JAMA Oncology | Original Investigation

Safety and Survival Rates Associated With Ablative Stereotactic Radiotherapy for Patients With Oligometastatic Cancer
A Systematic Review and Meta-analysis

Eric J. Lehrer, MD, MS; Raj Singh, MD; Ming Wang, MS, PhD; Vernon M. Chinchilli, PhD; Daniel M. Trifiletti, MD; Piet Ost, MD, PhD; Shankar Siva, PhD, MBBS; Mao-bin Meng, MD, PhD; Leila Tchelebi, MD; Nicholas G. Zaorsky, MD, MS

IMPORTANCE The oligometastatic paradigm postulates that patients with a limited number of metastases can be treated with ablative local therapy to each site of disease with curative intent. Stereotactic ablative radiotherapy (SABR) is a radiation technique that has become widely used in this setting. However, prospective data are limited and are mainly from single institutional studies.

OBJECTIVE To conduct a meta-analysis to characterize the safety and clinical benefit of SABR in oligometastatic cancer.

DATA SOURCES A comprehensive search was conducted in PubMed/MEDLINE, Embase, Cochrane Database of Systematic Reviews, and Cumulative Index to Nursing and Allied Health Literature on December 23, 2019, that included prospective clinical trials and review articles that were published within the past 15 years.

STUDY SELECTION Inclusion criteria were single-arm or multiarm prospective trials including patients with oligometastatic cancer (ie, ≤5 sites of extracranial disease), and SABR was administered in less than or equal to 8 fractions with greater than or equal to 5 Gy/fraction.

DATA EXTRACTION AND SYNTHESIS The Population, Intervention, Control, Outcomes and Study Design; Preferred Reporting Items for Systematic Reviews and Meta-analyses; and Meta-analysis of Observational Studies in Epidemiology methods were used to identify eligible studies. Study eligibility and data extraction were reviewed by 3 authors independently. Random-effects meta-analyses using the Knapp-Hartung correction, arcsine transformation, and restricted maximum likelihood method were conducted.

MAIN OUTCOMES AND MEASURES Safety (acute and late grade 3-5 toxic effects) and clinical benefit (1-year local control, 1-year overall survival, and 1-year progression-free survival).

RESULTS Twenty-one studies comprising 943 patients and 1290 oligometastases were included. Median age was 63.8 years (interquartile range, 59.6-66.1 years) and median follow-up was 16.9 months (interquartile range, 13.7-24.5 months). The most common primary sites were prostate (22.9%), colorectal (16.6%), breast (13.1%), and lung (12.8%). The estimate for acute grade 3 to 5 toxic effect rates under the random-effects models was 1.2% (95% CI, 0%-3.8%; I^2 = 50%; 95% CI, 3%-74%; and τ = 0.20%; 95% CI, 0.00%-1.43%), and the estimate for late grade 3 to 5 toxic effects was 1.7% (95% CI, 0.2%-4.6%; I^2 = 54%; 95% CI, 11%-76%; and τ = 0.25%; 0.01%-1.00%). The random-effects estimate for 1-year local control was 94.7% (95% CI, 88.6%-98.6%; I^2 = 90%; 95% CI, 86%-94%; and τ = 0.81%; 95% CI, 0.36%-2.38%]). The estimate for 1-year overall survival was 85.4% (95% CI, 77.1%-92.0%; I^2 = 82%; 95% CI, 71%-88%; and τ = 0.72%; 95% CI, 0.30%-2.09%) and 51.4% (95% CI, 42.7%-60.1%; I^2 = 58%; 95% CI, 17%-78%; and τ = 0.20%; 95% CI, 0.02%-1.21%) for 1-year progression-free survival.

CONCLUSIONS AND RELEVANCE In this meta-analysis, SABR appears to be relatively safe in patients with oligometastatic cancer with clinically acceptable rates of acute and late grade 3 to 5 toxic effects less than 13% and with clinically acceptable rates of 1-year local control overall survival, and progression-free survival. These findings are hypothesis generating and require validation by ongoing and planned prospective clinical trials.

JAMA Oncol. doi:10.1001/jamaoncol.2020.6146
Published online November 25, 2020.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Authors: Nicholas G. Zaorsky, MD, MS, Department of Radiation Oncology, Penn State Cancer Institute, 500 University Dr, Hershey, PA 17033 (nicholaszaorsky@gmail.com); Eric J. Lehrer, MD, MS, Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Pl, Box 1236, New York, NY 10029 (eric.lehrer@mountsinai.org).

Local therapies have previously had limited utility in the context of metastatic cancer owing to an inability to account for radiologically occult sites of disease. The traditional treatment of patients with metastatic solid tumors involved the use of systemic therapies with the goal of delaying disease progression and extending overall survival (OS).[1,2] In 1995, Hellman and Weichselbaum[3] at the University of Chicago formally defined the oligometastatic paradigm. This paradigm suggests that in certain tumors, anatomic and physiologic factors may limit and concentrate the number of metastases to single or few organs. This concept has been recently expanded in the context of patients with synchronous oligometastatic disease or those with oligoprogressive cancer (defined as patients with the majority of the disease being stable or responding to therapy with a limited number of sites exhibiting progression).[4] Subsequent work building on this hypothesis has found that distinct molecular subgroups exist that, in combination with clinical risk factors, define subpopulations who may preferentially benefit from aggressive local therapy and potentially delay tumor seeding of other sites and the development of more aggressive phenotypes.[5]

Stereotactic ablative radiotherapy (SABR) involves the delivery of a high dose of radiation in a highly conformal manner.[6] SABR is a noninvasive local therapy that is frequently used to target tumors in a variety of sites, such as the brain, lungs, liver, and bone. Should critical healthy tissues be adjacent to lesions being considered for local therapy, more protracted hypofractionated courses may be used to minimize the risk of potential toxic effects. In the context of oligometastatic cancer, SABR presents a novel opportunity for aggressive therapy for select patients with the potential for durable disease control without delaying systemic therapy given the minimal number of toxic effects with SABR. The low rates of toxic effects reported with SABR are notable thus far given the necessity of recognizing the importance of quality of life in the context of patients with limited life expectancy. Worldwide, the use of SABR is increasing[7,8]; in addition, combining SABR with newer systemic therapies (eg, immune checkpoint inhibitors) in the setting of oligometastatic cancer has become more widely adopted.[9-12]

Many studies have explored the role of SABR in the management of oligometastatic cancer.[13-33] Although these studies are prospective, they are largely single institutional trials and consist of many different types of histologic cancers and treatment sites, which may result in inherent selection bias. As a result, it is difficult to integrate these studies into clinical practice. Therefore, our aim in this study was to better characterize the safety and clinical benefit of SABR by pooling published prospective studies in which patients received SABR in the management of oligometastatic cancer via a meta-analysis to aid clinical decision-making. We hypothesized that SABR is safe and clinically beneficial when used in the setting of oligometastatic cancer.

Key Points

Question Is stereotactic ablative radiotherapy safe and clinically beneficial in the management of oligometastatic cancer?

Findings This meta-analysis of 21 trials comprising 943 patients and 1290 oligometastases found that stereotactic ablative radiotherapy was associated with rates of clinically significant acute and late toxic effects of less than 13% and with clinically acceptable rates of 1-year local control overall survival, and progression-free survival. These findings were noted among a heterogeneous group of patients treated in prospective trials.

Meaning The findings of this study suggest that stereotactic ablative radiotherapy is generally safe and well tolerated in the oligometastatic setting and remains a viable treatment option in appropriately selected patients; further study addressing sources of heterogeneity is warranted.

Methods

Evidence Acquisition

The Population, Intervention, Control, Outcomes and Study Design method was used to define literature inclusion criteria (eTable 1 in the Supplement).[34-36] The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline was used.[37] In addition, the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline was used.[38] A comprehensive search was conducted in PubMed/MEDLINE, Embase, Cochrane Database of Systematic Reviews, and Cumulative Index to Nursing and Allied Health Literature on December 23, 2019, which included prospective clinical trials and review articles that were published within the past 15 years. The search strategy applied was *oligometastatic* or *oligometastases* and *prospective* and *radiation* and *stereotactic*, which was used by 3 of us (E.J.L., R.S., and N.G.Z.) independently across the databases. In addition, references in review articles were closely examined for possible inclusion of studies into the meta-analysis. The results of a search of ClinicalTrials.gov is presented in eTable 2 in the Supplement.

Inclusion criteria included prospective trials with (1) patients with oligometastatic cancer (defined as ≤5 extracranial metastases), (2) multiarm or single-arm prospective clinical trial, (3) all patients in a treatment arm underwent SABR (defined as ≤8 fractions with ≥5 Gy/fraction), and (4) at least the primary outcome measure (grade 3-5 acute/late toxic effects) or at least 1 of the secondary outcome measures (1-year local control [LC], 1-year OS, or 1-year progression-free survival [PFS]) was reported. Exclusion criteria included (1) retrospective study design, (2) studies involving nonhuman subjects, (3) works not published in English, and (4) unfinished documents.

Centre for Evidence-Based Medicine levels of evidence were assigned next to each of the included studies.[39] **Table 1** depicts treatment and patient characteristics,[13-33] and **Table 2** presents outcomes of the studies.[13-19,21-33]

Outcome Measures and Data Extraction

The primary outcome measure was the incidence of grade 3 to 5 acute and late toxic effects. The secondary outcome measures were 1-year LC, 1-year OS, and 1-year PFS.

