Original Article

Comparison of stereotactic body radiotherapy and radiofrequency ablation for early-stage non-small cell lung cancer: a systematic review and meta-analysis

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Background: Stereotactic body radiation therapy (SBRT) and radiofrequency ablation (RFA) are recommended for patients with inoperable early-stage non-small cell lung cancer (NSCLC), with both offering promising results. However, it is largely unknown which of these two treatment modalities provides superior benefits for patients. Therefore, this systematic review and meta-analysis compared clinical outcomes and safety between SBRT and RFA in patients with inoperable early-stage NSCLC.

Methods: Eligible studies published between 2001 and 2020 were obtained through a comprehensive search of the PubMed, Medline, Embase, and Cochrane Library databases. Original English-language studies on the treatment of early-stage NSCLC with SBRT or RFA were included. Local control (LC) rates, overall survival (OS) rates, and adverse events were obtained by pooled analyses.

Results: Eighty-seven SBRT studies (12,811 patients) and 18 RFA studies (1,535 patients) met the eligibility criteria. For SBRT, the LC rates (with 95% confidence intervals) at 1, 2, 3, and 5 years were 98% (97–98%), 95% (95–96%), 92% (91–93%), and 92% (91–93%), respectively, which were significantly higher than those for RFA [75% (69–82%), 31% (22–39%), 67% (58–76%), and 41% (30–52%), respectively] ($P<0.01$). There were no significant differences in short-term OS between SBRT and RFA [1-year OS rate: 87% (86–88%) versus 89% (88–91%), $P=0.07$; 2-year OS rate: 71% (69–72%) versus 69% (64–74%), $P=0.42$]. Regarding long-term OS, the 3- and 5-year OS rates for SBRT were 58% (56–59%) and 39% (37–40%), respectively, which were significantly ($P<0.01$) superior to those for RFA [48% (45–51%) and 21% (19–23%), respectively]. The most common complication of SBRT was radiation pneumonitis (grade ≥2), making up 9.1% of patients treated with SBRT, while pneumothorax was the most common complication of RFA, making up 27.2% of patients treated with RFA.

Discussion: Compared with RFA, SBRT has superior LC and long-term OS rates but similar short-term OS rates. Prospective randomized trials with large sample sizes comparing the efficacy of SBRT and RFA are warranted.

Keywords: Stereotactic body radiotherapy (SBRT); radiofrequency ablation (RFA); meta-analysis

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Introduction

Stereotactic body radiotherapy (SBRT) is a non-invasive treatment, which is generally delivered in high doses per fraction over one to five sessions (1). SBRT, also known as stereotactic ablative radiotherapy (SABR), is recommended as a standard treatment for patients with inoperable early-stage non-small cell lung cancer (NSCLC) by the latest National Comprehensive Cancer Network (NCCN) guidelines (2) (version 4.2021). The recent multicenter, single-arm, prospective phase II trial RTOG (Radiation Therapy Oncology Group) 0236 reported outstanding outcomes of SBRT, with 5-year primary local control (LC) and overall survival (OS) rates of 92.7% and 40.0%, respectively (3,4). Furthermore, RTOG 0915, a randomized phase II multicenter study, demonstrated that patients with medically inoperable stage I peripheral NSCLC can achieve 5-year primary tumor control and OS rates of 92.2% and 41.1%, respectively, with a regimen of 48 Gy delivered in 4 fractions (5).

Radiofrequency ablation (RFA), a minimally invasive image-guided percutaneous ablation technique, provides another option for patients with medically inoperable NSCLC (6). RFA has been proved to be feasible and safe when given as an outpatient treatment or during a short hospital stay in a highly suitable group of patients (7,8). For instance, the RAPTURE study, a prospective multicenter clinical trial, used RFA to treat 13 patients with early-stage NSCLC, and reported a 2-year OS rate of 75% (9). Recently, a prospective multicenter Alliance study involving 51 patients with stage IA NSCLC reported an OS rate of 69.8% and a local tumor recurrence-free rate of 59.8% after 2 years of follow-up (10). In both trials, RFA was shown to have tolerable toxicities. Furthermore, a prospective multicenter phase II trial (11) published in 2018 arrived at a similar conclusion.

However, despite the majority of the above-mentioned studies on SBRT and RFA having a prospective design, their sample sizes were small. To date, few studies have performed a pooled analysis concerning the clinical outcomes and toxicities of SBRT or RFA, and detailed comparison of the two treatments is lacking (12,13). Moreover, with the broad use of SBRT in patients with inoperable early-stage NSCLC (14), and the development of well-rounded techniques for SBRT and RFA, the survival outcomes of patients treated with SBRT or RFA may be getting better than before. Therefore, we conducted a systematic review and pooled analysis to compare LC, OS and toxicities between SBRT and RFA for the treatment of patients with inoperable early-stage NSCLC.

We present the following article in accordance with the PRISMA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-6256/rc) (15).

Methods

Search strategy

A systematic search was conducted for relevant studies published between 2001 and 2020 in electronic databases including PubMed, Embase, Medline, and the Cochrane Library. The subject terms "non-small cell lung cancer/carcinoma" or "NSCLC" was combined with the following specific terms: "stereotactic body radiation therapy", "stereotactic body radiotherapy", "stereotactic ablative radiation therapy", "stereotactic ablative radiotherapy", "stereotactic radiosurgery", "hypo-fractionated radiotherapy", "SABR", "SBRT", "radiofrequency ablation", "thermal ablation", "early stage", "stage I", "T1", and "T2". The reference lists of the obtained studies were also checked.

Selection criteria

The inclusion criteria for studies were as follows: (I) English-language original articles published in peer-reviewed journals; (II) patients with stage I NSCLC [according to the American Joint Committee on Cancer (AJCC) cancer staging system] who were unsuitable for surgery; and (III) clinical outcomes were reported or explored on the basis of published articles. The following were excluded: (I) case reports, comments, editorials, and reviews; (II) studies with fewer than 15 patients treated with SBRT or fewer than 5 patients treated with RFA; (III) SBRT studies with fraction number >8 and fraction dose ≤8 Gy; and (IV) studies involving patients who received other treatments, including surgery, chemotherapy,

radiotherapy, and immunotherapy.

Articles were independently screened and then selected by two reviewers. In cases of studies overlapping, only the study with the most comprehensive data was selected when the patient populations were from the same institution, based on consensus between the two reviewers. However, if the patient populations were from a different period or received different regimens, all the related studies were included for analysis. If differences in opinion between the two reviewers needed to be resolved, a third reviewer (YP Xu) was consulted.

