Int J Clin Exp Pathol 2017;10(6):6179-6188
www.ijcep.com /ISSN:1936-2625/IJCEP0050202

Review Article

Meta-analysis of hypofractionated radiotherapy versus conventional radiotherapy in locally advanced non-small-cell lung cancer

Jie Liu[1*], Hongyan Cheng[2*], Chi Zhang[3*], Wangshu Dai[3], Xiaolin Ge[3], Liping Xu[3], Zhaoyue Zhang[3], Xinchen Sun[3]

[1]Department of Radiotherapy, The Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, China; Departments of [2]General Medicine, [3]Radiotherapy, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China. [*]Equal contributors.

Received February 6, 2017; Accepted March 22, 2017; Epub June 1, 2017; Published June 15, 2017

Abstract: Purpose: For inoperable locally advanced non-small cell lung cancer (LA-NSCLC), the efficacy of hypofractionated radiotherapy (Hypo-RT) has not been clearly established. The present meta-analysis was performed to estimate the effect of Hypo-RT on survival outcomes and toxicity in inoperable locally advanced non-small cell lung cancer. Material and methods: We performed a meta-analysis of patients with LA-NSCLC using Hypo-RT versus conventional RT, with the endpoints studied being overall survival (OS), progression-free survival (PFS), locoregional failure, distant failure and toxicity. Results: Data from six trials with 1211 patients were extracted. There were no significant differences in overall survival (HR 0.97; 95% CI, 0.86-1.10; P=0.64), progression-free survival (HR 1.03; 95% CI, 0.85 to 1.25; P=0.76), locoregional failure (HR 1.12; 95% CI, 0.83 to 1.49; P=0.46) or distant failure (HR 1.02; 95% CI, 0.73 to 1.43; P=0.92). Hypo-RT significantly reduced the risk of esophagitis toxicity from 13% to 24% (OR 0.32; 95% CI, 0.19 to 0.54; P < 0.0001) and reduced the risk of pneumonitis toxicity by 2% (OR 0.58; 95% CI, 0.34 to 0.99; P=0.05). Conclusion: Hypo-RT was not inferior to conventional RT in patients who had inoperable LA-NSCLC. With advanced technologies, it reduced the occurrence of toxicity. It is also convenient and safe. However, there was no evidence that this treatment improved the survival rate or decreased treatment failure.

Keywords: Locally advanced non-small cell lung cancer (LA-NSCLC), hypofractionated radiotherapy (Hypo-RT), survival outcome, toxicity

Introduction

Lung cancer is one of the most malignant tumors with the highest lethality worldwide [1]. More than 80% of lung cancers are non-small-cell lung cancers, of which one third are locally advance [2]. For inoperable locally advanced non-small-cell lung cancer (LA-NSCLC), radiotherapy alone or radiotherapy combined with chemotherapy is the main treatment regimen, and according to the RTOG 7,301 trial, conventional radiotherapy uses fractionated radiation doses of 60 to 66 Gy and 2 Gy per fraction [3]. However, the therapeutic effect is disappointing: the 5-year overall survival (OS) rate is only 13% to 16% [4].

To improve the overall survival and local control of LA-NSCLC, several trials have been conducted with dose escalations and have reported promising results [5-7]. However, the RTOG 0617 trial suggested that patients who received higher doses showed worse survival rates, with a median survival time of only 28 months [8, 9]. Extension of treatment time contributes to these negative results due to the accelerated repopulation of cancer cells [10].

Hyperfractionated and Hypo-RT were developed to shorten the overall treatment time (OTT) while delivering a sufficient biologically effective dose (BED). Hyperfractionated RT (Hyper-RT) delivers a treatment two or more times per day with a reduced dose per fraction. A significant survival benefit has been observed with Hyper-RT compared to conventional RT [11], but there are still several obstacles to its widespread use, including increased dose schedules and complicated logistics, as well as appropriate use of chemotherapy between the treatments. Hypo-RT delivers a higher dose of radiotherapy per fraction with only one dose

