Check for updates

OPEN ACCESS

EDITED BY Sunil Krishnan, Mayo Clinic Florida, United States

REVIEWED BY

Giuseppe Roberto D'Agostino, Humanitas Research Hospital, Italy Mihai Teodor Georgescu, Carol Davila University of Medicine and Pharmacy, Romania

*CORRESPONDENCE Chao Pan panchao@xmu.edu.cn Ritsuko Komaki DrKomakiCox@gmail.com

[†]These authors share first authorship

RECEIVED 25 March 2023 ACCEPTED 19 October 2023 PUBLISHED 17 November 2023

CITATION

Liao X, Kishi K, Du K, Komaki R, Mizoe J, Aikawa G, Zheng W and Pan C (2023) Risk factors of local control in adrenal metastases treated by stereotactic body radiation therapy - a systematic review and meta-analysis. *Front. Oncol.* 13:1193574. doi: 10.3389/fonc.2023.1193574

COPYRIGHT

© 2023 Liao, Kishi, Du, Komaki, Mizoe, Aikawa, Zheng and Pan. This is an openaccess article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Risk factors of local control in adrenal metastases treated by stereotactic body radiation therapy - a systematic review and meta-analysis

Xuehong Liao^{1,2†}, Kazushi Kishi^{3†}, Kaixin Du^{4,5†}, Ritsuko Komaki⁶*, Junetsu Mizoe⁷, Gosuke Aikawa⁷, Wei Zheng¹ and Chao Pan¹*

¹Department of Pathology, Zhongshan Hospital, Xiamen University, Xiamen, China, ²Department of Pathology, School of Medicine, Sapporo Medical University, Sapporo, Japan, ³Department of Radiation Oncology, National Disaster Medical Center, National Hospital Organization (NHO), Incorporated Administrative Agency 3256 Tachitawa City, Tokyo, Japan, ⁴Department of Radiation Oncology, Xiamen Humanity Hospital Fujian Medical University, Xiamen, China, ⁶Department of Radiation Oncology, Faculty of Medicine, Hokkaido University, Sapporo, Hokkaido, Japan, ⁶Department of Radiation Oncology, Emeritus of The University of Texas M.D. Anderson Cancer Center, Baylor College of Medicine, Hokkaido Ohno Memorial Hospital, Sapporo, Japan

Purpose: This study is aimed to explore risk factors affect the therapy outcomes of adrenal metastases (AM) for stereotactic body radiation therapy (SBRT) and guide clinical dose selection.

Methods and materials: PubMed, Embase and Web of Science were searched in September 22, 2022 in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA). Subgroup analysis and meta-regression were used to search for sources of heterogeneity and identify risky outcomes factors. Publication bias test and sensitivity analysis were also conducted.

Results: Thirty-three studies with full text from 2009 to 2022 about AM with SBRT on 1483 patients were included. Pooled 1- and 2-year local control (LC) and overall survival(OS) were 81.7% (95% confidence interval [CI], 75.6%-86.5%), 62.8% (95% CI, 53.8%-71.8%), 67.4% (95%CI, 61.8%-73.1%) and 46.5% (95%CI, 40.4%-52.6%), respectively. Biological effective dose (BED, α/β =10Gy) and dose per fraction affected 1-year LC (Qm=23.89, 15.10; *P*<0.0001, 0.0001). In the range of 60-80Gy (BED₁₀), the group of dose per fraction \geq 9Gy achieved the excellent 1-year LC (< 9Gy: \geq 9Gy =78%, 91%; χ^2 = 10.16, *P* = 0.001). Tracking technology significantly affected 1- and 2-year OS (Qm = 5.73, 8.75; *P* = 0.017, 0.003) and high tracking adoption group showed excellent 1- and 2- year OS (78.7% [95%CI, 68.6%- 88.9%]; and 62.9% [95%CI, 53.1%-72.7%]).

Conclusion: Increasing the dose per fraction appropriately may help control locally AM lesious. Tracking technology might contribute to improve survival of advanced patients with AM. But these results need prospective studies to verify them.

KEYWORDS

adrenal metastases, SBRT (stereotactic body radiation therapy), fractionation dose, tracking, oligometastases

Introduction

The adrenal glands are a common site of metastasis., accounting for up to 38% of metastastatic cancers (1), with melanomas (50%), lung and breast cancers (30-40%), and renal and gastrointestinal tumors (10-20%) (2) being commonly affected due to the adrenal glands' rich blood supply (3). Advanced imaging and close follow-up programs for cancer patients have led to a rise in their detection, typically at the oligometastatic stage. Targeted local therapies are gaining popularity as ablative therapy may improve outcomes in patients with limited systemic disease burden (1, 2). A paired analysis of 62 patients with isolated AM found that SBRT and laparoscopic adrenalectomy had similar outcomes and survival rates (4), but complications occurred in 37.9% of patients, including ileus or gastroparesis, wound problems, pneumonia, and heart arrhythmia (5). Stereotactic body radiation therapy (SBRT) enables conformal delivery of ablative radiation doses using single or a small number of fractions, resulting in a more effective radio biologic dose (6). SBRT has become an important treatment option for adrenal metastases, with its low toxicity and ability to maintain adrenal function.

However, there are currently no specific clinical guidelines established for SBRT in AM. This has resulted in considerable diversity in prescription doses and fractionation plans in clinical settings (7), with notable fluctuations in 1-year and 2-year LC rates, spanning from 44% to 100% and 27% to 100%, respectively (8) Consequently, it is critical to investigate risk factors and develop reliable models to guide clinical dose selection.

Methods and materials

We conducted a systematic search for relevant studies in PubMed, Embase, and Web of Science, including those published up to July 2022 and updating the search until September 22, 2022. Thirty-three studies published between 2009 and 2022 were included, covering 1483 patients with 1660 lesions (3, 7, 9–38). The screening flow diagram was shown in Supplementary Figure A and clinicopathologic characteristics in Supplementary Table A. The search query used was "stereotactic OR radiosurgery OR sbrt OR sabr OR knife) AND (adrenal/exp OR adrenal) AND (metastasis/exp OR metastasis OR metastases/exp OR metastases OR metastatic)" (39). We excluded studies that did not report treatment outcomes or toxicity data specific to SBRT for AM, studies that did not grade toxicities according to Common Terminology Criteria for Adverse Events (CTCAE) criteria or define radiological responses according to the Response Evaluation Criteria in Solid Tumors criteria (RECIST) criteria, studies without BED₁₀ information, redundant data or those reporting on fewer than 5 patients, or non-English reports were excluded. We followed PRISMA guidelines. Survival outcomes were calculated per patient, while the LC rate was calculated per metastatic lesion. Some outcome values were obtained from local control probability curves using Engauge Digitizer. SBRT was defined as the delivery of higher fractional doses of radiation than conventional fractionation (>1.8-2.5Gy) in a relatively small number of fractions (39). Local control was defined as the absence of progression at the treatment site. Oligometastatic disease defined as limited metastatic disease burden with 5 or fewer lesions in 2 or fewer organ sites. Synchronous metastases were defined as those present at the time of first diagnosis or appearing within 6 months. Since some criteria differed between studies, we performed simple calculations, such as calibrating technology adoption rates based on patients rather than lesions in some studies (7, 32). Biological effective doses were calculated by following quation:

$$BED = nd[1 + d/(a/\beta)]$$

where *d* is the single radiation dose, *n* is the number of fractions, and we picked up $\alpha/\beta = 10$ Gy.

A pooled analysis based on maximum likelihood estimation was used to determine weighted study level rates of 1,2-year LC and 1,2year OS, and subgroup analysis and meta-regression were conducted to explore possible sources of heterogeneity among study results. Qm was used to assess the degree of heterogeneity (variation) among the effect sizes of individual studies. Significant risk factors identified through meta-regression testing also need to undergo collinearity detection. We reported the total number of adverse events rather than estimating a pooled statistic because the reported rates of grade 3+ toxicity were uniformly low and frequently zero.

Statistical analysis

A pooled analysis based on maximum likelihood estimation was used to determine weighted study level rates of 1,2-year LC and 1,2year OS. The metaprop function in the meta package (version 5.5-0) in R was used to perform a meta-analysis of binomial proportions (version 4.2.1). Subgroup analysis and meta-regression were respectively conducted using meta and metaregression function in the meta package. Variable correlation examination was performed by using *scatterplotMatrix* function in the car package (version3.1.0). Qm was used to assess the degree of heterogeneity (variation) among the effect sizes of individual studies. Cases with missing covariates were automatically excluded from regression analyses. The difference in BED10 between different groups was compared using an independent samples t-test by SPSS (version 22.0).

Results

Out of 915 records, we included 33 studies published between 2009 and 2022 that reported outcomes for 1483 patients with 1660 lesions of AM. The median follow-up was 13.4 months, ranging from 0 to 124 months, and the median OS was 19 months, ranging from 0.4 to 171 months. The median total dose was 36Gy(10-70Gy) and the median number of fraction was 4.5(1-18). The median dose per fraction was 7.5Gy, ranging from 2 to 30Gy, and the median BED10 was 71.4Gy, ranging from 20 to 180Gy. Among the patients, 61% had were primary lung cancer patients, and 91% were oligometastatic or oligoprogressive patients. Ninety-four percentage of the studies included data on the

method of diagnosis, and only three studies reported biopsy tissue confirmation along with fiducial placement. Out of 1483 patients, only 19 (1.3%) patients reported grade3+ toxicity response, and out of 1401 patients, 22 patients (1.6%) experienced adrenal insufficiency. For more detailed information, please refer to Table A in the Supplement Tables. The pooled 1- and 2- year LC were 82% (95% CI, 76%-87%) and 63% (95% CI, 54%-72%), respectively, and the pooled 1- and 2- year OS were 67% (95%CI, 62%-73%) and 47% (95%CI, 40%-53%), respectively. The forest plots, funnel plots and sensitivity analysis were shown in Figures B–D in the Supplement Figures.

BED_{10} and dose per fraction were significant influence factors of LC

We analyzed the variables about technique, prescription dose and treatment method, or fractionation function to identify sources of heterogeneity for pooled 1- or 2-year LC. As shown in Table 1, BED₁₀, dose per fraction and SCLC were significant influence factors of 1-year LC (Qm = 23.89, 15.10, 4.37; P<0.001,< 0.001, 0.037). Only BED₁₀ play a crucial part for 2-year LC (Qm = 7.72; P = 0.006). We analyzed the correlation and showed there were moderate negative relation between SCLC and BED₁₀ (The coefficient= -0.34, Figure 1),

TABLE 1 Analysis of clinicopathological factors affecting the outcome by meta regression.

Variable	Moderators	d.f.	Qm	p-value	Variable	Moderators	d.f.	Qm	p-value
	Age	1(27)	0.01	0.926		Age	1(28)	0.85	0.356
1-year local control	Male	1(25)	0.68	0.409	1-year overall survival	Male	1(26)	0.50	0.479
	Right adrenal	1(21)	0.74	0.391		Right adrenal	1(22)	0.00	0.969
	Bilateral	1(27)	2.01	0.156		Bilateral	1(28)	0.05	0.823
	Concurrent therapy	1(8)	2.53	0.112		Concurrent therapy	1(11)	0.01	0.905
	SCLC	1(20)	4.37	0.037		SCLC	1(20)	2.40	0.121
	Melanoma	1(24)	0.07	0.791		Melanoma	1(24)	1.31	0.253
	Solitary	1(16)	2.94	0.087		Solitary	1(17)	0.42	0.519
	Synchronous	1(15)	1.52	0.218		Synchronous	1(15)	0.21	0.650
	Prescribed dose	1(26)	1.20	0.273		Prescribed dose	1(27)	0.11	0.741
	Fractions	1(25)	1.41	0.236		Fractions	1(26)	1.80	0.180
	Dose per fraction	1(26)	15.10	<.001		Dose per fraction	1(27)	3.10	0.078
	BED ₁₀	1(27)	23.89	<.001		BED ₁₀	1(28)	1.95	0.163
	PTV	1(18)	2.89	0.089		PTV	1(18)	0.15	0.703
	GTV	1(25)	0.72	0.396		GTV	1(26)	1.98	0.160
	Tumor size	1(7)	0.03	0.861		Tumor size	1(7)	0.52	0.473
	Tracking technology	1(25)	3.31	0.069		Tracking technology	1(26)	5.73	0.017
	Age	1(24)	0.17	0.684		Age	1(27)	2.40	0.121
2-year local control	Male	1(22)	0.48	0.490	2-year overall survival	Male	1(25)	0.02	0.895
	Right adrenal	1(18)	0.51	0.473		Right adrenal	1(21)	0.39	0.534

(Continued)

TABLE 1 Continued

Variable	Moderators	d.f.	Qm	p-value	Variable	Moderators	d.f.	Qm	p-value
	Bilateral	1(24)	1.02	0.313		Bilateral	1(27)	1.33	0.249
	Concurrent therapy	1(8)	0.09	0.761	-	Concurrent therapy	1(11)	1.65	0.199
	SCLC	1(17)	0.03	0.871	-	SCLC	1(19)	10.04	0.002
	Melanoma	1(21)	1.03	0.310	-	Melanoma	1(23)	0.03	0.863
	Solitary	1(15)	1.85	0.174		Solitary	1(17)	0.68	0.409
	Synchronous	1(13)	0.32	0.570	-	Synchronous	1(15)	1.69	0.194
	Prescribed dose	1(23)	0.82	0.365	-	Prescribed dose	1(26)	0.10	0.755
	Fractions	1(22)	0.23	0.629		Fractions	1(25)	3.21	0.073
	Dose per fraction	1(23)	1.35	0.245	-	Dose per fraction	1(26)	6.60	0.010
	BED ₁₀	1(24)	7.72	0.006		BED ₁₀	1(27)	2.82	0.093
	PTV	1(16)	0.47	0.491		PTV	1(17)	4.87	0.027
	GTV	1(24)	0.13	0.718		GTV	1(26)	8.20	0.004
	Tumor size	1(6)	1.42	0.233		Tumor size	1(7)	1.27	0.261
	Tracking technology	1(22)	0.34	0.559		Tracking technology	1(25)	8.75	0.003

SCLC, small cell lung cancer; PTV, planning target volume; GTV, gross tumor volume. The red shading mean that significantly difference (p < 0.05).



