Stereotactic body radiotherapy versus surgery for early-stage non-small cell lung cancer: an updated meta-analysis involving 29,511 patients included in comparative studies

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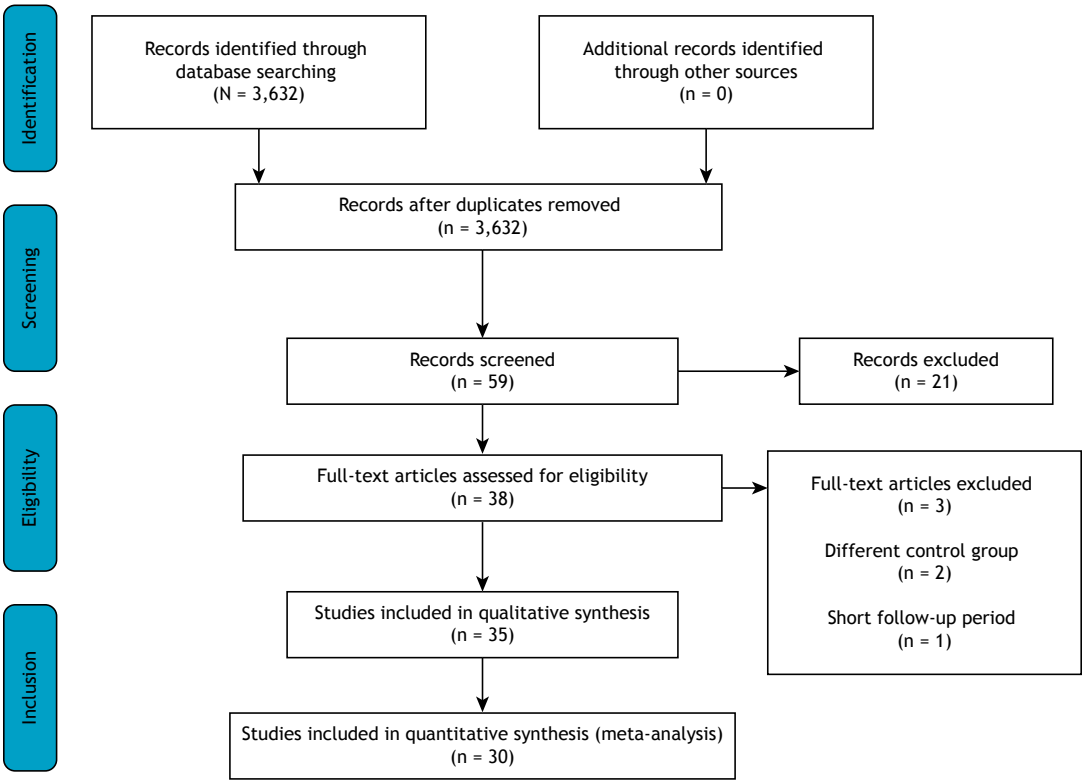

Figure S1. Flow chart of the study selection process.

Table S1. Characteristics of the studies included in the present meta-analysis.

Study	Study design	Clinical stage	Patients		SBRT dose	Type of surgery-%	Outcome
			SBRT	Surgery			
Grills et al.[19]	RS	T1/2aN0M0	58	69	48 Gy; 4 fx 60 Gy; 5 fx	SL-100	1y and 3y OS, LC, and CSS. Follow-up at 30 months for both groups.
Crabtree et al.[20]	RS PSM	T1/2aN0M0	57	57	54 Gy; 3 fx	Mixed-20 L-80	1y, 3y, and 5y OS, LC, and CSS. Follow-up at 19 and 31 months.
Palma et al.[21]	RS PSM	T1/2N0M0	60	60	60 Gy; 3-8 fx 54 Gy; 3 fx	Mixed-18 L-82	1y and 3y OS. Follow-up at 43 months.
Shirvani et al.[22]	RS PSM	T1/2N0M0	99 112	L-99 SL-112	NR	L-100 SL-100	OS, CSS, LC, RC, and DC. Follow-up at 38 months.