Data extraction

Relevant characteristics were extracted from each individual study, including the first author's name, publication year, country, study design, sample size, study participant age, study participant sex (the percentage of males), stage, and follow-up period. The information was independently extracted from the included studies by two reviewers. For SBRT studies, the radiation regimen, total dose, dose per fraction, number of fractions, and biologically effective dose (BED) were also extracted, and are displayed in *Table 1*. The BED was calculated using the equation: BED = $nd \times [\ 1 + d/(\alpha/\beta)\ ]$, in which d and n stand for the dose per fraction and number of fractions, respectively. The numerical value of α/β was 10 (100). Regarding clinical outcomes, the 1-, 2-, 3-, and 5-year LC and OS rates were also obtained. The LC rate was calculated based on freedom from local progression. Several studies did not report survival outcomes directly but included Kaplan-Meier survival curves, so the survival outcomes were extracted from these survival curves. During this analysis, we did not attempt to obtain missing data by contacting the studies' authors. Due to the occurrence of severe adverse effects (AEs) being infrequent for both SBRT and RFA, we only included common and grade 3–5 events on the basis of the Common Terminology Criteria for Adverse Events (CTCAE). We also estimated 95% confidence intervals (CIs) and proportions.

Statistical analysis

Both random effects and fixed effects models were used to conduct pooled analysis of the LC and OS rates for SBRT and RFA. The I^2 statistic was used to measure the degree of heterogeneity caused by variability in the true effect size. Statistical analysis was performed using the SPSS software (version 22.0, IBM Corp.) and R software (version 4.0.3; http://www.Rproject.org). Meta-analysis was conducted using the R package "*meta*". Forest plots were created using the *metaprop* function in the "*meta*" package, and funnel plots were constructed with the *funnel* function to estimate the publication bias. Egger's tests were performed to estimate the indexes of funnel asymmetry; when a funnel plot was not significantly asymmetrical, trim-and-fill analyses (101) were performed. A two-sided $P<0.05$ was deemed to represent the level of statistical significance.

Results

Literature search and characteristics

The search process is shown in *Figure 1*. A total of 2,090 articles published between 2001 and 2020 were identified through the initial database search. Of these articles, 275 reviews, 144 comments, 76 case reports, 43 editorials, and 27 meta-analyses were excluded. A further 1,352 articles were excluded based on the screening of their titles and abstracts. The remaining 173 studies were assessed on the basis of their full texts. After the exclusion of overlapping studies, studies presenting insufficient data, and studies with an inappropriate population, treatment, or size, 105 studies were finally included in the meta-analysis. Among them were 87 SBRT studies involving 12,811 patients (*Table 1*) and 18 RFA studies involving 1,525 patients (*Table 2*). There were no controlled trials or randomized studies comparing clinical outcomes between patients with early-stage NSCLC treated with SBRT and RFA. All the selected articles were single-arm observational articles or compassion studies.

The sample sizes of the SBRT studies ranged from 16 to 1,096 (median 71; mean 147) and those of the RFA studies ranged from 7 to 967 (median 33; mean 147). Patients treated with SBRT were significantly older than those treated with RFA (74.9±3.0 *vs.* 71.6±4.1 years, respectively, $P\leq0.001$). Significant sex differences were observed between the SBRT and RFA cohorts (percentage of males, 58.2% *vs.* 52.0%, $P\leq0.001$). The mean follow-up time of the RFA studies was longer than that of the SBRT studies (34.2 *vs.* 29.3 months). Regarding the SBRT treatment regimen, the total dose ranged from 30 to 70 Gy, and the number of fractions ranged from 1 to 10.

LC rates of patients treated with SBRT and RFA

Sixty-six SBRT and seven RFA studies reported the LC rate. For SBRT, 20 studies (2,132 patients), 31 studies

Table 1 Characteristics of the included SBRT studies

Author	Year	Country	Study design	Sample size	Median/mean age [range]	Male (%)	Stage	Dose range	BED	F/U [mo]
Nagata (16)	2005	Japan	P	45	77 [57–87, IA]	74	I (TNM not clear)	12 Gy ×4	105.6	30 [6–71]
Nyman (17)	2006	Sweden	R	45	74 [58–84]	57	I (TNM not clear)	15 Gy ×3	112.5	43 [24–74]
Timmerman (18)	2006	USA	R	70	70 [51–86]	74	I (TNM not clear)	20 Gy ×3	180	17.5 [0.6–44]
Zimmermann (19)	2006	Germany	R	68	76 [59–92]	71	I (TNM not clear)	12 Gy ×3; 7 Gy ×5	84.4; 59.5	17 [3–44]
Koto (20)	2007	Japan	P	31	77 [60–83]	81	I (TNM not clear)	15 Gy ×3; 7.5 Gy ×8	112.5; 105	32 [4–87]
Onishi (21)	2007	Japan	R	257	74 [39–92]	NA	I (TNM not clear)	4.4w35/1–14 Fx	117 [100–180]	38 [2–128]
Fritz (22)	2008	Germany	R	40	74 [59–82]	80	I (TNM not clear)	30 Gy ×1	120 Gy (isocenter)	20 [6–61.5]
Lagerwaard (23)	2008	The Netherlands	R	206	73	57	I (TNM not clear)	20 Gy ×3; 12 Gy ×5; 7.5 Gy ×8	132	12
Onimaru (24)	2008	Japan	P	41	76 [52–85]	69	I (TNM not clear)	10 Gy ×4; 12 Gy ×4	80; 105.6	27
Salazar (25)	2008	Japan	R	60	NA	NA	I (TNM not clear)	13 Gy ×4	119.6	NA
Baumann (26)	2009	Norway	P	57	75 [59–87]	44	I (TNM not clear)	15 Gy ×3	112.5	35 [4–47]
Fakiris (27)	2009	USA	P	70	NA	NA	I (TNM not clear)	20 Gy ×3 (IA); 22 Gy×3 (IB)	180; 211.2	50.2
Kopek (28)	2009	Denmark	R	88	72 [47–88]	50	I (TNM not clear)	15/22.5 Gy ×3	112.5; 219.5	44 [1.6–96.5]
Stephans (29)	2009	US	R	56	72 [49–89]	52	I (TNM not clear)	10 Gy ×5	100	19.8
Takeda (30)	2009	Japan	R	63	78 [56–91]	63	I (TNM not clear)	10 Gy ×5	100	31 [10–72]
Baba (31)	2010	Japan	R	124	77 [29–89]	68	I (TNM not clear)	11 Gy ×4 (1.6%); 12 Gy ×4; 13 Gy ×4	92.4; 105.6; 119.6	26 [7–66]
Bradley (32)	2010	Italy	P	91	71 [31–93]	47	I (TNM not clear)	18 Gy ×3	151.2	18 [6–42]
Burdick (33)	2010	USA	R	72	74 [44–89]	52	I (AJCC 6th)	20 Gy ×3; 10 Gy ×5; 5 Gy ×10	180; 100; 75	36
Dunlap (34)	2010	USA	R	40	73 [54–87]	NA	I (AJCC)	42–60/3–5 Fx	150	12.5 [2–35]
Hamamoto (35)	2010	Japan	R	52	78 [58–90]	70	I (TNM not clear)	12 Gy ×4	105.6	14 [3–34]
Ricardi (36)	2010	Italy	P	62	73 [53–83]	84	I (TNM not clear)	15 Gy ×3	112.5	28 [9–60.7]
Timmerman (3)	2010	USA	P	59	72 [48–89]	38	I (AJCC)	18 Gy ×3	151.2	34.4 [4.8–49.9]
van der Voort van Zyp (37)	2010	The Netherlands	P	39	77 [55–87]	NA	I (TNM not clear)	20 Gy ×3	180	17
Bral (38)	2011	Belgium	P	40	73 [54–86]	83	I (AJCC 6th)	20 Gy ×3; 15 Gy ×4	180; 150	16 [5–33]

