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A meta-analysis comparing stereotactic body radiotherapy vs conventional radiotherapy in inoperable stage I non-small cell lung cancer

Can Li, MD[a,b], Li Wang, MD[a,b], Qian Wu, MD[b], Jiani Zhao, MD[b], Fengming Yi, MD[c], Jianjun Xu, MD[a], Yiping Wei, MD, PhD[a,*], Wenxiong Zhang, MD[a,*]

Abstract

Background: Stereotactic body radiotherapy (SBRT) superseded conventional radiotherapy (CRT) for the treatment of patients with inoperable early stage non-small cell lung cancer (NSCLC) over a decade ago. However, the direct comparisons of the outcomes of SBRT and CRT remain controversial. This meta-analysis was performed to compare the survival and safety of SBRT and CRT in patients with inoperable stage I NSCLC.

Methods: We systematically searched the Cochrane Library, Embase, PubMed, Web of Science, Ovid MEDLINE, ScienceDirect, Scopus and Google Scholar for relevant articles. Overall survival (OS), progression-free survival (PFS), lung cancer-specific survival (LCSS), local control rate (LCR) and adverse effects (AEs) were the primary outcomes.

Results: We identified 11,110 articles, 17 of which were eventually included in this study; these 17 articles had 17,973 patients (SBRT: 7395; CRT: 10,578). Compared to CRT for the treatment of inoperable stage I NSCLC, SBRT had superior survival in terms of OS (hazard ratio [HR]: 0.66, 95% confidence interval [CI]: 0.62-0.70, $P < .00001$), LCSS (HR: 0.42 [0.35-0.50], $P < .00001$), and PFS (HR: 0.34 [0.25-0.48], $P < .00001$). The 4-year OS rate (OSR); 4-year LCSS rate (LCSSR); 3-year local control rate (LCR); 5-year PFS rate (PFSR) with SBRT were all higher than those with CRT. With regard to all-grade AEs, the SBRT group had a significantly lower rate of dyspnea, esophagitis and radiation pneumonitis; no significant difference was found in grade 3-5 AEs (risk ratio [RR]: 0.68 [0.30-1.53], $P = .35$).

Conclusions: With better survival and a lower rate of dyspnea, esophagitis and radiation pneumonitis than CRT, SBRT appears to be more suitable for patients with inoperable stage I NSCLC.

Abbreviations: 3DCRT = 3D conformal radiotherapy, AEs = adverse effects, AHRT = accelerated hypofractionated radiotherapy, BED = biologically effective dose, CFRT = conventional fractionated radiotherapy, CI = confidence interval, CRT = conventional radiotherapy, GRADE = the grading of recommendations assessment, development and evaluation system, HR = hazard ratio, LCR = local control rate, LCSS = lung cancer-specific survival, LCSSR = lung cancer-specific survival rate, NOS = Newcastle-Ottawa Scale, NSCLC = non-small cell lung cancer, OS = overall survival, OSR = overall survival rate, PFS = progression-free survival, PFSR = progression-free survival rate, PRISMA = preferred reporting items for systematic review and meta-analysis, RR = risk ratio, RCT = randomized controlled trial, SBRT = stereotactic body radiotherapy.

Keywords: stereotactic body radiotherapy, radiotherapy, stage I, non-small cell lung cancer, meta-analysis

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All analyses were based on previously published studies, and hence no ethical approval and patient consent were required.

All data generated or analyzed during this study are included in this manuscript and its Additional files.

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[a] Department of Thoracic Surgery, The Second Affiliated Hospital of Nanchang University, [b] Jiangxi medical college, Nanchang University, [c] Department of Oncology, The Second Affiliated Hospital of Nanchang University, Nanchang, China.

[*] Correspondence: Yiping Wei, Wenxiong Zhang, Department of Thoracic Surgery, The Second Affiliated Hospital of Nanchang University, 1 Minde Road, Nanchang 330006, China (e-mail: weiyip2000@hotmail.com, zwx123dr@126.com).

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1. Introduction

Lung cancer remains a major contributor to cancer-related mortality and cancer incidence worldwide[1]; its annual incidence is predicted to increase continually for at least the next few decades.[2] Recent advances in screening have made substantial progress with regard to detecting early-stage lung cancer.[3] As far as stage I non-small cell lung cancer (NSCLC) patients are concerned, the current standard therapy is surgery.[4] However, multiple comorbidities and poor physical performance status result in nearly 20% of stage I NSCLC patients being unable to tolerate surgery.[5] Conventional radiotherapy (CRT) has been used as the standard noninvasive strategy for more than a decade.[6] However, given the low 5-year survival of 10% to 22%,[7,8] CRT has long puzzled clinicians.

The past decade has seen great advances in stereotactic body radiotherapy (SBRT), and SBRT has gradually superseded CRT in clinical practice for the treatment of patients with inoperable early-stage NSCLC. The CHISEL trial reported that the rate of 2-year local control for inoperable Stage I NSCLC patients was 89% with SBRT compared with 65% with CRT.[9] However, Borst et al[10] demonstrated that SBRT had a significant dose-response relationship to radiation pneumonitis. In addition, the SPACE trial revealed that no apparent difference was observed in overall survival or local control between patients treated with SBRT and CRT.[11] It is controversial whether the SBRT can replace CRT.

This meta-analysis aimed to directly compare the efficacy and safety of CRT and SBRT for inoperable stage I NSCLC.

2. Materials and methods

The PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines guided the performance of this meta-analysis (Supplementary Digital Content, Table 1, http://links.lww.com/MD/E693).[12]

2.1. Search strategy

The following internet sources were used to retrieve the relevant literature:

(1) PubMed;
(2) Web of Science;
(3) Embase;
(4) Cochrane Library;
(5) Ovid MEDLINE;
(6) ScienceDirect;
(7) Scopus;
(8) Google Scholar.

We updated the last search on September 3, 2019. "Stereotactic body radiotherapy" and "lung neoplasms" were the key terms used in the search. The complete search is outlined in Appendix 1 (http://links.lww.com/MD/E698). For the further identification of eligible articles, we identified relevant references of the retrieved literature as well. We set no limitations on language.

2.2. Selection criteria

We performed this search pursuant to the PICOS guidelines:

(1) participants: stage I NSCLC patients who were inoperable, high-risk operable (the factors were:
   a. heart disease;
   b. advanced age;
   c. chronic obstructive pulmonary disease;
   d. poor performance status)[13–17,19,22,24,26,27] or refused surgical intervention;
(2) intervention and comparison: SBRT versus CRT (including conventional radiotherapy,[15,16,19,21,26] conventional fractionated radiotherapy,[17,20,23,25,27] 3D conformal radiotherapy,[9,11,13,14,18] and accelerated hypofractionated radiotherapy[13]);
(3) outcomes: OS (overall survival), OS rate (OSR), local control rate (LCR), lung cancer-specific survival (LCSS), LCSS rate (LCSSR), progression-free survival (PFS), PFS rate (PFSR) and adverse effects (AEs); and
(4) study design: RCTs and cohort studies.