Scatter plot matrix of correlation between variables. The figure contains linear and smooth fitted curves, and corresponding marginal distributions (kernel density maps and axonal whisker maps). single.dose=dose per fraction.

which might suggest the effect on 1-year LC by SCLC related to low BED_{10} . On the other sides, BED_{10} have a low correlation with dose per fraction (The coefficient =0.24, Figure 1). In conclusion, total dose and dose per fraction should be most important factors for LC.

The subgroup analysis results showed the group of $BED_{10} \ge$ 100Gy have an excellent 1-year LC (<70Gy: 70-99Gy: ≥100Gy = 69%: 86%: 96%, χ^2 = 33.74, *P*< 0.0001, Figure 2). In clinical practice, due to the presence of surrounding critical organs, we often cannot escalate the radiation dose without the support of tracking technology. The majority of studies still have a total prescription dose ranging from 60 to 80 Gy. Therefore, we further performed subgroup analysis in the range of 60-80Gy (BED₁₀) (N=21 studies, accounting for 64%) and the results showed 1-year LC in the group of dose per fraction \ge 9Gy (91%: 78%, $\chi^2 = 10.16$, *P*=0.001, Figure 3). On the other hand, dose per fraction \geq 9Gy have an excellent 1-year LC (≤5Gy: 5.1-8.9Gy: 9-14.9Gy: ≥ 15Gy = 68%: 75%: 90%: 94%, $\chi^2 = 27.93$, P =0.0001, Figure 4). Even in the low tracking adoption group (0-20% patients, most of them without tracking adoption (15/18)), dose per fraction still significantly affected 1-year LC (N=17 studies, Qm =13.93, P<0.001), which rules out the role of tracking technology in local control rates for AM.

The application of tracking significantly improved overall survival

As shown in Table 1, only tracking technology adoption has a strong correlation with 1-year OS (Qm=5.73; P = 0.017). SCLC, dose per fraction, tumor volume (PTV, GTV), tracking technology had strong effects on 2-year OS (Qm=10.04, 6.60, 4.87, 8.20, 8.75; P = 0.002, 0.010, 0.027, 0.004, 0.003). As shown in Figure 2, tracking technology adoption had a strong correlation with dose per fraction (The coefficient =0.61). But in the low tracking adoption (15/18)), dose per fraction didn't significantly affect 2-year OS (N =17 studies, Qm = 0.30, P = 0.584). The high-tracking adoption group received a median BED₁₀ of 69.4Gy. These results suggested that, with regard to overall survival, the impact of fractionation doses may be contingent upon the use of tracking technology rather than the tracking technology upon fractionation doses.

The total proportion of tracking technology is only 19.3% (257/ 1332) from published articles. High tracking adoption group got excellent 1-and 2-year OS (0-20% patients: 20%-80% patients: 80%-

Study	Events	Total				Proportion	95%-CI
Group = <70Gy							
A. Bavdoun-2021	37	57				0.65	[0.51: 0.77]
Daniel Buergy-2021	301	366		_		0.82	[0.78: 0.86]
Eabio Arcidiacono-2020	24	38	-		-T	0.63	[0 46: 0 78]
Jordan Torok-2011	6	ğ	-			0.67	[0.30.0.93]
Kim Buriakow 2019	22	20			_	0.59	[0.00, 0.00]
Marta Scorcotti 2012	22	30				0.50	[0.41, 0.74]
Michael Quieu 2012	24	30				0.07	[0.49, 0.01]
Michael Gulou-2012	10	25				0.43	[0.17, 0.77]
Sneema Chawla-2009	19	30				0.54	[0.37, 0.71]
Sonall Rudra-2013	9	13				0.69	[0.39; 0.91]
Theresa Voglhuber-2020	25	34				0.74	[0.56; 0.87]
Aysenur Elmali-2022	115	146		_		0.79	[0.71; 0.85]
Random effects model		783				0.69	[0.61; 0.75]
Heterogeneity: $I^2 = 72\%$, $\tau^2 = 0$.	1611, <i>p</i> < 0.01						
Group = 70-99Gy							
Alfred Haidenberger-2017	23	24				- 0.96	[0.79; 1.00]
Ciro Franzese-2021	127	149				0.85	0.79: 0.91
Corbin A.Helis-2020	25	29		-		- 0.86	[0.68: 0.96]
Diego A S Toesca-2018	36	39				- 0.92	[0 79 0 98]
Eren Celik-2016	q	15				0.60	[0.32 0.84]
Giuseppe Facondo-2021	17	25	-			0.00	[0.46: 0.85]
Edix Ebrot 2022	67	72				L 0.00	[0.40, 0.00]
Franco Cacamaccima 2012	52	58				- 0.00	[0.00, 0.90]
Kamran A Abmod 2012	12	12				- 0.90	[0.79, 0.90]
Kamian A. Anneu-2013	12	10			i 🖬 🗖	- 0.92	[0.04, 1.00]
Lalla Koenig-2020	24	28		_		- 0.86	[0.67; 0.96]
Leonid B. Resnko-2021	22	26				- 0.85	[0.65; 0.96]
Norio Katon-2018	19	21		-		- 0.90	[0.70; 0.99]
William W. Chance-2017	36	49		-		0.73	[0.59; 0.85]
Random effects model		548			-	0.86	[0.81; 0.90]
Heterogeneity: $I^2 = 52\%$, $\tau^2 = 0.1$	2360, <i>p</i> = 0.01						
Group = ≥100Gy							
Claire van Vliet-2022	52	54				- 0.96	[0.87; 1.00]
Cyrielle Scouarnec-2019	32	33				- 0.97	[0.84; 1.00]
Nicholas B. Figura-2020	43	45				- 0.96	[0.85; 0.99]
Random effects model		132			-	• 0.96	[0.91: 0.98]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, μ	0 = 0.95						
Random effects model		1463			-	0.82	[0.76: 0.86]
Heterogeneity: $l^2 = 73\%$ $\tau^2 = 0.0$	$6673 \ n < 0.01$		Г	Т	T	7 0.02	[0.1 0, 0.00]
Test for subgroup differences: ~	$c^2 = 33.74$ df = 1	2(n < 0.01) = 0	2 0.4	0.6	0.8	1	
reserver subgroup untereffices. χ	$_{2} = 55.74, \text{ of } = 7$	- (0 - 0.01) (2 0.4	0.0	0.0		

Study	Events	Total	Pr	oportion	95%-CI	Weight
Group = < 9Gy						
Theresa Voglhuber-2020	25	34	•	0.74	[0.56; 0.87]	5.5%
Sonali Rudra-2013	9	13		0.69	[0.39; 0.91]	3.2%
Aysenur Elmali-2022	115	146	_ _	0.79	0.71; 0.85]	8.0%
Kim Burjakow-2018	22	38	_	0.58	[0.41; 0.74]	5.3%
A. Baydoun-2021	37	57	_	0.65	0.51: 0.77	6.3%
Eren Celik-2016	9	15	_	0.60	[0.32: 0.84]	3.3%
Diego A.S. Toesca-2018	36	39		0.92	0.79: 0.981	7.5%
Corbin A.Helis-2020	25	29	_	0.86	[0.68: 0.96]	6.2%
Laila Koenig-2020	24	28	_	0.86	[0.67; 0.96]	6.1%
Ciro Franzese-2021	127	149		0.85	0.79: 0.911	8.3%
Random effects model		548		0.78	[0.70: 0.85]	59.8%
Heterogeneity: $I^2 = 70\%$, $\tau^2 = 0.0$	090, <i>p</i> < 0.01				• / •	
Group = ≥9Gy						
Alfred Haidenberger-2017	23	24		0.96	[0.79; 1.00]	7.7%
Leonid B. Reshko-2021	22	26	_	0.85	[0.65; 0.96]	5.8%
Giuseppe Facondo-2021	17	25		0.68	[0.46; 0.85]	4.6%
Norio Katoh-2018	19	21		0.90	0.70; 0.99]	6.2%
Franao Casamassima-2012	52	58	-	0.90	[0.79; 0.96]	7.7%
Felix Ehret-2022	67	72	_	0.93	[0.85; 0.98]	8.3%
Random effects model		226	-	0.91	[0.87; 0.95]	40.2%
Heterogeneity: $I^2 = 44\%$, $\tau^2 = 0.0$	002, <i>p</i> = 0.11					
Random effects model		774		0.82	[0.76; 0.88]	100.0%

FIGURE 3

The forest plot of subgroup analysis for 1-year local control by dose per fraction with the range of Biological effective dose (α/β =10)(60-80Gy).

Study	Events	Total	Proportion	959
Group = ≤5Gy				
Corbin A.Helis-2020	25	29		[0.68;
Kim Burjakow-2018	22	38	0.58	[0.41;
Laila Koenig-2020	24	28	0.86	0.67
Michael Guiou-2012	5	11	← 045	[0 17·
Sheema Chawla-2009	19	35	0.54	10 37·
Random effects model		141	0.69	[0.52:
Heterogeneity: $I^2 = 72\%$, $\tau^2 = 0.4$	685, <i>p</i> < 0.01			[0:0 1 ,
Group = 5 1-8 9Gv				
A Baydoun-2021	37	57	0.65	IO 51 ⁺
Ciro Franzoso 2021	127	149		[0.01,
Diego Δ S Toesca 2018	36	30		10.79
Fron Colik 2016		15		[0.79, [0.32
Eable Arcidiacone 2020	3	39	0.00	10.32,
Marta Scorpotti 2012	24	30	0.03	10.40
Sonali Dudra 2012	24	12	0.67	0.49,
Soliali Ruula-2013	9	13	0.09	0.59,
Milliam W. Chance 2017	20	34	0.74	0.50
William W. Chance-2017	30	49	0.73	[0.59,
Aysenur Eimail-2022	115	140	0.79	[0.71,
Random effects model	000 - 10.04	5/6	0.75	[0.68;
Heterogeneity: $I^{-} = 62\%$, $\tau^{-} = 0.1$	669, $p < 0.01$			
Group = 9-14.9Gy			_	
Claire van Vliet-2022	52	54	0.96	[0.87;
Giuseppe Facondo-2021	17	25	0.68	[0.46;
Franao Casamassima-2012	52	58	0.90	[0.79;
Kamran A. Ahmed-2013	12	13	0.92	[0.64;
Leonid B. Reshko-2021	22	26	0.85	[0.65;
Nicholas B. Figura-2020	43	45		[0.85;
Norio Katoh-2018	19	21	0.90	[0.70]
Random effects model		242		[0.82;
Heterogeneity: $I^2 = 58\%$, $\tau^2 = 0.4$	148, <i>p</i> = 0.03			- /
Group = ≥15Gy				
Alfred Haidenberger-2017	23	24	0.96	[0.79;
Cyrielle Scouarnec-2019	32	33		[0.84;
Felix Ehret-2022	67	72		0.85
Jordan Torok-2011	6	9	0.67	0.30
Random effects model		138	- 0.93	[0.87:
Heterogeneity: $I^2 = 60\%$, $\tau^2 = 0$,	o = 0.06			•,
Random effects model		1097	0.82	[0.75;
Hotorogonoity: $l^2 = 720/(\pi^2 = 0.7)$	004 0.04			

FIGURE 4

The forest plot of subgroup analysis for one-year local control by dose per fraction.

100% patients = 63%: 67%: 79%, c2 = 6.88; P=0.038; 41%: 46%: 63%, c2 = 12.72, P=0.002, Figures 5, 6). The side effects caused by the use of tracking technology accounted for 1.2% (3/257) of cases, all of which were associated with fiducial placement, including 1 case of spontaneous hematoma absorption, 1 case of pneumothorax, and 1 case requiring chest tube insertion, and these were concentrated in a single study (14). In high-tracking adoption group, the Grade 3+ toxicity response was 0.9% (2/213) and low-tracking adoption group, it was 1.1% (12/1091)(Differences were not statistically significant). Adrenal insufficiency morbidity was 1.8% (4/213) and 0.6% (6/979) separately because in high-tracking adoption group, three patients had only one remaining adrenal gland received SBRT.

Discussion

Delivery of high-dose on adrenal gland can be challenging due to the proximity of risk organs such as the duodenum, small intestine, and stomach, with dose limit violations potentially leading to lifethreatening complications (40). In clinical practice, compromises on target doses are necessary (4, 8). Moreover, the overuse of radiation can trigger the expression of certain proteins, such as Transforming Growth Factor (TGF), Indoleamine-pyrrole 2,3-dioxygenase (IDO), and Programmed cell Death-Ligand 1 (PD-L1), which contribute to an increase in immune-suppressive cells like Tregs and tumorassociated macrophages (TAMs) (41), and have harmful effects on the immune system's ability to fight cancer cells. Thus, seeking a dose scheme under 100Gy of BED10 not only helps to protect the surrounding organs at risk, but also helps to weaken the local immunosuppression around the tumor.

Our study underscores the importance of fractionated doses and emphasizes that fractionated doses should not be less than 9 Gy. When it is not feasible to achieve the currently recommended BED10 \geq 100 Gy total dose, our study offers a solution by increasing the fractionated dose. This finding aligns with experimental data (42-44), as doses greater than 8-10 Gy, as opposed to doses greater than 5 Gy, can result in rapid endothelial cell apoptosis, leading to extensive tumor cell death and severe hypoxia in the microenvironment.