Table 1 *(continued)*

Table 1 *(continued)*

Author	Year	Country	Study design	Sample size	Median/mean age [range]	Male (%)	Stage	Dose range	BED	F/U [mo]
Lanni (39)	2011	USA	R	45	76 [63–90]	40	I (TNM not clear)	12 Gy ×4; 12 Gy ×5	105.6; 140	36
Matsuo (40)	2011	Japan	R	101	77 [62–87]	73	I (TNM 7th)	12 Gy ×4	105.6	31.4 [4.2–118]
Nath (41)	2011	USA	R	58	79 [60–88]	63	I (TNM not clear)	10 Gy ×5; 12 Gy ×4; 13 Gy ×4	100; 105.6; 119.6	17 [4–42]
Turzer (42)	2011	Norway	R	36	74 [54–85]	28	I (TNM not clear)	15 Gy ×3	112.5	13.8 [0–21]
Widder (43)	2011	The Netherlands	P	202	76 [46–93]	73	I (TNM not clear)	20 Gy ×3; 12 Gy ×5; 7.5 Gy ×8	180; 140; 105	13
Senthi (44)	2012	The Netherlands	R	676	73 [47–92]	61	I (AJCC 6th)	20 Gy ×3 or 18 Gy ×3; 12 Gy ×5 or 11 Gy ×5; 7.5 Gy ×8	151.2; 115.5; 105	13
Taremi (45)	2012	Canada	P	108	73 [48–90]	49	I (TNM not clear)	20 Gy ×3; 18 Gy ×3; 12 Gy ×4; 7.5 Gy ×8; 5 Gy ×10	180; 151.2; 105.6; 105; 75	19.1 [1–55.7]
Abelson (46)	2012	USA	R	54	80 [58–93]	43	I (TNM not clear)	25–60/1–5 Fx	80–180	13.2 [3.2–60.5]
Chan (47)	2012	China	R	16	82 [71–90]	69	I (TNM not clear)	10 Gy ×5; 18 Gy ×3; 20 Gy ×3	100; 151.2; 180	22
Chang (48)	2012	USA	R	130	74 [48–91]	52	I (TNM not clear)	12.5 Gy ×4	106.3	26 [6–78]
Puri (49)	2012	USA	R	57	72 [50–94]	40	I (TNM not clear)	18 Gy ×3	151.2	NA
Satoh (50)	2012	Japan	P	57	NA	74	I (TNM not clear)	48–72 Gy	105.6; 119	27 [6–67]
Shibanoto (51)	2012	Japan	P	120	NA	NA	I (TNM not clear)	11 Gy ×4; 12 Gy ×4; 13 Gy ×4	92.4; 105.6; 119.6	36
Shirata (52)	2012	Japan	R	81	77 [54–90]	79	I (TNM not clear)	12 Gy ×4; 7.5 Gy ×8; 4 Gy ×15	192; 105; 84	30.4 [0.3–78.5]
Zhang (53)	2012	USA	R	68	72 [55–91]	56	I (TNM not clear)	12.5 Gy ×4	112.5	31 [6–71]
Guckenberger (54)	2013	Germany	R	582	72 [30–92]	70	I (TNM not clear)	12.5 Gy ×3; 15 Gy ×3	79.7; 112.5	21
Miyakawa (55)	2013	Japan	P	91	76 [61–86]	71	I (TNM not clear)	12 Gy ×4	105.6	39
Takahashi (56)	2013	Japan	R	32	NA	NA	I (TNM not clear)	12 Gy ×4; 7 Gy ×8	105.6; 100.8	21.2 [1.3–55.7]
Crabtree (57)	2014	USA	R	151	74	80	I (TNM not clear)	45–60 Gy	85.5–151.2	23.4
Ricardi (58)	2014	Italy	R	196	75 [48–91]	74	I (TNM not clear)	48–60 Gy/3–8 Fx	100–132	30
Rosen (59)	2014	USA	R	79	73 [27–92]	42	I (TNM not clear)	12 Gy ×4; 12 Gy ×5	105.6;132	27 [4–82]

Table 1 *(continued)*

Table 1 *(continued)*

Author	Year	Country	Study design	Sample size	Median/mean age [range]	Male (%)	Stage	Dose range	BED	F/U [mo]
Rwigema (60)	2014	USA	R	46	80 [42–95]	19	I (TNM not clear)	18 Gy ×3	151.2	16.8 [0.6–38.9]
Satoh (61)	2014	Japan	R	88	NA	68	I (TNM not clear)	48–70	96–119	33
Shultz (62)	2014	USA	R	117	77 [42–93]	55	I (AJCC 6th)	NA	112.5 [80–180]	17 [3–74]
Thibault (63)	2014	UK	R	180	NA	NA	I (TNM not clear)	48–60 Gy	NA	20.8 [0.2–52.1]
Yamashita (64)	2014	Japan	R	51	NA	NA	I (TNM not clear)	50–57 Gy	NA	8.9 [1.3–38.7]
Bahig (65)	2015	Canada	R	150	75 [55–95]	42	I (AJCC 7th)	40–60 Gy	180 [72–180]	22
Kishi (66)	2015	Japan	R	165	NA	73	I (UICC 7th)	12 Gy ×4	105.6	42 [4.8–159.6]
Koshy (67)	2015	USA	R	773	NA	45	I (TNM not clear)	NA	NA	68 [35–83]
Lindberg (68)	2015	Norway	P	38	75 [59–87]	46	I (AJCC 7th)	45–66 Gy	NA	NA
Mak (69)	2015	USA	R	75	74 [46–93]	45	I (TNM not clear)	18 Gy ×3; 10 Gy ×5; 12 Gy ×5	151.2; 100; 132	18.8
Mokhles (70)	2015	The Netherlands	R	73	67 [47–89]	58	I (AJCC 7th)	54–60 Gy	NA	30
Shen (71)	2015	China	R	50	NA	56	I (TNM not clear)	58–60 Gy	104–150 Gy	35 [3–45]
Videtic (72)	2015	USA	R	84	75	45	I (AJCC 6th)	34 Gy ×1; 12 Gy ×4	149.6; 105.6	30.2
Bhandari (73)	2016	USA	R	55	68 [51–87]	80	I (AJCC 7th)	50–62.5 Gy	100–180	23.8 [1.1–57.6]
Navarro-Martin (74)	2016	Spain	P	38	74 [52–89]	95	I (AJCC 6th)	18 Gy ×3	151.2	42 [1.4–66]
Shaverdian (75)	2016	USA	R	147	76 [41–93]	NA	I (TNM not clear)	18 Gy ×3; 12.5×4	151.2; 112.5	28.9
Zhao (76)	2016	China	R	1092	72 [33–94]	49	I (TNM not clear)	12.5 Gy ×4; 10 Gy ×7	112.5; 119	31.7 [14.8–51.3]
Awano (77)	2017	Japan	R	40	86 [56–95]	63	I (AJCC 7th)	36–48 Gy	68.4–105.6	14.5 [1–51]
Giuliani (78)	2017	Canada	P	734	76 [42–94]	50	I (AJCC 7th)	18–64 Gy	NA	16.8 [1.2–177.6]
Hörner-Rieber (79)	2017	Germany	R	126	73 [58–90]	69	I-IIb (TNM 8th)	NA	NA	22
Miyakawa (80)	2017	Japan	R	71	77 [55–89]	72	I (TNM 7th)	48–52 Gy	NA	44
Stam (81)	2017	Sweden	R	803	75 [41–92]	54	I (TNM not clear)	18 Gy ×3; 12 Gy ×4	151.2; 105.6	34.8 [0.1–121.5]
Tembhekar (82)	2017	Sweden	R	102	76	45	I (TNM not clear)	40–60 Gy	NA	27 [10–73]
Abreu (83)	2018	Brazil	R	54	75	76	I-IIb (TNM 7th)	45–60 Gy	80–180	17.8 [4–56.4]
Cornwell (84)	2018	USA	P	56	70 [64–78]	98	I (TNM not clear)	50–56 Gy	100–134.4	44.4