Data extraction was conducted and reviewed by 2 of us independently (E.J.L. and R.S.) and discussed with another of us (N.G.Z.). Data regarding outcome measures, as well as patient, study, histologic details, and treatment characteristics

Table 1. Patient and Study Characteristics

Source	CEBM level	No. (patients/lesions)	Age, median (range), y	Most common primary sites (No. of patients)	Treated sites (No. of lesions)	Treatment planning	No. of metastases	Follow-up, median (range)	LC/LPFS (95% CI)	PFS (95% CI)	OS (95% CI)	Grade 3-5 toxic effects
Sutera et al,[31] 2019	2b	147 (218)	66.4 (IQR, 59.9-74.6)	Lung (32), colon (31), head and neck (11), breast (13), prostate (11), kidney (8), esophagus (7), uterus (5), ovaries (5), bladder (5)	Lung (114), lymph nodes (36), bone (32), liver (15), adrenal (8), hilar mass (5), pelvic mass (3), head and neck (2), brain (2)	Median dose: 48 Gy (IQR, 41 Gy-54 Gy)	1-5	41.3 mo (IQR, 14.6 mo-59.0 mo)	1-y LPFS: 91%	Median PFS: 8.7 mo (6.6 mo-13.1 mo)	Median OS: 42.3 mo (27.4 mo-∞)	Acute: 2%
						Median fractions: 4 (IQR, 3-5)			5-y LPFS: 74%	1-y PFS: 44%	1-y OS: 84%	Late: 1.4%
						Median dose/fraction: 12 Gy (IQR, 9 Gy-12 Gy)				5-y PFS: 17%	5-y OS: 43%	
Salama et al,[28] 2012	2b	61 (113)	64.4	Lung (16), head and neck (5), breast (7), colorectal (6), renal (8), sarcoma (3), ovary (3), parotid (2), skin (2), small bowel (3), Ewing sarcoma (1), gallbladder (1), pituitary (1), thyroid (2), uterus (1)	Lung (41), lymph nodes (22), liver (22), bone (15), adrenal (9), soft tissue (3), pancreas (1)	Starting dose: 24 Gy/3 fractions; gradually escalated to 60 Gy/3 fractions	1-5	27.6 mo (0.2 mo-111.6 mo)	1-y LC: 7.2% (57.2%-76.1%)	1-y PFS: 33.3% (22.8%-46.1%)	1-y OS: 81.5% (71.1%-91.1%)	Acute: 3.3%
									2-y LC: 52.7% (41.1%-64.4%)	2-y PFS: 22.0% (12.8%-34.4%)	2-y OS: 56.7% (43.9%-68.9%)	Late: 9.8%
Nuyttens et al,[22] 2015	2b	30 (57)	66 (44-78)	Colorectal (19), breast (2), lung (2), melanoma (2), sarcoma (2), bladder (1), cervix (1), endometrial (1)	Lung (57)	Large peripheral: 60 Gy/3 fractions	1-5	36 mo (4 mo-60 mo)	1-y LC: 79% (80% CI: 67%-87%)	NR	1-y OS: 93.6%	Late: 10%
						Small peripheral: 30 Gy/1 fraction					2-y OS: 63% (43%-78%)	
						Central: 60 Gy/5 fractions					4-y OS: 38% (20%-56%)	
Iyengar et al,[18] 2018	1b	Systemic therapy (15) vs SABR and adjuvant chemotherapy (14; 31 lesions)	63.5 (51-78)	NSCLC (29)	Lung (17), mediastinum (4), liver (2), axilla (2), nasopharynx (1), adrenal (3)	1 fraction: 16-24 Gy, 3 fractions: 26.5-33 Gy, 5 fractions: 30-37.5 Gy	1-4	9.6 mo (2.4 mo-30.2 mo)	NR	Median PFS (SABR): 9.7 mo	Median OS (chemotherapy alone): 17 mo	Acute and late: 0%
										1-y PFS: 38.3%	Median OS (SABR): not reached	
										Median PFS (chemotherapy alone): 3.5 mo		

(continued)

Table 1. Patient and Study Characteristics (continued)

Source	CEBM level	No. (patients/lesions)	Age, median (range), y	Most common primary sites (No. of patients)	Treated sites (No. of lesions)	Treatment planning	No. of metastases	Follow-up, median (range)	LC/LPFS (95% CI)	PFS (95% CI)	OS (95% CI)	Grade 3-5 toxic effects
Iyengar et al,[17] 2014	2b	24 (52)	67 (56-86)	NSCLC (24)	Lung (18), mediastinum/hilum (13), adrenal (13), bone/spine/chest wall (13), liver/paracaval lymph nodes (8), nonmediastinal lymph nodes (5), kidney (1)	1 fraction: 19-24 Gy, 3 fractions: 27-33 Gy, 5 fractions: 35-40 Gy	1-6	11.6 mo	93.6% LC rate at last follow-up	Median PFS: 14.7 mo 1-y PFS: 53.6%	Median OS: 20.4 mo 1-y OS: 67.2%	Acute and late: 8.33%-16.66% (2 reported toxic effects with possible relation to SABR)[a]
Rusthoven et al,[26] 2009	2b	38 (63)	58 (29.9-83.3)	Colorectal (9), sarcoma (7), HCC (7), lung (5), melanoma (3), head and neck (3), breast (2), other (2)	Lung (63)	Phase I: dose escalation from 48-60 Gy/3 fractions	1-3 Lung	15.4 mo (6 mo-48 mo)	1-y LC: 100%	Median PFS: 8.4 mo	Median OS: 19 mo	Acute: 2.6%
						Phase II: 60 Gy/3 fractions			2-y LC: 96%		1-y OS: 65.9% 2-y OS: 39%	Late: 5.3%
Rusthoven et al,[27] 2009	2b	47 (63)	58.4 (26.6-91.5)	Colorectal (15), lung (10), breast (4), ovarian (3), esophageal (3), HCC (2), other (10)	Liver (63)	Phase I: dose escalation from 36-60 Gy/3 fractions	1-3 Liver	16 mo (6 mo-54 mo)	1-y LC: 95% (83.2%-98.9%)	Median PFS: 6.1 mo	Median OS: 20.5 mo	Acute: 0%
						Phase II: 60 Gy/3 fractions			2-y LC: 92% (76%-97.4%)		1-y OS: 67.2% 2-y OS: 30% (15.1%-47.2%)	Late: 2%
Wang et al,[32] 2012	2b	149 (166)	58 (20-88)	Renal (47), sarcoma (17), breast (15), NSCLC (15), thyroid (14), colon (6), melanoma (4), other (28), unknown (3)	Spine (166)	27-30 Gy/3 fractions (most common regimen)	1-2 Spinal	15.9 mo (IQR, 1.0 mo-91.6 mo)	1-y LC: 80.5% (72.9%-86.1%)	NR	Median OS: 23 mo (18.6 mo-27.2 mo)	8%[a]
									2-y LC: 72.4% (63.1%-79.7%)		1-y OS: 71.9% 2-y OS: 48.8%	
Scorsetti et al,[29] 2015	2b	42 (52)	Mean: 67 (43-87)	Colon (30), rectum (12)	Liver (52)	75 Gy/3 fractions	1-3 Liver	24 mo (4 mo-47 mo)	1-y LC: 95% (89%-100%)	Median PFS: 12 mo	Median OS: 29.2 mo	Acute and late: 0%
									2-y LC: 91% (82%-99%)	1-y PFS: 50.3%	1-y OS: 81.1%	
									3-y LC: 85% (73%-97%)	2-y PFS: 48% (32%-64%)	2-y OS: 65% (50%-80%)	

(continued)

Table 1. Patient and Study Characteristics (continued)

Source	CEBM level	No. (patients/lesions)	Age, median (range), y	Most common primary sites (No. of patients)	Treated sites (No. of lesions)	Treatment planning	No. of metastases	Follow-up, median (range)	LC/LPFS (95% CI)	PFS (95% CI)	OS (95% CI)	Grade 3-5 toxic effects
Garg et al,[15] 2012	2b	61 (63)	60 (34-78)	Renal (33), thyroid (10), sarcoma (6), breast (5), lung (3), other (6)	Spine (63)	16-24 Gy/1 fraction	1-2 Spinal	17.8 mo (1.2 mo-52.1 mo)	1-y LC: 91% 18-mo LC: 88%	NR	Median OS: 30 mo 1-y OS: 80.4% 18-mo OS: 64%	3.3%[a]
Chang et al,[14] 2004	2b	15 (19)	50 (18-75)	Renal (6), sarcoma (2), breast (2), thymoma (1), plasmacytoma (1), adenoid cystic (1), NSCLC (1), basal cell (1)	Spine (19)	30 Gy/5 fractions	1-2 Spinal	9 mo (6 mo-16 mo)	NR	NR	NR	Acute and late: 0%
Méndez Romero et al,[19] 2006	2b	17 (34)	63 (37-81)	Colorectal (14), carcinoid (1), breast (1), lung (1)	Liver (34)	30-37.5 Gy/3 fractions	1-4 Liver	12.9 mo (0.5 mo-31 mo)	1-y LC: 100% 2-y LC: 86%	NR	1-y OS: 85% 2-y OS: 62%	Acute: 12% Late: 6%
Milano et al,[20] 2009	2b	40 (curative intent)	48 (36-70)	Breast (40)	Liver (14), lung (12), bone (11), thoracic lymph nodes (9), pelvic or abdominal lymph nodes (2)	NR	1-5	NR	4-y LC: 89%	Median PFS: 23 mo 1-y PFS: 68.8% 2-y PFS: 44% 4-y PFS: 38%	Median OS: not reached 1-y OS: 92.7% 2-y OS: 76% 4-y OS: 59%	NR
Pasqualetti et al,[25] 2018	2b	51 (78)	NR	Prostate (51)	Lymph nodes (46), bone (32)	24 Gy/1 fraction (28 lesions), 27 Gy/3 fractions (50 lesions)	1-5	18.5 mo (3-103)	1-y LC: 98.7% 2-y LC: 97.4%	NR	NR	2%[a]
Ahmed et al,[13] 2013	2b	17 (21)	65 (50.6-79.7)	Prostate (17)	Bone (19), liver (1), lymph nodes (1)	Most common regimen: 20 Gy/1 fraction, dose range: 8-24 Gy; fraction range: 1-3	1-5	6 mo (2 mo-24 mo)	6-mo LC: 100%	NR	NR	Acute and late: 0%
Henke et al,[16] 2018	2b	11	64 (48-79)	Colorectal (4), NSCLC (2), HCC (1), NR (4)	Liver (5), adrenal gland (2), para-aortic lymph nodes (3)	Most common regimen: 50 Gy/5 fractions	1-3	15 mo (4 mo-22 mo)	3-mo LPFS: 95% 6-mo LPFS: 89.1%	1-y PFS: 45%	1-y OS: 91%	Acute and late: 0%

(continued)

Table 1. Patient and Study Characteristics (continued)