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Table S1. Characteristics of the studies included in the present meta-analysis. (Continued...)

Study	Study design	Clinical stage	Patients		SBRT dose	Type of surgery-%	Outcome
			SBRT	Surgery			
Robinson et al.[24]	RS PSM	T1-3N0M0	76	76	54 Gy; 3 fx 50 Gy; 5 fx 45 Gy; 3 fx	Mixed-5 L-95	1y and 3y OS, CSS, LC, RC, and DC. Follow-up at 50 months.
Varlotto et al.[25]	RS PSM	T1/2N0M0	77	77	48-60 Gy 3-5 fx	Mixed-7 L-93	1y 3y, and 5y OS, LC, RC, and DC. Follow-up at 19 and 30 months.
Verstegen et al.[26]	RS PSM	T1-3N0M0	64	64	54-60 Gy 3-12 fx	L-100	1y and 3y OS, LC, RC, PFS, and DC. Follow-up at 16 and 30 months.
Matsuo et al.[27]	RS PSM	T1/2aN0M0	53	53	48 Gy;4fx 60 Gy; 8 fx	SL-100	1y, 3y, and 5y OS, CSS, LC, RC, and DC. Follow-up at 64 and 80 months.
Crabtree et al.[28]	RS PSM	T1/2aN0M0	56	56	45 Gy; 5 fx 48 Gy; 4 fx 50 Gy; 5 fx 60 Gy; 5 fx	Mixed-22 L- 78	1y and 3y OS, LC, RC, PFS, and DC. Follow-up at 23 and 50 months.
Shirvani et al.[30]	RS PSM	T1/2bN0M0	251 53	251 53	NR	L-100 SL-100	1y, 2y, and 3y OS and CSS
Puri et al.[23]	RS PSM	T1/2N0M0	5,355	5,355	54 Gy; 3 fx	SL-100	3y and 5y OS and CSS. Follow-up at 17 and 28 months.
Hamaji et al.[31]	RS PSM	T1/2aN0M0	41	41	48 Gy; 4 fx	L-100	1y, 3y, and 5y OS, CSS, LC, RC, PFS and DC. Follow-up at 41 and 54 months.
Kastelijn et al.[32]	RS PSM	T1-3N0M0	53	175	54 Gy; 3 fx 60 Gy; 5 fx 60 Gy; 8 fx	Mixed-20 L-80	1y, 3y, and 5y OS, CSS, LRC, and RFS. Follow-up at 39 months
Chang et al.[9]	RCT	T1/2aN0M0	31	27	54-60 Gy; 3-5 fx	L-100	1y and 3y OS, LC, RC, PFS, and DC.
Ezer et al.[33]	RS PSM	T1/2N0M0	362	1,881	BED > 100 Gy10	SL-100	1y and 3y OS and CSS. Follow-up at 27 and 38 months.
Mokhles et al.[34]	RS PSM	T1/2aN0M0	73	73	54-60Gy 3-8fx	L-100	1y, 3y, and 5y OS, CSS, LRC, and RFS. Follow-up at 36 and 49 months
Smith et al.[35]	RS PSM	T1/2aN0M0	300 243	L-300 SL-243	NR	L-100 SL-100	1y and 3y OS and CSS. Follow-up at 44 and 49 months.
van der Berg et al.[36]	RS APC	T1/2aN0M0	197	143	60 Gy; 3-8 fx	Mixed-100	1y, 3y, and 5y OS, CSS, LRC, and RFS. Follow-up at 60 months.
Wang et al.[37]	RS PSM	T1N0M0	35	35	54-60 Gy; 3-8 fx	Mixed-40 L-60	1y, 3y, and 5y OS, CSS, LRC, and RFS.
Paul et al.[38]	RS PSM	T1/2N0M0	201	201	NR	SL-100	1y, 3y, and 5y OS, CSS, LRC, and RFS. Follow-up at 35 months.
Eba et al.[39]	RS PSM	T1N0M0	21	21	48 Gy;4 fx	L-100	1y, 3y, and 5y OS.