Table 1 *(continued)*

Table 1 *(continued)*

Author	Year	Country	Study design	Sample size	Median/mean age [range]	Male (%)	Stage	Dose range	BED	F/U [mo]
Jeon (85)	2018	Korea	R	53	74 [54–87]	76	I (TNM not clear)	50 Gy/3–8 Fx	60–160.5	37.1 [2.3–100.3]
Karasawa (86)	2018	Tokyo	R	56	79 [49–91]	70	I (TNM not clear)	12 Gy ×4	105.6	127.2
Lee (87)	2018	Korea	R	169	73	83	I (TNM not clear)	12 Gy ×4; 15 Gy ×4	105.6; 150	32 [2–195]
Lee (88)	2018	Korea	R	35	75 [60–89]	57	I (TNM not clear)	45–60 Gy	85.5–180	23 [3–77]
Ma (89)	2018	USA	R	159	76	48	I (TNM not clear)	30 Gy ×1; 48–60 Gy ×3	NA	22.2
Onimaru (90)	2018	Japan	R	28	NA	57	I (TNM 6th)	40–60 Gy	NA	46.8 [10.8–86.4]
Satoh (91)	2018	Japan	R	125	79 [58–89]	54	I (TNM not clear)	48–70 Gy	NA	39
Shintani (92)	2018	Japan	R	216	76 [49–91]	77	I (TNM 7th)	12 Gy ×4	105.6	NA
Shioyama (93)	2018	Japan	R	43	77 [56–88]	74	I (TNM 7th)	36–60 Gy	56–119.6	23.2 [4.5–114.6]
Timmerman (4)	2018	USA	P	59	NA	NA	I (TNM 7th)	18 Gy ×3	151.2	48
von Reibnitz (94)	2018	USA	R	398	77 [50–95]	46	I (TNM 7th)	9–10 Gy ×5; 12 Gy ×4; 18–20 Gy ×3	85.5–180	23.3 [2.2–75.2]
Baker (95)	2019	The Netherlands	R	586	75 [44–91]	62	I (TNM 7th)	40–60 Gy	NA	25
Nicosia (96)	2019	Germany	R	44	75 [57–88]	66	I (TNM 7th)	30 Gy ×1	120	34 [3–81]
Schonewolf (97)	2019	USA	R	186	72 [48–94]	50	I (AJCC 7th)	NA	NA	48
Videtic (5)	2019	USA	P	84	75	45	I (AJCC 6th)	12 Gy ×4; 34 Gy ×1	105.6; 149.6	48 [1.2–96]
Kwak (98)	2020	Korea	R	76	75 [48–90]	80	I (AJCC 7th)	36–63 Gy	NA	32 [5–142]
Mayne (99)	2020	USA	R	570	NA	NA	I (AJCC 7th)	NA	NA	27.6 [14.4–47]

SBRT, stereotactic body radiation therapy; BED, biological equivalent dose; F/U, follow-up; P, prospective; R, retrospective; NA, not available; USA, United States of America; UK, United Kingdom.

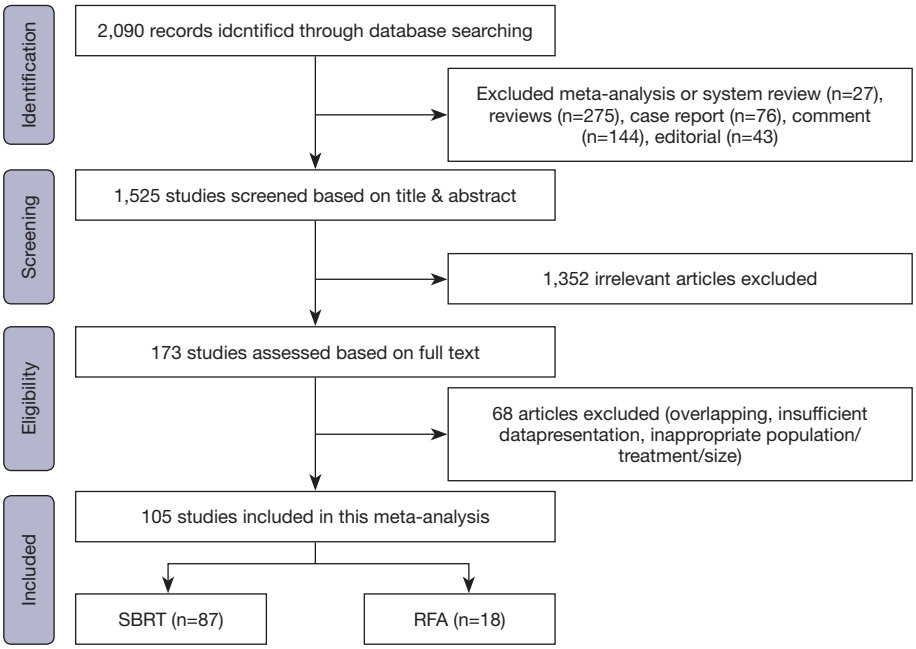

Figure 1 Flowchart of study selection.