Source	CEBM level	No. (patients/lesions)	Age, median (range), y	Most common primary sites (No. of patients)	Treated sites (No. of lesions)	Treatment planning	No. of metastases	Follow-up, median (range)	LC/LPFS (95% CI)	PFS (95% CI)	OS (95% CI)	Grade 3-5 toxic effects
Siva et al,[30] 2018	2b	33 (50)	70 (IQR, 67-75)	Prostate (33)	Bone (21), lymph nodes (12)	20 Gy/1 fraction	1-3	24 mo	1-y LPFS: 97% (91%-100%)	1-y PFS: 58% (43%-77%)	1-y OS: 100% (no deaths)	3%[a]
									2-y LPFS: 93% (84%-100%)	2-y PFS: 39% (25%-60%)		
Muacevic et al,[21] 2013	2b	40 (64)	66 (47-81)	Prostate (40)	Bone (64)	20.2 Gy/1 fraction (range: 16.5-22 Gy) (all 1 fraction)	1-2	Mean: 14 mo (3 mo-48 mo)	6-mo, 1-y, and 2-y LC: 95.5% (83%-98.8%)	NR	NR	NR
Ost et al,[23] 2018	1b	ADT alone (31) vs SABR and ADT (25)	60.8 (43-75)	Prostate (62)	Nodal (13 treated), distant metastasis (12 treated)	30 Gy/3 fractions	1-3	3-y (IQR, 2.3 y-3.8 y)	1-y LC: 100%	1-y PFS: 48% (28%-78%)	1-y OS: 100%	Acute and late: 0%
Palma et al,[24] 2019	1b	SABR: 66 (127) vs systemic therapy and palliative RT: 33	Standard of care: 69 (64-75), SABR: 67 (59-74)	SABR group: breast (13), colorectal (9), lung (12), prostate (14), other (18)	Adrenal (7), bone (45), liver (16), lung (55), other (4)	Allowable doses: 36-60 Gy/3-8 fractions, 16-24; Gy/1 fraction allowed for spinal or brain metastases	1-5	Standard of care: 25 mo (IQR, 19 mo-54 mo)	Standard of care: 49% with LC at last follow-up	Standard of care: 1-y PFS: 22.3%	Standard of care: 1-y OS: 87.6%	10.6%[a]
								SABR: 26 mo (IQR, 23 mo-27 mo; P = .09)	SABR: 75% with LC at last follow-up (P = .001)	SABR: 1-y PFS: 53%	SABR: 1-y OS: 84.1%	
David et al,[33] 2020	2b	15 (19)	63 (43-71)	Breast (15)	Bone (10), spine (9)	20 Gy/1 fraction (1 patient received 28 Gy in 2 fractions)	1-2	24 mo	1-y LPFS: 100%	1-y PFS: 80% (62%-100%)	NR	Acute: 20%
												Late: NR

Abbreviations: ADT, androgen deprivation therapy; CEBM, Centre for Evidence-Based Medicine; DFS, disease-free survival; HCC, hepatocellular carcinoma; IQR, interquartile range; LC, local control; LPFS, local progression-free survival; NA, not applicable; NR, not reported; NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; SABR, stereotactic ablative radiation.

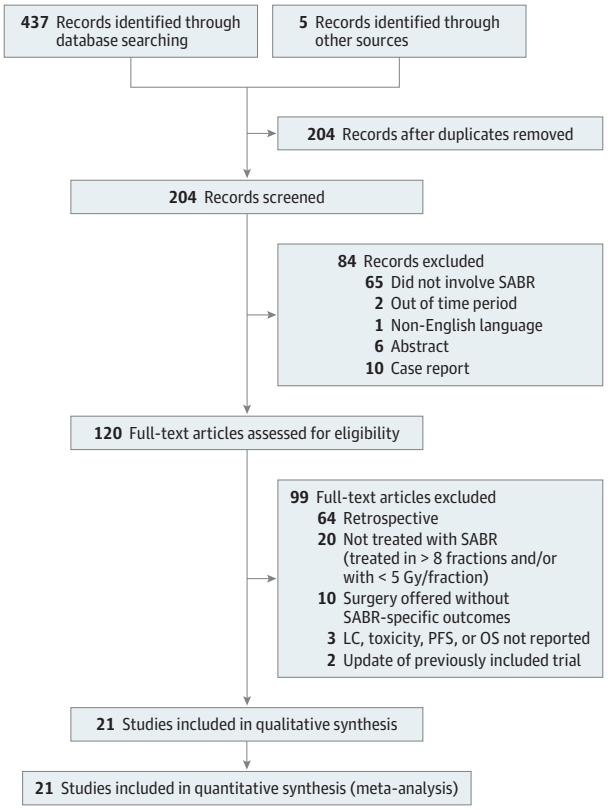
[a] Studies excluded from acute and late toxic effects analysis as they reported nonzero toxic effects that were not segmented into acute or late events.

Table 2. Details of Toxic Effects and Systemic Therapy

Source	Systemic therapy	Toxic effect details
Sutera et al,[31] 2019	All following SABR: 46.9% (chemotherapy), 12.2% (targeted therapies), 12.2% (immunotherapy)	Acute grade 3-5: dyspnea (1), dermatitis (1), anemia (1); late grade 3: ureter obstruction (1) Late grade 4: bowel obstruction (1) Improvement in QoL at 6 and 12 mo post-SABR (SS)
Salama et al,[28] 2012	80.3% Received systemic therapy before enrollment	Acute grade 3: 30 Gy to 2 liver lesions: nausea/vomiting after first SABR fraction requiring hospitalization and intravenous fluids; received prophylactic ondansetron and dexamethasone pre-SABR and post-SABR, intravenous prochlorperazine and 1 L of NS 42 Gy to 2 right lung lesions: fatigue resulting in decreased performance of ADLs 1 wk post-SABR and lasting for 4 d; fatigue resolved 2 wk post-SABR Late grade 3: 24 Gy to 3 para-aortic lymph nodes: GI bleed requiring hospitalization, blood transfusion, and laser coagulation 3 mo post-SABR 36 Gy to L4: neuritis developed requiring gabapentin and corticosteroid injections 1 mo after completing SABR and an L4 compression fracture 30 mo after completing SABR 36 Gy to right adrenal gland: partial adrenal insufficiency 31 mo post-SABR; the left adrenal gland was resected during previous radical nephrectomy; endocrinology service attributed the insufficiency to radiotherapy or a recent cortisone injection for arthritis with resultant transient adrenal suppression 42 Gy to right lung: radiation pneumonitis requiring supplemental oxygen and corticosteroids 24 Gy to right lung: late neuritis requiring nerve block after treatment of lesion adjacent to the thoracic spine (patient had thoracoscopy pain before radiotherapy) Possible grade 3 hepatic dysfunction 30 Gy to 3 liver metastases: patient with history of mild alcoholic cirrhosis; 1 lesion progressed and received RFA and also developed bulky retroperitoneal LAD that required additional radiotherapy. Subsequently developed elevation of LFT results, thrombocytopenia, hypoalbuminemia, ascites, and pericardial effusion. Given positivity of effusion cytology for cancer and inconclusive peritoneal washings, which was scored as disease progression and not toxic effect. 1 patient in 36-Gy cohort who was treated for a centrally located right upper lobe lung metastasis required hospitalization 10 mo post-SABR; bronchoscopy and computed tomography results were suspicious for recurrence; the patient was discharged and died a day later. This outcome was not scored as a grade 5 toxic effect; however, this dose regimen is no longer commonly practiced for central lung tumors because of its association with toxic effects. Rib fracture incidence increased with SABR dose: 0 in 24-Gy or 30-Gy cohorts; 36 Gy (1), 42 Gy (2), 48 Gy (1)
Nuyttens et al,[22] 2015	Chemotherapy was not allowed	Acute grade 3: fatigue (2 had grade 2 fatigue and 1 had grade 3 fatigue before SABR), chest pain (2: 1 had grade 1 chest pain before SABR); dyspnea (4: 1 had grade 1 and another had grade 2 dyspnea before SABR) Late grade 3: pain (1), fatigue (2: 1 had grade 2 fatigue before SABR), pneumonitis (1), rib fracture (3)
Iyengar et al,[18] 2018	4-6 cycles of first-line platinum-based chemotherapy with resultant SD or PR by RECIST	No grade 3 or higher adverse events were attributed to SABR; several grade 5 toxic effects occurred; however, none were attributable to study interventions
Iyengar et al,[17] 2014	Erlotinib; majority received platinum-based chemotherapy; docetaxel and pemetrexed was used in some patients as part of a doublet regimen	Only 2 of 24 grade 3-5 toxic events were definitely attributable to SABR: radiation pneumonitis and vertebral compression fracture; grade 4 hypoxia in 1 patient who died was possibly attributable to SABR The remainder of toxic effects were attributable to systemic therapy or progression of disease
Rusthoven, et al,[26] 2009	Systemic therapy not allowed 14 d before or after SABR	No cases of grade 4 or 5 toxic effects reported; none of the patients who died before the 6-mo follow-up had signs of treatment-related toxic effects Grade 3 pneumonitis in patient with NSCLC presented 7 mo post-SABR with increased dyspnea and oxygen requirements (lung V15 was 15.4 Gy) Left 6th rib fracture in patient with sarcoma 25 mo post-SABR; narcotic pain medications were not needed; the left 6th rib was included in the PTV and received a maximum dose of 76.4 Gy at the fracture site Grade 3 dermatitis in SCC of the base of the tongue 6 wk post-SABR was managed with NSAIDs and improved at 4-mo follow-up; the 30-Gy isodose extended to within 1 mm of the skin surface that corresponded to the area of desquamation

(continued)

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses Flow Diagram



Search methods and screening process used to screen and select eligible articles. There were initially 442 articles screened; 21 articles were eligible for inclusion in the meta-analysis. LC indicates local control; OS, overall survival; PFS, progression-free survival; SABR indicates stereotactic ablative radiotherapy.

were recorded as reported in Table 1 and Table 2. Rates of acute and late grade 3 to 5 toxic effects were largely based on the Radiation Oncology Therapy Group or the Common Terminology Criteria for Adverse Events.[40] In the case of toxic effects, if studies did not separate nonzero toxic effect rates into acute or late events, they were excluded from the analysis. However, if acute and late toxic effect rates were pooled together and reported as being 0, they were included in both the acute and late toxic effect analyses as 0%. When outcome measure rates were not reported in the article text, Kaplan-Meier curves were digitized using Plot Digitizer, version 2.6.8 (SourceForge) to extract the pertinent values at 1 year. This process was performed by 2 of us (E.J.L. and R.S.) independently and discussed with another of us (N.G.Z).

Individual study effect sizes were modeled as proportions in which the denominator was the total number of patients enrolled in the study and the numerator was the number of patients experiencing the particular outcome measure of interest. The numerator was calculated by multiplying the denominator by the percentage of patients experiencing the outcome measure of interest at a prespecified time. For example, if 100 patients were enrolled in a study and the 1-year OS rate was 85%, then the numerator would be 100 multiplied by 85%. For each forest plot, the numerator was rounded to the nearest whole number. Each proportion was then expressed as a percentage by dividing the denominator into the numerator.