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Table S1. Characteristics of the studies included in the present meta-analysis. (Continued...)

Study	Study design	Clinical stage	Patients		SBRT dose	Type of surgery-%	Outcome
			SBRT	Surgery			
Rosen et al.[40]	RS PSM	T1/2aN0M0	1,781	1,781		L-100	1y, 3y, and 5y OS. Follow-up at 29 and 32 months.
Yerokun et al.[41]	RS PSM	T1N0M0	1,584	1,584	NR	SL-100	1y, 3y, and 5y OS. Follow-up at 30 months.
Miyazaki et al.[42]	RS PSM	T1N0M0	27	27	48 Gy; 4 fx 60 Gy; 10 fx	Mixed-100	1y, 3y and 5y OS and CSS.
Albano et al.[43]	RS PSM	T1-3N0M0	48	64	48 Gy; 4 fx	L-100	1y, 3y and 5y OS and LC.
Cornwell et al.[44]	RS PSM	T1/2aN0M0	37	37	BED > 100	L-100	1y, 3y, and 5y OS, CSS, LRC, and RFS. Follow-up at 44 months.
Boyer et al.[29]	RS PSM	Stage I	400	400	NR	L-100	2y, 4y, 6y, 8y, and 10y OS and CSS
Bryant et al.[45]	RS	T1/2aN0M0	449	L-2,986 SL-634	BED > 100	L-100 SL-100	1y and 3y OS and CSS. Follow-up at 31 months.
Dong et al.[46]	RS PSM	T1/2aN0MO	66	66	BED > 100	Mixed	1y and 3y OS, CSS, and LRC.
Lin et al.[47]	RS PSM	T1/2aN0MO	45	45	NR	L-100	1y and 3y OS, CSS, and LRC.

SBRT: stereotactic body radiotherapy; RS: retrospective; fx: fraction; SL: sublobar resection; y: year; OS: overall survival; LC: local control; CSS: cancer-specific survival; PSM: propensity score matching; L: lobectomy; NR: not reported; RC: regional control; DC: disease control; PFS: progression-free survival; LRC: locoregional control; RFS: relapse-free survival;: RCT: randomized controlled trial; BED: biological effective dose; and APC: adjustment for prognostic covariates.

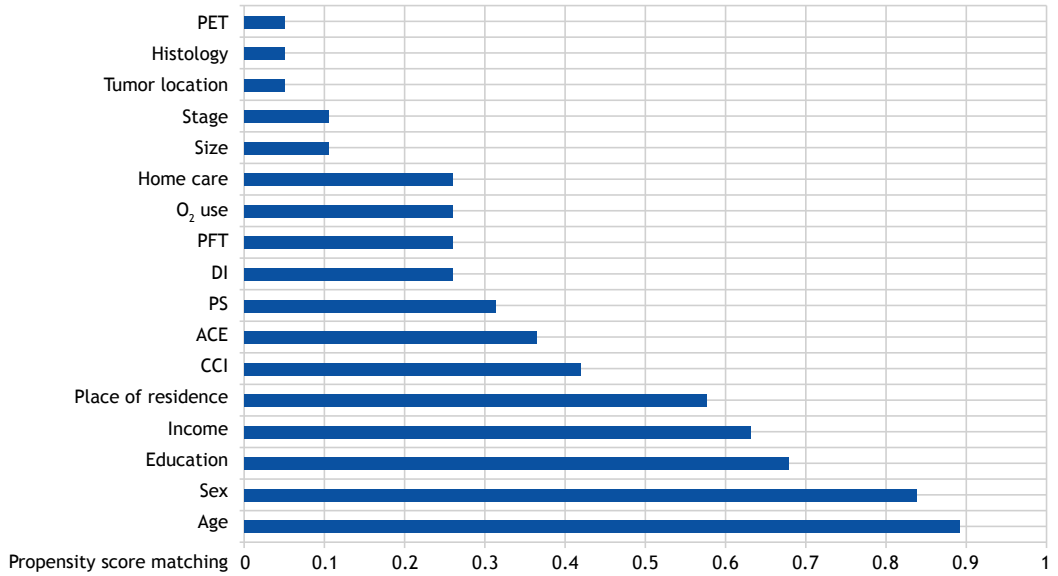

Figure S2. Description of the proportion of all covariates used in the studies to generate propensity score matching models. PFT: pulmonary function test; DI: diabetes; PS: performance status; ACE: Adult Comorbidity Evaluation; and CCI:. Charlson Comorbidity Index.

