist

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review incorporating a meta-analysis (or related form of meta-analysis).	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and synthesis methods, such as network meta-analysis. Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity. Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, including mention of why a network meta-analysis has been conducted.	4
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	No
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Additional file Table S2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	NA
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.	7
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • Handling of multi-arm trials; • Selection of variance structure; • Selection of prior distributions in Bayesian analyses; and • Assessment of model fit.	7

Table S1. CONT.

Section/Topic	Item #	Checklist Item	Reported on Page #
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • Alternative formulations of the treatment network; and • Use of alternative prior distributions for Bayesian analyses (if applicable).	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	NA
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	NA
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. Modified approaches may be needed to deal with information from larger networks.	8-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.	8-9
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, P values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	8
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth).	8-9
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	9-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).	11-12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	NA

PICOS = population, intervention, comparators, outcomes, study design.

Table S2. Search strategy

a: Search strategy in PubMed

#	Query
#1	"Lung Neoplasms"[mh]
#2	Pulmonary Neoplasms[tiab] OR Neoplasms, Lung[tiab] OR Lung Neoplasm[tiab] OR Neoplasm, Lung[tiab] OR Neoplasms, Pulmonary[tiab] OR Neoplasm, Pulmonary[tiab] OR Pulmonary Neoplasm[tiab] OR Lung Cancer[tiab] OR Cancer, Lung[tiab] OR Cancers, Lung[tiab] OR Lung Cancers[tiab] OR Pulmonary Cancer[tiab] OR Cancer, Pulmonary[tiab] OR Cancers, Pulmonary[tiab] OR Pulmonary Cancers[tiab] OR Cancer Of The Lung[tiab] OR Cancer Of Lung[tiab]
#3	"Small Cell Lung Carcinoma"[mh]
#4	Small Cell Lung Cancer[tiab] OR Carcinoma, Small Cell Lung[tiab] OR Small Cell Cancer Of The Lung[tiab] OR SCLC[tiab] OR Oat Cell Lung Cancer[tiab] OR Oat Cell Carcinoma Of Lung[tiab]
#5	#1 OR #2 OR #3 OR #4
#6	Limited[tiab] OR Limited-Stage[tiab] OR Limited Stage[tiab] OR Limited-Disease[tiab] OR Limited Disease[tiab] OR Nonmetastatic[tiab] OR Stage 1-3[tiab] OR Stage I-III[tiab]
#7	"Radiotherapy"[mh] OR Radiotherapies[tiab] OR Radiation Therapy[tiab] OR Radiation Therapies[tiab] OR Radiation Treatment[tiab] OR Targeted Radiotherapy[tiab] OR Targeted Radiation Therapy[tiab] OR Hypofractionated Radiotherapy[tiab] OR Hyperfractionated Radiotherapy[tiab] OR Conventionally Fractionated Radiotherapy[tiab] OR Standard Fractionation Radiotherapy[tiab] OR Once-Daily Radiotherapy[tiab] OR QD Radiation[tiab] OR Twice-Daily Radiotherapy[tiab] OR BID Radiation[tiab]
#8	#5 AND #6 AND #7

b: Search strategy in Embase

#	Query
#1	'Lung Cancer'/exp
#2	'Small Cell Lung Cancer'/exp
#3	'Small Cell Lung Cancer':ab,ti OR 'SCLC':ab,ti
#4	#1 OR #2 OR #3
#5	'Limited':ab,ti OR 'Limited-Stage':ab,ti OR 'Limited Stage':ab,ti OR 'Limited-Disease':ab,ti OR 'Limited Disease':ab,ti OR 'Nonmetastatic':ab,ti OR 'Stage 1-3':ab,ti OR 'Stage I-III':ab,ti
#6	'Radiotherapy'/exp OR 'Radiotherapies':ab,ti OR 'Radiation Therapy':ab,ti OR 'Radiation Therapies':ab,ti OR 'Radiation Treatment':ab,ti OR 'Targeted Radiotherapy':ab,ti OR 'Targeted Radiation Therapy':ab,ti OR 'Hypofractionated Radiotherapy':ab,ti OR 'Hyperfractionated Radiotherapy':ab,ti OR 'Conventionally Fractionated Radiotherapy':ab,ti OR 'Standard Fractionation Radiotherapy':ab,ti OR 'Once-Daily Radiotherapy':ab,ti OR 'QD Radiation':ab,ti OR 'Twice-Daily Radiotherapy':ab,ti OR 'BID Radiation':ab,ti
#7	#4 AND #5 AND #6