Table 2 Characteristics of the included RFA studies

Author	Year	Country	Study design	Sample size	Median/mean age [range]	Male (%)	Stage	F/U (mo)
Belfiore (102)	2004	Italy	R	33	66 [44–75]	79	I (TNM not clear)	12
Pennathur (103)	2007	USA	R	19	78 [68–88]	42	I (TNM not clear)	28 [9–52]
Simon (8)	2007	USA	R	75	69 [17–94]	57	I (TNM not clear)	21 [3–74]
Lencioni (9)	2008	Italy	P	33	67 [29–82]	76	I (TNM not clear)	15 [1–30]
Okuma (104)	2010	Japan	R	7	70 [31–94]	78	I (TNM not clear)	12 [3–60]
Zemlyak (7)	2010	USA	R	12	74 [62–83]	56	I (TNM not clear)	33
Ambrogi (105)	2011	Italy	P	59	74 [40–88]	79	I (TNM not clear)	46 [12–82]
Hess (106)	2011	France	R	15	64 [42–82]	60	I (TNM not clear)	17.6 [2–31]
Hiraki (107)	2011	Japan	R	50	75 [52–88]	58	I (TNM not clear)	37 [2–88]
Lee (108)	2011	Korea	R	16	73	75	I (TNM not clear)	56 [6–64]
Sofocleous (109)	2011	USA	R	12	65 [44–81]	67	I (TNM not clear)	23
Kim (110)	2012	Korea	R	8	72 [61–78]	88	I (TNM not clear)	108
Lanuti (111)	2012	USA	R	45	70 [51–89]	40	I (TNM not clear)	32 [2–75]
Ridge (112)	2014	USA	R	29	73 [55–86]	41	I (TNM not clear)	12
Ambrogi (113)	2015	Italy	R	62	76 [60–88]	73	I (TNM not clear)	42
Dupuy (10)	2015	USA	R	51	76 [60–89]	45	I (TNM not clear)	24
Lam (114)	2018	USA	R	967	74	46	I (TNM 7th)	62.5 [58.0–67.1]
Palussière (11)	2018	France	R	42	72	69	I (TNM not clear)	NA

RFA, radiofrequency ablation; F/U, follow-up; P, prospective; R, retrospective; NA, not available.

Table 3 Outcomes of pooled analysis for LC rates

Year	SBRT			RFA			P value
	Number of patients	LC rate (%)	95% CI (%)	Number of patients	LC rate (%)	95% CI	
1	2,123	98%	97–98%	156	75%	69–82%	0.01
2	4,783	95%	95–96%	85	31%	22–39%	0.01
3	4,828	92%	91–93%	83	67%	58–76%	0.01
5	3,504	92%	91–93%	44	41%	30–52%	0.01

SBRT, stereotactic body radiation therapy; RFA, radiofrequency ablation; CI, confidence interval; LC, local control.

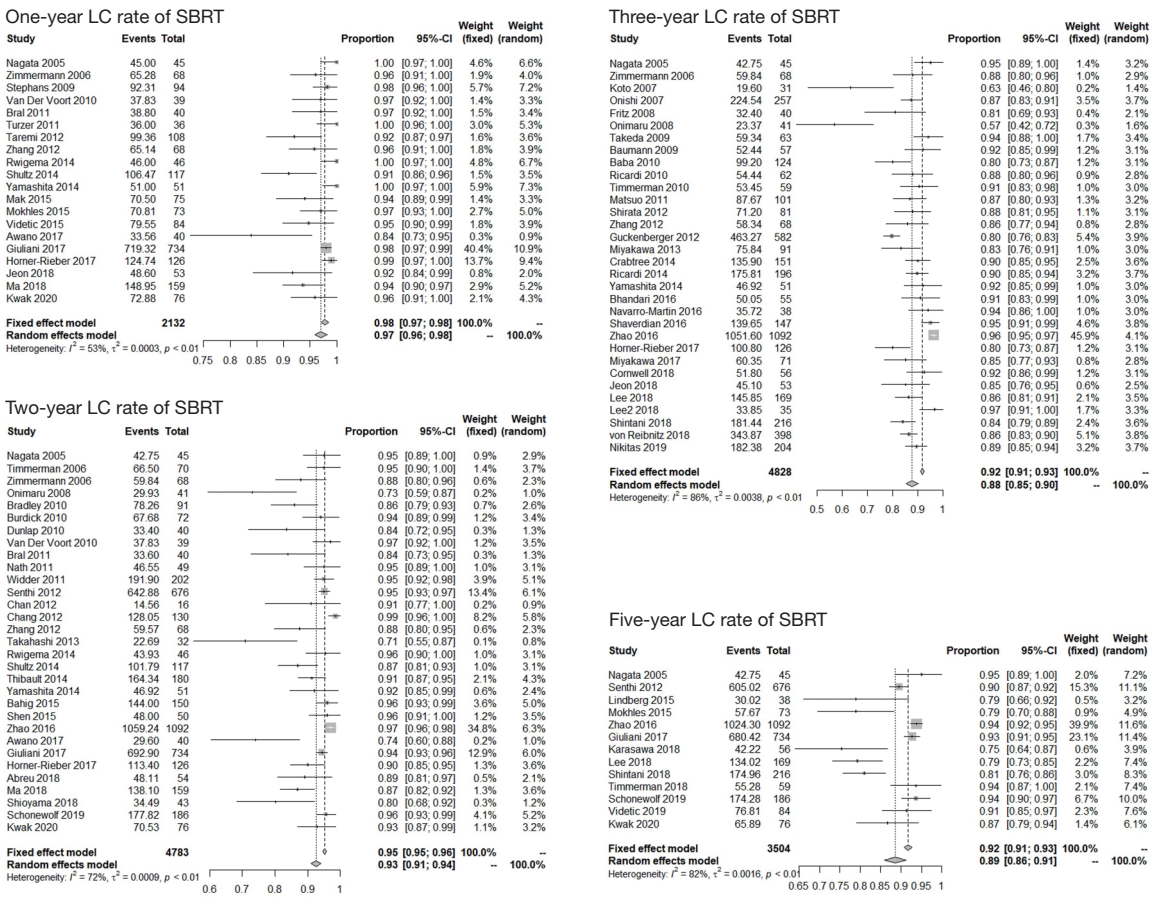

Figure 2 Meta-analysis (forest plot) of the LC rates in the SBRT studies. LC, local control; SBRT, stereotactic body radiation therapy.

(4,783 patients), 32 studies (4,828 patients), and 13 studies (3,504 patients) reported the LC rates at 1, 2, 3, and 5 years, respectively. For RFA, 6 articles (156 patients), 4 articles (85 patients), 3 articles (83 patients), and 3 articles (44 patients) reported the LC rates at 1, 2, 3, and 5 years, respectively. The pooled LC rates calculated by fixed effects model are shown in *Table 3*, *Figure 2*, and *Figure 3*. The LC rates (with 95% CIs) for SBRT at 1, 2, 3, and 5 years were 98% (97–98%), 95% (95–96%), 92% (91–93%), and 92% (91–93%), respectively, which were significantly higher than those for RFA [75% (69–82%), 31% (22–39%), 67% (58–76%), and 41% (30–52%); P<0.01].