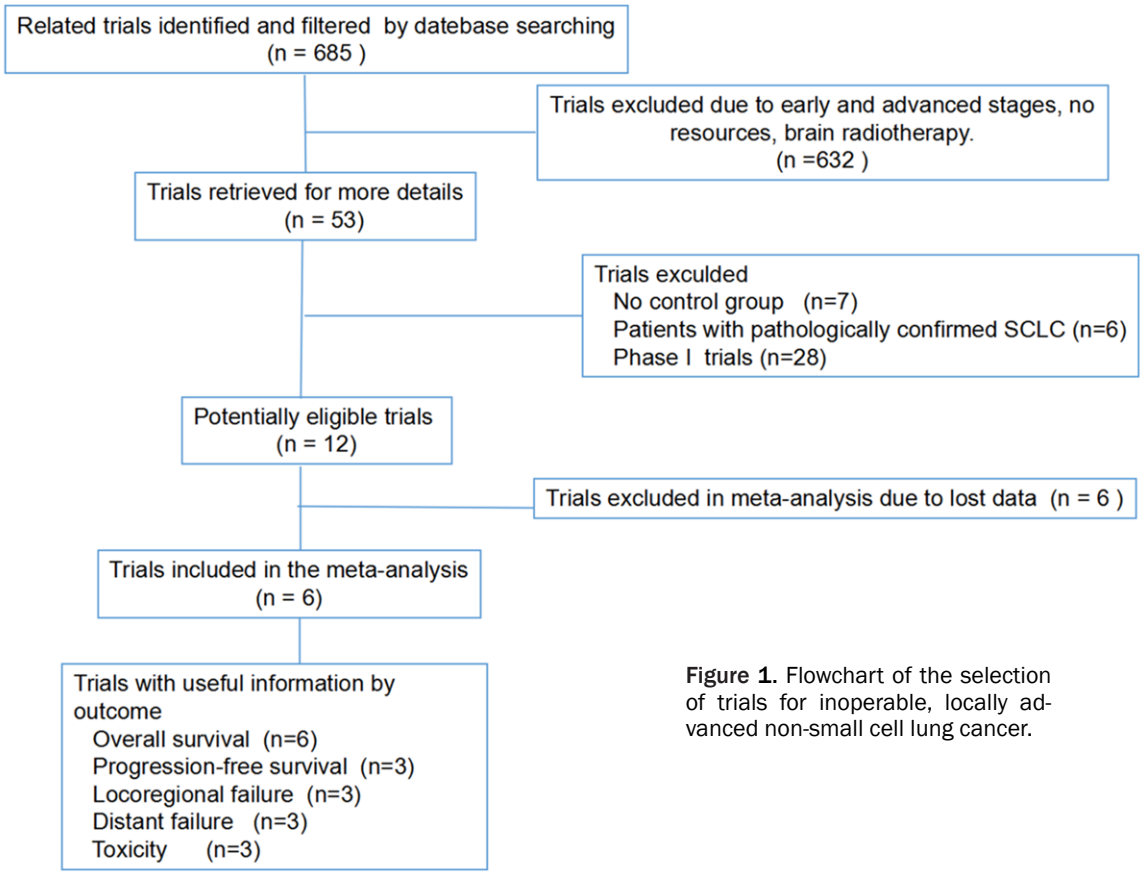


Figure 1. Flowchart of the selection of trials for inoperable, locally advanced non-small cell lung cancer.

per day. In recent years, Hypo-RT has been used in breast cancer and prostate cancer and has received considerable attention from clinicians and investigators [12, 13]. Although concerns exist about the severe side effects of Hypo-RT on lung tissue and the chest wall, the treatment holds promise because of the smaller number of fractions needed, the lower overall cost of treatment, and increased patient compliance, especially in busy radiation treatment centers. Furthermore, in the UK, Hypo-RT of 2.5 Gy per fraction has been the most widespread fractionation regimen for LA-NSCLC [14].

The present meta-analysis was performed to estimate the effect of Hypo-RT compared to conventional RT on survival outcomes and toxicity.

Materials and methods

Literature search strategy

A search was conducted with the index words "(radiotherapy dose) AND (non-small-cell lung carcinoma)" and "(hypofractionated RT) AND (non-small-cell lung cancer)" on PubMed, and published trials were included without language limitations. Each paper was carefully reviewed to prevent any data duplication.

Selection criteria and search strategy

Patients were eligible if they had locally advanced non-small-cell lung cancer and were not candidates for surgery, needing to receive radiotherapy instead. The studies also had to compare Hypo-RT (> 2 Gy per fraction, once daily) with conventional radiotherapy (1.8 to 2 Gy per fraction, 5 days per week). Patients who received concurrent chemotherapy (CT) were included.

Individual patient data

Data extraction was conducted for the items of gender, age, performance status, histology, tumor stage, number of patients, inclusion period, median follow-up, data on 1-, 2- and 3-year survival rates, PFS, local and distant failure, chemotherapy schedules and related toxicities

Table 1. Descriptions of included trials

Trial	No. Of patients	Inclusion Period	Median Follow-up (months)	RT Total Dose (Gy)	Dose per fractions (Gy)	Duration (weeks)	BED (Gy) (Exp/St)	CT	Patient characteristics
Steffen Appold 1999 [20]	298	1985-1994	NR	Experimental: 25 Standard: 60	5 2	1-2 6	37.5 72	NR	Stage III A, III B
LINH N. N GUYEN, M.D. 1999 [21]	55	1990-1994	13.5	Experimental: 45 Standard: 60-66	3 2	3 6-6.5	58.5 72-79.2	NR	Stage II A, II B, III A, III B
Stein Sundstrøm 2004 [22]	421	1993-1998	36	Experimental: 17 Experimental: 42 Standard: 50	8.5 2.8 2	1-2 3 5	31.45 53.76 60	Seven patients received palliative chemotherapy within 4 months	Stage III A, III B
Arya Amini 2012 [23]	300	1993-2009	NR	Experimental: 45 Standard: 60	3 2	3 6	58.5 72	Not mentioned	KPS 60-90, Stage III A, III B
Zheng-Fei Zhu, M.D. 2014 [24]	68	2006-2008	20	Experimental: 50 Standard: 60	2.5 2	4 6	83.7 76.4	*vinorelbine + cisplatin docetaxel + cisplatin	Age ≥ 18, KPS ≥ 70, Stage III A, III B
Jian He 2016 [25]	69	2011-2013	26.4	Experimental: 60 Standard: 60	3 2	4 6	78 72	+All patients received platinum-based CT	Age ≥ 18, PS 0-2, Weight loss < 10%