c: Search strategy in Cochrane Library

#	Query
#1	MeSH descriptor: [Lung Neoplasms] explode all trees
#2	MeSH descriptor: [Small Cell Lung Carcinoma] explode all trees
#3	((Lung OR Pulmon*) AND (Neoplas* OR Cancer OR Carcinoma* OR Tumour* OR Tumor*))
#4	(Small Cell Lung Cancer) OR (SCLC)
#5	#1 OR #2 OR #3 OR #4
#6	(Limited OR Limited-Stage OR Limited Stage OR Limited-Disease OR Limited Disease OR Nonmetastatic OR Stage I-III):ti,ab
#7	(Radiotherapy OR Radiotherapies OR Radiation Therapy OR Radiation Therapies OR Radiation Treatment OR Targeted Radiotherapy OR Targeted Radiation Therapy OR Hypofractionated Radiotherapy OR Hyperfractionated Radiotherapy OR Conventionally Fractionated Radiotherapy OR Standard Fractionation Radiotherapy OR Once-Daily Radiotherapy OR QD Radiation OR Twice-Daily Radiotherapy OR BID Radiation):ti,ab
#8	#5 AND #6 AND #7

d: Search strategy in Web of Science

#	Query
#1	TS=(" Lung Cancer" OR "Small Cell Lung Cancer" OR "SCLC" OR ((Lung OR Pulmon*) AND (Neoplas* OR Cancer OR Carcinoma* OR Tumour* OR Tumor*)))
#2	TS=("Limited" OR "Limited-Stage" OR "Limited Stage" OR "Limited-Disease" OR "Limited Disease" OR "Nonmetastatic" OR "Stage 1-3" OR "Stage I-III")
#3	TS=("Radiotherapy" OR "Radiotherapies" OR "Radiation Therapy" OR "Radiation Therapies" OR "Radiation Treatment" OR "Targeted Radiotherapy" OR "Targeted Radiation Therapy" OR "Hypofractionated Radiotherapy" OR "Hyperfractionated Radiotherapy" OR "Conventionally Fractionated Radiotherapy" OR "Standard Fractionation Radiotherapy" OR "Once-Daily Radiotherapy" OR "QD Radiation" OR "Twice-Daily Radiotherapy" OR "BID Radiation")
#4	#1 AND #2 AND #3

Table S3. Quality assessment of retrospective studies using the Newcastle-Ottawa scale

First author/year	Selection				Comparability		Outcome			Score
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	
Tomita/2010	–	*	*	*	*	*	*	*	–	7
Watkins/2010	–	*	*	*	*	–	*	*	–	6
Gazula/2014	*	*	*	*	*	–	*	*	–	7
Winther-Larsen/2015	–	*	*	*	*	*	*	*	–	7
Han/2015	–	*	*	*	*	*	*	*	–	7
Watkins/2020	*	*	*	*	*	*	*	–	–	7
Tan/2021	–	*	*	*	*	*	*	*	–	7
Shidal/2022	*	*	*	*	*	*	*	–	–	7
Videtic/2003	–	*	*	*	*	*	*	–	–	6
Socha/2015	–	*	*	*	*	–	*	*	–	6
Zhang/2017	–	*	*	*	*	*	*	*	–	7
Zayed/2020	–	*	*	*	*	*	*	*	–	7
Bettington/2013	*	*	*	*	*	–	*	–	–	6
Hu/2019	*	*	*	*	*	*	*	–	–	7
Yan/2021	*	*	*	*	*	*	*	*	–	8
Graabak/2021	*	*	*	*	*	*	*	–	–	7
Zhou/2022	–	*	*	*	*	–	*	*	–	6
Almahmudi/2020	*	*	*	*	*	*	*	–	–	7

Abbreviations: –, zero point; *, one point. Item 1, representativeness of the exposed cohort; item 2, selection of the non-exposed cohort; item 3, ascertainment of exposure; item 4, demonstration that outcome of interest was not present at start of study; item 5, comparability of cohorts on the basis of the design (study controls for the most important factor); item 6, comparability of cohorts on the basis of the design (study controls for other additional factor); item 7, assessment of outcome; item 8, follow-up long enough for outcomes to occur; item 9, adequacy of follow-up of cohorts.