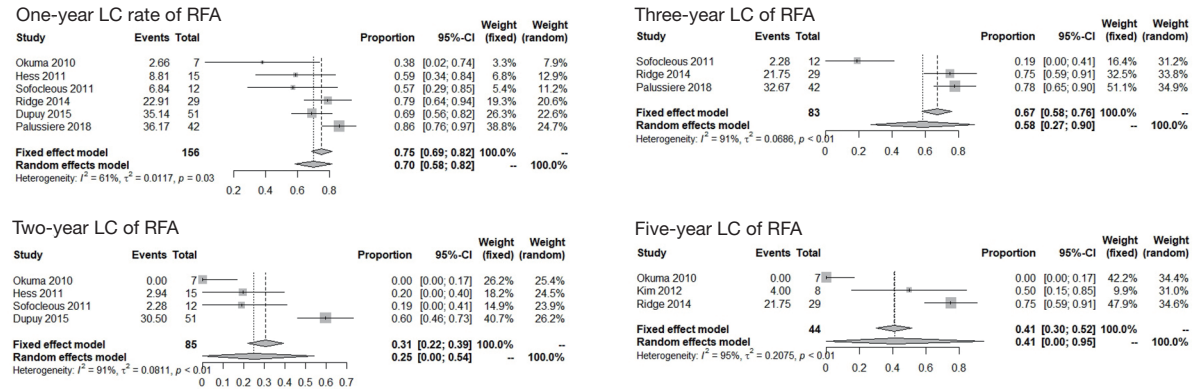

Figure 3 Meta-analysis (forest plot) of the LC rates in the RFA studies. LC, local control; RFA, radiofrequency ablation.

Table 4 Outcomes of pooled analysis for OS rates

Year	SBRT			RFA			P value
	Number of patients	OS rate (%)	95% CI (%)	Number of patients	OS rate (%)	95% CI	
1	2,703	87%	86–88%	1,461	89%	88–91%	0.07
2	5,587	71%	69–72%	348	69%	64–74%	0.42
3	6,939	58%	56–59%	1,289	48%	45–51%	0.01
5	4,269	39%	37–40%	1,278	21%	19–23%	0.01

SBRT, stereotactic body radiation therapy; RFA, radiofrequency ablation; CI, confidence interval; OS, overall survival.

OS rates of patients treated with SBRT and RFA

Eighty-two SBRT and 18 RFA studies reported OS outcomes. For SBRT, 27 articles (2,703 patients), 40 articles (5,587 patients), 45 articles (6,939 patients), and 22 articles (4,269 patients) reported the OS rate at 1, 2, 3, and 5 years, respectively. For RFA, 15 studies (1,461 patients), 11 studies (348 patients), 9 studies (1,289 patients), and 10 studies (1,278 patients) reported the OS rate at 1, 2, 3, and 5 years. The pooled OS rates calculated by fixed effects model are shown in *Table 4*, *Figure 4*, and *Figure 5*. Regarding short-term OS, no significant differences were observed between patients treated with SBRT and those treated with RFA at 1 year (P=0.07) or 2 years (P=0.42); for SBRT and RFA, the 1-year OS rates (with 95% CIs) were 87% (86–88%) and 89% (88–91%), respectively, and the 2-year OS rates were 71% (69–72%) and 69% (64–74%), respectively. Regarding long-term OS, the 3- and 5-year OS rates of patients treated with SBRT (with 95% CIs) were 58% (56–59%) and 39% (37–40%), respectively, and were significantly (P<0.01) superior to those of patients treated with RFA [48% (45–51%) and 21% (19–23%)], respectively.

AEs

Data on the overall incidence of AEs following treatment with SBRT or RFA were limited (*Table 5*). The most common complication of RFA was pneumothorax, making up 27.2% (95% CI, 23.2–31.1%) of patients treated with RFA, followed by hemoptysis and pleural effusion comprised 2.2% (95% CI, 0.9–3.5%) or 4.1% (95% CI, 2.2–5.9%). The rate of severe AEs related to SBRT (grade ≥3) was 5.8% (95% CI, 5.1–6.5%), with the most common severe AE (grade ≥2) being radiation pneumonitis, making up 9.1% (95% CI, 8.0–10.1%) of patients treated with SBRT. The incidence of radiation esophagitis (grade ≥3) was low, comprising only 0.2% (95% CI, 0.1–0.3%) of patients treated with SBRT, and the incidence of rib fracture was 4.0% (95% CI, 3.4–4.6%).

Sensitivity analysis and publication bias testing

After sensitivity analysis using the elimination method, no significant change was observed in the results, which indicated their robustness. Egger's test was performed on the indexes with more than three included studies, and the results showed no obvious publication bias (Table S1).