Abbreviations: RT, radiotherapy; BED, biologically effective dose; Exp, experimental CT; St, Standard; CT, Chemotherapy (unless otherwise specified, chemotherapy is concurrent with radiotherapy); KPS, Karnofsky performance status; NR, Not reported. *Experimental group: a maximum of 4 cycles of CT with vinorelbine 25 mg/m^2 on days 1 and 8 + cisplatin 25 mg/m^2 on days 1, 2, and 3; cycles were repeated in 21-day intervals. +Standard group: docetaxel (20 mg/m^2) + cisplatin (20 mg/m^2) weekly for 6 weeks; Consolidation regimen: docetaxel (35 mg/m^2) + cisplatin (35 mg/m^2), both on days 1 and 8, which was repeated every 3 weeks.

Table 2. Patient characteristics

Characteristics		Hypofractionated RT (n=561)		Standard RT (n=610)	
		No.	%	No.	%
Male sex		385	55	381	62.5
Median age, years		67.2 (36-100)		66.8 (32-95)	
Performance status (KPS)	≥ 70	439	62.7	519	85.1
	< 70	79	11.3	38	6.2
Histology	Squamous carcinoma	173	24.7	163	26.7
	Adenocarcinoma	126	18	118	19.3
	Others	87	12.4	66	10.8
Tumor Stage	II A	8	1.1	2	0.3
	II B	0	0	1	0.2
	III A	202	36.0	257	42.1
	III B	298	53.1	232	38.0

NOTE: Percentage values are unknown.

(particularly esophagitis and pneumonitis). Recent follow-up information was acquired to maintain balance between both arms. The data were strictly censored in cases of missing data and contradictions to standard measures. Queries were raised and solved by professional statisticians and investigators.

Statistical analysis

The endpoints in the meta-analysis were overall survival (OS), progression-free survival (PFS), locoregional failure, distant failure and toxicity. OS was defined as the time from random assignment to death or the end of follow-up. Progression-free survival was defined as the time from observation to the first event or to the end of follow-up for patients without progression. Time to locoregional failure was defined as the time from randomization to the time of the first event of local failure. When distant failure occurred before local failure, it was considered distant failure. Furthermore, patients with simultaneous locoregional and distant failures were included in distant failure analysis only. Toxicity was graded according to the WHO criteria or the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) criteria depending on the trial [15, 16]. Toxicity for grade ≥ 2 was achieved in this research. Data regarding treatment response were not included for analysis because of insufficient information.

The analyses were stratified by trials. A fixed-effects model with log-rank observed and expected number of events and the related variance was used to estimate the individual and pooled risk ratios (RRs) and 95% CIs [17]. The toxicity between groups was calculated using a fixed-effects model with odds ratios (ORs). χ^2 heterogeneity tests [18] were used to measure the heterogeneity among trials, and $I^2 \leq 50\%$ was considered eligible. The survival and absolute benefits were calculated via Peto's curves using annual death rates and ORs. We also analyzed the effect on patients who received chemotherapy.

The biologically effective dose (BED) that had a significant value in terms of overall survival and toxicity was calculated to compare the dose fractionation regimens and to adjust the overall treatment times as well as the time factors for related toxicity [19]. The Cox model was applied during the analysis.

All *P* values were two-sided. Analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC).

Results

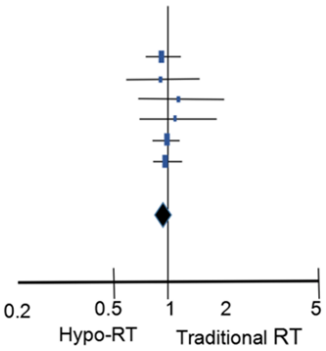
Description of trials

The different steps of the trial selection are presented in **Figure 1**. Six trials were identified and are shown in **Table 1**. Data were available for all trials. Chemotherapy (CT) was given concurrently with RT in two trials. Vinorelbine and cisplatin were given in the experimental group, while docetaxel and cisplatin were given in the standard group in both trials [24, 25]. In one

A

Study or Subgroup	Hypo-RT Events	Hypo-RT Total	Traditional RT Events	Traditional RT Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E/V)], Fixed, 95%CI	Hazard Ratio Exp[(O-E/V)], Fixed, 95%CI
Arya Amini 2012	104	119	146	181	-4.9	60.7	24.9%	0.92[0.72,1.19]	
Jian He 2016	23	34	21	34	-1	11	4.5%	0.91[0.51,1.65]	
LINH.N GUYEN,M.D.1999	16	34	20	35	1.7	8.9	3.7%	1.21[0.63,2.33]	
Steffen Appold 1999	24	29	24	26	1.2	12	4.9%	1.11[0.63,1.95]	
Stein Sundstrøm 2004	188	192	101	106	-1.8	65.7	27.0%	0.97[0.76,1.24]	
ZhengFei Zhu, M.D. 2014	281	291	122	130	-2.4	85.1	35.0%	0.97[0.79,1.20]	
Total(95%CI)		699		512			100%	0.97[0.86,1.10]	
Total events	636		434						