Tracking = 0-20% patients 0.40 [0.26; 0.56] 4.3% A. Baydoun-2021 131 326 0.40 [0.26; 0.56] 4.3% Dariel Buery-2021 131 326 0.40 [0.26; 0.56] 4.3% Ciro Franzese-2021 76 142 0.54 [0.45; 0.62] 5.0% Claire van Vilet-2022 31 51 0.61 [0.46; 0.74] 4.4% Giuseppe Facondo-2020 16 24 0.61 [0.46; 0.74] 4.4% Giuseppe Facondo-2021 16 24 0.67 [0.45; 0.84] 3.7% FRANAO CASAMASSIMA-2012 7 48 0.67 [0.45; 0.84] 3.7% Kim Bujakow-2018 14 33 0.42 [0.25; 0.61] 4.0% Kristin Plichta-2017 3 10 0.30 [0.07; 0.65] 2.7% Leonid B. Reshko-2021 7 23 0.30 [0.13; 0.53] 3.7% Maria Scorsetti-2012 2 2 34 0.51 [0.35; 0.67] 4.2% Nicholas B. Figura 2020 21 41 0.51 [0.35; 0.67] 4.2% ShEEMA CHAWLA-2009 8 30 0.7 [0.12; 0.46] 4.1% Sonali Rudra-2013 5 10 0.50 [0.19; 0.81] 2.4% Tracking = 20-80% patients 0.56 [0.29; 0.63] 4.0% 0.45 [0.29; 0.63] 4.0% Norio Katoh-2018 9 20 0.46 [0.29; 0.63] 4.0% 0.46 [0.29; 0.63] 4.1% Vililia W. Chance-2017 17 23 </th <th>Tracking = 0.20% patients 0 4. Baydoun-2021 19 47 A. Baydoun-2021 19 47 0.40 0.26; 0.56 4.3% Daniel Buergy-2021 16 12 0.40 0.25; 0.46 0.52 Claire van Vilet-2022 31 51 0.40 0.25; 0.46 0.44 0.45 0.52 50% Claire van Vilet-2022 31 51 0.40 0.25; 0.46 0.44 0.45 0.46 0.25 0.46 0.45 0.46 0.25 0.46 0.45 0.46 0.25 0.46 0.46 0.46 0.46 0.46 <td< th=""><th>Study</th><th>Events</th><th>Total</th><th></th><th>Proportion</th><th>95%-CI</th><th>Weight</th></td<></th>	Tracking = 0.20% patients 0 4. Baydoun-2021 19 47 A. Baydoun-2021 19 47 0.40 0.26 ; 0.56 4.3% Daniel Buergy-2021 16 12 0.40 0.25 ; 0.46 0.52 Claire van Vilet-2022 31 51 0.40 0.25 ; 0.46 0.44 0.45 0.52 50% Claire van Vilet-2022 31 51 0.40 0.25 ; 0.46 0.44 0.45 0.46 0.25 0.46 0.45 0.46 0.25 0.46 0.45 0.46 0.25 0.46 0.46 0.46 0.46 0.46 <td< th=""><th>Study</th><th>Events</th><th>Total</th><th></th><th>Proportion</th><th>95%-CI</th><th>Weight</th></td<>	Study	Events	Total		Proportion	95%-CI	Weight
A. Baydoun-2021 19 47 0.40 0.26, 0.56] 4.3% Daniel Buergy-2021 131 326 0.40 0.25, 0.66] 5.0% Claire van Vilet-2022 31 51 0.61 0.46 0.2% 0.558 4.3% Giuseppe Facondo-2020 15 37 0.41 0.25, 0.581 4.3% Kim Bujakow-2018 14 33 0.42 0.25, 0.581 4.3% Kim Bujakow-2018 14 33 0.42 0.25, 0.581 4.3% Kinstin Plichta-2017 3 10 0.67 0.45, 0.841 3.7% Leonid B. Reshko-2021 7 23 0.30 0.07, 0.651 2.7% Leonid B. Reshko-2021 7 23 0.30 0.16, 0.52 3.9% ShEEMA CHAWLA-2009 8 30 0.51 0.567 4.2% ShEEMA CHAWLA-2020 21 41 0.51 0.567 4.2% Wilham W. Chance-2017 18 43 0.42 0.27, 0.58 4.2% Random effects model 967 0.46 0.23, 0.683 4.0%	A Baydoun-2021 19 47 - 0.40 [0.26, 0.56] 4.3% Ciro Franzese-2021 76 142 0.45 [0.35, 0.46] 5.2% Ciro Franzese-2021 76 142 0.4 [0.45, 0.62] 5.0% Claire van Vilet-2022 31 51 - 0.61 [0.46, 0.74] 4.4% Frabio Arcidiacono-2020 15 37 - 0.41 [0.25, 0.58] 4.1% Giuseppe Facondo-2021 16 24 - 0.57 [0.45, 0.84] 3.7% FRANAO CASAMASSIMA-2012 7 48 - 0.15 [0.06; 0.28] 4.8% Kirn Buigkow-2018 14 33 - 0.42 [0.25, 0.61] 4.0% Kirstin Pilcha-2017 3 10 - 0.30 [0.07; 0.65] 2.7% Mata Scorsetti-2012 22 34 - 0.30 [0.07; 0.65] 2.7% Mata Scorsetti-2012 19 28 - 0.30 [0.07; 0.65] 2.7% Nicholas B. Figura-2020 21 41 - 0.51 [0.35, 0.67] 4.2% SHEEMA CHAWLA-2009 8 30 - 0.30 [0.13; 0.53] 3.7% Mitchael Guiou-2012 1 9 - 0.11 [0.00; 0.48] 3.5% SHEEMA CHAWLA-2009 8 30 - 0.51 [0.35; 0.67] 4.2% SHEEMA CHAWLA-2009 8 30 - 0.51 [0.35; 0.67] 4.2% Random effects model 967 - 0.46 [0.29; 0.63] 4.0% Norio Katoh-2017 18 43 - 0.46 [0.29; 0.63] 4.0% Norio Katoh-2018 9 20 - 0.41 [0.34; 0.48] 72.5% Heterogeneity: $l^2 = 0.9k$, $r^2 = 0.0175$, $p < 0.01$ Tracking = 20-80% patients Diego A.S. Toesca-2018 16 35 - 0.46 [0.29; 0.63] 4.0% Norio Katoh-2018 9 20 - 0.41 [0.34; 0.48] 72.5% Heterogeneity: $l^2 = 0.0, p = 0.96$ Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 - 0.46 [0.29; 0.63] 4.0% Niarbi Zubi Zubi Zubi Zubi Zubi Zubi Zubi Zu	Tracking = 0-20% patient	S		_			
Daniel Buergy-2021 131 326 0.40 [0.35, 0.46] 5.2% Ciro Franzese-2021 76 142 0.54 [0.45, 0.62] 5.0% Claire van Viiet-2022 31 51 0.41 [0.25, 0.58] 4.1% Giuseppe Facendo-20201 16 24 0.61 [0.46, 0.74] 4.4% FRANAO CASAMASSIMA-2012 7 48 0.42 [0.25, 0.61] 4.0% Kristin Pitchta-2017 3 10 0.30 [0.07, 0.65] 2.7% Laila K7nig-2020 9 28 0.32 [0.6, 0.52] 3.9% Leonid B. Reshko-2021 7 23 0.30 [0.3, 0.53] 3.7% Marta Scoretti-2012 22 34 0.65 [0.46, 0.08] 4.1% Sonaii Rudra-2013 5 10 0.30 [0.13, 0.53] 3.7% Michael Guiou-2012 1 9 0.11 [0.05, 0.67] 4.2% Sonaii Rudra-2013 5 10 0.50 [0.19, 0.55] 4.0% Norio Katch-2018 9 0.41 0.32 [0.29, 0.63] 4.0% </td <td>Daniel Buergy-2021 131 326 0.40 [0.35; 0.46] 5.2% Ciro Franzes-2021 76 142 0.40 [0.35; 0.46] 5.2% Claire van Vliet-2022 31 51 0.61 [0.46; 0.74] 4.4% Fabio Arcidiacono-2020 15 37 0.41 [0.25; 0.58] 4.1% Giuseppe Facondo-2021 16 24 0.41 [0.25; 0.58] 4.1% Giuseppe Facondo-2021 16 24 0.41 [0.25; 0.58] 4.1% Kristin Plichta-2017 1 3 10 0.50 [0.46] 0.52 1.7% Laita K?nig-2020 9 28 0.32 [0.16; 0.52] 3.9% Leonid B. Reshko-2021 7 23 0.30 [0.07; 0.56] 2.7% Mata Scorsetti-2012 2 2 34 0.65 [0.46] 0.80 4.1% Sonali Rudra-2013 5 10 0.13; 0.53 3.7% Milliam W. Chance-2017 18 43 0.00 0.05 [0.19; 0.81] 2.4% Thereas Voglhuber-2020 11 31 0.00 0.42 [0.27; 0.58] 4.2% Random effects model 967 Heterogeneity: $l^2 = 78\%$, $r^2 = 0.075$, $p = 0.96$ Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 0.44 0.65 [0.46] 0.38; 3.1% Morio Katoh-2018 9 20 0.44 [0.32; 0.68] 3.4% 0.45 [0.23; 0.68] 3.4% 0.46 [0.29; 0.63] 4.0% 0.46 [0.29; 0.63] 4.0% 0.46 [0.32; 0.59] 7.4% Heterogeneity: $l^2 = 78\%$, $r^2 = 0.075$, $p = 0.96$ Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 0.46 0.45 [0.23; 0.68] 3.4% 0.46 [0.32; 0.69] 7.4% Heterogeneity: $l^2 = 78\%$, $r^2 = 0.000$ 7.5 0.01 Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 0.46 0.45 [0.32; 0.59] 7.4% Heterogeneity: $l^2 = 78\%$, $r^2 = 0.096$ Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 0.48 3.1% 0.46 [0.39; 0.52] 100.0% Random effects model 199 Heterogeneity: $l^2 = 78\%$, $r^2 = 0.000$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 79\%$, $r^2 = 0.000$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 79\%$, $r^2 = 0.000$, $p = 0.09$ Random effects model 199</td> <td>A. Baydoun-2021</td> <td>19</td> <td>47</td> <td></td> <td>0.40</td> <td>[0.26; 0.56]</td> <td>4.3%</td>	Daniel Buergy-2021 131 326 0.40 [0.35; 0.46] 5.2% Ciro Franzes-2021 76 142 0.40 [0.35; 0.46] 5.2% Claire van Vliet-2022 31 51 0.61 [0.46; 0.74] 4.4% Fabio Arcidiacono-2020 15 37 0.41 [0.25; 0.58] 4.1% Giuseppe Facondo-2021 16 24 0.41 [0.25; 0.58] 4.1% Giuseppe Facondo-2021 16 24 0.41 [0.25; 0.58] 4.1% Kristin Plichta-2017 1 3 10 0.50 [0.46] 0.52 1.7% Laita K?nig-2020 9 28 0.32 [0.16; 0.52] 3.9% Leonid B. Reshko-2021 7 23 0.30 [0.07; 0.56] 2.7% Mata Scorsetti-2012 2 2 34 0.65 [0.46] 0.80 4.1% Sonali Rudra-2013 5 10 0.13; 0.53 3.7% Milliam W. Chance-2017 18 43 0.00 0.05 [0.19; 0.81] 2.4% Thereas Voglhuber-2020 11 31 0.00 0.42 [0.27; 0.58] 4.2% Random effects model 967 Heterogeneity: $l^2 = 78\%$, $r^2 = 0.075$, $p = 0.96$ Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 0.44 0.65 [0.46] 0.38; 3.1% Morio Katoh-2018 9 20 0.44 [0.32; 0.68] 3.4% 0.45 [0.23; 0.68] 3.4% 0.46 [0.29; 0.63] 4.0% 0.46 [0.29; 0.63] 4.0% 0.46 [0.32; 0.59] 7.4% Heterogeneity: $l^2 = 78\%$, $r^2 = 0.075$, $p = 0.96$ Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 0.46 0.45 [0.23; 0.68] 3.4% 0.46 [0.32; 0.69] 7.4% Heterogeneity: $l^2 = 78\%$, $r^2 = 0.000$ 7.5 0.01 Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 0.46 0.45 [0.32; 0.59] 7.4% Heterogeneity: $l^2 = 78\%$, $r^2 = 0.096$ Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 0.48 3.1% 0.46 [0.39; 0.52] 100.0% Random effects model 199 Heterogeneity: $l^2 = 78\%$, $r^2 = 0.000$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 79\%$, $r^2 = 0.000$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 79\%$, $r^2 = 0.000$, $p = 0.09$ Random effects model 199	A. Baydoun-2021	19	47		0.40	[0.26; 0.56]	4.3%
Ciro Franzese-2021 76 142 0.54 $[0.45, 0.62]$ 5.0% Claire van Viiet-2022 31 51 0.64 $[0.46, 0.74]$ 4.4% Fabio Arcidiacono-2020 15 37 0.41 $[0.25, 0.58]$ 4.1% Giuseppe Facondo-2021 16 24 0.67 $[0.45, 0.84]$ 3.7% FRANAO CASAMASSIMA-2012 7 48 0.01 $[0.67, 0.62]$ 5.0% Kim Burjakow-2018 14 33 0.42 $[0.25, 0.61]$ 4.0% Kristin Plichta-2017 3 10 0.30 $[0.07, 0.65]$ 2.7% Laila K?nig-2020 9 28 0.42 $[0.25, 0.61]$ 4.0% Michael Guiou-2012 7 23 0.30 $[0.13, 0.53]$ 3.7% Marta Scorsetti-2012 22 34 0.65 $[0.46, 0.80]$ 4.1% Nicholas B. Figura-2020 21 41 0.51 $[0.35, 0.67]$ 4.2% SHEEMA CHAWLA-2009 8 30 0.27 $[0.12, 0.46]$ 8.5% Nicholas B. Figura-2020 21 41 0.51 $[0.35, 0.67]$ 4.2% SHEEMA CHAWLA-2009 8 30 0.27 $[0.12, 0.46]$ 8.5% Norio Katon-2017 18 43 0.42 0.27, 0.58] 4.2% Random effects model 967 0.41 $[0.34; 0.48]$ 7.25% Heterogeneity: $I^2 = 78\%$, $\tau^2 = 0.0175$, $\rho < 0.01$ Tracking = 80-100% patients Diego A.S. Toesca-2018 16 35 Norio Katon-2018 9 20 0.46 $[0.29; 0.63]$ 4.0% O.45 $[0.23; 0.68]$ 3.4% O.45 $[0.23; 0.68]$ 3.4% O.45 $[0.23; 0.68]$ 3.4% O.46 $[0.29; 0.63]$ 4.0% O.46 $[0.38; 0.88]$ 3.1% Cyrielle Scourance-2017 17 7 23 O.74 $[0.52; 0.90]$ 3.8% O.67 $[0.38; 0.88]$ 3.1% Cyrielle Scourance-2017 17 7 23 O.74 $[0.52; 0.90]$ 3.8% O.67 $[0.38; 0.88]$ 3.1% Cyrielle Scourance-2019 19 31 Feix Chect-2022 38 55 O.46 $[0.29; 0.63]$ 4.0% O.46 $[0.39; 0.52]$ 100.0% Heterogeneity: $I^2 = 79\%$, $\tau^2 = 0.0060$, $p = 0.09$ Random effects model 199 Heterogeneity: $I^2 = 79\%$, $\tau^2 = 0.00060$, $p = 0.09$ Random effects model 199 Heterogeneity: $I^2 = 79\%$, $\tau^2 = 0.00060$, $p = 0.09$ Random effects model 199 Heterogeneity: $I^2 = 79\%$, $\tau^2 = 0.00060$, $p = 0.09$ Random effects model 199 Heterogeneity: $I^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$	Ciro Franzese-2021 76 142 0.54 [0.45, 0.62] 5.0% Claire van Vilet-2022 31 51 0.61 [0.46, 0.74] 4.4% Fabio Arcidiacono-2020 15 37 0.61 [0.46, 0.74] 4.4% Guiseppe Facondo-2021 16 24 0.67 [0.45, 0.62] 5.0% FRANAO CASSMMASSIMA-2012 7 48 0.41 [0.25, 0.58] 4.1% Kim Burjakow-2018 14 33 0.44 0.42 [0.25, 0.61] 4.0% Kristin Piichta-2017 3 10 # 0.42 [0.25, 0.61] 4.0% Lenid B. Reshko-2021 7 23 0.30 [0.07, 0.65] 2.7% Leidi K?nig-2020 21 41 0.51 [0.30, 0.07, 0.65] 2.7% Leidi K?nig-2020 21 41 0.51 [0.35, 0.67] 4.2% Nicholas B. Figura-2020 21 41 0.51 [0.35, 0.67] 4.2% Sonali Ruidra-2013 5 10 0.55 4.0% 0.44 [0.29, 0.63] 4.0% William W. Chance-2017	Daniel Buergy-2021	131	326		0.40	[0.35; 0.46]	5.2%
Claire van Vliet.2022 31 51 $0.46 (0.74) 4.4\%$ Fabio Arcidiacono-2020 15 37 $0.41 (0.25, 0.58) 4.1\%$ Giuseppe Facondo-2021 16 24 $0.41 (0.25, 0.58) 4.1\%$ Kim Burjakow-2018 14 33 $0.41 (0.25, 0.58) 4.1\%$ Kim Burjakow-2018 14 33 $0.41 (0.25, 0.58) 4.1\%$ Kim Burjakow-2017 3 10 $0.42 (0.25, 0.61) 4.0\%$ Leonid B. Reshko-2021 7 23 $0.32 (0.16, 0.52) 3.9\%$ Leonid B. Reshko-2021 7 23 $0.32 (0.16, 0.52) 3.9\%$ Leonid B. Reshko-2021 7 23 $0.32 (0.16, 0.52) 3.9\%$ Nicholas B. Figura-2020 21 41 $0.51 (0.35, 0.67) 4.2\%$ Nicholas B. Figura-2020 11 31 $0.53 (0.19, 0.55) 4.0\%$ Nicholas B. Figura-2020 11 31 $0.53 (0.19, 0.55) 4.0\%$ Numina W. Chance-2017 18 43 $0.42 (0.27, 0.58) 4.2\%$ Random effects model 967 $0.41 (0.34; 0.48) 72.5\%$ Heterogeneity: $l^2 = 78\%$, $t^2 = 0.0175$, $p < 0.01$ Tracking = 80-100% patients Diego A.S. Toesca-2018 16 35 $0.46 (0.29, 0.63) 4.0\%$ Norio Katoh-2018 9 20 $0.45 (0.23, 0.68) 3.4\%$ Random effects model 55 $0.41 (0.34; 0.48) 72.5\%$ Heterogeneity: $l^2 = 0\%$, $t^2 = 0, p = 0.98$ Tracking = 80-100% patients Diego A.S. Toesca-2017 17 23 $0.44 (0.45 (0.23, 0.68) 3.4\%$ Random effects model 199 Heterogeneity: $l^2 = 0\%$, $t^2 = 0.0000$, $p = 0.09$ Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 $0.47 (0.52; 0.90) 3.8\%$ Kianzhi Zhao-2020 37 75 $0.61 (0.48, 0.48) (0.45 (0.23; 0.59) 7.4\%$ Heterogeneity: $l^2 = 0.0000$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 70\%$, $t^2 = 0.0000$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 70\%$, $t^2 = 0.0000$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 70\%$, $t^2 = 0.0000$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 70\%$, $t^2 = 0.0000$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 70\%$, $t^2 = 0.0000$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 70\%$, t^2	Claire van Vilet-2022 31 51 $(-1, -1, -1, -1, -1, -1, -1, -1, -1, -1, $	Ciro Franzese-2021	76	142	÷	0.54	[0.45; 0.62]	5.0%