Protocols, abstracts, meta-analyses, animal experiments, articles with duplicated data and studies without original data were excluded.

2.3. Data extraction

The following data were extracted independently by 2 investigators: first author, country, publication year, number of participants, participant characteristics (age, sex, tumor size, TNM stage, histology, performance status (PS), medically inoperable rate), treatment characteristics (type, dose, time), median follow-up, study design, antitumor efficacy indices (OS, OSR, LCSS, LCSSR, LCR, PFS, and PFSR) and the types and quantity of AEs (all-grade AEs and grade 3-5 AEs). Disagreements on any terms were resolved by a third investigator.

2.4. Quality assessment

The 5-point Jadad scale was adopted to evaluate the quality of the RCTs; it consisted of three sections, namely, randomization, masking and accountability. Studies with scores ≥ 3 were assessed as being of high quality.[28]

The Newcastle-Ottawa Scale (NOS, 9 points) was adopted to determine the cohort study quality; it contained three sections, namely, selection, comparability and exposure. Studies with scores between 8 and 9 were assessed as being of high quality; studies with scores between 6-7 were assessed as being of medium quality.[29]

The grading of recommendations assessment, development and evaluation (GRADE) system was use to explore the quality of the data; it consisted of five sections, namely, inconsistency, indirectness, imprecision, risk of bias and publication bias. Data were assessed as being of high, medium, low or very low quality.[30]

2.5. Statistical analysis

Stata 14.0 (Stata Corp) and Review Manager 5.3 (The Nordic Cochrane Center) were utilized to perform this meta-analysis. To analyze the OS, LCSS and PFS, hazard ratios (HRs, HRs > 1 favored the CRT arm) and 95% confidence interval (CIs) were applied. HR, OSR, LCSSR, LCR, PFSR were extracted directly from the included articles and indirectly from Kaplan–Meier curves, pursuant to the methods proposed by Tierney et al.[31] Risk ratios (RRs) and their 95% CIs were used for AEs (RRs > 1 favored the CRT arm) as well as the OSR, LCSSR, LCR, and PFSR (RR > 1 favored the SBRT arm). To clarify whether the

results would change by region, sex, age, stage, PS, histology, CRT type, SBRT fraction dose, biologically effective dose (BED) of SBRT, medically inoperable rate, treatment time or study design, subgroup analyses of OS, LCSS and PFS were performed. We utilized the χ^2 test and I^2 statistic to assess heterogeneity. A $P < .1$ (on the χ^2 test) or $I^2 > 50\%$ reflected evident heterogeneity and a random-effects model was used; otherwise the fixed-effects model was used. Begg rank correlation[32] and Egger linear regression tests[33] were utilized to assess publication bias; $P < .05$ indicated statistical significance.

3. Results

3.1. Search results and study quality assessment

On the last search on September 3, 2019, 11,110 potentially qualified studies were initially identified. After strict screening, 17 studies (2 RCTs,[9,11] 2 prospective cohorts[13,14] and 13 retrospective cohorts[15–27]) involving 17,973 patients (SBRT, 7395; CRT, 10,578) were included in this analysis (Fig. 1). In total, 8/17 studies included all medically inoperable patients, 12/17 studies analyzed the reasons patients were deemed inoperable. Table 1 summarizes the basic characteristics and chief evaluation indexes of the involved articles. Of the 17 articles, 10 were high quality and 7 were medium quality (Supplementary Digital Content, Table 2, http://links.lww.com/MD/E694). The GRADE approach indicated that the evidence was all in the low- and very low-quality categories (Supplementary Digital Content, Table 3, http://links.lww.com/MD/E695).

3.1.1. Antitumor efficacy. Fourteen articles focused on OS (heterogeneity: $P = .29$, $I^2 = 15\%$). SBRT showed significant superiority in OS (HR: 0.66 [0.62-0.70], $P < .00001$) compared with CRT (Fig. 2A). The subgroup analyses revealed that the