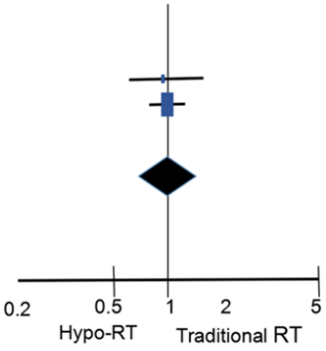
Heterogeneity. Chi^2=0.84, df=5(P=0.97), I^2=0%
Test for overall effect Z=0.46(P=0.64)



B

Study or Subgroup	Hypo-RT Events	Hypo-RT Total	Traditional RT Events	Traditional RT Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E/V)], Fixed, 95%CI	Hazard Ratio Exp[(O-E/V)], Fixed, 95%CI
Arya Amini 2012	110	119	157	181	4.1	0	Not estimate		
Jian He 2016	24	34	23	34	-0.5	11.7	11.2%	0.96[0.54,1.70]	
ZhengFei Zhu, M.D. 2014	159	187	221	250	3.6	92.5	88.8%	1.04[0.85,1.27]	
Total(95%CI)		340		465			100%	1.03[0.85,1.25]	
Total events	293		401						

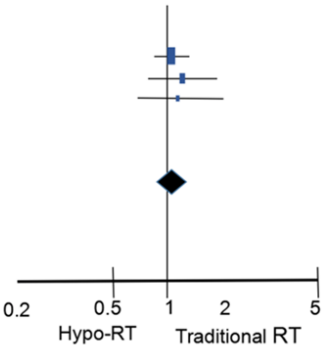
Heterogeneity. Chi^2=0.07, df=1(P=0.79), I^2=0%
Test for overall effect Z=0.30(P<0.76)



C

Study or Subgroup	Hypo-RT Events	Hypo-RT Total	Traditional RT Events	Traditional RT Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E/V)], Fixed, 95%CI	Hazard Ratio Exp[(O-E/V)], Fixed, 95%CI
Arya Amini 2012	47	119	78	181	2.6	29.3	64.1%	1.09[0.76,1.57]	
LINH.N GUYEN,M.D.1999	15	26	22	29	2.4	8.9	19.5%	1.31[0.68,2.53]	
ZhengFei Zhu, M.D. 2014	15	34	15	34	0	7.5	16.4%	1.00[0.49,2.05]	
Total(95%CI)		179		244			100%	1.12[0.83,1.49]	
Total events	77		115						

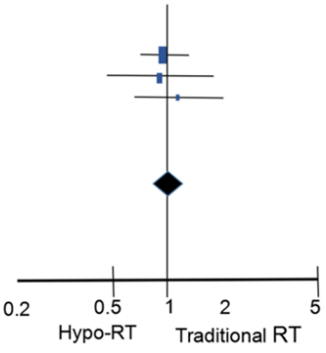
Heterogeneity. Chi^2=0.33, df=2(P=0.85), I^2=0%
Test for overall effect Z=0.74(P=0.46)



D

Study or Subgroup	Hypo-RT Events	Hypo-RT Total	Traditional RT Events	Traditional RT Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E/V)], Fixed, 95%CI	Hazard Ratio Exp[(O-E/V)], Fixed, 95%CI
Arya Amini 2012	32	119	47	181	-0.7	19	56.9%	0.96[0.61,1.51]	
LINH.N GUYEN,M.D.1999	12	26	12	29	-0.7	6	18.0%	0.89[0.40,1.98]	
ZhengFei Zhu, M.D. 2014	15	34	19	34	2	8.4	25.1%	1.27[0.65,2.50]	
Total(95%CI)		179		244			100%	1.02[0.73,1.43]	
Total events	59		78						

Heterogeneity. Chi^2=0.57, df=2(P=0.75), I^2=0%
Test for overall effect Z=0.10(P=0.92)