Fabio Arcidiacono-2020 15 37 0.41 [0.25] 0.58 4.1% Giuseppe Facondo-2021 16 24 0.67 [0.45] 0.84 3.7% FRANAO CASAMASSIMA-2012 7 48 0.67 [0.45] 0.84 3.7% Kim Burjakow-2018 14 33 0.41 [0.67] 0.45 0.84 3.7% Kim Burjakow-2017 3 10 0.30 [0.07] 0.65 2.7% Leonid B. Reshko-2021 7 23 0.30 [0.13] 0.53 3.7% Matta Scorsetti-2012 22 34 0.65 [0.46] 0.80 4.1% Michael Guiou-2012 1 9 0.30 [0.13] 0.53 3.7% Michael Guiou-2012 1 9 0.51 [0.35] 0.67] 4.2% Sonali Rudra-2013 5 10 0.51 [0.35] 0.67] 4.2% Random effects model 967 0.35 [0.19] 0.81] 2.4% Norio Katoh-2018 9 20 0.46 [0.22] 0.63] 4.0% Norio Katoh-2018 9 20 0.46 [0.22] 0.63] 4.0% <	Fabio Arcidiacono-2020 15 37 0.41 0.25; 0.58] 4.1% Giuseppe Facondo-2021 16 24 0.67 0.45; 0.68] 3.7% FRANAO CASAMASSIMA-2012 7 48 0.55 0.67 0.45; 0.84] 3.7% Kim Burjakow-2018 14 33 0 0.57 0.067; 0.45; 0.84] 3.7% Laila K?nig-2020 9 28 0.51 0.06; 0.28] 4.8% Marta Scorsetti-2012 22 34 0.30 0.07; 0.65; 2.7% Laila K?nig-2020 21 41 0.51 0.065 0.46; 0.80] 4.1% Michael Guiou-2012 1 9 0.31 0.11 0.00; 0.48] 3.5% Nicholas B. Figura-2020 21 41 0.51 0.35; 0.67] 4.2% ShEEEMA CHAWLA-2009 8 30 0.51 0.019; 0.55] 4.0% William W. Chance-2017 18 43 0.45 0.22; 0.63] 4.0% Norio Katoh-2018 9 20 0.45 0.23; 0.68] 3.4% Oxif I 0.42; 0.78] 4.2%	Claire van Vliet-2022	31	51		0.61	[0.46; 0.74]	4.4%
Giuseppe Facondo-2021 16 24 0.67 (0.45; 0.84] 3.7% FRANAO CASAMASSIMA-2012 7 48 0.15 (0.06; 0.28] 4.8% Kim Bujakow-2018 14 33 0.42 (0.25; 0.61] 4.0% Laila K?nig-2020 9 28 0.30 (0.07; 0.65] 2.7% Laila K?nig-2020 9 28 0.32 (0.16; 0.52] 3.9% Leonid B. Reshko-2021 7 23 0.30 (0.07; 0.65] 2.7% Marta Scorsetti-2012 22 34 0.65 (0.46; 0.80) 4.1% Sichael S. Figura-2020 21 41 0.51 (0.35; 0.67] 4.2% SHEEMA CHAWLA-2009 8 30 0.27 (0.12; 0.46] 4.1% Sonali Rudra-2013 5 10 0.51 (0.35; 0.67] 4.2% Random effects model 967 0.45 (0.45; 0.28] 3.4% Random effects model 967 0.44 (0.45 (0.32; 0.68] 3.4% Norio Katoh-2018 9 20 0.44 (0.45 (0.32; 0.68] <td< td=""><td>Giuseppe Facondo-2021 16 24 0.67 [0.45; 0.84] 3.7% FRANAO CASAMASSIMA-2012 7 48 0.15 [0.06; 0.28] 4.8% Kirstin Plichta-2017 3 10 0.15 [0.06; 0.28] 4.8% Laila K?nig-2020 9 28 0.30 [0.07; 0.65] 2.7% Laila K?nig-2020 9 28 0.30 [0.07; 0.65] 2.7% Marta Scorsetti-2012 1 9 0.32 [0.16; 0.52] 3.9% Michael Guiou-2012 1 9 0.51 [0.55; 0.67] 4.2% ShEEMA CHAWLA-2009 8 30 0.11 [0.00; 0.48] 3.5% Shteevalue 9 0.11 [0.00; 0.48] 3.5% 0.51 [0.35; 0.67] 4.2% Shteevalue 9 0.11 0.01 0.50 [0.19; 0.81] 2.4% Shteevalue 9 0.41 0.35 0.19 0.51 0.35 0.19 0.55 0.40 0.51 0.35 0.19 0.51 0.55 0.40 0.55 0.61 0.42 0.27</td></td<> <td>Fabio Arcidiacono-2020</td> <td>15</td> <td>37</td> <td></td> <td>0.41</td> <td>[0.25; 0.58]</td> <td>4.1%</td>	Giuseppe Facondo-2021 16 24 0.67 [0.45; 0.84] 3.7% FRANAO CASAMASSIMA-2012 7 48 0.15 [0.06; 0.28] 4.8% Kirstin Plichta-2017 3 10 0.15 [0.06; 0.28] 4.8% Laila K?nig-2020 9 28 0.30 [0.07; 0.65] 2.7% Laila K?nig-2020 9 28 0.30 [0.07; 0.65] 2.7% Marta Scorsetti-2012 1 9 0.32 [0.16; 0.52] 3.9% Michael Guiou-2012 1 9 0.51 [0.55; 0.67] 4.2% ShEEMA CHAWLA-2009 8 30 0.11 [0.00; 0.48] 3.5% Shteevalue 9 0.11 [0.00; 0.48] 3.5% 0.51 [0.35; 0.67] 4.2% Shteevalue 9 0.11 0.01 0.50 [0.19; 0.81] 2.4% Shteevalue 9 0.41 0.35 0.19 0.51 0.35 0.19 0.55 0.40 0.51 0.35 0.19 0.51 0.55 0.40 0.55 0.61 0.42 0.27	Fabio Arcidiacono-2020	15	37		0.41	[0.25; 0.58]	4.1%
FRANAO CASAMASSIMA-2012 7 48	FRANAO CASAMASSIMA-2012 7 48	Giuseppe Facondo-2021	16	24		0.67	[0.45; 0.84]	3.7%
Kim Burjakow-2018 14 33 0.42 [0.25; 0.61] 4.0% Kristin Plichta-2017 3 10 0.30 [0.07; 0.65] 2.7% Laila K?nig-2020 9 28 0.30 [0.07; 0.65] 2.7% Marta Scorsetti-2012 22 34 0.51 [0.46; 0.80] 4.1% Michael Guiou-2012 1 9 0.11 [0.00; 0.48] 3.5% Nicholas B. Figura-2020 21 41 0.51 [0.35; 0.67] 4.2% SHEEMA CHAWLA-2009 8 30 0.27 [0.12; 0.46] 4.1% Sonali Rudra-2013 5 10 0.50 [0.19; 0.81] 2.4% Theresa VogIhuber-2020 11 31 0.50 [0.19; 0.85] 4.0% William W. Chance-2017 18 43 0.42 [0.27; 0.58] 4.2% Random effects model 967 0.41 [0.34; 0.48] 72.5% Heterogeneity: $l^2 = 0.80\%$ patients 0.45 [0.32; 0.69] 7.4% Norio Katoh-2018 9 20 0.45 [0.32; 0.63] 4.0%	Kim Burjakow.2018 14 33	FRANAO CASAMASSIMA	-2012 7	48		0.15	[0.06; 0.28]	4.8%
Kristin Plichta-2017 3 10 0.30 $[0.07; 0.65]$ 2.7% Laila K?nig-2020 9 28 0.32 $[0.16; 0.52]$ 3.9% Leonid B. Reshko-2021 7 23 0.30 $[0.07; 0.65]$ 2.7% Marta Scorsetti-2012 2 34 0.30 $[0.07; 0.65]$ 3.9% Micholas B. Figura-2020 21 41 0.51 $[0.35; 0.67]$ 4.2% Sonali Rudra-2013 5 10 0.51 $[0.35; 0.67]$ 4.2% Sonali Rudra-2013 5 10 0.55 $[0.19; 0.81]$ 2.4% Nicholas B. Figura-2020 11 31 0.45 $[0.27; 0.58]$ 4.2% Random effects model 967 0.41 $[0.34; 0.48]$ 72.5% Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ 74 $[0.32; 0.59]$ 4.0% Tracking = 20-80% patients 0.45 $[0.32; 0.59]$ 4.0% Alfred Haidenberger-2017 17 23 0.74 $[0.52; 0.90]$ 3.8% Cyrielle Scouarnec-2019 19 31 0.45 $[0.32; 0.63]$ 4.0%	Kristin Plichta-2017 3 10 1 0.30 $[0.07; 0.65]$ 2.7% Laila K?nig-2020 9 28 1 0.32 $[0.16; 0.52]$ 3.9% Leonid B. Reshko-2021 7 23 1 0.30 $[0.07; 0.65]$ 2.7% Marta Scorsetti-2012 22 34 0.65 $[0.46; 0.80]$ 4.1% Michael Guiou-2012 1 9 0.11 $[0.07; 0.48]$ 3.5% Nicholas B. Figura-2020 21 41 0.51 $[0.35; 0.67]$ 4.2% Sonali Rudra-2013 5 10 0.27 $[0.12; 0.46]$ 4.1% William W. Chance-2017 18 43 0.55 $[0.97; 0.58]$ 4.0% Norio Katoh-2018 9 20 0.46 $[0.29; 0.63]$ 4.0% Norio Katoh-2018 9 20 0.46 $[0.29; 0.63]$ 4.0% Norio Katoh-2018 9 20 0.46 $[0.29; 0.63]$ 4.0% Cyrielle Scouarnec-2019 19 31 0.45 $[0.23; 0.59]$ 7.4% Heterogeneity: $l^2 = 50\%$, $t^2 = 0.0060$, $p = 0.0$	Kim Burjakow-2018	14	33		0.42	[0.25; 0.61]	4.0%
Laila K?nig-2020 9 28 0.32 [0.16; 0.52] 3.9% Leonid B. Reshko-2021 7 23 0.30 [0.13; 0.53] 3.7% Marta Scorsetti-2012 2 34 0.55 [0.46; 0.80] 4.1% Michael Guiou-2012 1 9 0.55 [0.46; 0.80] 4.1% Nicholas B. Figura-2020 21 41 0.11 [0.00; 0.48] 3.5% ShtEEMA CHAWLA-2009 8 30 0.11 [0.35; 0.67] 4.2% Sonali Rudra-2013 5 10 0.15 [0.16; 0.52] 3.9% William W. Chance-2017 18 43 0.11 [0.00; 0.48] 3.5% Notic Nance-2017 18 43 0.11 [0.35; 0.67] 4.2% Random effects model 967 0.15 [0.16; 0.52] 4.0% Noric Katch-2018 9 20 0.41 [0.34; 0.48] 72.5% Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 Alfred Haidenberger-2017 17 723 Alfred Haidenberger-2017 17 723 Alfred Haidenberger-2017 17 75 Random effects model 199 Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0.0060$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0006$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0006$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0006$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0006$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0006$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0006$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0006$, $p = 0.09$ Random effects model 1221 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ Test for subgroup differences: $x_2 = 12.72$, $df = 2 (p < 0.01)0.2$ 0.4 0.6 0.8	Laia K ² nig-2020 9 28 0.32 [0.16; 0.52] 3.9% Leonid B. Reshko-2021 7 23 0.30 [0.13; 0.53] 3.7% Marta Scorsetti-2012 22 34 0.55 [0.46; 0.80] 4.1% Michael Guiou-2012 1 9 0.55 [0.46; 0.80] 4.1% ShtEEMA CHAWLA-2009 8 30 0.27 [0.12; 0.46] 4.1% Sonali Rudra-2013 5 10 0.50 [0.19; 0.51] 4.2% ShtEEMA CHAWLA-2009 8 30 0.27 [0.12; 0.46] 4.1% William W. Chance-2017 18 43 0.42 [0.27; 0.58] 4.2% William W. Chance-2017 18 43 0.42 [0.27; 0.58] 4.2% Marta Scorsetti-2017 18 43 0.42 [0.27; 0.58] 4.2% Mitchael effects model 967 0.41 [0.34; 0.48] 72.5% Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ Tracking = 20-80% patients Diego A.S. Toesca-2018 16 35 0.45 [0.23; 0.68] 3.4% Random effects model 55 0.46 [0.29; 0.63] 4.0% Norio Katoh-2018 9 20 0.45 [0.23; 0.68] 3.4% Cyrielle Scouarnec-2019 19 31 0.45 [0.23; 0.59] 7.4% Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.96$ Tracking = 80-100% patients Afred Haidenberger-2017 17 23 0.45 [0.23; 0.68] 3.1% EREN CELIK-2016 10 15 0.67 [0.38; 0.88] 3.1% Felix Ehret-2022 38 55 0.67 [0.38; 0.81] 4.6% Xianzhi Zhao-2020 37 75 0.49 [0.55; 0.81] 4.6% Xianzhi Zhao-2020 37 75 0.49 [0.55; 0.81] 4.6% Atterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ Test for subgroup differences: $\chi_2^2 = 12.72$, df $= 2(p < 0.01)0.2$ 0.4 0.6 0.8	Kristin Plichta-2017	3	10		0.30	[0.07; 0.65]	2.7%
Leonid B. Reshko-2021 7 23 0.30 [0.13; 0.53] 3.7% Marta Scorsetti-2012 22 34 0.65 [0.46; 0.80] 4.1% Michael Guiou-2012 1 9 0.11 [0.00; 0.48] 3.5% Nicholas B. Figura-2020 21 41 0.51 [0.03; 0.67] 4.2% SHEEMA CHAWLA-2009 8 30 0.27 [0.12; 0.46] 4.1% Sonali Rudra-2013 5 10 0.50 [0.19; 0.81] 2.4% Theresa VogIhuber-2020 11 31 0.55 [0.19; 0.55] 4.0% William W. Chance-2017 18 43 0.42 [0.27; 0.58] 4.2% Random effects model 967 0.41 [0.34; 0.48] 72.5% Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ 72 0.46 [0.29; 0.63] 4.0% Norio Katch-2018 9 20 0.45 [0.23; 0.68] 3.4% Ox45 [0.23; 0.68] 3.4% 0.45 [0.23; 0.68] 3.4% Ox46 [0.29; 0.63] 4.0% 0.45 [0.23; 0.52] 0.4	Leonid B. Reshko-2021 7 23 Marta Scorsetti-2012 22 34 Michael Guiou-2012 1 9 Nicholas B. Figura-2020 21 41 Sonali Rudra-2013 5 10 Theresa Voglhuber-2020 11 31 Theresa Voglhuber-2020 11 31 Tracking = 20-80% patients Diego A.S. Toesca-2018 16 35 Diego A.S. Toesca-2018 16 35 Diego A.S. Toesca-2018 16 35 Diego A.S. Toesca-2017 17 23 Cyrielle Scouarnec-2019 19 31 EREN CELIK-2016 10 15 Feix Ehret-2022 38 55 Xianzhi Zhao-2020 37 75 Theresa model 199 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0060$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0020$, $p < 0.01$ Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.2 0.4 0.6 0.8	Laila K?nig-2020	9	28		0.32	[0.16; 0.52]	3.9%
Marta Scorsetti-2012 22 34 0.65 0.46; 0.80] 4.1% Michael Guiou-2012 1 9 0.11 0.05 0.65 0.46; 0.80] 4.1% Nicholas B. Figura-2020 21 41 0.51 0.057; 0.67] 4.2% Sonali Rudra-2013 5 10 0.51 0.35; 0.67] 4.2% Sonali Rudra-2013 5 10 0.55 0.46; 0.48] 3.5% William W. Chance-2017 18 43 0.42 0.27; 0.58] 4.2% Micholas S. Toesca-2018 967 0.42 0.42 0.27; 0.58] 4.2% Norio Katoh-2018 9 20 0.46 0.29; 0.63] 4.0% Norio Katoh-2018 9 20 0.45 0.23; 0.68] 3.4% Alfred Haidenberger-2017 17 23 0.46 0.29; 0.63] 4.0% Cyrielle Scouance-2019 19 31 0.46 0.29; 0.63] 4.0% Kitred Haidenberger-2017 17 23 0.46 0.45 0.38; 0.88] 3.1% Gelin CELK-2016 10 15	Marta Scorsetti-2012 22 34 0.65 0.46; 0.80] 4.1% Micholas B. Figura-2020 21 41 0.11 0.00; 0.48] 3.5% Nicholas B. Figura-2020 21 41 0.65 0.46; 0.80] 4.1% Sonali Rudra-2013 5 10 0.27 0.12; 0.46] 4.1% Sonali Rudra-2013 5 10 0.50 0.19; 0.81] 2.4% William W. Chance-2017 18 43 0.42 0.27; 0.58] 4.2% March Scoreative Proceed Proced Proceed Proceed Proceed Proceed Proceed Pr	Leonid B. Reshko-2021	7	23		0.30	[0.13; 0.53]	3.7%
Michael Guiou-2012 1 9 0.11 $[0.00; 0.48]$ 3.5% Nicholas B. Figura-2020 21 41 0.51 $0.35; (0.67]$ 4.2% SHEEMA CHAWLA-2009 8 30 0.57 $0.27; (0.12; 0.46]$ 4.1% Sonai Rudra-2013 5 10 0.50 $0.27; (0.12; 0.46]$ 4.1% Sonai Rudra-2013 5 10 0.50 $0.27; (0.53; (0.67)]$ 4.2% Theresa Voghuber-2020 11 31 0.50 $0.50; (0.19; 0.85]$ 4.0% William W. Chance-2017 18 43 0.46 $0.29; 0.63]$ 4.0% Random effects model 967 90 0.46 $0.29; 0.63]$ 4.0% Norio Katoh-2018 9 20 0.46 $0.29; 0.63]$ 4.0% Random effects model 55 0.46 $0.45; (0.23; 0.68]$ 3.4% Heterogeneity: $l^2 = 0\%, \tau^2 = 0, p = 0.96$ 0.46 $0.29; 0.63; 0.48]$ 3.5% Tracking = 80-100% patients 0.46 $0.45; 0.23; 0.68; 0.31, 4.6\%$ $0.67; 0.38; 0.88]$ 3.1% Gyriele Scouarnec-2019 19	Michael Guiou-2012 1 9 0.11 $[0.00; 0.48]$ 3.5% Nicholas B. Figura-2020 21 41 0.51 $[0.35; 0.67]$ 4.2% ShEEMA CHAWLA-2009 8 30 0.51 $[0.35; 0.67]$ 4.2% Sonali Rudra-2013 5 10 0.50 $[0.19; 0.81]$ 2.4% Theresa Voglhuber-2020 11 31 0.55 $[0.19; 0.55]$ 4.0% Random effects model 967 967 0.41 $[0.34; 0.48]$ 72.5% Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ 72.5% 4.2% 0.44 $[0.29; 0.63]$ 4.0% Norio Katoh-2018 9 20 0.45 $[0.23; 0.68]$ 3.4% Norio Katoh-2018 9 20 0.45 $[0.23; 0.63]$ 4.0% Random effects model 55 0.45 $[0.42; 0.78]$ 3.9% 0.61 $[0.42; 0.78]$ 3.9% Viriele Scouarnec-2019 19 31 0.67 $[0.38; 0.61]$ 4.7% 0.63 $[0.55; 0.81]$ 4.6% Kandom effects model 199 199 0.46	Marta Scorsetti-2012	22	34		0.65	[0.46; 0.80]	4.1%