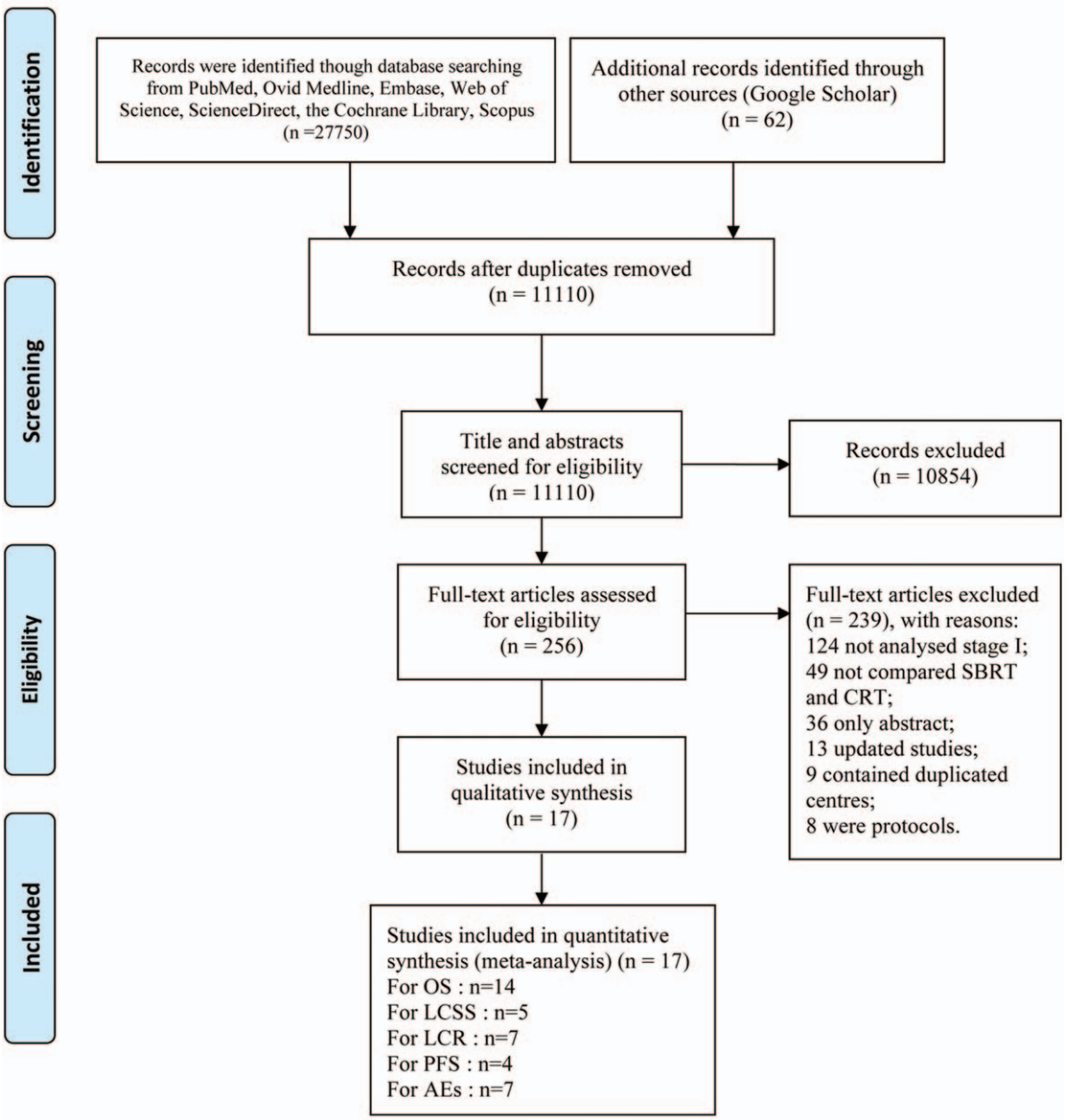

Figure 1. Flow chart of study selection.

Table 1

Characteristics of included studies.

Study		Country	Time	Stage	CRT type	Patients (n)	Age (yr)	Size (mm)	Doses Selection	OTT (wk)	BED (Gy)	Follow up (mo)	Design
2011	Lanni[13]	USA	2002.01-2008.04	T1-T2N0M0	SBRT	45	76	–	48 Gy in 4 F or 60 Gy in 5 F	–	–	36	PC
					CFRT	41	76	–	70 Gy in 35 F	–	–		
2011	Wildder[14]	USA	2006.11-2009.11	T1-T2N0M0	SBRT	202	76	28	60 Gy in 3-8 F	–	105-132	13	PC
					3DCRT	27	71	27	70 Gy in 35 F	–	84		
2012	Shirvani[15]	USA	2001-2007	T1-T2aN0M0	SBRT	124	80	25	–	–	–	38.4	RC
					CRT	1613	81	25	–	–	–		
2013	Jeppesen[16]	Denmark	1998.07-2012.06	T1-T2N0M0	SBRT	100	73	–	45/50/66 Gy in 3 F	1.3	112-211	35.4	RC
					CRT	32	70	–	80 Gy in 35 or 40 F (once/day, 5 F/week)	7-8	96-98		
2014	Mitera[17]	Canada	2002.01-2010.06	T1-T2N0M0	SBRT	118	74	–	–	–	–	24	RC
					CFRT	50	75	–	–	–	–		
2014	Tong[18]	China	2012-2013	T1-T2aN0M0	SBRT	30	75	–	42-60 Gy in 3F	–	100.8-180	12	RC
					3DCRT	38	76	–	60 Gy in 30 F (once/day, 5 F/week)	–	72		
2015	Liu[19]	Canada	2005.01-2012.01	T1-T2N0M0	SBRT	77	77	–	–	–	–	30.4	RC
					CRT	193	77	–	–	–	–		
2015	Koshy[20]	USA	2003-2006	T1-T2N0M0	SBRT	773	75	–	–	–	–	21	RC
					CFRT	5375	75	–	60 Gy in 1.8-2 Gy/F	–	–		
2015	Valle[21]	USA	2007-2011	T1-T2aN0M0	SBRT	184	–	–	–	–	–	–	RC
					CRT	64	–	–	–	–	–		
2016	Nyman[11]	Swedish	2007-2011	T1-T2N0M0	SBRT	49	73	–	22 Gy/F (at the isocenter)	1	112.5	37	RCT
					3DCRT	53	75	–	70 Gy in 35 F (once/day, 5 F/week)	7	84		
2017	Boyer[22]	USA	2001.01-2011.01	T1-T2aN0M0	SBRT	468	73	–	–	–	–	80.9	RC
					CFRT	1203	72	–	–	–	–		
2017	Tu[23]	China	2007-2013	T1-T2N0M0	SBRT	69	78	–	25-34 Gy/F or 45-60 Gy/3 F, or 48-50 Gy/4 F, or 50-55 Gy/5 F, or 60-70 Gy/8-10 F	–	–	28	RC
					CFRT	169	75	–	60-70 Gy in 1.8-2 Gy/F	–	–		
2018	Karasawa[24]	Japan	2003.10-2010.12	T1-T2N0M0	SBRT	56	79	28	48 Gy in 4 F	1	105.6	127.2	RC
					AHRT	103	78	28	75 Gy in 25 F	5	97.5		
2018	Reibnitz[25]	USA	1990-2013	T1-T2N0M0	SBRT	398	77	–	54 Gy in 3 F or 48 Gy in 4 F	–	105.6	24.4	RC
					CFRT	127	74	–	66 Gy in 33 F or 50 Gy in 20 F	–	89.2		
2019	Ball[9]	Australia	2010.01-2015.06	T1-T2aN0M0	SBRT	66	74	25	54 Gy in 3 F or 4 F of 48 Gy in 12 Gy (if tumour < 2 cm from the chest wall)	1.5-2	–	29	RCT
					3DCRT	35	75	28	66 Gy in 33 Gy F or 50 Gy in 20 F (once/day)	4-6.5	–		
2019	Driessen [26]	Netherland	2010-2015	T1-T2aN0M0	SBRT	3049	74	–	–	–	–	58	RC
					CRT	738	74	–	–	–	–		
2019	Phillips[27]	UK	2015.01-2017.01	T1-T2aN0M0	SBRT	1587	82	–	50 Gy or more in 8 or fewer F	–	–	–	RC
					CFRT	717	82	–	50 Gy or more in over 10 F	–	–		

3DCRT = 3-dimensional conformal radiotherapy, AHRT = accelerated hypofractionated radiotherapy, BED = biologically efffective dose, CFRT = conventional fractionated radiotherapy, CRT = conventional radiotherapy, F = fraction(s), OTT = overall treatment time, PC = prospective cohort, RC = retrospective cohort, RCT = randomized controlled trial, SBRT = stereotactic body radiotherapy, – = not available.