Table S2. Summary of previous meta-analyses in the literature and of the present meta-analysis.

Meta-analysis	Studies included and sample size	Outcomes evaluated	Publication bias Heterogeneity/outcomes	Conclusion
Zhang et al.[13]	6 retrospective studies (PSM) 864 patients SBRT (n = 432) Surgery (n = 432)	LC, OS, CSS, and DC at 1 and 3 years	No publication bias No significant difference in 1-year OS; significant differences in favor of surgery group in 3-year OS	Patients with early stage NSCLC treated with SBRT had DFS, LC, and DC similar to those of patients treated with surgery, but worse 3-year OS on a matched-pair analysis
Wen et al.[11]	11 retrospective studies 3,124 patients matched SBRT (n = 1,087) Surgery (n = 2,037)	LC, RC, OS, CSS, PFS, and DC, without time specification	Not evaluated OS was significantly higher in the surgery group, but there were no significant differences in LC and CSS between the groups	Treatment for early-stage NSCLC should be personalized
Li et al.[12]	15 retrospective studies and randomized trials 7,089 patients SBRT (n = 2,986) Surgery (n = 4,894)	LC, RC, OS, CSS, PFS, and DC at 5 years	No publication bias OS and RFS were significantly higher in the surgery group, unlike LC and DC	Patients with T1-3N0M0 NSCLC should preferably be treated by surgery prior to SBRT/SABR
Chen et al.[10]	16 retrospective studies and randomized trials 19,882 patients SBRT (n = 9,941) Surgery (n = 9,941)	OS and CSS	Publication bias OS was significantly higher in the surgery group (highly heterogenous); no differences in CSS between the groups	Surgery produces better survival with similar CSS when compared with SBRT
Cao et al.[14]	23 retrospective studies 17,888 patients SBRT (n = 8,946) Surgery (n = 8,942)	LC, OS, CSS, and PFS at 3 years	Not evaluated High heterogeneity for OS and CSS No subgroup analysis without heterogeneity	Surgery is superior to SBRT in terms of mid- and long-term clinical outcomes
Present meta-analysis	30 retrospective studies and randomized clinical trials 29,511 patients SBRT (n =12.365) Surgery (n = 17.146)	LC, OS, and CSS at 3 years	Publication bias for OS in favor of surgery, but not for CSS High heterogeneity for OS and CSS, but none in the subgroup analyses	3y OS was significantly higher in the surgery group, but influenced by significant publication bias and heterogeneity. Subgroup analysis showed no difference for 3y CSS regarding sublobar resection or T1N0 patients

PSM: propensity score matching; SBRT: stereotactic body radiotherapy; LC: local control; OS: overall survival; CSS: cancer-specific survival; DC: disease control; NSCLC: non-small cell lung cancer; DFS: disease-free survival; RC: regional control; PFS: progression-free survival; RFS: relapse-free survival; and SABR: stereotactic ablative body radiotherapy.