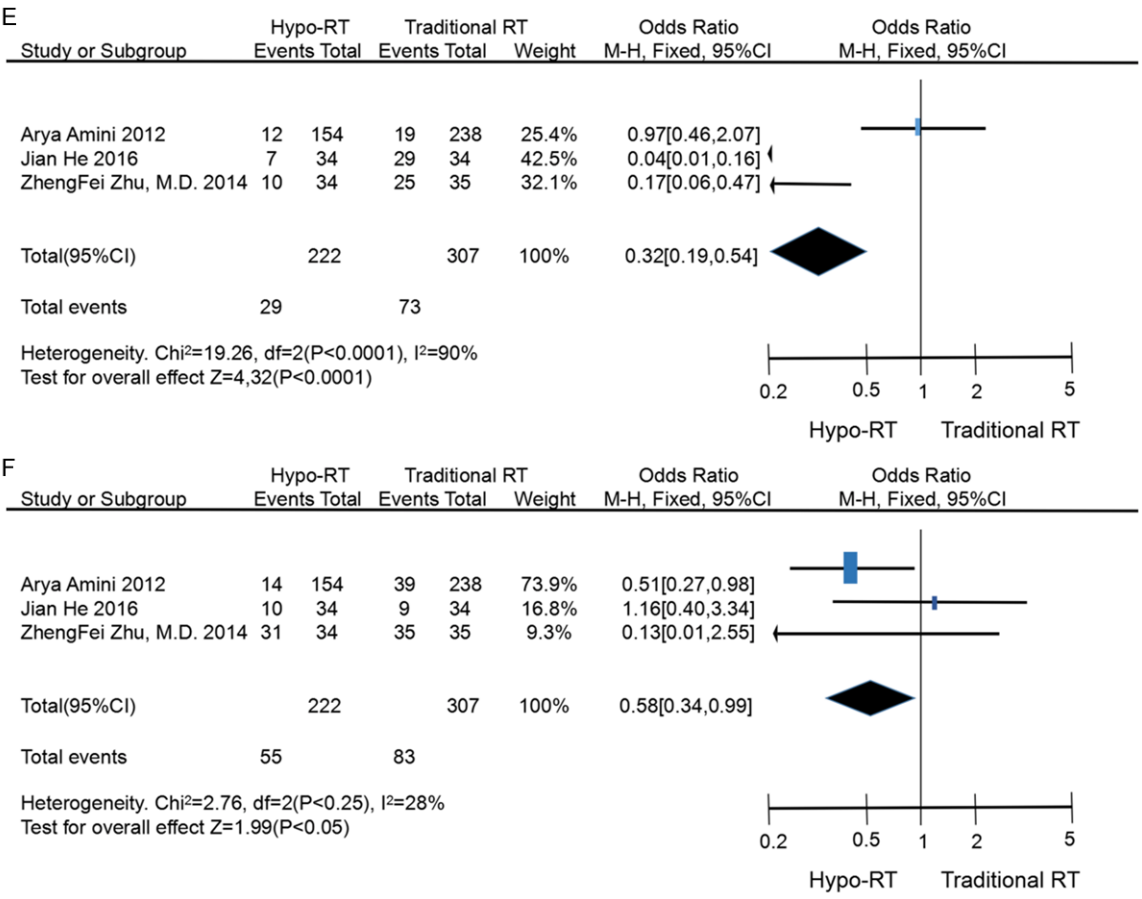


Figure 2. Forest plots of the meta-analysis on hypofractionated RT versus conventional RT. A. Overall survival; B. Progression-free survival; C. Local failure; D. Distant failure; E. Toxicity of esophagitis; F. Toxicity of pneumonitis. The center of each blue square shows the HR for each trial, and the horizontal line represents its 95% CI; the size of the square is proportional to the amount of information from the trial. The black diamond represents the pooled HRs. We use the fixed-effect model. RT, radiation therapy; O-E, Observed-expected.

trial, patients received CT, but the agents were not defined [22].

A total of 65% of patients were male, and the average age was 67.2 years in the hypofractionated group and 66.8 years in standard group. The studies were divided into two groups based on Karnofsky performance status (KPS): KPS ≥ 70 (82%) and < 70 (10%) (one trial did not report the KPS information [20]. Most patients (more than 98%) had stage III cancer. The patients' characteristics were well balanced between the two groups (**Table 2**).

Overall survival

Overall survival results were based on six trials with 1,211 patients and 1,070 deaths. The survival rate in the Hypo-RT group was 9.01% at 3 years, which was lower than that for standard radiotherapy (15.23%) (**Figure 3A**). There were no significant differences in the risk of death (HR 0.97; 95% CI, 0.86-1.10; P=0.64; **Figure 2A**), or in the heterogeneity of the effect of treatment between the trials (heterogeneity test, P=0.97, I^2=0%).

Progression-free survival

Analysis of PFS was based on 805 patients and 694 events. The HR was 1.03 (95% CI, 0.85 to 1.25; P=0.76; **Figure 2B**). Similar to OS, PFS in the Hypo-RT group was lower than that associated with standard radiotherapy (18.72% vs 23.2%) at 2 years, but an absolute increase of 3.4% at 3 years was observed with Hypo-RT. There was no evidence of heterogeneity in the effect of treatment between the trials (heterogeneity test, P=0.79, I^2=0%).