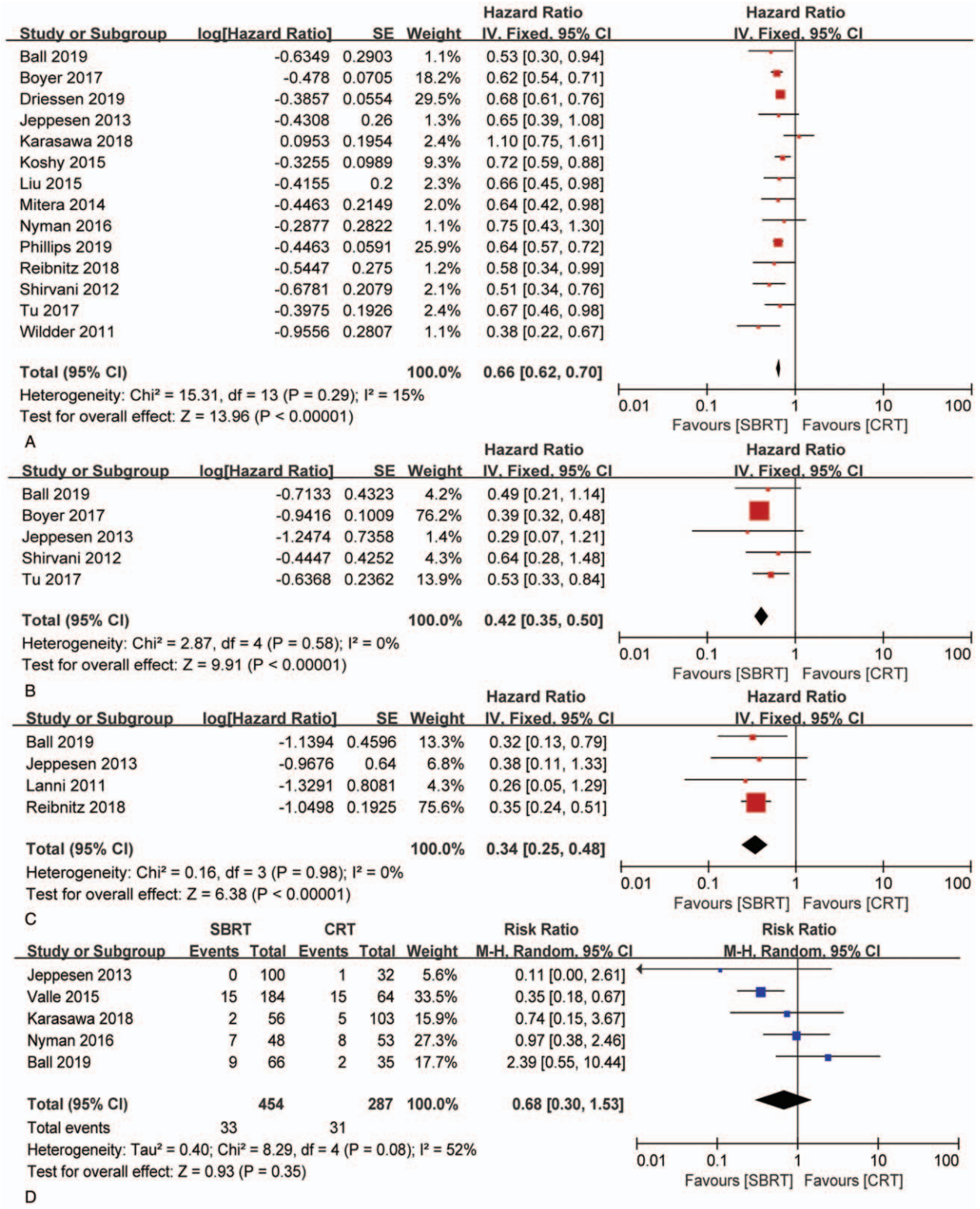

Figure 2. Forest plot of HRs for OS (A), LCSS (B), PFS (C) and forest plots of RRs for grade 3–5 AEs (D) associated with SBRT versus CRT.

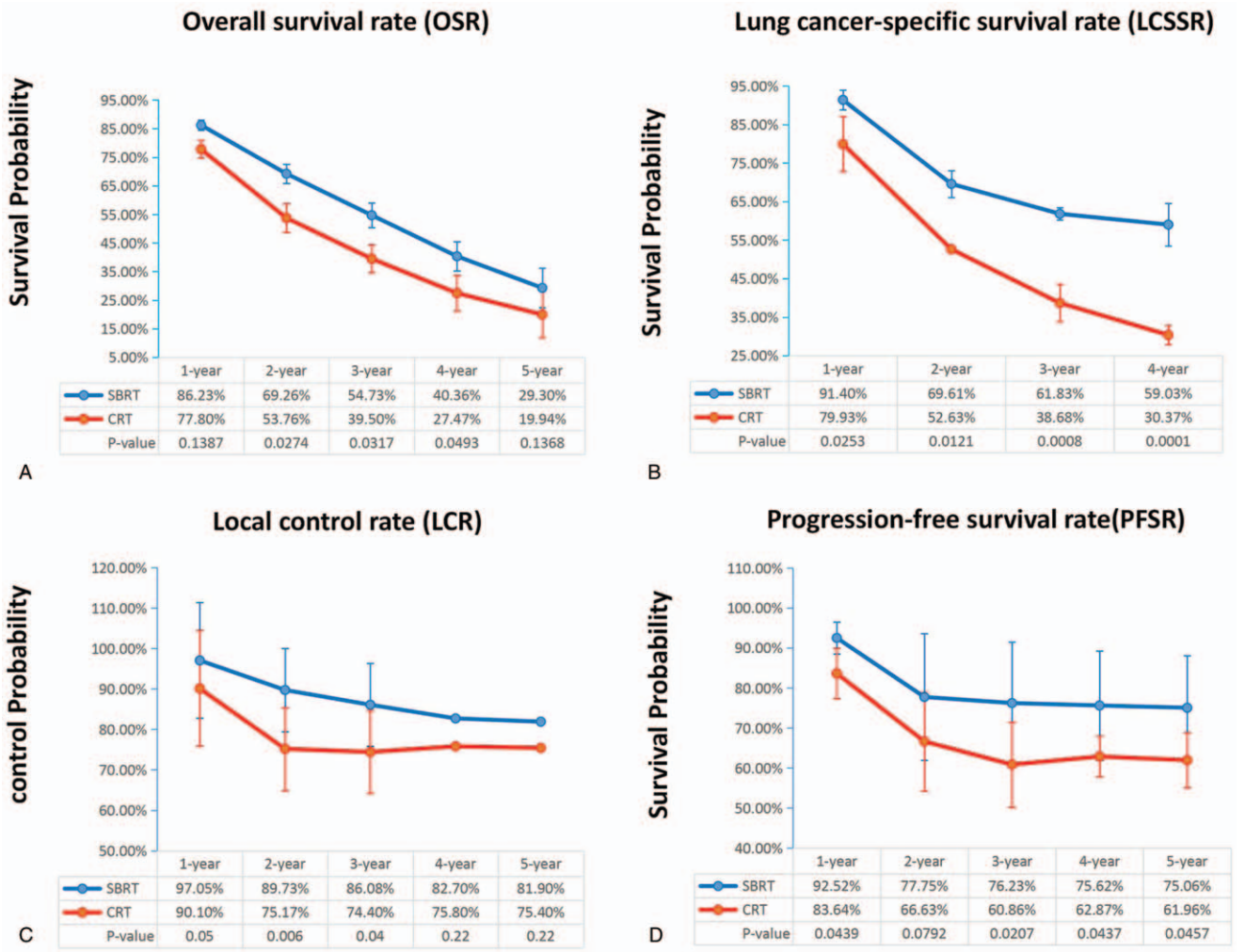

Figure 3. Broken-line graphs of OSR (A), LCSSR (B), LCR (C) and PFSR (D) associated with SBRT vs CRT.