Statistical Analysis

Statistical analyses were performed using R Studio, version 1.1.383 (R Foundation for Statistical Computing).[41] The Meta-analysis for R (metafor) package, version 2.4-0[42] and the General Package for Meta-Analysis (meta), version 4.13-0[43] were used to perform the random effects meta-analyses, tests for heterogeneity (I^2 and τ), generation of prediction intervals, generation of funnel plots, and tests for publication bias. The angular transformation was used and a 0.5 continuity correction was applied for studies with an event probability of 0 or 1.[44] In addition, the restricted maximum likelihood method and the Knapp-Hartung adjustment were used.[45] Weighted random-effects models were used to determine an overall summary estimate for each outcome measure and were depicted on a forest plot with its corresponding 95% CI and associated 95% prediction interval (PI). A random-effects approach was chosen over a fixed-effects approach because using random effects is often the preferred technique when performing a meta-analysis to guide patient treatment decisions.[46,47] Forest plots were generated when 3 or more studies were included in each group. The R code used to generate each of these analyses is provided in the eMethods in the Supplement.

Heterogeneity was assessed using the I^2 and τ statistics.[48,49] Although significant heterogeneity was considered present if I^2>50%, there are shortcomings of the I^2 statistic, such as its high sensitivity to individual study sample sizes; therefore, we also provided τ, which is the SD of the random effect, to quantify study heterogeneity, which has been calculated using an arcsine transformation, with the value ranging from 0 to π.[50-52] An inverse transform $(\sin[\tau/2])^2$ was used to express τ as a percentage in the article.

In addition, PIs were included because they are particularly insightful in this setting, with a 95% PI providing a prediction region for a single future study.[52] The presence of publication bias was assessed with the use of funnel plots, and the *t* test was based on weighted linear regression, whereby the null hypothesis was rejected for $P < .05$.[53] The data sets for each outcome measure are provided in eTables 3-7 in the Supplement.

Results

Study Characteristics

Twenty-one prospective trials comprising 943 patients who underwent SABR for the treatment of 1290 oligometastases were included in the meta-analysis (**Figure 1**). The trials were published between 2004 and 2020 as reported in Table 1.[13-33] Patients underwent treatment in the US,[13-18,20,25-28,31,32] Canada,[24] Europe,[19,21-24,29] and Australia.[24,30,33] The median patient age was 63.8 years (interquartile range [IQR], 59.6-66.1 years). Median follow-up was 16.9 months (IQR, 13.7-24.5 months).

Table 2. Details of Toxic Effects and Systemic Therapy (continued)

Source	Systemic therapy	Toxic effect details
Rusthoven, et al,[27] 2009	Systemic therapy not allowed 14 d before or after SABR	No instances of grade 4 or 5 toxic effects None of the 7 patients who died before assessed for local control had any evidence of treatment-related toxic effects 1 Grade 3 soft tissue toxic effect was seen in a patient who required narcotic analgesics, hyperbaric oxygen, and debridement 6 mo after SABR
Wang, et al,[32] 2012	Systemic radiotherapy or chemotherapy allowed within 30 d of SABR; patients receiving bisphosphonates or hormone therapy were excluded	Grade 3: nausea (1), vomiting (1), diarrhea (1), fatigue (1), noncardiac chest pain (3), dysphagia (1), neck pain (1), diaphoresis (1), pain associated with tongue edema and trismus (2) No grade 4 toxic effects were reported and no radiation-related spinal cord myelopathy was observed during the study
Scorsetti et al,[29] 2015	All patients received chemotherapy after diagnosis of metastatic disease; 42% of patients received chemotherapy post-SABR	No grade 3-5 toxic effects were observed
Garg et al,[15] 2012	Patients who received chemotherapy within 30 d of SABR were excluded	Grade 4 toxic effect in a patient who developed hemicord syndrome 11 mo post-SABR requiring use of wheelchair Grade 3 toxic effect in a patient who developed L5 radiculopathy 9 mo post-SABR requiring the use of a cane and pain medication
Chang et al,[14] 2004	Patients who received systemic radiotherapy or chemotherapy within 30 d of SABR were excluded	No neurotoxicity or grade 3-4 toxic effects were observed in any patients
Méndez Romero et al,[19] 2006	NR	Nonclassic radiation-induced liver disease (2) Grade 3 asthenia (1; however, this patient received chemotherapy and surgery before SABR, which may have contributed to his presentation) Grade 3 late GI bleeding event (1)
Milano et al,[20] 2009	90% of patients received chemotherapy and/or hormone therapy prior to trial enrollment; 80% received chemotherapy and/or hormone therapy post-SABR	NR
Pasqualetti et al,[25] 2018	Chemotherapy and/or hormonal therapies were administered post-SABR only after the occurrence of >3 synchronous active lesions	Grade 3 vertebral fracture (1)
Ahmed et al,[13] 2013	Hormone therapy allowed	No grade 3-5 acute or late toxic effects reported
Henke et al,[16] 2018	No systemic therapy allowed within 1 wk of SABR; no investigative agents allowed.	No grade 3-5 acute or late SABR-related toxic effects reported Grade 4 anemia and thrombocytopenia related to receiving full-dose gemcitabine and FOLFIRINOX after completing SABR (2)
Siva et al,[30] 2018	Hormone therapy allowed; previous cytotoxic chemotherapy was an exclusion factor	Grade 3 spinal fracture requiring instrumentation (1)
Muacevic et al,[21] 2013	8% of patients received chemotherapy and 19% received hormone therapy before SABR	Mild nausea following SABR that was treated with oral antiemetics (5), clinically silent rib fracture (1); 1 patient with progressive spinal metastasis developed neurologic deficits
Ost et al,[23] 2018	Patients were ineligible if they experienced a PSA relapse while on hormone therapy, earlier cytotoxic agent for prostate cancer, or treatment within 30 d before SABR with an agent known to influence PSA	No grade 2 or higher toxic effects were observed
Palma et al,[24] 2019	Chemotherapy or targeted therapies were not permitted within 4 wk before SABR but could be resumed after SABR was completed	Grade 5 (3): subdural hematoma after repair of gastric ulcer in a patient with Crohn disease receiving corticosteroid therapy; pulmonary abscess at site of treated lesion 1 y after undergoing SABR, and patient refused treatment; radiation-associated pneumonitis 2 mo after SABR administered to 2 chest lesions, 1 of which was central; unknown if patient had history of interstitial lung disease Grade 3: pain (3) and dyspnea (1)
David et al,[33] 2020	Patients were ineligible if they had previous high-dose radiotherapy administered to an area to be treated, visceral metastases, treatment with cytotoxic chemotherapy within 3 wk of SABR, or evidence of spinal cord compression or spinal instability	Grade 3: ALT level increase (1), anemia (1) Grade 4: obesity (1) Reported in final statistical report

Abbreviations: ADLs, activities of daily living; GI, gastrointestinal; LAD, lymphadenopathy; LFT, liver function test; NS, normal saline; NSAIDs, nonsteroidal anti-inflammatory drugs; NSCLC, non–small cell lung cancer; PR, partial response; PSA, prostate-specific antigen; PTV, planning tumor volume; QoL, quality of life; RECIST, response evaluation criteria in solid tumors; RFA, radiofrequency ablation; SABR, stereotactic ablative radiotherapy; SCC, squamous cell carcinoma; SD, stable disease; SS, statistically significant; V15, volume receiving 15 Gy and higher.

The most common primary sites were the prostate (22.9%), colorectal (16.6%), breast (13.1%), and lung (12.8%). The most frequently treated lesions by SABR site were bone and/or spine (44.8%), lung (29.2%), liver (13.1%), and lymph nodes (12.2%). Of the 21 studies included, 2 solely evaluated non-small cell lung cancer (NSCLC) oligometastases,[17,18] 2 solely evaluated breast cancer oligometastases,[20,33] 5 solely evaluated prostate cancer oligometastases,[13,21,23,25,30] and the remaining 12 trials evaluated multiple tumor histologic characteristics.[14-16,19,22,24,26-29,31,32] The most common definition of acute toxic effects was events occurring within 3 months (range, 3-6 months) of completing radiotherapy.

Acute Grade 3 to 5 Toxic Effects

Twelve studies provided rates of acute grade 3 to 5 toxic effects after SABR.[13,14,16,18,19,23,26-29,31,33] Rates of development of acute grade 3 to 5 toxic effects ranged from 0%[14,16,18,23,27,29] to 20%.[33] Mixed primary tumor histologic findings were evaluated in 8 studies,[14,16,19,26-29,31] prostate cancer oligometastases were evaluated in 2 studies,[13,23] breast cancer oligometastases were solely evaluated in 1 study,[33] and NSCLC oligometastases were solely evaluated in 1 study.[18] **Figure 2**A depicts the forest plot for all 12 studies reporting the incidence of acute grade 3 to 5 toxic effects; the estimated incidence under the random-effects model was 1.2% (95% CI, 0%-3.8%; 95% PI, 0%-10.1%; I^2 = 50%; 95% CI, 3%-74%; and τ = 0.20%; 95% CI, 0.00%-1.43%). Figure 2A also shows the corresponding funnel plot in which the *P* value of the weighted linear regression test was <.001, indicating the presence of publication bias. Forest plots were not generated by histologic characteristics because only 2 studies[13,23] solely evaluated acute grade 3 to 5 toxic effects for prostate cancer oligometastases; both of these trials reported rates of 0%. In addition, only 1 study solely evaluated breast cancer [33] and NSCLC[18] oligometastases and reported acute grade 3 to 5 toxic effects, with rates of 20% for breast cancer and 0% for NSCLC.

Late Grade 3 to 5 Toxic Effects

Twelve studies provided rates of late grade 3 to 5 late toxic effects after SABR.[13,14,16,18,19,22,23,26-29,31] Rates of late toxic effects ranged from 0%[13,14,16,18,23,27,29,31] to 10%.[22] Mixed primary tumor histologic characteristic were evaluated in 9 studies,[14,16,19,22,26-29,31] prostate cancer oligometastases were solely evaluated in 2 studies,[13,23] and NSCLC oligometastases were solely evaluated in 1 study.[18] Figure 2B depicts the forest plot for all 12 studies reporting the incidence of late grade 3 to 5 toxic effects; the estimated incidence of late grade 3 to 5 toxic effects was 1.7% (95% CI, 0.2%-4.6%; 95% PI, 0%-12.5%; I^2 = 54%; 95% CI, 11%-76%; and τ = 0.25%; 95% CI, 0.01%-1.00%). Figure 2B also shows the corresponding funnel plot in which the *P* value of the weighted linear regression test was 0.39, indicating an absence of publication bias. Forest plots were not generated by histologic findings because only 2 studies[13,23] solely evaluated late grade 3 to 5 toxic effects for prostate cancer oligometastases; both of these trials reported rates of 0%. In addition, forest plots were not generated for NSCLC because only 1 study[18] solely evaluated this histologic finding exclusively. Incidence of late grade 3 to 5 toxic effects in that single study was 0%. Further details regarding toxic effects and systemic therapy are presented in Table 2.