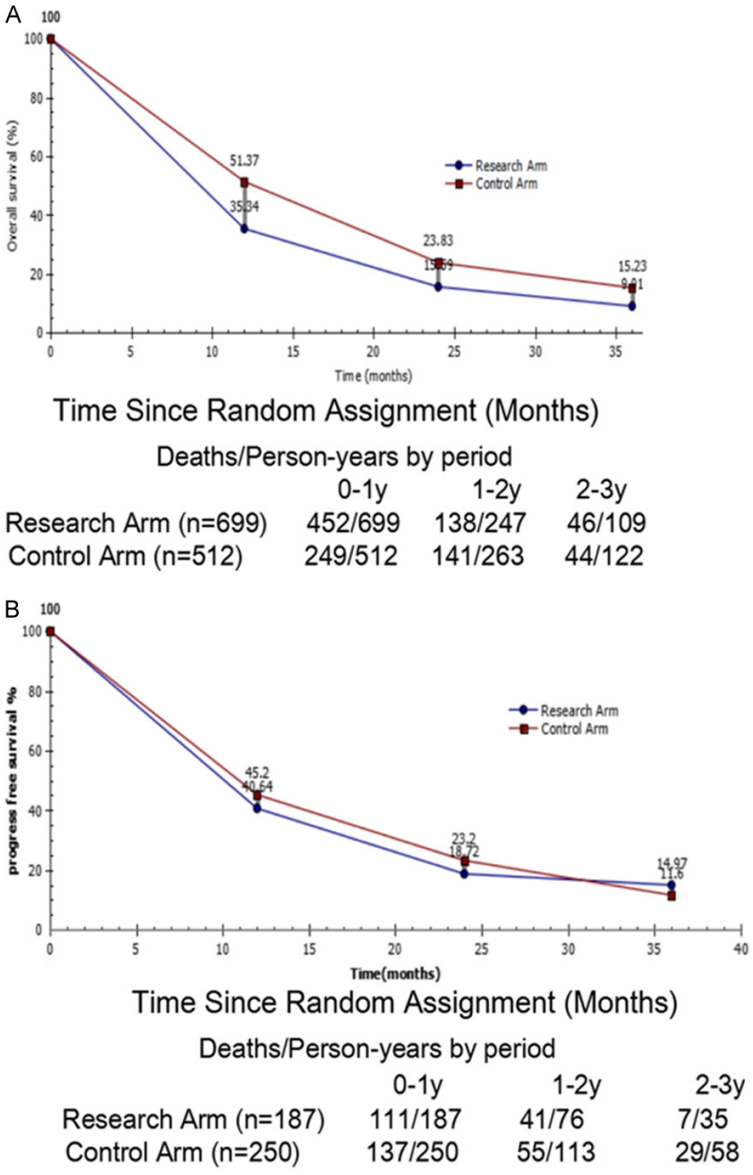


Figure 3. Survival curves for the non-small-cell lung cancer trials: A. Overall survival; B. Progression-free survival; "Research Arm" indicates the Hypo-RT group; "Control Arm" indicates the conventional RT group.

Locoregional and distant failure

Both locoregional and distant progression analyses were based on 3 trials [21, 23, 24] with 423 patients total. There was no evidence that Hypo-RT influenced locoregional failure (192 events, HR 1.12; 95% CI, 0.83 to 1.49; P=0.46) or distant failure (137 events, HR 1.02; 95% CI, 0.73 to 1.43; P=0.92, **Figure 2B** and **2C**). For these two end points, no evidence of heterogeneity was observed (I^2=0%).

Toxicity

Data were available for 529 patients (89%) with esophagitis and pneumonitis toxicity. Hypo-RT decreased the risk of esophagitis toxicity from 24% to 13% (data not shown) (OR 0.32; 95% CI, 0.19 to 0.54; P < 0.0001). However, obvious heterogeneity was observed between the arms (I^2=90%).

On the other hand, there was a significant benefit in terms of pneumonitis toxicity (OR 0.58; 95% CI, 0.34 to 0.99; P=0.05), with a 2% benefit (data not shown), and no evidence of heterogeneity was observed (I^2=28%). Overall, Hypo-RT significantly reduced the risk of esophagitis and pneumonitis toxicity. Severe hematologic toxicity was reported in trials with CT [24, 25], which principally influenced overall results. A comparison of other toxicities between the two arms was not performed because of insufficient data.

Discussion

This meta-analysis extracted data from six trials with 1,211 patients total who had locally advanced non-small cell lung cancer. The results suggested that Hypo-RT led to significant relative decreases of 11% and 2% in esophagitis and pneumonitis, respectively, compared to conventional radiotherapy. These decreases are likely due to the shortened duration of radiotherapy and the use of advanced technologies. We found no differences in overall survival, progression-free survival, local failure or distant failure between the two groups, confirming that Hypo-RT is not inferior to conventional RT.

A significant increase in the survival rate of lung cancer associated with Hyper-RT has been

reported [11], but Hypo-RT showed no positive results in terms of survival outcome. In fact, the survival rate of the Hypo-RT group was lower than that of the standard group after three years (**Figure 3A**), and PFS prior to 31 months was also lower (**Figure 3B**). Several possible explanations exist for these results of our exploratory analysis. The sample size was limited (1211 patients for OS, 805 patients for PFS), following-up with patients is exceedingly difficult (especially for trials performed in early 1990s), data are often lost in retrospective analyses, there is a tendency to treat patients with poor PS, and the mortality of lung cancer is very high.

A dominating challenge in lung cancer is that local failure remains uncontrolled. A previous meta-analysis of hyper-RT supported the conclusion that more aggressive radiotherapy is associated with improvements, which was discussed in the findings of many trials included in that study [11]. An absolute survival benefit of 4.5% at 5 years secondary to decreased local failure was reported in a study comparing concurrent and sequential chemoradiotherapy in patients with LA-NSCLC [26], but a similar result was not found in this meta-analysis. Furthermore, the low statistical power (only 421 patients), the ambiguity of the definition of failure and the occurrence of distant failure that may have exceeded local failure could be additional explanations for the poor survival outcomes observed in this study.

We calculated the biologically effective dose (BED) of each radiation regimen to compare the effects of the treatments. A previous study suggested an absolute benefit of 5.1% for 3-year survival using a BED $\geq$ 55 Gy [11]. This observation may account for the poor survival outcomes in some Hypo-RT arms that used a lower BED and were included in the present meta-analysis.