1-year OSR (86.23% vs 77.80%; RR: 1.10 [0.97-1.26], $P=.1387$), 2-year OSR (69.26% vs 53.76%; RR: 1.28 [1.02-1.60], $P=.0274$), 3-year OSR (54.73% vs 39.50%; RR: 1.38 [1.02-1.85], $P=.0317$), 4-year OSR (40.36% vs 27.47%; RR: 1.48 [0.99-2.21], $P=.0493$), and 5-year OSR (29.30% vs 27.47%; RR: 1.45 [0.88-2.39], $P=.1368$) were higher in the SBRT group than in the CRT group (Fig. 3A, Fig. 4A).

Five articles evaluated LCSS (heterogeneity: $P=.58$, $I^2=0$). SBRT showed significant superiority in LCSS (HR: 0.42 [0.35-0.50], $P<.00001$) compared with CRT (Fig. 2B). The subgroup analyses showed that the 1-year LCSSR (91.40% vs 79.93%; RR: 1.14 [1.01-1.28], $P=.0253$), 2-year LCSSR (69.61% vs 52.63%; RR: 1.32 [1.05-1.65], $P=.0121$), 3-year LCSSR (61.83% vs 38.68%; RR: 1.59 [1.19-2.12], $P=.0008$), and 4-year LCSSR (59.03% vs 30.37%; RR: 1.97 [1.40-2.77], $P<.0001$) were higher in the SBRT group than in the CRT group (Figs. 3B and 4B).

Seven articles evaluated LCR (heterogeneity: $P=.61$, $I^2=0$). SBRT showed significant superiority in LCR (RR: 1.12 [1.06-1.19], $P<.00001$) compared with CRT. The subgroup analyses demonstrated that the 1-year LCR (97% vs 90%; RR: 1.08 [1.00-1.16], $P=.05$), 2-year LCSSR (90% vs 75%; RR: 1.20 [1.05-1.37], p=0.006), 3-year LCSSR (86% vs 74%; RR: 1.16 [1.01-1.34], $P=.04$), and 4-year LCSSR (83% vs 76%; RR: 1.09 [0.95-1. 26], $P=.22$) were higher in the SBRT group than in the CRT group (Figs. 3C and F4C).

Four articles compared PFS (heterogeneity: $P=.98$, $I^2=0$). SBRT showed significant superiority in PFS (HR: 0.34 [.25-0.48], $P<.00001$) compared with CRT (Fig. 2C). The subgroup analyses showed that the 1-year PFSR (92.52% vs 83.64%; RR: 1.11 [1.00-1.22], $P=.0439$), 2-year PFSR (77.75% vs 66.63%; RR: 1.16 [0.98-1.38], $P=.0792$), 3-year PFSR (76.23% vs 60.86%; RR: 1.25 [1.03-1.51], $P=.0207$), 4-year PFSR (75.62% vs 62.87%; RR: 1.21 [1.00-1.45], $P=.0437$), and 5-year PFSR (75.06% vs 61.96%; RR: 1.21 [1.00-1.46], $P=.0457$) were higher in the SBRT group than in the CRT group (Figs. 3D and 4D).

3.1.2. Adverse effects. Six articles compared all-grade AEs[9,11,13,20,22,23] (Supplementary Digital Content, Table 4, http://links.lww.com/MD/E696). The 10 most commonly reported AEs in all grades were pneumonitis, dyspnea, cough, fibrosis, acute kidney disease, radiation pneumonitis, skin reactions, fatigue, and chest wall pain (Table 2). SBRT was associated with a significantly lower risk of dyspnea (RR: 0.77 [0.62-0.97], $P=.02$), radiation pneumonitis (RR: 0.52 [0.32-0.84], $P=.0007$) and esophagitis