1-Year LC

Fourteen studies provided rates of LC at 1 year after SABR.[15,19,21-23,25-33] Rates of 1-year LC ranged from 67.2%[29] to 100%.[19,23,26,33] Mixed primary tumor histologic characteristics were evaluated in 9 studies,[15,19,22,26-29,31,32] prostate cancer oligometastases were solely evaluated in 4 studies,[21,23,25,30] and breast cancer oligometastases were solely evaluated in 1 study.[33] **Figure 3**A depicts the forest plot for 1-year LC for all 14 studies; the estimated rate of 1-year LC was 94.7% (95% CI, 88.6%-98.6%; 95% PI, 63.8%-100%; I^2 = 90%; 95% CI, 86%-94%; and τ = 0.81%; 95% CI, 0.36%-2.38%). Figure 3A also shows the corresponding funnel plot in which the *P* value of the weighted linear regression test was 0.45, indicating the absence of publication bias. A subgroup analysis was conducted for prostate cancer oligometastases. eFigure 1A in the Supplement depicts the forest plot for 1-year LC for the 4 studies examining prostate cancer oligometastases; the estimated rate of 1-year LC was 97.9% (95% CI, 93.1%-100%; 95% PI, 90%-100%; I^2 = 21%; 95% CI, 0%-88%; and τ = 0.01%; 95% CI, 0%-2.86%). eFigure 1B in the Supplement shows the corresponding funnel plot in which the *P* value of the weighted linear regression test was 0.79, indicating the absence of publication bias. A forest plot was not generated for the breast cancer studies, because only 1 study solely evaluated patients with breast cancer oligometastases and reported a 100% LC rate at 1 year after SABR.[33]

1-Year OS

Fifteen studies provided rates of OS at 1 year after SABR.[15-17,19,20,22-24,26-32] Rates of 1-year OS ranged from 65.9%[26] to 100%.[23,30] Mixed primary tumor histologic characteristics were evaluated in 11 studies,[15,16,19,22,24,26-29,31,32] prostate cancer oligometastases were solely evaluated in 2 studies,[23,30] breast cancer oligometastases were solely evaluated in 1 study,[20] and lung cancer oligometastases were solely evaluated in 1 study.[17] Figure 3B depicts the forest plot for 1-year OS for all 15 studies; the estimated 1-year OS was 85.4% (95% CI, 77.1%-92.0%; 95% PI, 50.9%-100%; I^2 = 82%; 95% CI, 71%-88%; and τ = 0.72%; 95% CI, 0.30%-2.09%). Figure 3B also shows the corresponding funnel plot in which the *P* value of the weighted linear regression test was 0.87, indicating an absence of publication bias. Forest plots were not generated by histologic factors because only 2 studies[23,30] solely evaluated 1-year OS for prostate cancer oligometastases, both of which reported rates of 100%. In addition, only 1 study solely evaluated breast cancer[20] and NSCLC[17] oligometastases and reported 1-year OS rates of 92.7% for breast cancer and 67.2% for NSCLC.

1-Year PFS

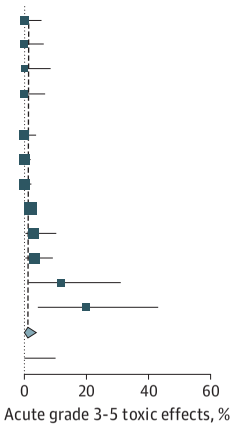
Eleven studies provided rates of PFS at 1 year after SABR.[16-18,20,23,24,28-31,33] Rates of 1-year PFS ranged from 33.3%[28] to 80.0%.[33] Mixed primary tumor histologic characteristics were examined in 5 studies,[16,24,28,29,31] prostate cancer oligometastases were solely evaluated in 2 studies,[23,30]

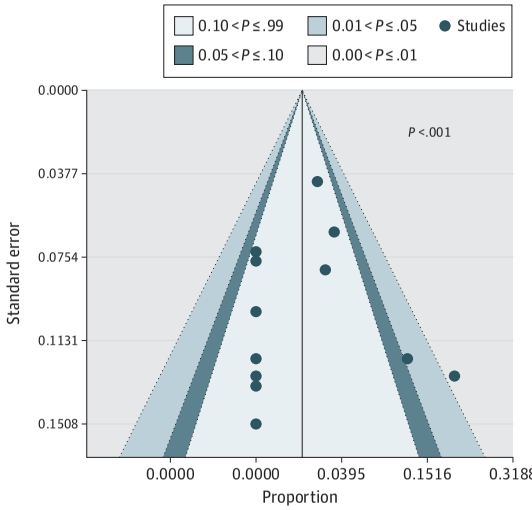
Figure 2. Safety

A Acute grade 3-5 toxic effects

Source	Cases, n	Total patients, n	Median age, y	Median dose	Acute grade 3-5 toxic effects, % (95% CI)
Ahmed et al,[13] 2013 (prostate)	0	17	65.0	20 Gy/1 fx; 8-24 Gy/1-3 fx	0.0 (0.0-5.5)
Chang et al,[14] 2004 (mixed)	0	15	50.0	30-37.5 Gy/3 fx	0.0 (0.0-6.3)
Henke et al,[16] 2018 (mixed)	0	11	64.0	50 Gy/5 fx	0.0 (0.0-8.5)
Iyengar et al,[18] 2018 (NSCLC)	0	14	63.5	16-24 Gy/1 fx; 26.5-33 Gy/3 fx; 30-37.5 Gy/5 fx	0.0 (0.0-6.7)
Ost et al,[23] 2018 (prostate)	0	25	70.0	30 Gy/3 fx	0.0 (0.0-3.8)
Rusthoven et al,[27] 2009 (mixed)	0	47	58.4	Ph I: 36-60 Gy/3 fx; Ph 2: 60 Gy/3 fx	0.0 (0.0-2.0)
Scorsetti et al,[29] 2015 (mixed)	0	42	67.0	75 Gy/3 fx	0.0 (0.0-2.3)
Sutera et al,[31] 2019 (mixed)	3	147	66.4	48 Gy/4 fx	2.0 (0.4-4.9)
Rusthoven et al,[26] 2009 (mixed)	1	38	58.0	Ph I: 48-60 Gy/3 fx; Ph 2: 60 Gy/3 fx	2.6 (0.0-10.0)
Salama et al,[28] 2012 (mixed)	2	61	64.4	20-60 Gy/3 fx	3.3 (0.3-9.2)
Méndez Romero et al,[19] 2006 (mixed)	2	17	63.0	30-37.5 Gy/3 fx	11.8 (1.3-31.1)
David et al,[33] 2020 (breast)	3	15	63.0	20 Gy/1 fx; 28 Gy/2 fx	20.0 (4.4-43.1)
Random-effects model		449			1.2 (0.0-3.8)
Prediction interval					(0.0-10.1)

Heterogeneity: I^2 = 50% (95% CI, 3%-74%), τ = 0.20% (95% CI, 0.00-1.43), χ^2_{11} = 22.09 (*P* =.02)

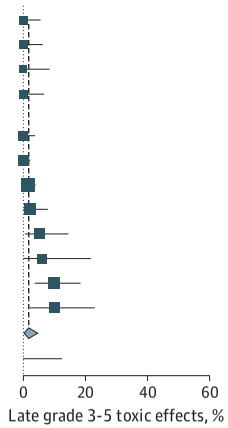


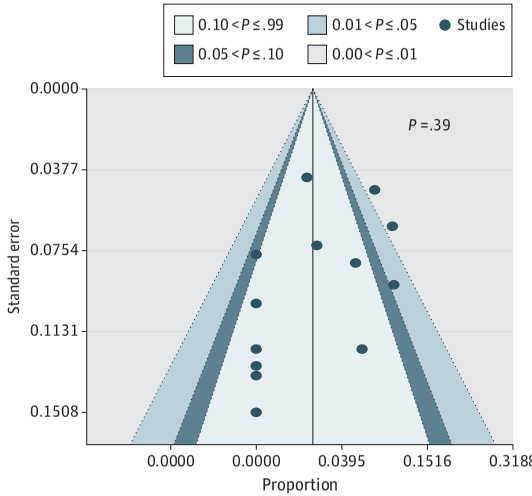


B Late grade 3-5 toxic effects

Source	Cases, n	Total patients, n	Median age, y	Median dose	Late grade 3-5 toxic effects, % (95% CI)
Ahmed et al,[13] 2013 (prostate)	0	17	65.0	20 Gy/1 fx; 8-24 Gy/1-3 fx	0.0 (0.0-5.5)
Chang et al,[14] 2004 (mixed)	0	15	50.0	30-37.5 Gy/3 fx	0.0 (0.0-6.3)
Henke et al,[16] 2018 (mixed)	0	11	64.0	50 Gy/5 fx	0.0 (0.0-8.5)
Iyengar et al,[18] 2018 (NSCLC)	0	14	63.5	16-24 Gy/1 fx; 26.5-33 Gy/3 fx; 30-37.5 Gy/5 fx	0.0 (0.0-6.7)
Ost et al,[23] 2018 (prostate)	0	25	70.0	30 Gy/3 fx	0.0 (0.0-3.8)
Scorsetti et al,[29] 2015 (mixed)	0	42	67.0	75 Gy/3 fx	0.0 (0.0-2.3)
Sutera et al,[31] 2019 (mixed)	2	147	66.4	48 Gy/4 fx	1.4 (0.1-3.9)
Rusthoven et al,[27] 2009 (mixed)	1	47	58.4	Ph I: 36-60 Gy/3 fx; Ph 2: 60 Gy/3 fx	2.1 (0.0-7.9)
Rusthoven et al,[26] 2009 (mixed)	2	38	58.0	Ph I: 48-60 Gy/3 fx; Ph 2: 60 Gy/3 fx	5.3 (0.5-14.5)
Méndez Romero et al,[19] 2006 (mixed)	1	17	63.0	30-37.5 Gy/3 fx	5.9 (0.0-21.7)
Salama et al,[28] 2012 (mixed)	6	61	64.4	20 Gy/1 fx; 28 Gy/2 fx	9.8 (3.7-18.4)
Nuyttens et al,[22] 2015 (mixed)	3	30	66.0	60 Gy/3 fx; 30 Gy/1 fx	10.0 (2.0-23.0)
Random-effects model		464			1.7 (0.2-4.6)
Prediction interval					(0.0-12.5)

Heterogeneity: I^2 = 54% (95% CI, 11%-76%), τ = 0.25% (95% CI, 0.01%-1.00%), χ^2_{11} = 23.79 (*P* =.01)





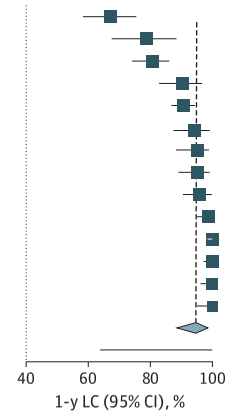
A, Weighted random-effects model depicting acute grade 3 to 5 toxic effects for 12 studies. In the acute grade 3 to 5 toxic effects funnel plot, each blue circle represents 1 of the 12 included studies, with the study effect size proportions on the x-axis and corresponding SE on the y-axis. Publication bias was detected with *P* < .001 for the weighted linear regression test. B, Weighted random-effects model depicting late-grade 3 to 5 toxic effects for 12 studies. In the late grade 3 to 5 toxic effect funnel plot, each blue circle represents 1 of the 12 included studies, with the study effect size proportions on the x-axis and corresponding SE on the y-axis. Publication bias was not detected with *P* = .39 for the weighted linear regression test. The number of cases in each forest plot was rounded to the nearest whole number. fx indicates fraction; NR, not reported; NSCLC, non–small cell lung cancer; and Ph, phase.