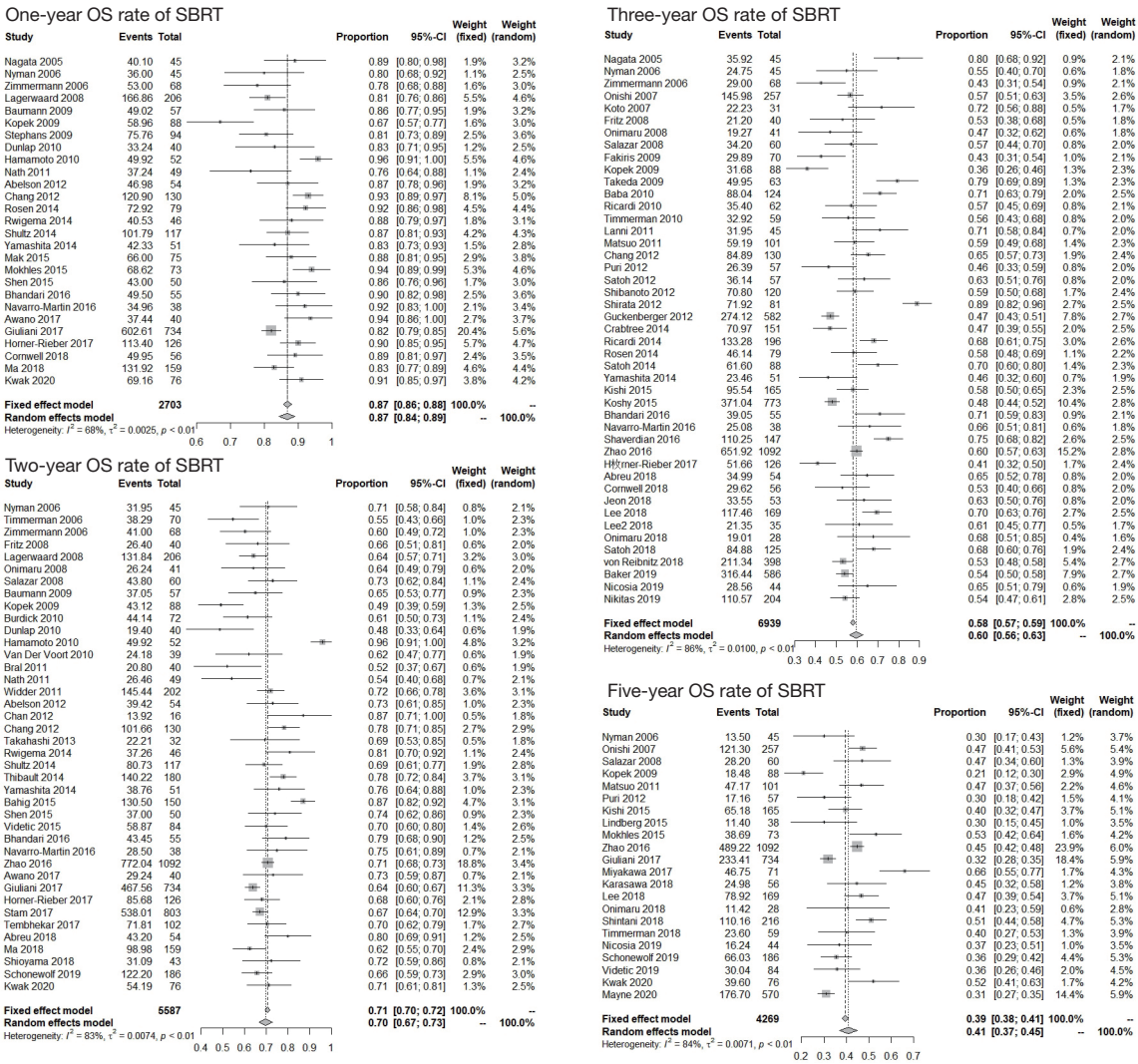

Figure 4 Meta-analysis (forest plot) of the OS rates in the SBRT studies. OS, overall survival; SBRT, stereotactic body radiation therapy.

Discussion

A total of 105 studies, including 87 SBRT studies and 18 RFA studies, were selected to compare the clinical outcomes and AEs of SBRT and RFA in patients with medically inoperable early-stage NSCLC. This comprehensive review revealed that patients who received SBRT had higher 1-, 2-, 3-, and 5-year LC rates than patients treated with RFA (P<0.01). After 1 (P=0.07) and 2 (P=0.42) years, the two groups of patients had comparable OS, whereas the 3- and 5-year OS rates were significantly higher in patients treated with SBRT (P<0.01). A low incidence of severe AEs was reported in both the SBRT and RFA groups.

Several previous reviews or meta-analyses have compared the outcomes of SBRT and RFA. However, no reviews or pooled analyses comparing the two have been reported in the past 5 years. In 2012, Bilal *et al.* (115) conducted a literature review of nine RFA studies and seven SBRT studies to compare SBRT and RFA, and found that SBRT had lower local progression rates than did RFA (3.5–14.5% *vs.* 23.7–43%). They also observed that while the two treatment modalities had similar 1-year OS (68.2–95% *vs.* 81–85.7%), the SBRT cohort had a higher 5-year OS rate (47%) than the RFA cohort (20.1–27%), which was in line with the results of the present study. However, Bilal *et al.* did not utilize statistical methods to compare LC or OS between the two treatments. In 2016, Bi *et al.* (12) screened relevant

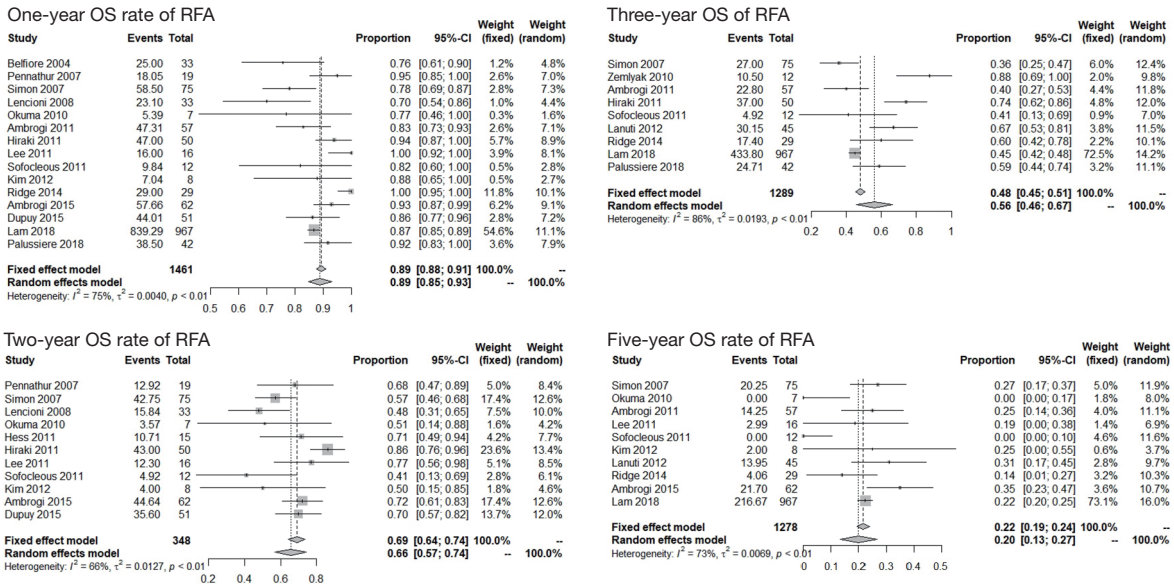

Figure 5 Meta-analysis (forest plot) of the OS rates in the RFA studies. OS, overall survival; RFA, radiofrequency ablation.

Table 5 Summary of AEs

Treatment	AE	No. of events	No. of patients	Events percentage (%)	95% CI (%)
SBRT	RP grade 2–5	270	2,982	9.1	(8.0–10.1)
	RP grade 3–5	112	4,244	2.6	(2.2–3.1)
	Rib fracture	163	4,093	4.0	(3.4–4.6)
	RE grade 3–5	6	3,244	0.2	(0.1–0.3)
	Total grade 3–5	242	4,205	5.8	(5.1–6.5)
RFA	Pneumothorax	132	486	27.2	(23.2–31.1)
	Hemoptysis	10	453	2.2	(0.9–3.5)
	Pleural effusion	18	441	4.1	(2.2–5.9)

AE, adverse events; SBRT, stereotactic body radiation therapy; RFA, radiofrequency ablation; RP, radiation pneumonitis; RE, radiation esophagitis; CI, confidence interval..

studies published from 2000 to 2012, and subsequently conducted a systemic review and pooled analysis of 31 SBRT studies and 13 RFA studies. They found that the rates of LC at 1, 2, 3, and 5 years for SBRT were significantly higher than those for RFA (97%, 92%, 88%, and 86% *vs.* 77%, 48%, 55%, 42%, respectively; P<0.001), which was consistent with the findings of the present study. However, in contrast with our study results, Bi *et al.* reported similar OS rates between the two treatment modalities, even at 3 and 5 years. These differences may be attributable to the fact that the OS rates reported in Bi *et al.*'s study were estimated pooled ratios calculated by a regression model and were not the actual pooled values. Other reasons may be that only 31 SBRT and 13 RFA studies were included, and all of them were published before 2012; since 2012, the utilization and popularity of SBRT techniques have increasingly expanded. Therefore, prospective studies containing large sample sizes to compare the clinical results of SBRT and RFA are warranted in the future to validate the findings of the present study.