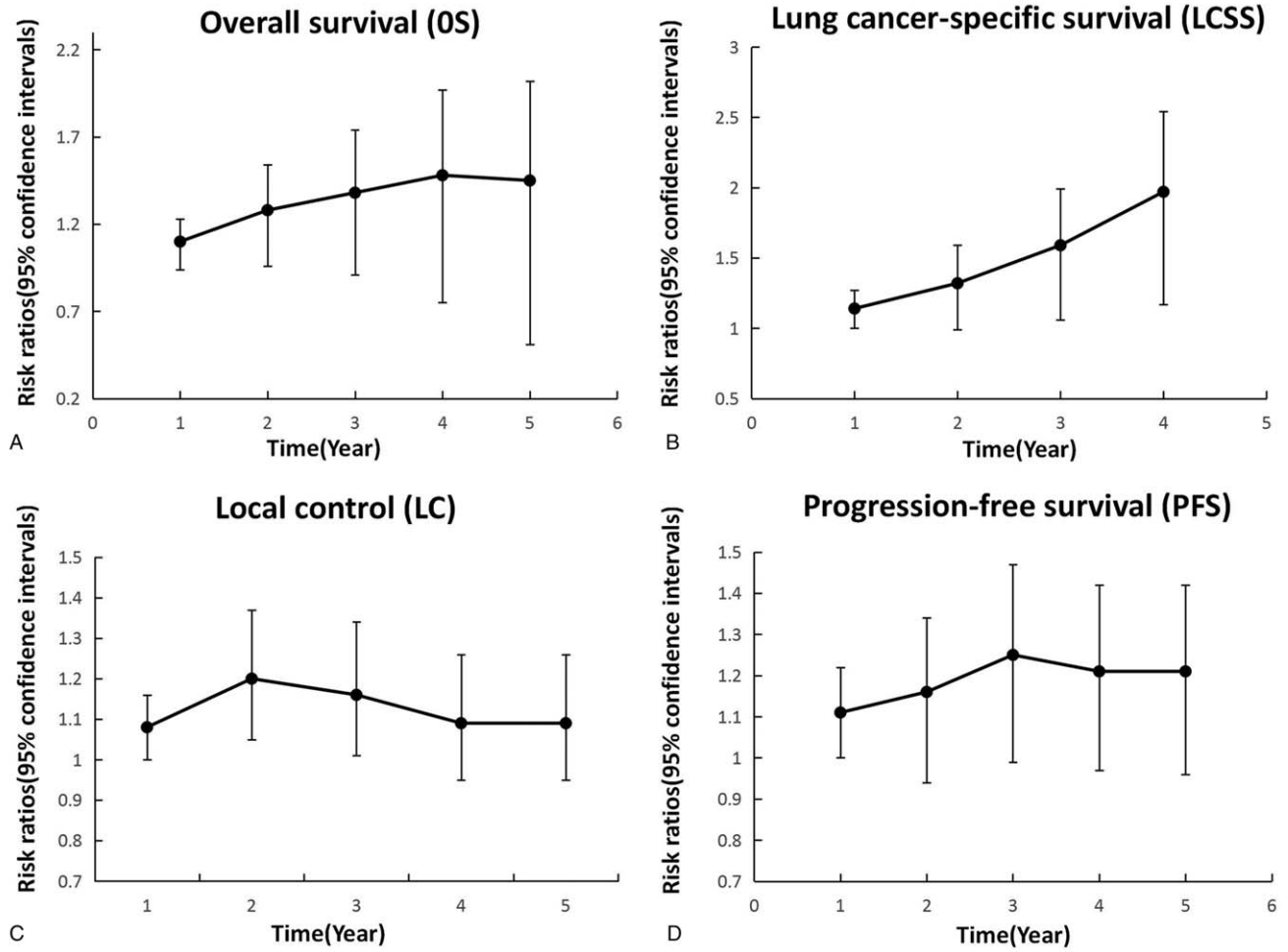

Figure 4. Broken-line graphs of RRs for OSR (A), LCSSR (B), LCR (C) and PFSR (D) associated with SBRT vs CRT.

(RR: 0.30 [0.12-0.74], $P = .009$) than CRT; no significant difference was found in the other AEs.

Five articles referred to grade 3–5 AEs,[9,11,13,20,23] in which SBRT was associated with no obvious difference (RR: 0.68 [0.30-1.53], $P = .35$) when compared with CRT (heterogeneity: $P = .08$, $I^2 = 52\%$, Fig. 2D) (Supplementary Digital Content, Table 5, http://links.lww.com/MD/E697). Dyspnea, cough, radiation pneumonitis, fatigue, chest wall pain, lung infection, pain, cataracts, hypoxia and weight loss were the 10 most commonly reported grade 3–5 AEs induced by SBRT and CRT (Table 3), among which we observed no significant differences.

3.1.3. Subgroup analysis. Subgroup analyses for OS, LCSS and PFS were performed in order to explore whether the better

Table 2

Top 10 adverse effects (all grades) associated with SBRT versus CRT.

	SBRT (event/total)		CRT (event/total)					Heterogeneity	
Adverse effects					Total	RR (95% CI)	*P* value	I^2 (%)	*P* value
Pneumonitis	56/922	6.10%	91/1490	6.10%	6.10%	0.92 (0.49, 1.74)	.8	53	.09
Dyspnoea	64/922	6.90%	65/1490	4.40%	5.30%	0.77 (0.62, 0.97)	.02	0	.81
Cough	60/922	6.50%	49/1490	3.30%	4.50%	0.98 (0.65, 1.48)	.91	55	.14
Fibrosis	46/922	5.00%	36/1490	2.40%	3.40%	1.08 (0.77, 1.52)	.66	0	.47
Acute kidney disease	19/922	2.10%	61/1490	4.10%	3.30%	0.80 (0.48, 1.32)	.39	NA	NA
Radiation Pneumonitis	27/952	2.80%	46/1528	3.00%	2.90%	0.52 (0.32, 0.84)	.007	0	.48
Skin reactions	24/922	2.60%	44/1490	3.00%	2.80%	0.40 (0.10, 1.64)	.2	91	.001
Fatigue	33/922	3.60%	21/1490	1.40%	2.20%	0.83 (0.58, 1.20)	.32	NA	NA
Stroke	9/922	1.00%	22/1490	1.50%	1.30%	1.05 (0.49, 2.27)	.9	NA	NA
Chest wall pain	21/922	2.30%	5/1490	0.30%	1.10%	2.23 (0.92, 5.40)	.08	NA	NA

CI = confidence interval, CRT = conventional radiotherapy, RR = risk ratios, SBRT = stereotactic body radiotherapy.

Table 3

Top 10 adverse effects (grade 3-5) associated with SBRT versus CRT.

Grade 3-5 adverse effects	SBRT (event/total)		CRT (event/total)		Total	RR (95% CI)	*P* value	Heterogeneity	
								I^2(%)	*P* value
Dyspnoea	15/454	3.30%	9/287	3.10%	3.20%	0.98 (0.45, 2.16)	.96	0	.67
Cough	3/454	0.70%	0/287	0.00%	0.40%	2.95 (0.33, 26.20)	.33	0	.93
Radiation pneumonitis	0/484	0.00%	3/325	0.90%	0.40%	0.18 (0.01, 3.35)	.25	NA	NA
Fatigue	1/454	0.20%	0/287	0.00%	0.10%	1.61 (0.07, 38.56)	.77	NA	NA
Chest wall pain	0/454	0.00%	1/287	0.30%	0.10%	0.18 (0.01, 4.28)	.29	NA	NA
Lung infection	1/454	0.20%	0/287	0.00%	0.10%	1.61 (0.07, 38.56)	.77	NA	NA
Pain	0/454	0.00%	1/287	0.30%	0.10%	0.18 (0.01, 4.28)	.29	NA	NA
Cataract	1/454	0.20%	0/287	0.00%	0.10%	1.61 (0.07, 38.56)	.77	NA	NA
Hypoxia	1/454	0.20%	0/287	0.00%	0.10%	1.61 (0.07, 38.56)	.77	NA	NA
Weight loss	1/454	0.20%	0/287	0.00%	0.10%	1.61 (0.07, 38.56)	.77	NA	NA

CI = confidence interval, CRT = conventional radiotherapy, NA = not available, RR = risk ratios, SBRT = stereotactic body radiotherapy.

Table 4

Subgroup analysis for overall survival, lung cancer-specific survival and progression-free survival.