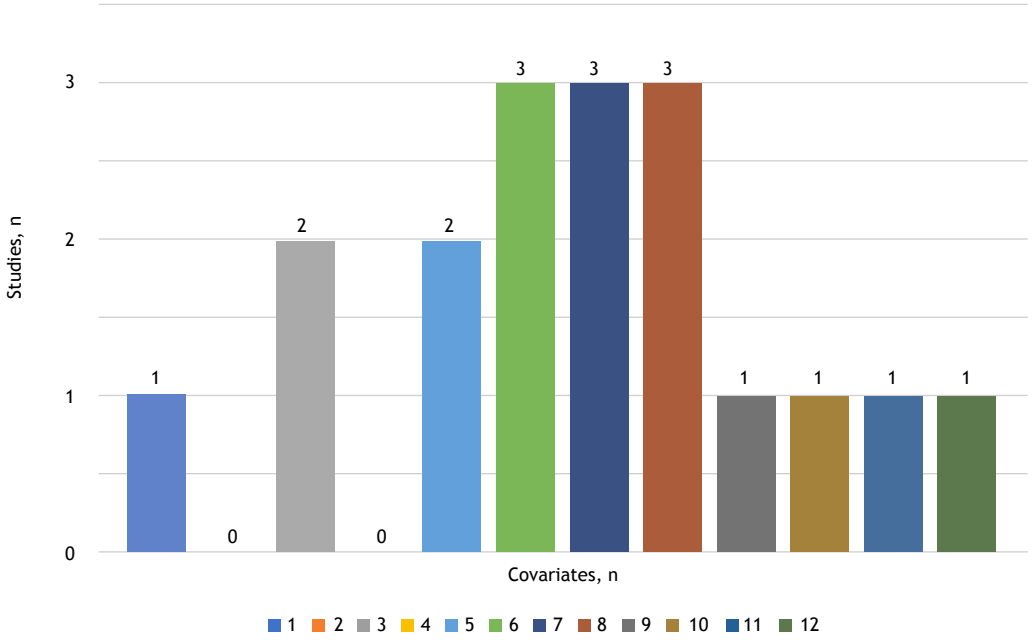

Figure S3. Number of covariates used in propensity score matching model per number of studies included in the meta-analysis.

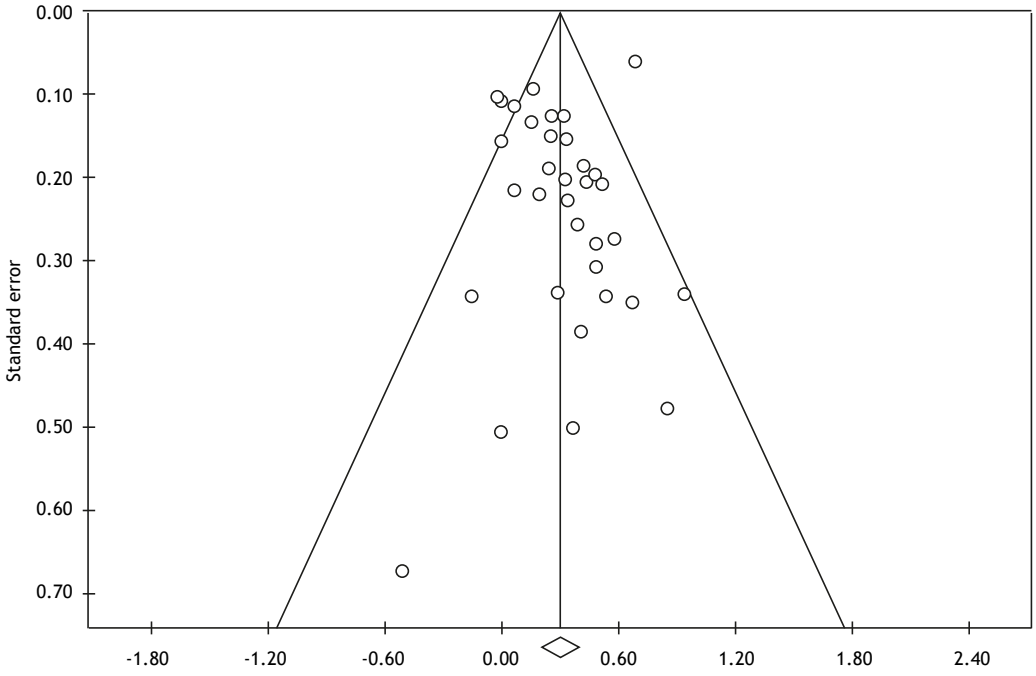

Figure S4. Funnel plot of publication bias for three-year overall survival.