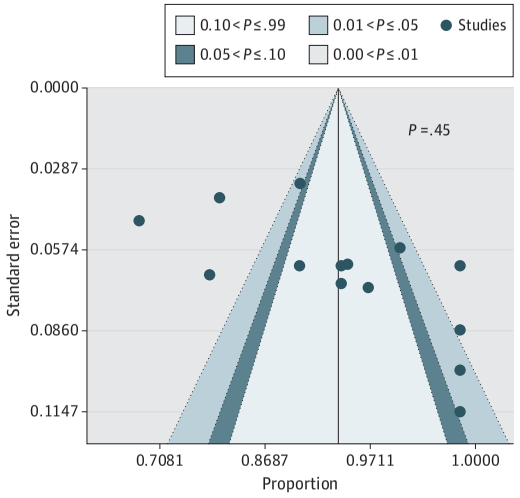
Figure 3. Clinical Benefit

A 1-y Local control

Source	Cases, n	Total patients, n	Median age, y	Median dose	1-y LC (95% CI), %
Salama et al,[28] 2012 (mixed)	76	113	64.4	20-60 Gy/3 fx	67.3 (58.3-75.5)
Nuyttens et al,[22] 2015 (mixed)	45	57	66.0	60 Gy/3 fx; 30 Gy/1 fx	78.9 (67.6-88.5)
Wang et al,[32] 2012 (mixed)	134	166	58.0	27-30 Gy/3 fx	80.7 (74.1-86.2)
Garg et al,[15] 2012 (mixed)	57	63	61.0	16-24 Gy/1 fx	90.5 (82.8-96.8)
Sutera et al,[31] 2019 (mixed)	198	218	66.4	48 Gy/4 fx	90.8 (86.9-94.4)
Scorsetti et al,[29] 2015 (mixed)	49	52	67.0	75 Gy/3 fx	94.2 (87.5-99.2)
Rusthoven et al,[27] 2009 (mixed)	60	63	58.4	Ph I: 36-60 Gy/3 fx; Ph 2: 60 Gy/3 fx	95.2 (88.3-99.0)
Muacevic et al,[21] 2013 (prostate)	61	64	66.0	20.2 Gy/1 fx	95.3 (89.1-99.2)
Siva et al,[30] 2018 (prostate)	48	50	70.0	20 Gy/1 fx	96.0 (90.5-99.9)
Pasqualetti et al,[25] 2018 (prostate)	77	78	NR	24 Gy/1 fx; 27 Gy/3 fx	98.7 (95.0-100)
Rusthoven et al,[26] 2009 (mixed)	63	63	58.0	Ph I: 48–60 Gy/3 fx; Ph 2: 60 Gy/3 fx	100 (98.5-100)
Méndez Romero et al,[19] 2006 (mixed)	34	34	63.0	30-37.5 Gy/3 fx	100 (97.2-100)
Ost et al,[23] 2018 (prostate)	25	25	70.0	30 Gy/3 fx	100 (96.2-100)
David et al,[33] 2020 (breast)	19	19	63.0	20 Gy/1 fx	100 (95.0-100)
Random-effects model		1065			94.7 (88.6-98.6)
Prediction interval					(63.8-100)

Heterogeneity: I^2 = 90% (95% CI, 86%-94%), τ = 0.81% (95% CI, 0.36%-2.38%), χ^2_{13} = 135.99 (*P* <.01)

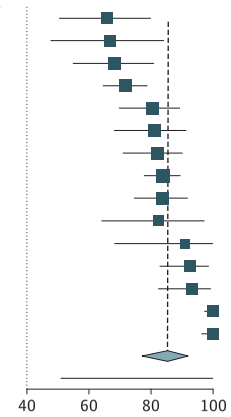


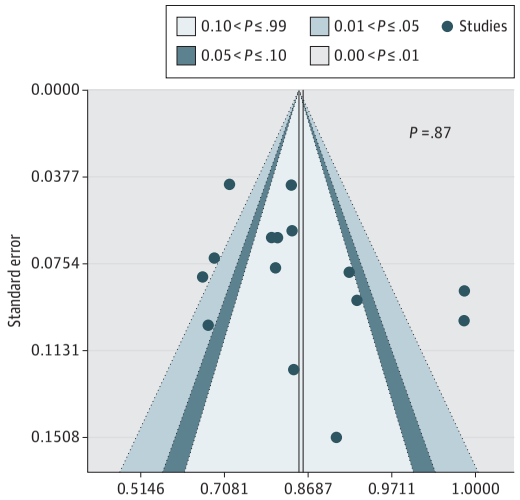


B 1-y Overall survival

Source	Cases, n	Total patients, n	Median age, y	Median dose	1-y OS (95% CI), %
Rusthoven et al,[26] 2009 (mixed)	25	38	58.0	Ph I: 48-60 Gy/3 fx; Ph 2: 60 Gy/3 fx	65.8 (50.3-79.9)
Iyengar et al,[17] 2014 (NSCLC)	16	24	67.0	19-24 Gy/1fx; 27-33 Gy/3 fx; 35-40 Gy/5 fx	66.7 (47.6-84.1)
Rusthoven et al,[27] 2009 (mixed)	32	47	58.4	Ph I: 36-60 Gy/3 fx; Ph 2: 60 Gy/3 fx	68.1 (54.8-80.9)
Wang et al,[32] 2012 (mixed)	107	149	58.0	27-30 Gy/3 fx	71.8 (64.4-78.8)
Garg et al,[15] 2012 (mixed)	49	61	61.0	16-24 Gy/1 fx	80.3 (69.6-89.3)
Scorsetti et al,[29] 2015 (mixed)	34	42	67.0	75 Gy/3 fx	81.0 (68.0-91.3)
Salama et al,[28] 2012 (mixed)	50	61	64.4	20-60 Gy/3 fx	82.0 (70.9-90.2)
Sutera et al,[31] 2019 (mixed)	123	147	66.4	48 Gy/4 fx	83.7 (77.7-89.5)
Palma et al,[24] 2019 (mixed)	56	66	67.0	36-60 Gy/3-8 fx; 16-24 Gy/1fx	83.6 (74.5-91.8)
Méndez Romero et al,[19] 2006 (mixed)	14	17	63.0	30-37.5 Gy/3 fx	82.4 (64.0-97.2)
Henke et al,[16] 2018 (mixed)	10	11	64.0	50 Gy/5 fx	90.9 (68.1-100)
Milano et al,[20] 2009 (breast)	37	40	48.0	NR	92.5 (82.7-98.6)
Nuyttens et al,[22] 2015 (mixed)	28	30	66.0	60 Gy/3 fx; 30 Gy/1 fx	93.3 (82.3-99.4)
Siva et al,[30] 2018 (prostate)	33	33	70.0	20 Gy/1 fx	100 (97.1-100)
Ost et al,[23] 2018 (prostate)	25s	25	70.0	30 Gy/3 fx	100 (96.2-100)
Random-effects model		791			85.3 (77.0-92.0)
Prediction interval					(50.8-100)

Heterogeneity: I^2 = 82% (95% CI, 71%-88%), τ = 0.72% (95% CI, 0.30%-2.09%), χ^2_{14} = 75.85 (*P* <.01)





A, Weighted random-effects model depicting 1-year local control (LC) for 13 studies. In the 1-year LC funnel plot, each blue circle represents 1 of the 13 included studies, with the study effect size proportions on the x-axis and corresponding SE on the y-axis. Publication bias was not detected with *P* = .45 for the weighted linear regression test. B, Weighted random-effects model depicting 1-year overall survival (OS) for 15 studies. In the 1-year OS funnel plot, each blue circle represents 1 of the 15 included studies, with the study effect size proportions on the x-axis and corresponding SE on the y-axis. Publication bias was not detected with *P* = .87 for the weighted linear regression test. The number of cases in each forest plot was rounded to the nearest whole number. fx indicates fraction; NR, not reported; NSCLC, non–small cell lung cancer; and Ph, phase.

breast cancer oligometastases were solely evaluated in 2 studies,[20,33] and lung cancer oligometastases were solely evaluated in 2 studies.[17,18] eFigure 2A in the Supplement depicts the forest plot for 1-year PFS for all 11 studies; the estimated 1-year PFS was 51.4% (95% CI, 42.7%-60.1%; 95% PI, 29.1%-73.5%; I^2 = 58%; 95% CI, 17%-78%; τ = 0.20%; 95% CI, 0.02%-1.21%). eFigure 2B in the Supplement shows the corresponding funnel plot in which the *P* value of the weighted linear regression test was 0.40, indicating an absence of publication bias. Forest plots were not generated by histologic factors because only 2 studies reported 1-year PFS for prostate (48%-85%), breast (68%-80%), and NSCLC (38.3%-53.6%) oligometastases.

Discussion

There have been reports dating back to the 1930s that patients with limited metastatic disease may respond favorably to curative local therapy (eg, radiotherapy or surgery).[54,55] To date, there have been several single-institution trials assessing the safety and efficacy of SABR in the oligometastatic setting.[13-32] To our knowledge, this is the only meta-analysis exploring the role of SABR prospectively administered in the setting of oligometastatic cancer. Our analysis suggests that SABR is generally well tolerated and of clinical benefit.