Group	OS				LCSS				PFS			
	No.of studies	HR (95% CI)	*P value*	I^2 (%)	No. of studies	HR (95% CI)	*P value*	I^2 (%)	No. of studies	HR (95% CI)	*P value*	I^2 (%)
Total	14	0.66 (0.62-0.70)	<.00001	15	5	0.42 (0.35-0.50)	<.00001	0	4	0.34 (0.25-0.48)	<.00001	0
Region												
Asia	2	0.86 (0.53-1.39)	.54	69	1	0.53 (0.33-0.84)	.007	–	–	–	–	–
Europe	4	0.66 (0.61-0.72)	<.00001	0	1	0.29 (0.07-1.21)	.09	–	1	0.38 (0.11-1.33)	.13	–
North American	7	0.63 (0.57-0.70)	<.00001	4	2	0.40 (0.33-0.49)	<.00001	23	2	0.34 (0.24-0.50)	<.00001	0
Oceania	1	0.53 (0.30-0.94)	.03	–	1	0.49 (0.21-1.14)	0.1	–	1	0.32 (0.13-0.79)	.01	-
Gender												
Female	4	0.67 (0.57-0.79)	<.00001	0	1	0.64 (0.28-1.48)	0.3	–	2	0.34 (0.24-0.50)	<.00001	0
Male	9	0.66 (0.58-0.74)	<.00001	35	4	0.41 (0.34-0.49)	<0.00001	0	2	0.34 (0.16-0.71)	.004	0
Age												
≤75	6	0.65 (0.60-0.71)	<.00001	0	3	0.39 (0.32-0.47)	<.00001	0	2	0.34 (0.16-0.71)	.004	0
75-80	6	0.69 (0.55-0.86)	.001	53	1	0.53 (0.33-0.84)	.007	–	2	0.34 (0.24-0.50)	<.00001	0
≥80	2	0.63 (0.56-0.70)	<.00001	13	1	0.64 (0.28-1.48)	0.3	–	–	–	–	–
T Stage												
T1	9	0.68 (0.62-0.74)	<.00001	15	3	0.39 (0.32-0.47)	<.00001	0	4	0.34 (0.25-0.48)	<.00001	0
T2	2	0.67 (0.51-0.87)	.003	0	1	0.53 (0.33-0.84)	.007	–	–	–	–	–
PS												
0-1	1	0.53 (0.30-0.94)	.03	–	1	0.49 (0.21-1.14)	.1	-	1	0.32 (0.13-0.79)	.01	–
0-2+	7	0.66 (0.59-0.72)	<.00001	47	2	0.50 (0.32-0.78)	.002	0	3	0.35 (0.24-0.49)	<.00001	0
Histology												
Adenocarcinoma	5	0.67 (0.60-0.74)	<.00001	45	3	0.50 (0.34-0.74)	.0005	0	3	0.35 (0.25-0.49)	<.00001	0
Squamous	3	0.64 (0.58-0.71)	<.00001	32	2	0.40 (0.33-0.49)	<.00001	23	–	–	–	–
CRT Type												
CRT	4	0.67 (0.60-0.74)	<.00001	0	2	0.52 (0.25-1.08)	.08	0	1	0.38 (0.11-1.33)	.13	–
CFRT	6	0.65 (0.60-0.70)	<.00001	0	2	0.41 (0.34-0.49)	<.00001	29	1	0.35 (0.24-0.51)	<.00001	–
3DCRT	3	0.53 (0.36-0.78)	.001	29	1	0.49 (0.21-1.14)	.1	–	2	0.31 (0.14-0.67)	.003	–
AHRT	1	1.10 (0.75-1.61)	.63	–	–	–	–	–	–	–	–	–
Medically Inoperable												
Inoperable	8	0.70 (0.62-0.80)	<.00001	38	3	0.50 (0.34-0.74)	.005	0	3	0.32 (0.17-0.63)	.0009	0
Unclear	6	0.65 (0.60-0.69)	<.00001	0	2	0.40 (0.33-0.49)	<.00001	23	1	0.35 (0.24-0.51)	<.00001	–
SBRT Fraction Dose												
10 Gy ≤ dose<15 Gy	5	0.66 (0.59-0.73)	.003	0	1	0.49 (0.21-1.14)	.1	–	3	0.34 (0.24-0.48)	<.00001	0
≥ 20 Gy	3	0.58 (0.42-0.78)	.0005	37	1	0.29 (0.07-1.21)	.09		1	0.38 (0.11-1.33)	.13	–
SBRT BED												
100 - 150 Gy	4	0.67 (0.42-1.07)	.09	71	–	–	–	–	1	0.35 (0.24-0.51)	<.00001	–
100 - 200+ Gy	1	0.65 (0.39-1.08)	.1	–	1	0.29 (0.07-1.21)	.09	–	1	0.38 (0.11-1.33)	.13	–
Treatment Time												
-2010	10	0.65 (0.60-0.72)	<.00001	36	3	0.40 (0.33-0.48)	<.00001	0	3	0.35 (0.24-0.49)	<.00001	0
2010 - 2015	2	0.67 (0.61-0.75)	<.00001	0	1	0.49 (0.21-1.14)	.1	–	1	0.32 (0.13-0.79)	.01	–
2015 -	1	0.64 (0.57-0.72)	<.00001	–	–	–	–	–	–	–	–	–
Study Design												
PC	1	0.38 (0.22-0.67)	.0007	–	–	–	–	–	1	0.26 (0.05-1.29)	.1	–
RC	11	0.66 (0.62-0.70)	<.00001	8	4	0.41 (0.35-0.49)	<.00001	0	2	0.33 (0.12-0.88)	.03	0
RCT	2	0.63 (0.43-0.94)	.02	0	1	0.49 (0.21-1.14)	.1	–	1	0.32 (0.13-0.79)	.01	–

– = not available, 3DRT = 3-dimensional conformal radiotherapy, AHRT = accelerated hypofractionated radiotherapy, BED = biologically effective dose, CI = confidence interval, CRT = conventional fractionated radiotherapy, HR = hazard ratio, LCSS = lung cancer-specific survival, OS = overall survival, PC = prospective cohort, PFS = progression-free survival, PS = performance status, RC = retrospective cohort, RCT = randomized controlled trial.

efficacy with SBRT existed among subgroups stratified by the following variables: region, sex, age, stage, PS, histology, study design, CRT type, SBRT fraction dose, BED of SBRT, medically inoperable rate, and treatment time. The vast majority of subgroup differences in OS, LCSS and PFS between the SBRT and CRT groups were significant (Table 4).

3.1.4. Sensitivity analysis. We assessed the stability and sensitivity of these results by evaluating the impact of each article on the pooled results. The OS (Supplementary Digital Content, Fig. 1A, http://links.lww.com/MD/E699), LCSS (Supplementary Digital Content, Fig. 1B, http://links.lww.com/MD/E699) and PFS (Supplementary Digital Content, Fig. 1C, http://links.lww.com/MD/E699) results were stable.

3.1.5. Publication bias. We concluded that no publication bias existed in the evaluation of OS (Supplementary Digital Content, Fig. 2A, http://links.lww.com/MD/E700), LCSS (Supplementary Digital Content, Fig. 2B, http://links.lww.com/MD/E700) or PFS (Supplementary Digital Content, Fig. 2C, http://links.lww.com/MD/E700), according to the *P* values from Egger test (OS: 0.702; LCSS: 0.464; PFS: 0.375) and Begg test (OS: 0.101; LCSS: 0.308; PFS: 0.806).

4. Discussion

Early-stage NSCLC accounts for approximately 10% to 20% of new NSCLC diagnoses, and the figure is continually rising due to the implementation of the new NSCLC screening guidelines.[3] SBRT has improved substantially during the past decade, and it has supplanted CRT and gained popularity among early-stage inoperable NSCLC patients.[34] However, several debates still exist concerning whether SBRT can completely replace CRT. This meta-analysis is the first to directly compare SBRT with CRT in patients with inoperable stage I NSCLC. The outcomes revealed that the patients who were administered SBRT had superior OS, LCSS, LCR and PFS when compared with the patients who received CRT. In addition, the subgroup results were also statistically significant and in favor of better survival with SBRT. The analyses also demonstrated that the SBRT group had a significantly lower risk of dyspnea, radiation pneumonitis and esophagitis among all-grade AEs, though there was no apparent difference in the rate of grade 3–5 AEs between the SBRT and CRT groups.