Based on this meta-analysis, the application of Hypo-RT leads to significant relative decreases of 11% and 2% in esophagitis and pneumonitis toxicity, respectively, in patients with LA-NSCLC. This result may be incredible because of previous work showing that toxicity is more severe using aggressive RT. However, the efficacy of RT, especially for late toxicity, was associated not only with total radiation dose but also with radiation treatment duration. Many studies have indicated the importance of shortening the treatment duration to prevent cell repopulation [27]. Furthermore, the use of advanced technologies such as image-guided RT, intensity-modulated RT, helical tomotherapy, positron emission tomography, and dose-guided RT may contribute to the accuracy of RT delivery and avoid severe adverse effects on the lung and esophagus [25, 28-30]. Comparisons with other related toxicities, such as dysphagia, dermatitis, nausea/vomiting, anorexia, fatigue and hematological effects, were not performed due to insufficient data. High heterogeneity in comparing esophagitis between the two groups was observed, and this may be secondary to the tendency to use Hypo-RT as a palliative therapy for patients.

Some limitations in this meta-analysis should be considered. First, most of the included trials had relatively small sample sizes that made the results lack robust statistical power. Small trials may more easily lead to overestimates of efficacy than larger trials. Therefore, our conclusion should be considered with caution. Second, several differences in patient characteristics between the groups existed, including Karnofsky performance status (KPS), tumor histology, and chemotherapy regimens. These elements may increase heterogeneity or result in an inaccurate result, similar to the result on esophagitis despite the positive outcome. Third, there were some limitations regarding the data collection, such as insufficient information on the relationship between deaths and patient characteristics. Several reports have described improved prognostic effects of performance status and weight loss in lung cancer [31], which could not be presented in this study. Similarly, the toxicity endpoints were reported differently in each trial; thus, we could only extract information on esophagitis and pneumonitis. Despite these limitations, our results showed that Hypo-RT is an acceptable treatment option for patients who have LA-NSCLC. Hypo-RT with advanced technologies reduced the occurrence of toxicity. Further randomized studies are needed to judge whether the use of Hypo-RT for inoperable LA-NSCLC improves survival and local control compared to conventional RT.

Disclosure of conflict of interest

None.

Address correspondence to: Xinchen Sun, Department of Radiotherapy, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China. Tel: 8613770662828; E-mail: sun13770662828@163.com

References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.

[2] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63: 11-30.

[3] Perez CA, Stanley K, Rubin P, Kramer S, Brady L, Perez-Tamayo R, Brown GS, Concannon J, Rotman M, Seydel HG. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lungs. Preliminary report by the radiation therapy oncology group. Cancer 1980; 45: 2744-2753.

[4] Curran WJ Jr, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, Movsas B, Wasserman T, Rosenthal SA, Gore E, Machtay M, Sause W, Cox JD. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst 2011; 103: 1452-60.

[5] Bradley J, Graham MV, Winter K, Purdy JA, Komaki R, Roa WH, Ryu JK, Bosch W, Emami B. Toxicity and outcome results of RTOG 9311: a phase I-II dose escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. Int J Radiat Oncol Biol Phys 2005; 61: 318-28.

[6] Rosenzweig KE, Fox JL, Yorke E, Amols H, Jackson A, Rusch V, Kris MG, Ling CC, Leibel SA. Results of a phase I dose-escalation study using three-dimensional conformal radiotherapy in the treatment of inoperable non-small cell lung carcinoma. Cancer 2005; 103: 2118-27

[7] Bradley JD, Moughan J, Graham MV, Byhardt R, Govindan R, Fowler J, Purdy JA, Michalski JM, Gore E, Choy H. A phase I/II radiation dose escalation study with concurrent chemotherapy for patients with inoperable stages I to III non-small-cell lung cancer: phase I results of RTOG 0117. Int J Radiat Oncol Biol Phys 2010; 77: 367-72.

[8] Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, Bogart J, Hu C, Forster K, Magliocco A, Kavadi V, Garces YI, Narayan S, Iyengar P, Robinson C, Wynn RB, Koprowski C, Meng J, Beitler J, Gaur R, Curran W Jr, Choy H. A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy with or without cetuximab for stage III nonesmall cell lung cancer: results on radiation dose in RTOG 0617. J Clin Oncol 2013; 31: 7501.

[9] Movsas B, Hu C, Sloan J, Bradley J, Komaki R, Masters G, Kavadi V, Narayan S, Michalski J, Johnson DW, Koprowski C, Curran WJ Jr, Garces YI, Gaur R, Wynn RB, Schallenkamp J, Gelblum DY, MacRae RM, Paulus R, Choy H. Quality of life analysis of a radiation dose-escalation study of patients with non-small-cell lung cancer: a secondary analysis of the radiation therapy oncology group 0617 randomized clinical trial. JAMA Oncol 2016; 2: 359-67.

[10] Fowler JF, Chappell R. Non-small cell lung tumors repopulate rapidly during radiation therapy. Int J Radiat Oncol Biol Phys 2000; 46: 516-7.