Two of the largest prospective trials published to date examining the potential benefit of SABR in the setting of oligometastatic prostate cancer have been Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence (STOMP)[23] and Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer (ORIOLE 2).[56] The STOMP trial randomized patients with oligometastatic prostate cancer to surveillance with salvage androgen deprivation therapy or upfront metastasis-directed therapy comprising SABR or surgery followed by salvage androgen deprivation therapy.[23] In the metastasis-directed therapy arm, the patients treated with SABR experienced 1-year LC and OS rates of 100%, with an absence of acute and late toxic effects. Updated findings noted 5-year androgen deprivation therapy-free survival rates of 34% for the metastasis-directed therapy and 8% for the observation arms (*P* = .06).[57] Similarly, the recently reported ORIOLE 2 trial that randomized patients with oligometastatic prostate cancer to SABR vs observation noted a significant 5-year PFS benefit in favor of SABR (not reached vs 5.8 months, *P* = .002), with no grade 3 or greater level of toxic effects reported.[56]

Among other primary tumor types, one of the largest trials assessing the potential role of SABR is the Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers (SABR-COMET) trial, which randomized patients with oligometastatic or oligoprogressive cancer among a variety of histologic characteristics in a 2:1 fashion to SABR or standard of care palliative treatments.[24] On initial reporting, PFS (hazard ratio, 0.47; 95% CI, 0.40-0.76; *P* = .001) was found to be superior in the SABR arm, with a 1-year PFS of 53% with 3 patients dying from treatment-related toxic effects. A recent update found that 5-year OS was significantly higher in patients within the SABR arm (42.3%) compared with patients who did not receive SABR (17.7%) (*P* = .006), as was 5-year PFS (17.3% vs 3.2%, *P* = .001).[58] Other trials have noted significant benefits among tumors with other histologic characteristics. Iyengar et al,[18] in the setting of patients with oligometastatic NSCLC, noted a median PFS of 9.7 months with the addition of SABR to systemic therapy vs 3.5 months in patients randomized to receive chemotherapy alone (*P* = .01). Additional planned and ongoing trials investigating the role of SABR in oligometastatic cancer can be found in eTable 2 in the Supplement, with many focusing on specific primary tumor histologic characteristics or expanding the use of SABR for patients with up to 10 lesions, such as the case with SABR-COMET-10.[59]

The results of this work provide evidence in support of SABR across a variety of primary tumor histologic characteristics given its excellent LC and perhaps more importantly low overall rates of severe acute and late toxic effects, which is particularly important in the context of patients with metastatic disease and limited life expectancies. However, the low rates of toxic effects are likely to be a result of well-selected patients. Lesions treated with SABR in the trials included in our analysis were similarly likely well selected such that relevant dose and volume constraints for critical structures could be met to minimize the risk of potential toxic effects. In addition, the potential quality-of-life detriments from potential SABR-related toxic effects, as well as potential delays of systemic therapies that compose the backbone of the management of metastatic disease, are also important considerations. Thus, patient selection is critical in determining which populations of patients with oligometastatic or oligoprogressive cancer have the most to gain from the addition of SABR to systemic therapy.

In addition to clinical patient-specific factors, such as performance status, the volume and number of metastatic deposits, whether patients presented with synchronous or metachronous disease, the location of metastatic deposits, and primary tumor subtype, further studies aim to examine the molecular phenotype of metastases that will estimate outcomes for patients who are more likely to benefit.[60-62]

Prior work by Lussier et al[63] noted distinct microRNA expressions between patients with oligometastatic or polymetastatic progression in the lung, which may aid in identifying patient populations at risk for rapid progression. Another study of note, the TRACERx Renal study, compared matched biopsies of primary renal cell carcinoma and metastases and noted that loss of chromosome 9q was associated with both development of metastasis and poorer outcomes compared with metastasis biopsies with more heterogeneity.[64] Pitroda et al[5] used specific molecular features among patients with metastatic colorectal cancer with liver metastases to identify 10-year OS rates in low- (94%), intermediate- (45%), and high-risk (19%) patient populations, highlighting the need to consider molecular phenotypes as well as patient-specific prognostic factors in clinical decision-making. Each of these works exhibited the need for further study to better define distinct phenotypes of metastatic lesions across a variety of tumor histologic char-

acteristics to aid in patient selection and identification of subgroups that have the most to gain from SABR.

Limitations

Our work has limitations. First, we did not have access to individual patient data. Therefore, we were unable to adjust for patient-specific covariates. We aimed to mitigate this limitation by including only prospective studies in the meta-analysis. Second, our median follow-up for all studies was 16.9 months, which may be an inadequate time to comprehensively record all late toxic effects. Third, although there was largely an absence of publication bias, this factor was observed in our analysis of acute toxic effects.

Although our analysis provides evidence in support of using SABR in the oligometastatic setting, a significant amount of heterogeneity was observed. This large amount of heterogeneity was likely present because the prospective data presently available were not limited to a single tumor histologic type, the studies had varying inclusion and exclusion criteria, and the studies primarily involved treatment to different sites. Future prospective studies should aim to further stratify these factors to better elucidate sources of heterogeneity, which would allow for SABR to be tailored in a more individualized manner.

Conclusions

The findings of this meta-analysis are not meant to be viewed as definitive evidence that SABR is safe and effective in all patients with oligometastatic cancer. Rather, we recommend that clinicians continue to exercise their best clinical judgment and offer this therapy in appropriately selected patients, typically those with low-volume metastatic disease, favorable initial responses to systemic therapy, and good performance status. Our analysis was intended to be hypothesis generating as we await the results of further prospective trials. Initiatives are under way to further classify oligometastatic disease based on patient-level and treatment characteristics that influence OS in patients undergoing SABR.[65]

In this meta-analysis, SABR appeared to be safe and effective in the setting of oligometastatic cancer. Rates of acute and late grade 3 to 5 toxic effects were commonly less than 10%, with clinically acceptable rates of local LC OS and PFS at 1 year posttreatment. Therefore, we recommend that clinicians consider this therapy in selected patients with oligometastatic cancer. Ongoing prospective studies will further explore potential sources of heterogeneity, allowing for a more individualized approach to this therapy.

ARTICLE INFORMATION

Accepted for Publication: September 15, 2020.

Published Online: November 25, 2020. doi:10.1001/jamaoncol.2020.6146

Author Affiliations: Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, New York (Lehrer); Department of Radiation Oncology, Virginia Commonwealth University, Richmond (Singh); Department of Public Health Sciences, Penn State University, Hershey, Pennsylvania (Wang, Chinchilli, Zaorsky); Department of Radiation Oncology, Mayo Clinic, Jacksonville, Florida (Trifiletti); Department of Radiotherapy and Experimental Cancer Research, Ghent University, Belgium (Ost); Sir Peter McCallum Department of Oncology, The University of Melbourne, Parkville, Victoria, Australia (Siva); Cyberknife Center and Key Laboratory of Cancer Prevention and Therapy, Department of Radiation Oncology, Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Tianjin, China (Meng); Department of Radiation Oncology, Penn State Cancer Institute, Hershey, Pennsylvania (Tchelebi, Zaorsky).

Author Contributions: Drs Lehrer and Zaorsky had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Lehrer and Singh contributed equally to this work.
Concept and design: Lehrer, Singh, Chinchilli, Trifiletti, Ost, Zaorsky.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Lehrer, Singh, Chinchilli, Trifiletti, Siva, Zaorsky.
Critical revision of the manuscript for important intellectual content: Lehrer, Singh, Wang, Trifiletti, Ost, Siva, Meng, Tchelebi, Zaorsky.
Statistical analysis: Lehrer, Singh, Wang, Chinchilli.
Administrative, technical, or material support: Singh, Ost, Meng, Zaorsky.
Supervision: Siva, Zaorsky.

Conflict of Interest Disclosures: Dr Trifiletti reported receiving support from Novocure for clinical trial research and personal fees from Springer Nature Inc. Dr Siva is supported by a National Health and Medical Research Council fellowship. Dr Zaorsky is supported by the National Institutes of Health LRP 1 L30 CA231572-01. Dr Zaorsky received personal fees from Springer Nature Inc and Weatherby Healthcare. No other disclosures were reported.

REFERENCES

1. Ettinger DS, Aisner DL, Wood DE, et al. NCCN guidelines insights: non–small cell lung cancer, version 5.2018. *J Natl Compr Canc Netw*. 2018;16(7):807-821. doi:10.6004/jnccn.2018.0062

2. Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E, Group EGW; ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23(suppl 7):vii11-vii19. doi:10.1093/annonc/mds232

3. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. 1995;13(1):8-10. doi:10.1200/JCO.1995.13.1.8

4. Lievens Y, Guckenberger M, Gomez D, et al. Defining oligometastatic disease from a radiation oncology perspective: an ESTRO-ASTRO consensus document. *Radiother Oncol*. 2020;148:157-166. doi:10.1016/j.radonc.2020.04.003

5. Pitroda SP, Khodarev NN, Huang L, et al. Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis. *Nat Commun*. 2018;9(1):1793. doi:10.1038/s41467-018-04278-6

6. Timmerman RD, Herman J, Cho LC. Emergence of stereotactic body radiation therapy and its impact on current and future clinical practice. *J Clin Oncol*. 2014;32(26):2847-2854. doi:10.1200/JCO.2014.55.4675

7. Bartlett EK, Simmons KD, Wachtel H, et al. The rise in metastasectomy across cancer types over the past decade. *Cancer*. 2015;121(5):747-757. doi:10.1002/cncr.29134

8. Lewis SL, Porceddu S, Nakamura N, et al. Definitive stereotactic body radiotherapy (SBRT) for extracranial oligometastases: an international survey of >1000 radiation oncologists. *Am J Clin Oncol*. 2017;40(4):418-422. doi:10.1097/COC.0000000000000169

9. Bernstein MB, Krishnan S, Hodge JW, Chang JY. Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach? *Nat Rev Clin Oncol*. 2016;13(8):516-524. doi:10.1038/nrclinonc.2016.30

10. Zaorsky NG, Lehrer EJ, Kothari G, Louie AV, Siva S. Stereotactic ablative radiation therapy for oligometastatic renal cell carcinoma (SABR ORCA): a meta-analysis of 28 studies. *Eur Urol Oncol*. 2019;2(5):515-523. doi:10.1016/j.euo.2019.05.007

11. Lehrer EJ, McGee HM, Peterson JL, et al. Stereotactic radiosurgery and immune checkpoint inhibitors in the management of brain metastases. *Int J Mol Sci*. 2018;19(10):E3054. doi:10.3390/ijms19103054

12. Lehrer EJ, Peterson J, Brown PD, et al. Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: an international meta-analysis of individual patient data. *Radiother Oncol*. 2019;130:104-112. doi:10.1016/j.radonc.2018.08.025

13. Ahmed KA, Barney BM, Davis BJ, Park SS, Kwon ED, Olivier KR. Stereotactic body radiation therapy in the treatment of oligometastatic prostate cancer.