Nicholas B. Figura-2020 21 41 0.51 [0.35; 0.67] 4.2% ShEEMA CHAWLA-2009 8 30 0.27 [0.12; 0.46] 4.1% Sonali Rudra-2013 5 10 0.50 [0.19; 0.81] 2.4% Theresa Voglhuber-2020 11 31 0.55 [0.9; 0.55] 4.0% William W. Chance-2017 18 43 0.42 [0.27; 0.58] 4.2% Random effects model 967 0.42 [0.27; 0.58] 4.2% Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ 0.46 [0.29; 0.63] 4.0% Norio Katoh-2018 9 20 0.46 [0.29; 0.63] 4.0% Norio Katoh-2018 9 20 0.45 [0.23; 0.68] 3.4% Random effects model 55 0.45 [0.42; 0.78] 3.9% EREN CELIK-2016 10 15 0.61 [0.42; 0.78] 3.9% Gyrielle Scouarnec-2019 19 31 0.61 [0.42; 0.78] 3.9% Kinzhi Zhao-2020 37 75 0.44 [0.49 [0.38; 0.61] 4.7%	Nicholas B. Figura-2020 21 41 0.51 $[0.35; 0.67]$ 4.2% SHEEMA CHAWLA-2009 8 30 0.50 $[0.19; 0.81]$ 2.4% Sonali Rudra-2013 5 10 0.50 $[0.19; 0.81]$ 2.4% Dheresa VogIhuber-2020 11 31 0.50 $[0.19; 0.81]$ 2.4% William W. Chance-2017 18 43 0.50 $[0.19; 0.55]$ 4.0% William W. Chance-2017 18 43 0.42 $[0.27; 0.58]$ 4.2% Random effects model 967 0.42 $[0.27; 0.58]$ 4.2% Random effects model 967 0.41 $[0.34; 0.48]$ 72.5% Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ Tracking = 20-80% patients Diego A.S. Toesca-2018 16 35 0.46 $[0.29; 0.63]$ 4.0% Norio Katoh-2018 9 20 0.45 $[0.23; 0.68]$ 3.4% Random effects model 55 0.41 $[0.34; 0.48]$ 72.5% Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0.96$ Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 0.45 $[0.42; 0.78]$ 3.9% Cyrielle Scouarnec-2019 19 31 0.45 $[0.42; 0.78]$ 3.9% EREN CELIK-2016 10 15 0.67 0.38; 0.88] 3.1% Golf $[0.42; 0.78]$ 3.9% Cyrielle Scouarnec-2019 19 31 0.46 $[0.39; 0.52]$ 100.0% Random effects model 199 Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0202$, $p < 0.01$ Test for subgroup differences: $\chi_2^2 = 12.72$, $df = 2$ ($p < 0.01$)0.2 0.4 0.6 0.8	Michael Guiou-2012	1	9 -		0.11	[0.00; 0.48]	3.5%
SHEEMA CHAWLA-2009 8 30 Sonali Rudra-2013 5 10 Theresa Voghuber-2020 11 31 William W. Chance-2017 18 43 Random effects model 967 Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ Tracking = 20-80% patients Diego A.S. Toesca-2018 16 35 Norio Katoh-2018 9 20 Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 Cyrielle Scouarnec-2019 19 31 EREN CELIK-2016 10 15 Felix Ehret-2022 38 55 Xianzhi Zhao-2020 37 75 Kianzhi Zhao-2020 37 75 Random effects model 199 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0060$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0060$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0000$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.00202$, $p < 0.01$ Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.2 0.4 0.6 0.8	SHEEMA CHAWLA-2009 8 30 Sonali Rudra-2013 5 10 Theresa Voglhuber-2020 11 31 William W. Chance-2017 18 43 Random effects model 967 Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ Tracking = 20-80% patients Diego A.S. Toesca-2018 16 35 Norio Katoh-2018 9 20 Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 Cyrielle Scouarnec-2019 19 31 Felix Ehret-2022 38 55 Xianzhi Zhao-2020 37 75 Kandom effects model 199 Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0000$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0000$, $p = 0.09$ Random effects model 1221 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.2 0.4 0.6 0.8	Nicholas B. Figura-2020	21	41	 ••	0.51	[0.35; 0.67]	4.2%
Sonali Rudra-2013 5 10 Theresa Voghuber-2020 11 31 Theresa Voghuber-2020 11 31 Random effects model 967 Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ Tracking = 20-80% patients Diego A.S. Toesca-2018 16 35 Norio Katoh-2018 9 20 Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 Cyrielle Scouarnec-2019 19 31 EREN CELIK-2016 10 15 Felix Ehret-2022 38 55 Xianzhi Zhao-2020 37 75 Random effects model 199 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0060$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0060$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0060$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0060$, $p = 0.09$ Construction of the state of the s	Sonali Rudra-2013510Theresa VogInuber-20201131William W. Chance-20171843Random effects model967Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ Tracking = 20-80% patientsDiego A.S. Toesca-201816Diego A.S. Toesca-201816Norio Katch-20189Norio Katch-20189Heterogeneity: $l^2 = 0, p = 0.96$ Tracking = 80-100% patientsAlfred Haidenberger-201717Cyrielle Scouarnec-201919Sianzhi Zhao-202037Xianzhi Zhao-202037Kandom effects model199Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0000$, $p = 0.09$ Random effects model199Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ Test for subgroup differences: $\chi_2^2 = 12.72$, $df = 2 (p < 0.01)0.2$ 0.440.450.45[0.39; 0.52]100.0%	SHEEMA CHAWLA-2009	8	30		0.27	[0.12; 0.46]	4.1%
Theresa Voglhuber-2020 11 31 0.35 [0.19; 0.55] 4.0% William W. Chance-2017 18 43 0.42 [0.27; 0.58] 4.2% Random effects model 967 967 0.41 [0.34; 0.48] 72.5% Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ Tracking = 20-80% patients 0.46 [0.29; 0.63] 4.0% Diego A.S. Toesca-2018 16 35 0.46 [0.29; 0.63] 4.0% Norio Katoh-2018 9 20 0.45 [0.23; 0.68] 3.4% Random effects model 55 0.45 [0.32; 0.59] 7.4% Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0, p = 0.96$ 0.45 [0.22; 0.90] 3.8% Cyrielle Scouarnec-2019 19 31 0.61 [0.42; 0.78] 3.9% Cyrielle Scouarnec-2020 37 75 0.63 0.67 [0.38; 0.61] 4.7% Random effects model 199 199 0.63 [0.55; 0.61] 4.6% 0.63 [0.53; 0.73] 20.1% Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$	Theresa Voghuber-2020 11 31 William W. Chance-2017 18 43 Random effects model 967 Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ Tracking = 20-80% patients Diego A.S. Toesca-2018 16 35 Norio Katch-2018 9 20 Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.96$ Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 Alfred Haidenberger-2019 19 31 EREN CELIK-2016 10 15 Felix Ehret-2022 38 55 Xianzhi Zhao-2020 37 75 Random effects model 199 Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0060$, $p = 0.09$ Random effects model 1221 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.2 0.4 0.6 0.8	Sonali Rudra-2013	5	10		0.50	[0.19; 0.81]	2.4%
William W. Chance-2017 18 43 0.42 [0.27; 0.58] 4.2% Random effects model 967 0.41 [0.34; 0.48] 72.5% Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ 0.46 [0.29; 0.63] 4.0% Tracking = 20-80% patients 0.46 [0.29; 0.63] 4.0% Norio Katoh-2018 9 20 0.45 [0.23; 0.68] 3.4% Random effects model 55 0.45 [0.22; 0.63] 4.0% Norio Katoh-2018 9 20 0.45 [0.32; 0.59] 7.4% Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.96$ 0.45 [0.32; 0.59] 7.4% Tracking = 80-100% patients 0.46 [0.42; 0.78] 3.9% Cyrielle Scournec-2019 19 31 0.61 [0.42; 0.78] 3.9% EREN CELIK-2016 10 15 0.67 [0.38; 0.61] 4.7% Nanzhi Zhao-2020 37 75 0.49 [0.38; 0.61] 4.7% Random effects model 199 199 0.46 [0.39; 0.52] 100.0% Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$	William W. Chance-201718430.42 $[0.27; 0.58]$ 4.2%Random effects model967967967967941913Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ 72.5%942Tracking = 20-80% patients920941943Diego A.S. Toesca-201816359920945Norio Katoh-2018920945945945Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.96$ 967946946946Tracking = 80-100% patients910919191Alfred Haidenberger-2017172393946Cyrielle Scouarnec-201919319394Felix Ehret-202238559494Xianzhi Zhao-202037759494Random effects model1999496Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ 9090Random effects model12219496Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ 9093Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.20.40.60.8	Theresa Voglhuber-2020	11	31		0.35	[0.19; 0.55]	4.0%
Random effects model 967 0.41 [0.34; 0.48] 72.5% Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ 0.41 [0.34; 0.48] 72.5% Tracking = 20-80% patients 0.46 [0.29; 0.63] 4.0% Diego A.S. Toesca-2018 16 35 0.46 [0.29; 0.63] 4.0% Norio Katoh-2018 9 20 0.45 [0.23; 0.68] 3.4% Random effects model 55 0.45 [0.32; 0.59] 7.4% Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0, p = 0.96$ 0.45 [0.32; 0.59] 7.4% Tracking = 80-100% patients 0.61 [0.42; 0.78] 3.9% Cyrielle Scouarnec-2019 19 31 0.61 [0.42; 0.78] 3.9% EREN CELIK-2016 10 15 0.67 [0.38; 0.88] 3.1% Felix Ehret-2022 38 55 0.69 [0.55; 0.81] 4.6% Xianzhi Zhao-2020 37 75 0.46 [0.39; 0.52] 100.0% Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ 0.46 [0.39; 0.52] 100.0% Random effects model 1221 0.46 [0.39; 0.52] 100.0% Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ 0.46 [0.39; 0.52] 100.0%	Random effects model9670.41 [0.34; 0.48]72.5%Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ Tracking = 20-80% patients0.46 [0.29; 0.63]4.0%Diego A.S. Toesca-201816350.46 [0.29; 0.63]4.0%Norio Katoh-20189200.45 [0.23; 0.68]3.4%Random effects model550.45 [0.32; 0.59]7.4%Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0, p = 0.96$ 0.41 [0.34; 0.48]72.5%Tracking = 80-100% patients0.46 [0.29; 0.63]4.0%Alfred Haidenberger-201717230.45 [0.32; 0.59]Cyrielle Scouarnec-201919310.61 [0.42; 0.78]Felix Ehret-202238550.67 [0.38; 0.88]Xianzhi Zhao-202037750.63 [0.53; 0.73]Random effects model199199Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0202, p < 0.01$ 0.40 [0.39; 0.52]Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 (p < 0.01)0.2	William W. Chance-2017	18	43		0.42	[0.27; 0.58]	4.2%
Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ Tracking = 20-80% patients Diego A.S. Toesca-2018 16 35 0.46 [0.29; 0.63] 4.0% Norio Katoh-2018 9 20 0.45 [0.23; 0.68] 3.4% Random effects model 55 0.45 [0.32; 0.59] 7.4% Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.96$ Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 0.45 [0.32; 0.59] 7.4% EREN CELIK-2016 10 15 0.61 [0.42; 0.78] 3.9% 0.61 [0.42; 0.78] 3.9% 0.67 [0.38; 0.88] 3.1% 0.69 [0.55; 0.81] 4.6% 0.69 [0.55; 0.81] 4.6% 0.69 [0.55; 0.81] 4.6% 0.49 [0.38; 0.61] 4.7% 0.63 [0.53; 0.73] 20.1% Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.2 0.4 0.6 0.8	Heterogeneity: $l^2 = 78\%$, $\tau^2 = 0.0175$, $p < 0.01$ Tracking = 20-80% patients Diego A.S. Toesca-2018 16 35 Norio Katoh-2018 9 20 Random effects model 55 Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.96$ Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 Cyrielle Scouarnec-2019 19 31 EREN CELIK-2016 10 15 Felix Ehret-2022 38 55 Xianzhi Zhao-2020 37 75 Random effects model 199 Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.2 0.4 0.6 0.8	Random effects model		967	\sim	0.41	[0.34; 0.48]	72.5%
Tracking = 20-80% patients Diego A.S. Toesca-2018 16 35 Norio Katoh-2018 9 20 Random effects model 55 Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.96$ 0.46 [0.29; 0.63] 4.0% Tracking = 80-100% patients 0.45 [0.32; 0.59] 7.4% Alfred Haidenberger-2017 17 23 0.74 [0.52; 0.90] 3.8% Cyrielle Scouarnec-2019 19 31 0.61 [0.42; 0.78] 3.9% EREN CELIK-2016 10 15 0.67 [0.38; 0.88] 3.1% Felix Ehret-2022 38 55 0.49 [0.38; 0.61] 4.7% Nianzhi Zhao-2020 37 75 0.46 [0.39; 0.52] 100.0% Heterogeneity: $I^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ 0.46 [0.39; 0.52] 100.0% Random effects model 199 0.46 [0.39; 0.52] 100.0% Heterogeneity: $I^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ 0.46 [0.39; 0.52] 100.0%	Tracking = 20-80% patients 0.46 [0.29; 0.63] 4.0% Diego A.S. Toesca-2018 16 35 Norio Katoh-2018 9 20 Random effects model 55 Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.96$ 0.46 [0.29; 0.63] 4.0% Tracking = 80-100% patients 0.45 [0.23; 0.68] 3.4% Alfred Haidenberger-2017 17 23 Cyrielle Scouarnec-2019 19 31 EREN CELIK-2016 10 15 Felix Ehret-2022 38 55 Xianzhi Zhao-2020 37 75 Random effects model 199 Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ Random effects model 199 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.2 0.4 0.6 0.8	Heterogeneity: $I^2 = 78\%$, $\tau^2 =$	0.0175, <i>p</i> < 0.01					