Besides performing comparative analysis of the two therapeutic modalities, our study also conducted pooled

analyses of survival outcomes in SBRT and RFA cohorts. For SBRT, 87 articles from the past 20 years, involving 11,827 patients, were included to calculate the pooled outcomes, which supports the credibility of the present pooled results. Furthermore, our pooled results echo the results of a number of prospective studies. Recently, the prospective RTOG 0236 study (3,4) in the setting of inoperable early-stage NSCLC reported 3- and 5-year LC rates of 97.6% and 92.7%, respectively, and 3- and 5-year OS rates of 55.8% and 40.0%, respectively, which are in line with our findings (5-year LC rate: 92%; 3- and 5-year OS rates: 58% and 39%, respectively). Another randomized prospective study, RTOG 0915 (5), also reported similar 5-year LC and OS rates (93.2% and 41.1%, respectively) in patients treated with 48 Gy in 4 fractions. The RTOG 0236 and RTOG 0915 trials were conducted by the North American Cooperative Group with criteria relating to SBRT, and were used to develop the infrastructure and offer high-quality treatment across multiple centers (116). Given the similar results found in this current study, it is reasonable to generalize our findings for a large population.

The present study included 18 studies on RFA from the past 20 years, involving 1,525 patients, for pooled analysis. In view of fewer articles reporting the outcomes of RFA than of SBRT in the treatment of medically inoperable early-stage NSCLC, it can be inferred that RFA is less frequently utilized and popular than SBRT. In 2008, the first prospective multicenter clinical trial, the RAPTURE study (9), reported a 2-year OS rate of 75%, which is in accordance with the 69% 2-year OS rate observed in our study. In 2015, another prospective study reported by Dupuy *et al.* (10) showed similar 2-year OS and LC rates of 69.8% and 59.8%, respectively. However, our study reported an LC rate of only 31% after 2 years, which may be attributable to the fact that only 4 studies and 85 patients were included in the pooled analysis for the 2-year LC rate of RFA. Recently, a prospective multicenter phase II trial (11) described LC and OS rates of 81.25% and 58.3%, respectively, after 3 years, which were higher than the rates observed in our study (67% and 48%, respectively). Although this prospective study revealed RFA to produce good clinical results, the sample size was only 32, which may not be sufficient to prove the suitability of RFA for patients with inoperable early-stage NSCLC. Therefore, despite the findings of these previous studies and our pooled analysis on RFA, further investigation is still warranted.

In terms of AEs, both treatment modalities have advantages and disadvantages which need to be weighed up by a multidisciplinary team. The major toxicities of RFA are pneumothorax, hemoptysis, and pleural effusion, which usually occur roughly 30 days after the treatment. The AEs of SBRT, which include radiation pneumonitis, rib fracture, and chest pain (117), often occur 2 to 3 months after radiation. Bi *et al.* (12) performed a pooled analysis of AEs for both modalities, and they found that the most common complication of RFA was pneumothorax, occurring in 31% of patients. They also discovered that severe AEs (grade ≥3) occurred in 6.9% of patients in the SBRT cohort, with the most common severe complication (grade ≥3) of SBRT being radiation pneumonitis, which was reported in 2.2% of patients. Our current study produced similar results regarding AEs, with the rates of severe AEs (grade ≥3) and severe radiation pneumonitis (grade ≥2) for SBRT being 5.8% and 9.1%, respectively, and the rate of pneumothorax for RFA being 27.2%. Summarizing AEs of SBRT or RFA can offer guidance and inform treatment during the surveillance and follow-up of patients with inoperable early-stage NSCLC.

With the rapid development of immune therapy utilized in the field of treatment for patients with lung cancer, the combination of SBRT or RFA and immunotherapy has gradually become a rational option. Both SBRT and RFA can modulate the immune function and regulate the immune microenvironment. SBRT has been proved to play an important role in the immunomodulatory process (118). Specifically, on the one hand, SBRT can activate the innate immune microenvironment by expressive upregulation of immunogenic markers, production of immunogenic cell deaths (ICDs) and release of enough tumor-associated antigens (TAAs). (119-125). On the other hand, SBRT can also elicit adaptive immune responses by acting as situ vaccine to induce the priming of cytotoxic T lymphocytes (CTLs) and the release of related cytokines, such as IFN-γ, which plays a vital role in the inhabitation of metastatic lesion progression (126). The expression of IFN-γ related genes has been demonstrated to have significantly correlation with the distant non-irradiated tumor response (127), which is also famous as abscopal effect (123,128). As far as the immune effect generated by RFA, similar to SBRT, RFA can alter the immunogenic nature, increase the TAAs released by tumor necrosis, and promote T cell trafficking to TME (129-132), thus activating the immune system. However, such positive immune effect seems to last about 4 weeks after ablative therapy (133).

A few clinical researches have shown that SBRT combined with immunotherapy can obtain favorable

benefits in term of several survival outcomes, such as ORR (objective response rate), median PFS and median OS (127,134). However, the combined therapy of SBRT and PD-1 (programmed death-1)/PD-L1(programmed death-ligand 1) inhibitors still face some challenges concerning the optimal dose or fraction, the suitable schedule of the combined therapy, and the rational irradiated target and volume. In term of RFA, several clinical trials have also revealed more potent response for the additional immune therapy to the RFA than either PD-1/PD-L1 or RFA alone (135,136). Unfortunately, incomplete ablation may induce the aggressive growth of the residual tumor lesion, the upregulation of suppressive T cell caused by the release of IL-10 and TGF-β, and the acceleration of tumor recurrence (137-139).

There are several limitations in this study. First, due to the nature of systematic reviews and pooled analyses, heterogeneity, caused by factors such as demographic variables, study design, radiation regimen or delivery technique disparity, and variation in clinical outcome definitions, was present. However, this systematic review and pooled analysis including more than 14,000 patients can, to a certain degree, offer benefit in the guidance of treatment options (140). Second, our current pooled analysis included studies published between 2000 and 2020, and the techniques of both SBRT and RFA may have evolved during those two decades, which could have resulted in inconsistencies between the studies. Third, SBRT may offer a suitable option for salvage treatment (141), but the current study did not include articles focusing on this area. However, Steber *et al.* (142) found that SBRT alone offered similar or even superior LC to RFA and SBRT combined.

Conclusions

This systematic review and pooled analysis have revealed that compared to RFA, SBRT has superior LC rates and long-term OS rates, but similar short-term OS rates. Prospective randomized trials or studies with large sample sizes are needed to validate these findings.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-21-6256/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-21-6256/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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