Front Oncol. 2013;2:215. doi:10.3389/fonc.2012.00215

14. Chang EL, Shiu AS, Lii MF, et al. Phase I clinical evaluation of near-simultaneous computed tomographic image–guided stereotactic body radiotherapy for spinal metastases. *Int J Radiat Oncol Biol Phys*. 2004;59(5):1288-1294. doi:10.1016/j.ijrobp.2004.04.025

15. Garg AK, Shiu AS, Yang J, et al. Phase 1/2 trial of single-session stereotactic body radiotherapy for previously unirradiated spinal metastases. *Cancer*. 2012;118(20):5069-5077. doi:10.1002/cncr.27530

16. Henke L, Kashani R, Robinson C, et al. Phase I trial of stereotactic MR-guided online adaptive radiation therapy (SMART) for the treatment of oligometastatic or unresectable primary malignancies of the abdomen. *Radiother Oncol*. 2018;126(3):519-526. doi:10.1016/j.radonc.2017.11.032

17. Iyengar P, Kavanagh BD, Wardak Z, et al. Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non–small-cell lung cancer. *J Clin Oncol*. 2014;32(34):3824-3830. doi:10.1200/JCO.2014.56.7412

18. Iyengar P, Wardak Z, Gerber DE, et al. Consolidative radiotherapy for limited metastatic non–small-cell lung cancer: a phase 2 randomized clinical trial. *JAMA Oncol*. 2018;4(1):e173501. doi:10.1001/jamaoncol.2017.3501

19. Méndez Romero A, Wunderink W, Hussain SM, et al. Stereotactic body radiation therapy for primary and metastatic liver tumors: a single institution phase I-II study. *Acta Oncol*. 2006;45(7):831-837. doi:10.1080/02841860600897934

20. Milano MT, Zhang H, Metcalfe SK, Muhs AG, Okunieff P. Oligometastatic breast cancer treated with curative-intent stereotactic body radiation therapy. *Breast Cancer Res Treat*. 2009;115(3):601-608. doi:10.1007/s10549-008-0157-4

21. Muacevic A, Kufeld M, Rist C, Wowra B, Stief C, Staehler M. Safety and feasibility of image-guided robotic radiosurgery for patients with limited bone metastases of prostate cancer. *Urol Oncol*. 2013;31(4):455-460. doi:10.1016/j.urolonc.2011.02.023

22. Nuyttens JJ, van der Voort van Zyp NC, Verhoef C, et al. Stereotactic body radiation therapy for oligometastases to the lung: a phase 2 study. *Int J Radiat Oncol Biol Phys*. 2015;91(2):337-343. doi:10.1016/j.ijrobp.2014.10.021

23. Ost P, Reynders D, Decaestecker K, et al. Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: a prospective, randomized, multicenter phase II trial. *J Clin Oncol*. 2018;36(5):446-453. doi:10.1200/JCO.2017.75.4853

24. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet*. 2019;393(10185):2051-2058. doi:10.1016/S0140-6736(18)32487-5

25. Pasqualetti F, Panichi M, Sainato A, et al. Image-guided stereotactic body radiotherapy in metastatic prostate cancer. *Anticancer Res*. 2018;38(5):3119-3122. doi:10.21873/anticanres.12572

26. Rusthoven KE, Kavanagh BD, Burri SH, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. *J Clin Oncol*. 2009;27(10):1579-1584. doi:10.1200/JCO.2008.19.6386

27. Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol*. 2009;27(10):1572-1578. doi:10.1200/JCO.2008.19.6329

28. Salama JK, Hasselle MD, Chmura SJ, et al. Stereotactic body radiotherapy for multisite extracranial oligometastases: final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease. *Cancer*. 2012;118(11):2962-2970. doi:10.1002/cncr.26611

29. Scorsetti M, Comito T, Tozzi A, et al. Final results of a phase II trial for stereotactic body radiation therapy for patients with inoperable liver metastases from colorectal cancer. *J Cancer Res Clin Oncol*. 2015;141(3):543-553. doi:10.1007/s00432-014-1833-x

30. Siva S, Bressel M, Murphy DG, et al. Stereotactic ablative body radiotherapy (SABR) for oligometastatic prostate cancer: a prospective clinical trial. *Eur Urol*. 2018;74(4):455-462. doi:10.1016/j.eururo.2018.06.004

31. Sutera P, Clump DA, Kalash R, et al. Initial results of a multicenter phase 2 trial of stereotactic ablative radiation therapy for oligometastatic cancer. *Int J Radiat Oncol Biol Phys*. 2019;103(1):116-122. doi:10.1016/j.ijrobp.2018.08.027

32. Wang XS, Rhines LD, Shiu AS, et al. Stereotactic body radiation therapy for management of spinal metastases in patients without spinal cord compression: a phase 1-2 trial. *Lancet Oncol*. 2012;13(4):395-402. doi:10.1016/S1470-2045(11)70384-9

33. David S, Tan J, Savas P, et al. Stereotactic ablative body radiotherapy (SABR) for bone only oligometastatic breast cancer: a prospective clinical trial. *Breast*. 2020;49:55-62. doi:10.1016/j.breast.2019.10.016

34. Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. *ACP J Club*. 1995;123(3):A12-A13.

35. Ebell M. Information at the point of care: answering clinical questions. *J Am Board Fam Pract*. 1999;12(3):225-235. doi:10.3122/jabfm.12.3.225

36. Huang X, Lin J, Demner-Fushman D. Evaluation of PICO as a knowledge representation for clinical questions. *AMIA Annu Symp Proc*. 2006;359-363.

37. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62(10):1006-1012. doi:10.1016/j.jclinepi.2009.06.005

38. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting: Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-2012. doi:10.1001/jama.283.15.2008

39. Howick J. Levels of evidence. Oxford Centre for Evidence-Based Medicine; March 2009.

40. National Cancer Institute; DCTD Division of Cancer Treatment and Diagnosis. Common Terminology Criteria for Adverse Events, version 4.03. Updated September 21, 2020. Accessed December 23, 2019. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

41. Studio R. Integrated development environment for R. 2015. Accessed October 23, 2020. https://rstudio.com/products/rstudio/

42. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Statistical Software*. 2010;36(3):1-48. doi:10.18637/jss.v036.i03

43. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health*. 2019;22(4):153-160. doi:10.1136/ebmental-2019-300117

44. Freeman MF, Tukey JW. Transformations related to the angular and the square root. *Ann Mathematical Statistics*. 1950;21:607-611. doi:10.1214/aoms/1177729756

45. Langan D, Higgins JPT, Jackson D, et al. A comparison of heterogeneity variance estimators in simulated random-effects meta-analyses. *Res Synth Methods*. 2019;10(1):83-98. doi:10.1002/jrsm.1316

46. Ades AE, Lu G, Higgins JP. The interpretation of random-effects meta-analysis in decision models. *Med Decis Making*. 2005;25(6):646-654. doi:10.1177/0272989X05282643

47. Fleiss JL, Gross AJ. Meta-analysis in epidemiology, with special reference to studies of the association between exposure to environmental tobacco smoke and lung cancer: a critique. *J Clin Epidemiol*. 1991;44(2):127-139. doi:10.1016/0895-4356(91)90261-7

48. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558. doi:10.1002/sim.1186

49. Cochran WG. The combination of estimates from different experiments. *Biometrics*. 1954;10:110-129. doi:10.2307/3001666

50. Rücker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I^2 in assessing heterogeneity may mislead. *BMC Med Res Methodol*. 2008;8:79. doi:10.1186/1471-2288-8-79

51. Serghiou S, Goodman SN. Random-effects meta-analysis: summarizing evidence with caveats. *JAMA*. 2019;321(3):301-302. doi:10.1001/jama.2018.19684

52. IntHout J, Ioannidis JP, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open*. 2016;6(7):e010247. doi:10.1136/bmjopen-2015-010247

53. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. *JAMA*. 2006;295(6):676-680. doi:10.1001/jama.295.6.676

54. Barney JD, Churchill EJ. Adenocarcinoma of the kidney with metastasis to the lung: cured by nephrectomy and lobectomy. *J Urol*. 1939;42(3):269-276. doi:10.1016/S0022-5347(17)71516-9

55. Milas L, Hunter N, Withers HR. Concomitant immunity to pulmonary metastases of a murine fibrosarcoma: influence of removal of primary tumor by radiation or surgery, of active specific immunization and treatment with *Corynebacterium granulosum*. *Int J Radiat Oncol Biol Phys*. 1976;1(11-12):1171-1178. doi:10.1016/0360-3016(76)90090-0

56. Phillips R, Shi WY, Deek M, et al. Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: the ORIOLE phase 2 randomized clinical trial. *JAMA Oncol*. 2020;6(5):650-659. doi:10.1001/jamaoncol.2020.0147

57. Ost P, Reynders D, Decaestecker K, et al. Surveillance of Metastasis-Directed Therapy For Oligometastatic Prostate Cancer Recurrence (STOMP): five-year results of a randomized phase II trial [abstract]. *J Clin Oncol*. 2020;38(6 suppl):10. doi:10.1200/JCO.2020.38.6_suppl.10

58. Palma DA, Olson R, Harrow S, et al. Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: long-term results of the SABR-COMET phase II randomized trial. *J Clin Oncol*. 2020;38(25):2830-2838. doi:10.1200/JCO.20.00818

59. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of 4-10 oligometastatic tumors (SABR-COMET-10): study protocol for a randomized phase III trial. *BMC Cancer*. 2019;19(1):816. doi:10.1186/s12885-019-5977-6

60. Fode MM, Høyer M. Survival and prognostic factors in 321 patients treated with stereotactic body radiotherapy for oligo-metastases. *Radiother Oncol*. 2015;114(2):155-160. doi:10.1016/j.radonc.2014.12.003

61. Pembroke CA, Fortin B, Kopek N. Comparison of survival and prognostic factors in patients treated with stereotactic body radiotherapy for oligometastases or oligoprogression. *Radiother Oncol*. 2018;127(3):493-500. doi:10.1016/j.radonc.2018.04.022

62. Franzese C, Comito T, Toska E, et al. Predictive factors for survival of oligometastatic colorectal cancer treated with stereotactic body radiation therapy. *Radiother Oncol*. 2019;133:220-226. doi:10.1016/j.radonc.2018.10.024

63. Lussier YA, Khodarev NN, Regan K, et al. Oligo- and polymetastatic progression in lung metastasis(es) patients is associated with specific microRNAs. *PLoS One*. 2012;7(12):e50141. doi:10.1371/journal.pone.0050141

64. Turajlic S, Xu H, Litchfield K, et al; PEACE; TRACERx Renal Consortium. Tracking cancer evolution reveals constrained routes to metastases: TRACERx Renal. *Cell*. 2018;173(3):581-594.e12. doi:10.1016/j.cell.2018.03.057

65. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol*. 2020;21(1):e18-e28. doi:10.1016/S1470-2045(19)30718-1