Diego A.S. Toesca-2018 16 35 0.46 [0.29; 0.63] 4.0% Norio Katoh-2018 9 20 0.45 [0.23; 0.68] 3.4% Random effects model 55 0.45 [0.23; 0.68] 3.4% Heterogeneity: $J^2 = 0\%$, $\tau^2 = 0$, $p = 0.96$ 0.45 [0.23; 0.69] 7.4% Tracking = 80-100% patients 0.45 [0.22; 0.90] 3.8% Cyrielle Scouarnec-2019 19 31 0.61 [0.42; 0.78] 3.9% EREN CELIK-2016 10 15 0.61 [0.42; 0.78] 3.9% Vianzhi Zhao-2020 37 75 0.69 [0.55; 0.81] 4.6% Xianzhi Zhao-2020 37 75 0.49 [0.38; 0.61] 4.7% Heterogeneity: $J^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ 0.46 [0.39; 0.52] 100.0% Heterogeneity: $J^2 = 79\%$, $\tau^2 = 0.2022$, $p < 0.01$ 0.40 0.45 [0.39; 0.52] 100.0% Tracking = 2 (p < 0.01)0.2	Diego A.S. Toesca-201816350.46 $[0.29; 0.63]$ 4.0%Norio Katoh-20189200.45 $[0.23; 0.68]$ 3.4%Random effects model55550.45 $[0.32; 0.59]$ 7.4%Heterogeneity: $l^2 = 0\%, \tau^2 = 0, p = 0.96$ 777230.45 $[0.32; 0.59]$ 7.4%Tracking = 80-100% patientsAlfred Haidenberger-201717230.74 $[0.52; 0.90]$ 3.8%Cyrielle Scouarnec-201919310.61 $[0.42; 0.78]$ 3.9%EREN CELIK-201610150.67 $[0.38; 0.88]$ 3.1%Felix Ehret-202238550.69 $[0.55; 0.81]$ 4.6%Xianzhi Zhao-202037750.49 $[0.38; 0.61]$ 4.7%Random effects model1991990.63 $[0.53; 0.73]$ 20.1%Heterogeneity: $l^2 = 50\%, \tau^2 = 0.0060, p = 0.09$ 0.46 $[0.39; 0.52]$ 100.0%Random effects model12210.46 $[0.39; 0.52]$ 100.0%Heterogeneity: $l^2 = 79\%, \tau^2 = 0.0202, p < 0.01$ 0.40.60.80.46	Tracking = 20-80% patien	nts					
Norio Katoh-2018 9 20 3.4% Random effects model 55 0.45 0.45 0.23 ; 0.68 3.4% Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.96$ $\tau^2 = 0\%$, $\tau^2 = 0.96$ 0.45 0.45 0.23 ; 0.59 7.4% Tracking = 80-100% patients 0.45 0.23 ; 0.68 3.4% 0.45 0.23 ; 0.59 7.4% Alfred Haidenberger-2017 17 23 0.74 $(0.52; 0.90)$ 3.8% 0.61 $(0.42; 0.78]$ 3.9% 0.61 $(0.42; 0.78]$ 3.9% 0.61 $(0.42; 0.78]$ 3.9% 0.61 $(0.42; 0.78]$ 3.9% 0.61 $(0.42; 0.78]$ 3.9% 0.61 $(0.42; 0.78]$ 3.9% 0.61 $(0.42; 0.78]$ 3.9% 0.61 $(0.42; 0.78]$ 3.9% 0.69 $(0.55; 0.81]$ 4.6% 0.49 $(0.38; 0.61]$ 4.7% 0.63 $(0.53; 0.73]$ 20.1% Random effects model 199 1221 0.46 $(0.39; 0.52]$ 100.0% 0.46 $(0.39; 0.52]$ 100.0% 0.46 $(0.39; 0.52]$ 100.0% 0.46	Norio Katoh-20189200.45 $[0.23; 0.68]$ 3.4% Random effects model550.45 $[0.32; 0.59]$ 7.4% Heterogeneity: $l^2 = 0\%, \tau^2 = 0, p = 0.96$ 0.45 $[0.32; 0.59]$ 7.4% Tracking = 80-100% patients0.45 $[0.32; 0.59]$ 7.4% Alfred Haidenberger-201717230.61 $[0.42; 0.78]$ 3.9% Cyrielle Scouarnec-201919310.61 $[0.42; 0.78]$ 3.9% EREN CELIK-201610150.67 $[0.38; 0.88]$ 3.1% Felix Ehret-202238550.69 $[0.55; 0.81]$ 4.6% Xianzhi Zhao-202037750.49 $[0.38; 0.61]$ 4.7% Random effects model1991990.63 $[0.53; 0.73]$ 20.1% Heterogeneity: $l^2 = 50\%, \tau^2 = 0.0060, p = 0.09$ 12210.46 $[0.39; 0.52]$ 100.0% Random effects model12210.46 $[0.39; 0.52]$ 100.0% Heterogeneity: $l^2 = 79\%, \tau^2 = 0.0202, p < 0.01$ 1221 0.46 $[0.39; 0.52]$ 100.0%	Diego A.S. Toesca-2018	16	35		0.46	[0.29; 0.63]	4.0%
Random effects model 55 0.45 [0.32 ; 0.59] 7.4% Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.96$ 0.45 [0.32 ; 0.59] 7.4% Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 0.74 [0.52 ; 0.90] 3.8% Cyrielle Scouarnec-2019 19 31 0.61 [0.42 ; 0.78] 3.9% EREN CELIK-2016 10 15 0.67 [0.38 ; 0.88] 3.1% Felix Ehret-2022 38 55 0.67 [0.38 ; 0.88] 3.1% Xianzhi Zhao-2020 37 75 0.49 [0.38 ; 0.61] 4.7% Random effects model 199 0.63 [0.53 ; 0.73] 20.1% Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ 0.46 [0.39 ; 0.52] 100.0% Random effects model 1221 0.46 [0.39 ; 0.52] 100.0% Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ 0.46 [0.39 ; 0.52] 100.0%	Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.96$ 550.45 $[0.32; 0.59]$ 7.4%Tracking = 80-100% patientsAlfred Haidenberger-20171723Cyrielle Scouarnec-20191931EREN CELIK-20161015Felix Ehret-20223855Xianzhi Zhao-20203775Random effects model199Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ 1221Random effects model1221Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.20.40.60.8	Norio Katoh-2018	9	20		0.45	[0.23; 0.68]	3.4%
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.96$ Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 Cyrielle Scouarnec-2019 19 31 EREN CELIK-2016 10 15 Felix Ehret-2022 38 55 Xianzhi Zhao-2020 37 75 Random effects model 199 Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ Random effects model 1221 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.2 0.4 0.6 0.8	Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.96$ Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 Cyrielle Scouarnec-2019 19 31 EREN CELIK-2016 10 15 Felix Ehret-2022 38 55 Xianzhi Zhao-2020 37 75 Random effects model 199 Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ Random effects model 1221 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.2 0.4 0.6 0.8	Random effects model		55		0.45	[0.32; 0.59]	7.4%
Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 Cyrielle Scouarnec-2019 19 31 EREN CELIK-2016 10 15 Felix Ehret-2022 38 55 Xianzhi Zhao-2020 37 75 Random effects model 199 Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ 0.46 Random effects model 1221 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ 0.4 Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.2 0.4 0.6	Tracking = 80-100% patients Alfred Haidenberger-2017 17 23 Cyrielle Scouarnec-2019 19 31 EREN CELIK-2016 10 15 Felix Ehret-2022 38 55 Xianzhi Zhao-2020 37 75 Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ 0.61 0.62 Random effects model 199 Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0000$, $p = 0.09$ 0.46 [0.39; 0.52] 1000% 0.46 [0.39; 0.52] 100.0%	Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$	0, <i>p</i> = 0.96					
Alfred Haidenberger-2017 17 23 0.74 [0.52; 0.90] 3.8% Cyrielle Scouarnec-2019 19 31 0.61 [0.42; 0.78] 3.9% EREN CELIK-2016 10 15 0.67 [0.38; 0.88] 3.1% Felix Ehret-2022 38 55 0.69 [0.55; 0.81] 4.6% Xianzhi Zhao-2020 37 75 0.49 [0.38; 0.61] 4.7% Random effects model 199 0.63 [0.53; 0.73] 20.1% Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ 0.46 [0.39; 0.52] 100.0%	Alfred Haidenberger-2017 17 23 0.74 [0.52; 0.90] 3.8% Cyrielle Scouarnec-2019 19 31 0.61 [0.42; 0.78] 3.9% EREN CELIK-2016 10 15 0.67 [0.38; 0.88] 3.1% Felix Ehret-2022 38 55 0.67 [0.38; 0.88] 3.1% Xianzhi Zhao-2020 37 75 0.49 [0.38; 0.61] 4.7% Random effects model 199 0.63 [0.55; 0.73] 20.1% Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ 0.46 [0.39; 0.52] 100.0% Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ 0.4 0.6 0.8	Tracking = 80-100% patie	ents					
Cyrielle Scouarnec-2019 19 31 0.61 $[0.42; 0.78]$ 3.9% EREN CELIK-2016 10 15 0.67 $[0.38; 0.88]$ 3.1% Felix Ehret-2022 38 55 0.69 $[0.55; 0.81]$ 4.6% Xianzhi Zhao-2020 37 75 0.63 $[0.53; 0.73]$ 20.1% Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ 0.46 $[0.39; 0.52]$ 100.0% Random effects model 1221 0.46 $[0.39; 0.52]$ 100.0% Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ 0.40.6 0.8 0.46 $[0.39; 0.52]$ 100.0%	Cyrielle Scouarnec-2019 19 31 EREN CELIK-2016 10 15 Felix Ehret-2022 38 55 Xianzhi Zhao-2020 37 75 Random effects model 199 Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ Random effects model 1221 Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.2 0.4 0.6 0.8 0.61 [0.42; 0.78] 3.9% 0.67 [0.38; 0.88] 3.1% 0.69 [0.55; 0.81] 4.6% 0.49 [0.38; 0.61] 4.7% 0.63 [0.53; 0.73] 20.1% 0.46 [0.39; 0.52] 100.0%	Alfred Haidenberger-2017	17	23		- 0.74	[0.52; 0.90]	3.8%
EREN CELIK-2016 10 15 0.67 0.038; 0.88] 3.1% Felix Ehret-2022 38 55 0.69 0.55; 0.81] 4.6% Xianzhi Zhao-2020 37 75 0.69 0.63 0.65 0.46 0.46 0.45 0.46 0.45 0.46 0.45 0.46 0.45 0.46 0.45 0.46 0.45 0.46 0.45 0.46 0.45 0.46 0.45 <	EREN CELIK-20161015Felix Ehret-20223855Xianzhi Zhao-20203775Random effects model199Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ 0.67Random effects model1221Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.20.40.60.8	Cyrielle Scouarnec-2019	19	31		0.61	[0.42; 0.78]	3.9%
Felix Ehret-2022 38 55 0.69 0.055 0.81 4.6% Xianzhi Zhao-2020 37 75 0.49 0.38 0.61 4.7% Random effects model 199 0.63 [0.53] 0.73 20.1% Heterogeneity: $I^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ 0.46 [0.39] 0.46 [0.39] 0.52] 100.0% Heterogeneity: $I^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ 0.4 0.6 0.8 0.46 [0.39] 0.52] 100.0%	Felix Ehret-202238550.69 $(0.55; 0.81]$ 4.6%Xianzhi Zhao-202037750.49 $(0.38; 0.61]$ 4.7%Random effects model1990.63 $(0.53; 0.73]$ 20.1%Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ 0.63 $(0.53; 0.73]$ 20.1%Random effects model12210.46 $(0.39; 0.52]$ 100.0%Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ 0.40.60.8	EREN CELIK-2016	10	15		0.67	[0.38; 0.88]	3.1%
Xianzhi Zhao-2020 37 75 0.49 [0.38; 0.61] 4.7% Random effects model 199 0.63 [0.53; 0.73] 20.1% Heterogeneity: $I^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ 0.40 [0.39; 0.52] 100.0% Random effects model 1221 0.46 [0.39; 0.52] 100.0% Heterogeneity: $I^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ 0.4 0.6 0.8	Xianzhi Zhao-202037750.49 $(0.38; 0.61]$ 4.7%Random effects model1990.63 $(0.53; 0.73]$ 20.1% Heterogeneity: $l^2 = 50\%, \tau^2 = 0.0060, p = 0.09$ 12210.46 $(0.39; 0.52]$ 100.0%Random effects model12210.46 $(0.39; 0.52]$ 100.0%Heterogeneity: $l^2 = 79\%, \tau^2 = 0.0202, p < 0.01$ 0.40 $(0.39; 0.52]$ 100.0%	Felix Ehret-2022	38	55		0.69	[0.55; 0.81]	4.6%
Random effects model 199 0.63 [0.53; 0.73] 20.1% Heterogeneity: $I^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ 0.63 [0.53; 0.73] 20.1% Random effects model 1221 0.46 [0.39; 0.52] 100.0% Heterogeneity: $I^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ 0.40 [0.39; 0.52] 100.0% Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.2 0.4 0.6 0.8	Random effects model1990.63 [0.53; 0.73]20.1%Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ 12210.46 [0.39; 0.52]100.0%Random effects model12210.46 [0.39; 0.52]100.0%Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ 0.46 [0.39; 0.52]100.0%Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.20.40.60.8	Xianzhi Zhao-2020	37	75		0.49	[0.38; 0.61]	4.7%
Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ Random effects model Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.2 0.4 0.6 0.8 0.46 [0.39; 0.52] 100.0%	Heterogeneity: $l^2 = 50\%$, $\tau^2 = 0.0060$, $p = 0.09$ Random effects model Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.2 0.4 0.6 0.8 0.46 [0.39; 0.52] 100.0%	Random effects model		199	\sim	0.63	[0.53; 0.73]	20.1%
Random effects model12210.46 [0.39; 0.52] 100.0%Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ 0.46 [0.39; 0.52] 100.0%Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.20.40.60.8	Random effects model12210.46 [0.39; 0.52] 100.0%Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ 11Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.20.40.60.8	Heterogeneity: $I^2 = 50\%$, $\tau^2 =$	0.0060, p = 0.09)				
Heterogeneity: $I^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.2 0.4 0.6 0.8	Heterogeneity: $l^2 = 79\%$, $\tau^2 = 0.0202$, $p < 0.01$ Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.2 0.4 0.6 0.8	Random effects model		1221		0.46	[0.39; 0.52]	100.0%
Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$) 0.2 0.4 0.6 0.8	Test for subgroup differences: $\chi_2^2 = 12.72$, df = 2 ($p < 0.01$)0.2 0.4 0.6 0.8	Heterogeneity: $I^2 = 79\%$, $\tau^2 =$	$0.0202, p < 0.0^{\circ}$	l I				
		Test for subgroup differences	$\chi_2^2 = 12.72$, df =	= 2 (p <	0.01)0.2 0.4 0.6 0.8			