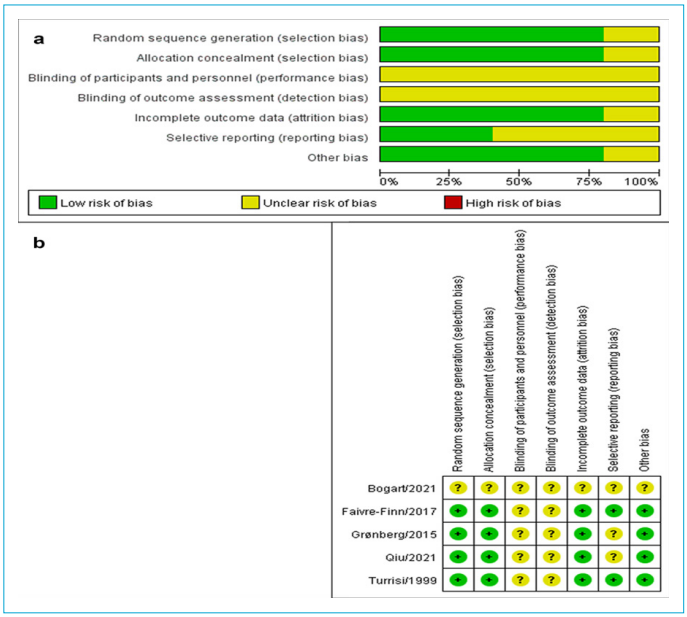

Figure S1. Assessment of risk of bias for randomized controlled trials. **(a)** Methodological quality graph: authors' judgment about each methodological quality item presented as percentages across all included studies; **(b)** Methodological quality summary: authors' judgment about each methodological quality item for each included study, "+" low risk of bias; "?" unclear risk of bias; "-" high risk of bias.

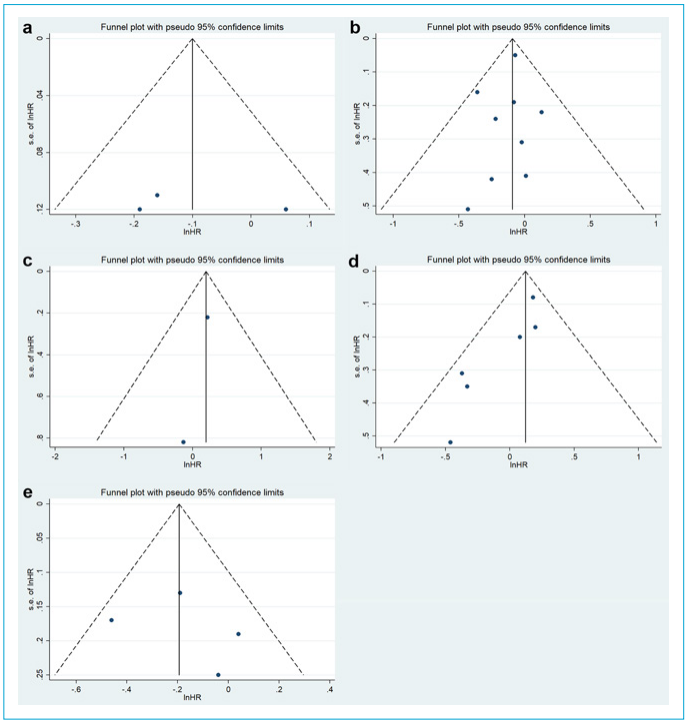

Figure S2. Funnel plots of publication bias. **(a)** Hyper-TRT vs Con-TRT in RCTs; **(b)** Hyper-TRT vs Con-TRT in retrospective studies; **(c)** Hypo-TRT vs Hyper-TRT in RCTs; **(d)** Hypo-TRT vs Hyper-TRT in retrospective studies; **(e)** Hyper-TRT vs Con-TRT. Hyper: hyperfractionated; Con: conventionally fractionated; Hypo: hypofractionated; TRT: thoracic radiotherapy.