The main benefit of SBRT treatment is the significantly better survival (OS, LCSS, LCR and PFS). Compared with CRT, SBRT had obvious advantages in OSR-4y, LCSSR-4y, LCR-3y and PFSR-5y in our study. Navarro-Martin et al[35] found that the 3-year OSR was 66%. In addition, Timmerman et al[36] showed the 5-year OSR and 5-year PFSR with SBRT were 40.0% and 25.5%, respectively, in the RTOG 0236 Trial. However, the SPACE trial[9] indicated no apparent difference in local control or OS after directly comparing SBRT and CRT. We speculated that the superior survival with SBRT could be due to many reasons. First, SBRT delivers high doses (e.g., 3 fractions of 15–22 Gy) of radiation that precisely and directly target tumors for ablation, while CRT is based on a protracted treatment with minimal 1.8 to 2.0 dose-per-fraction sizes.[37] Additionally, the most common SBRT dose-fractionation schedules provide a BED of at least 100 Gy to achieve antitumor efficacy, while the BED of CRT usually reaches 80 Gy or less, which is not high enough to completely kill all the tumor cells in the gross target volume, resulting in a lower rate of long-term local control.[38] Finally, with highly accurate doses delivered during minimal courses of therapy, SBRT prevents tissues within the irradiation volume from radiation injury to some extent. CRT involves 6 to 7 weeks of daily radiation; as these doses are above the radiation tolerance, the accumulated dose injuries inevitably lead to some degree of lung fibrosis.[39] Our subgroup analyses showed that SBRT led to better survival than CRT, conventional fractionated radiotherapy (CFRT) and 3D conformal radiotherapy (3DCRT), though not in the subgroup of patients who received accelerated hypofractionated radiotherapy (AHRT). We also found that the patients with a performance status score of 0-1, patients aged $\leq$75 years, males, patients with squamous histology and patients who received an SBRT fraction dose $\geq$20 Gy were predicted to have relatively better survival. Additionally, residence in Asian or European regions, age between 75 and 80, and a fraction dose of 10 to 15 Gy were also likely to influence the outcomes. In terms of AHRT subgroup results, we surmised that several schedules with an adequately high BED of fractionated and accelerated CRT could achieve tumor control rates similar to those achieved with SBRT. The differences in the SPACE trial concerning survival may be attributed to the lower BED in the SBRT group with the 3 prescribed fractions of 45 Gy. However, a worse performance status (24% PS > 2) of the patients treated in the SPACE trial cannot be ignored. As van Baardwijk et al stated, the high BED in SBRT could also be considered "overkill."[40] Overall, SBRT appears to lead to better survival in patients with inoperable stage I NSCLC.

Our meta-analysis demonstrated that the risk of toxicity was low in both the SBRT and CRT groups. Our subgroup analyses indicated that SBRT induced significantly lower rates of dyspnea, radiation pneumonitis and esophagitis in all-grade AEs while there were no significant difference in grade 3–5. For the statistical difference, we suspected the difference might because the special courses and doses of SBRT and CRT treatment. Both BED are rather "safe", there were rarely treatment-related deaths and the majority of the AEs were mostly grade 1–2. This may illustrate the low correlation in grade 3–5 AEs. For SBRT, higher fraction dose and less fractions meant more of the ray was precisely concentrated on the tumor regions with less harm to normal structures and tissues, which effectively promoted a declined probability and quantity of AEs. Additionally, the suitable BED effectively meant that latent radiotherapy damage and lung fibrosis could be avoided during a shorter treatment time. While CRT with lower BED struggles to get enough efficacy to kill tumor cells in the gross target volume via a longer course treatment involving 6 to 7 weeks of daily radiation. Accumulated dose injuries inevitably lead to some grade 1–2 AEs. In the published literature, it has been reported that tumors located in the central lung may enhance the risks associated with SBRT due to the potential damage to the mediastinal tissues; for instance, there may be an increased risk of pleural effusion, pneumonitis and lung capacity reduction. In addition, related rare AEs are tracheobronchial injury, esophageal ulcer and myeleterosis.[41–45] When the tumors are near the brachial plexus nerve, severe damage could result in neuropathic pain and brachial palsy.[46] For tumors near the chest wall, the latent complications are rib fractures and chest wall pain[47]; therefore, the SBRT dose should be limited to 30 to 35 Gy. SBRT seems to be acceptable for patients with tumors located in the peripheral lung but away from chest wall; however, radiation pneumonitis is the most common complication in these patients.[36] It is accepted that, in SBRT, 4 to 10 fractions are safe and effective, yet 3 fractions with 54 to 60 Gy pose a risk that needs to be avoided.[48] The prospective RTOG 0813 study reported that no serious toxicities occurred at

the maximum tolerated dose (50 Gy) in 5-fraction regimens.[49] However, particular attention should be paid to tumors abutting the bronchial tree and esophagus to avoid severe toxicity. In summary, compared with CRT, SBRT is a safer treatment strategy.

Several limitations exist in the present meta-analysis. First and foremost, the articles we included were all in the English language; therefore, there may have been language bias. Additionally, while most of the 17 articles were of medium- and high- quality, the 2 RCTs included in the analysis could have weakened the study conclusions. Moreover, attention should be paid to the significant heterogeneity that existed in the analyses of all-grade and grades 3–5 AEs, which might have reduced the reliability of the results. Furthermore, we obtained the data pertaining to grades 3–5 AE mainly from 2 RCTs, which may have led to representativeness bias. Finally, the CRT types and the treatment doses were diverse, which perhaps increased the heterogeneity and decreased the quality, although subgroup analyses were conducted. Accordingly, we suggest that determining the suitable dose for tumors in each anatomical region should be considered in future studies.

5. Conclusions

Our study illustrated that SBRT tends to lead to better survival (OS, LCSS, LCR and PFS) and carries lower risks of dyspnea, radiation pneumonitis and esophagitis than CRT for patients with inoperable stage I NSCLC. The subgroup analyses indicated that a 0-1 patient performance status and suitable BED predicted an improved prognosis. Given the inherent limitations of the present study, the conclusions need to be confirmed in more large-scale high-quality RCTs.

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Author contributions

Can Li had full access to all of the data in the manuscript and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Acquisition, analysis, or interpretation of data: All authors.
Concept and design: All authors.
Critical revision of the manuscript for important intellectual content: Can Li, Li Wang, Qian Wu, Jiani Zhao, Fengming Yi and Jianjun Xu.
Drafting of the manuscript: Can Li and Wenxiong Zhang.
Statistical analysis: Can Li and Wenxiong Zhang.
Supervision: Yiping Wei and Wenxiong Zhang.

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