The forest plot of subgroup analysis for 1-year overall survival by tracking technology adoption rate.

07

Tracking = 0-20% patients A. Baydoun-2021 Daniel Buergy-2021 Ciro Franzese-2021 Claire van Vliet-2022	33 208 103 39	47 326		0.70	ra 55 a aai	
A. Baydoun-2021 Daniel Buergy-2021 Ciro Franzese-2021 Claire van Vliet-2022	33 208 103 39	47 326		0.70	TO EE 0 001	
Daniel Buergy-2021 Ciro Franzese-2021 Claire van Vliet-2022	208 103 39	326		0.10	[0.55; 0.83]	4.1%
Ciro Franzese-2021 Claire van Vliet-2022	103 39			0.64	[0.58; 0.69]	4.9%
Claire van Vliet-2022	39	142	÷	0.73	[0.64: 0.80]	4.8%
E 1 : 1 : 1 0000		51		0.76	10.63: 0.871	4.3%
Fablo Arcidiacono-2020	20	37		0.54	[0.37:0.71]	37%
Giuseppe Eacondo-2021	21	24		0.88	[0.68: 0.97]	4 1%
FRANAO CASAMASSIMA-2012	2 19	48		0.40	[0.26, 0.55]	4.0%
Kamran A Ahmed-2013	8	13		0.62	[0.32, 0.86]	2.5%
Kim Burjakow-2018	14	33		0.42	[0.25, 0.61]	3.6%
Kristin Plichta_2017	3	10 -	-	0.30	[0.07:0.65]	2.3%
Laila K2nig-2020	13	28		0.46	[0.28: 0.66]	3.4%
Leonid B Reshko-2021	15	23		0.40	[0.20, 0.00]	3 3%
Marta Scorsetti_2012	23	34		0.68	[0.49: 0.83]	3.7%
Michael Guiou-2012	5	ä		0.56	[0.43, 0.03]	2.0%
Nicholas B. Eigura 2020	20	11		0.00	[0.54: 0.84]	1.0%
SHEEMA CHAMI A 2000	13	30		0.71	[0.34, 0.04]	3.5%
Sonali Pudra 2013	0	10		- 0.00	[0.25, 0.05]	3.0%
Thorosa Voglbubor 2020	20	21		0.90	[0.35, 1.00]	2.6%
William W. Chanco 2017	20	42		0.05	[0.43, 0.01]	2.0%
Rendem offecte model	20	43	~	0.05	[0.49, 0.79]	5.9%
Heterogeneity: $I^2 = 72\%$, $\tau^2 = 0.016$	61, p < 0.0	1		0.05	[0.56, 0.70]	00.070
Tracking = 20-80% patients						
Diego A.S. Toesca-2018	19	35		0.54	[0.37: 0.71]	3.6%
Diego A S Toesca-2018	19	35		0.54	[0 37·0 71]	3.6%
Norio Katoh-2018	16	20		0.80	[0.56: 0.94]	3.5%
Random effects model		90		0.63	[0.46: 0.79]	10.8%
Heterogeneity: $I^2 = 65\%$, $\tau^2 = 0.014$	40, p = 0.06	6			,	
Tracking = 80-100% patients						
Alfred Haidenberger-2017	18	23		0.78	[0.56; 0.93]	3.6%
Cyrielle Scouarnec-2019	25	31	+ · ·	0.81	[0.63; 0.93]	4.0%
EREN CELIK-2016	14	15		- 0.93	[0.68; 1.00]	4.1%
Felix Ehret-2022	44	55		0.80	[0.67; 0.90]	4.4%
Xianzhi Zhao-2020	47	75		0.63	[0.51; 0.74]	4.3%
Random effects model		199		0.79	[0.69; 0.89]	20.4%
Heterogeneity: $I^2 = 70\%$, $\tau^2 = 0.00\%$	91, p < 0.0	1				
Random effects model		1269	<u> </u>	0.66	[0.60; 0.72]	100.0%
Heterogeneity: $I^{2} = 74\%$, $\tau^{2} = 0.017$	$70, p < 0.0^{\circ}$	1				
Test for subgroup differences: χ_2^2 =	= 6.88, df =	2(p = 0)	.030.2 0.4 0.6 0.8			

Furthermore, the release of tumor antigens during the death or dying process of tumor cells post high fractionated radiation can trigger an anti-tumor immune response within weeks to months, contributing to the formation of a local immune environment (45, 46). There is evidence that in animal experiments, a dose of 8-10 Gy is optimal, as fractionated radiation at 8 Gy, combined with CTLA-4 inhibitors, can induce a distant effect (47).