[11] Mauguen A, Le Péchoux C, Saunders MI, Schild SE, Turrisi AT, Baumann M, Sause WT, Ball D, Belani CP, Bonner JA, Zajusz A, Dahlberg SE, Nankivell M, Mandrekar SJ, Paulus R, Behrendt K, Koch R, Bishop JF, Dische S, Arriagada R, De Ruysscher D, Pignon JP. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. J Clin Oncol 2012; 30: 2788-97.

[12] Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, Shelley W, Grimard L, Bowen J, Lukka H, Perera F, Fyles A, Schneider K, Gulavita S, Freeman C. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010; 362: 513-520.

[13] Zhu Z, Zhang J, Liu Y, Chen M, Guo P, Li K. Efficacy and toxicity of external-beam radiation therapy for localised prostate cancer: a network meta-analysis. Br J Cancer 2014; 110: 2396-404.

[14] Prewett SL, Aslam S, Williams MV, Gilligan D. The management of lung cancer: a UK survey of oncologists. Clin Oncol (R Coll Radiol) 2012; 24: 402-9.

[15] World Health Organization: WHO handbook for reporting results of cancer treatment. Geneva, Switzerland: WHO Offset Publication; 1979. pp. 48.

[16] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the radiation therapy oncology group (RTOG) and the European organisation for research and treatment of cancer (EORTC). Int J Radiat Oncol Biol Phys 1995; 31: 1341-1346.

[17] Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of randomised clinical trials. Prog Cardiovasc 1985; 27: 335-371.

[18] Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patient from 52 randomized clinical trialsnon-small cell lung cancer collaborative group. BMJ 1995; 311: 899-909.

[19] Healy J. In regard to Machtay et al. Int J Radiat Oncol Biol Phys 2012; 84: 302-3.
[20] Appold S, Baumann M, Neidt F, Herrmann T. Results of irradiation of inoperable stage III non-small cell lung cancer with 25 Gy in five fractions. Strahlenther Onkol 1999; 175: 267-270.
[21] Nguyen LN, Komaki R, Allen P, Schea RA, Milas L. Effectiveness of accelerated radiotherapy for patients with inoperable non-small cell lung cancer (NSCLC) and borderline prognostic factors without distant metastasis: a retrospective review. Int J Radiat Oncol Biol Phys 1999; 44: 1053-1056.
[22] Sundstrøm S, Bremnes R, Aasebø U, Aamdal S, Hatlevoll R, Brunsvig P, Johannessen DC, Klepp O, Fayers PM, Kaasa S. Hypofractionated palliative radiotherapy (17 Gy per two fractions) in advanced non-small-cell lung carcinoma is comparable to standard fractionation for symptom control and survival: a national phase III trial. J Clin Oncol 2004; 22: 801-10.
[23] Amini A, Lin SH, Wei C, Allen P, Cox JD, Komaki R. Accelerated hypofractionated radiation therapy compared to conventionally fractionated radiation therapy for the treatment of inoperable non-small cell lung cancer. Radiat Oncol 2012; 7: 33.
[24] Zhu ZF, Ma HL, Fan M, Bao Y, Zhuang TT, Chen M, Jiang GL, Fu XL. Sequential chemoradiotherapy with accelerated hypofractionated radiotherapy compared to concurrent chemoradiotherapy with standard radiotherapy for locally advanced non-small cell lung cancer. Technol Cancer Res Treat 2014; 13: 269-75.
[25] He J, Huang Y, Chen Y, Shi S, Ye L, Hu Y, Zhang J, Zeng Z. Feasibility and efficacy of helical intensity-modulated radiotherapy for stage III non-small cell lung cancer in comparison with conventionally fractionated 3D-CRT. J Thorac Dis 2016; 8: 862-71.
[26] Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, Belderbos J, Clamon G, Ulutin HC, Paulus R, Yamanaka T, Bozonnat MC,Uitterhoeve A, Wang X, Stewart L, Arriagada R, Burdett S, Pignon JP. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010; 28: 2181-90.
[27] Cox JD, Pajak TF, Asbell S, Russell AH, Pederson J, Byhardt RW, Emami B, Roach M 3rd. Interruptions of high-dose radiation therapy decrease long-term survival of favorable patients with unresectable non-small cell carcinoma of the lung: analysis of 1244 cases from 3 radiation therapy oncology group (RTOG) trials. Int J Radiat Oncol Biol Phys 1993; 27: 493-8.
[28] Pirtoli L, Bindi M, Bellezza A, Pepi F, Tucci E. Unfavorable experience with hypofractionated radiotherapy in unresectable lung cancer. Tumori 1992; 78: 305-10.
[29] Le Pechoux C. Role of postoperative radiotherapy in resected nonesmall cell lung cancer: a reassessment based on new data. Oncologist 2011; 16: 672-81.
[30] De Ruysscher D, Faivre-Finn C, Nestle U, Hurkmans CW, Le Péchoux C, Price A, Senan S. European organisation for research and treatment of cancer recommendations for planning and delivery of high-dose, high-precision radiotherapy for lung cancer. J Clin Oncol 2010; 28: 5301-10.
[31] Feld R, Abratt R, Graziano S, Jassem J, Lacquet L, Ninane V, Paesmans M, Rocmans P, Schiepers C, Stahel R, Stephens R. Pretreatment minimal staging and prognostic factors for non-small cell lung cancer. Lung Cancer 1997; 17 Suppl 1: S3-S10.