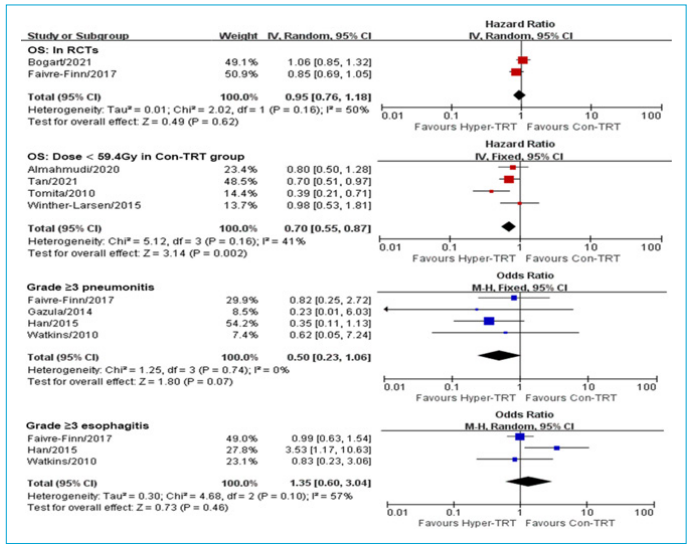

Figure S3. Outcomes of Hypo-TRT vs Con-TRT when removing the old study by Turrisi et al (published in 1999). Hypo, hypofractionated; Con, conventionally fractionated; TRT, thoracic radiotherapy; CI, confidence interval.

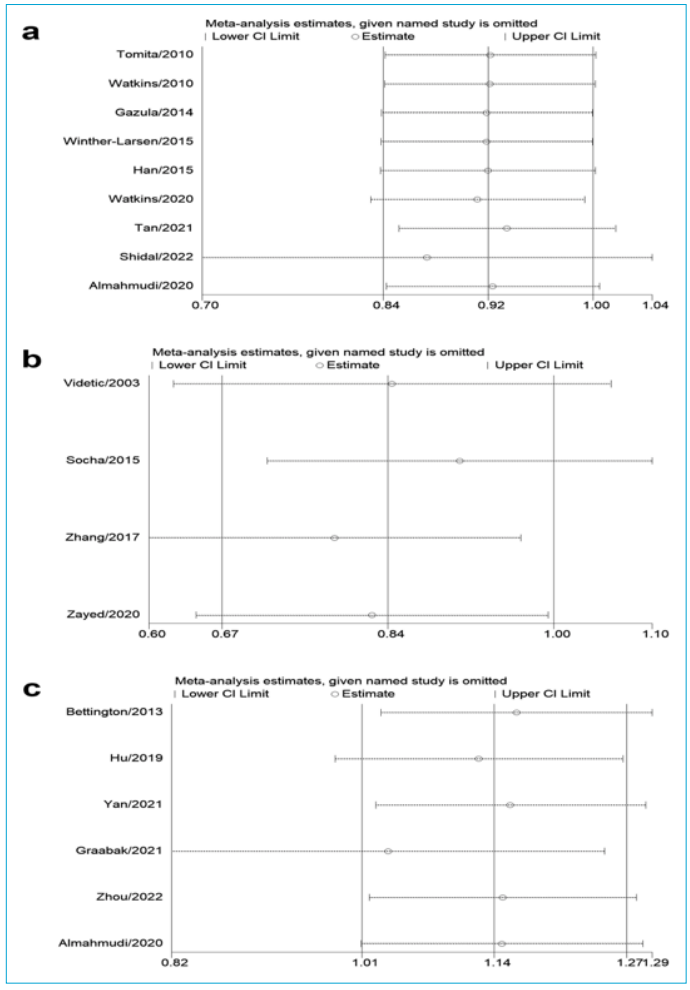

Figure S4. Sensitivity analysis. **(a)** Hyper-TRT vs Con-TRT; **(b)** Hyper-TRT vs Con-TRT; **(c)** Hypo-TRT vs Hyper-TRT. Hyper, hyperfractionated; Con, conventionally fractionated; Hypo, hypofractionated; TRT, thoracic radiotherapy.