Our research demonstrates that the utilization of tracking technology not only contributes to extending the survival of patients with AM but is also highly safe. Real-time monitoring and tracking of tumor location is an emerging technology to enhance the precision of tumor radiotherapy (48). This technology allows for high-dose, highaccuracy irradiation of the tumor, improving treatment effectiveness while avoiding "off-target" effects in the target area, and reducing adverse effects on surrounding tissues (48, 49). A study published in the journal Nature Cancer suggests that damage to tissues caused by "offtarget" radiotherapy can locally activate neutrophils in the normal repair process and Notch signal transduction, which can promote cancer metastasis and reduce overall survival (50). For under-irradiated tumors cells, insufficient radiation fails to kill them; instead, it enhances its malignancy and promotes invasion and metastasis (51, 52).

Therefore, the application of real-time tracking technology is essential, especially for patients with AM. We found that 91% of AM patients fall within the current definition of oligometastasis. Multiple studies have shown that aggressive treatment in oligometastatic patients can significantly extend survival (53–55). However, regrettably, the use rate of tracking technology is only 19% (257/ 1332) and the importance of tracking technology urgently needs to be widely promoted. Of course, we also need to be vigilant about selection bias. Because this portion of patients in the high fiducial adoption group may also have better medical support, which could potentially influence the overall survival outcome. Nevertheless, we cannot deny the importance of adopting tracking radiation therapy, and we hope that prospective studies in the future will confirm our findings.

We are the first to propose a study on the focus of fractional dose and tracking technology in the treatment of AM using SBRT.

William C. Chen et al (39) collected 39 studies between 2009 and 2019 to perform first meta-analyze on AM by SBRT. They only analyzed the relationship between the total dose (BED10) and local control, as well as overall survival, and reached the conclusion that dose escalation contributes to local control. They did not analyze and find the significance of fractionation dose and tracking techniques, perhaps due to the inclusion of a large number of abstracts with insufficient information in their study. To extract more data and ensure data accuracy, we excluded all studies that had only abstracts and lacked full texts. Furthermore, due to the recent advancements in tracking technology and the development of imaging techniques, many new articles (14/out of 33) on SBRT treatment for AM have emerged. Therefore, there is an urgent need for updated meta-analyses in this regard.

Our study has some limitations that need to be acknowledged. The inconsistencies in radiation techniques and dosimetry, and the inherent biological inaccuracies in calculating BED by linearquadratic (LQ) formulas, mean that the reported doses are only informative and should be carefully considered. As our study is a retrospective analysis, it cannot establish causal relationships, and more prospective studies are needed to verify our findings. The results of meta model-based estimates should be interpreted with caution, given the heterogeneity of tumor control estimates extracted from the literature and the variability of diametric data reporting, as well as the definitions and statistical methods used to report tumor control. Despite our efforts to collect data of the same quality, there were still some differences in detail.

Conclusions

SBRT is a safe technique. Constrained by organs at risk, the clinical dose for treating AM often falls within the range of 40-80 Gy, especially in centers with low tracking adoption rates. But we recommend that the minimum dose per fraction should be set around 9 Gy to ensure treatment efficacy. Additionally, the use of tracking techniques may improve the survival rates of advanced AM patients and is strongly recommended. Prospective studies are needed to validate these discoveries.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

XL had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: KK. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: all authors. Critical revision of the manuscript for important intellectual content: KK and RK. Statistical analysis: XL. Obtained funding: CP. Administrative, technical, or material support: KK, CP. Supervision: KK, CP, RK. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by grants 2021CXB022 from Medical Innovation Project of Fujian Province of China.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1193574/ full#supplementary-material

References

3. Desai A, Rai H, Haas J, Witten M, Blacksburg S, Schneider JG. A retrospective review of cyberKnife stereotactic body radiotherapy for adrenal tumors (Primary and metastatic): winthrop university hospital experience. *Front Oncol* (2015) 5:185. doi: 10.3389/fonc.2015.00185

4. Howell GM, Carty SE, Armstrong MJ, Stang MT, McCoy KL, Bartlett DL, et al. Outcome and prognostic factors after adrenalectomy for patients with distant adrenal metastasis. *Ann Surg Oncol* (2013) 20:3491–6. doi: 10.1245/s10434-013-3050-2

^{1.} Franzese C, Franceschini D, Cozzi L, D'Agostino G, Comito T, De Rose F, et al. Minimally invasive stereotactical radio-ablation of adrenal metastases as an alternative to surgery. *Cancer Res Treat* (2017) 49:20–8. doi: 10.4143/crt.2016.057

^{2.} Salama JK, Hasselle MD, Chmura SJ, Malik R, Mehta N, Yenice KM, 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) 118:2962–70. doi: 10.1002/cncr.26611

5. Metman MJH, Viëtor CL, Seinen AJ, Berends AMA, Hemmer PHJ, Kerstens MN, et al. Outcomes after surgical treatment of metastatic disease in the adrenal gland; valuable for the patient? *Cancers* (2022) 14:156. doi: 10.3390/cancers14010156

6. 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

 Baydoun A, Chen H, Poon I, Badellino S, Dagan R, Erler D, et al. Outcomes and toxicities in oligometastatic patients treated with stereotactic body radiotherapy for adrenal gland metastases: A multi-institutional retrospective study. *Clin Transl Radiat Oncol* (2021) 33:159–64. doi: 10.1016/j.ijrobp.2021.07.1319

8. Borghesi S, Casamassima F, Aristei C, Grandinetti A, Di Franco R. Stereotactic radiotherapy for adrenal oligometastases. *Rep Pract Oncol Radiother* (2022) 27:52–6. doi: 10.5603/RPOR.a2021.0104

9. Chance WW, Nguyen Q-N, Mehran R, Welsh JW, Gomez DR, Balter P, et al. Stereotactic ablative radiotherapy for adrenal gland metastases: Factors influencing outcomes, patterns of failure, and dosimetric thresholds for toxicity. *Pract Radiat Oncol* (2017) 7:E195–203. doi: 10.1016/j.prro.2016.09.005

10. Ahmed KA, Barney BM, Macdonald OK, Miller RC, Garces YI, Laack NN, et al. Stereotactic body radiotherapy in the treatment of adrenal metastases. *Am J Clin Oncolcancer Clin Trials* (2013) 36:509–13. doi: 10.1097/COC.0b013e3182569189

11. Arcidiacono F, Aristei C, Marchionni A, Italiani M, Fulcheri CPL, Saldi S, et al. Stereotactic body radiotherapy for adrenal oligometastasis in lung cancer patients. *Br J Radiol* (2020) 93. doi: 10.1259/bjr.20200645

12. Buergy D, Wuerschmidt F, Gkika E, Hoerner-Rieber J, Knippen S, Gerum S, et al. Stereotactic or conformal radiotherapy for adrenal metastases: Patient characteristics and outcomes in a multicenter analysis. *Int J Cancer* (2021) 149:358–70. doi: 10.1002/ijc.33546

13. Burjakow K, Fietkau R, Putz F, Achterberg N, Lettmaier S, Knippen S, et al. Fractionated stereotactic radiation therapy for adrenal metastases: contributing to local tumor control with low toxicity. *Strahlentherapie Und Onkol* (2019) 195:236–45. doi: 10.1007/s00066-018-1390-3

14. Casamassima F, Livi L, Masciullo S, Menichelli C, Masi L, Meattini I, et al. Stereotactic radiotherapy for adrenal gland metastases: University of florence experience. *Int J Radiat Oncol Biol Phys* (2012) 82:919–23. doi: 10.1016/j.ijrobp.2010.11.060

15. Celik E. Robot-assisted extracranial stereotactic radiotherapy of adrenal metastases in oligometastatic non-small cell lung cancer. *AR* (2017) 37. doi: 10.21873/anticanres.11954

16. Chawla S, Chen Y, Katz AW, Muhs AG, Philip A, Okunieff P, et al. Stereotactic body radiotherapy for treatment of adrenal metastases. *Int J Radiat Oncol Biol Phys* (2009) 75:71–5. doi: 10.1016/j.ijrobp.2008.10.079

17. Ehret F, Kaul D, Kufeld M, Vom Endt C, Budach V, Senger C, et al. Robotic stereotactic body radiotherapy for the management of adrenal gland metastases: a bi-institutional analysis. *J Cancer Res Clin Oncol* doi: 10.1007/s00432-022-03943-0

18. Elmali A, Akkus Yildirim B, Cengiz M, Cengiz M, Yuce Sari S, Onal HC, et al. Stereotactic radiotherapy for adrenal metastases: a multi-institutional review of patient characteristics and outcomes. Turkish Society for Radiation Oncology SBRT Group Study (TROD SBRT 10-004). *Oncol Res Treat* (2022). doi: 10.1159/000527052

19. Facondo G, Vullo G, Valeriani M, Ascolese AM, De Sanctis V, Osti MF. Stereotactic body radiation therapy (SBRT) for patients with oligometastatic/ oligoprogressive adrenal metastases: Outcomes and toxicities profile in a monoinstitutional study. *Cancer Treat Res Commun* (2021) 29:100481-1. doi: 10.1016/j.ctarc.2021.100481

20. Figura NB, Oliver DE, Mohammadi H, Martinez K, Grass GD, Hoffe SE, et al. Novel dose escalation approaches for stereotactic body radiotherapy to adrenal oligometastases A single-institution experience. *Am J Clin Oncol-Cancer Clin Trials* (2020) 43:107–14. doi: 10.1097/COC.00000000000634

21. Franzese C, Nicosia L, Facondo G, Lo Faro L, Cuccia F, Vullo G, et al. Stereotactic body radiation therapy for adrenal gland metastases: outcome and predictive factors from a multicenter analysis. *Clin Exp Metastasis* (2021) 38:511–8. doi: 10.1007/s10585-021-10124-9

22. Gamsiz H, Beyzadeoglu M, Sager O, Demiral S, Dincoglan F, Uysal B, et al. Evaluation of stereotactic body radiation therapy in the management of adrenal metastases from non-small cell lung cancer. *Tumori* (2015) 101:98–103. doi: 10.5301/tj.5000222

23. Guiou M, Mayr NA, Kim EY, Williams T, Lo SS. Stereotactic body radiotherapy for adrenal metastases from lung cancer. *J Radiat Oncol* (2012) 1:155–63. doi: 10.1007/s13566-012-0037-8

24. Haidenberger A, Heidorn S-C, Kremer N, Muacevic A, Fuerweger C. Robotic radiosurgery for adrenal gland metastases. *Cureus* (2017) 9. doi: 10.7759/cureus.1120

25. Helis CA, Hughes RT, Nieto K, Ufondu A, Daugherty EC, Farris MK. Adrenal SBRT: a multi-institutional review of treatment outcomes and toxicity. *Clin Exp Metastasis* (2020) 37:585–92. doi: 10.1007/s10585-020-10052-0

26. Holy R, Piroth M, Pinkawa M, Eble MJ. Stereotactic Body Radiation Therapy (SBRT) for treatment of adrenal gland metastases from non-small cell lung cancer. *Strahlentherapie Und Onkol* (2011) 187:245–51. doi: 10.1007/s00066-011-2192-z

27. Katoh N, Onishi H, UChinami Y, Inoue T, Kuriyama K, Nishioka K, et al. Realtime tumor-tracking radiotherapy and general stereotactic body radiotherapy for adrenal metastasis in patients with oligometastasis. *Technol Cancer Res Treat* (2018) 17. doi: 10.1177/1533033818809983 28. Koenig L, Haefner MF, Katayama S, Koerber SA, Tonndorf-Martini E, Bernhardt D, et al. Stereotactic body radiotherapy (SBRT) for adrenal metastases of oligometastatic or oligoprogressive tumor patients. *Radiat Oncol* (2020) 15. doi: 10.1186/s13014-020-1480-0

29. Plichta K, Camden N, Furqan M, Abu Hejleh T, Clamon GH, Zhang J, et al. SBRT to adrenal metastases provides high local control with minimal toxicity. *Adv Radiat Oncol* (2017) 2:581–7. doi: 10.1016/j.adro.2017.07.011

30. Reshko LB, Gaskins JT, Silverman CL, Dunlap NE. Stereotactic body radiation therapy (SBRT) of adrenal gland metastases in oligometastatic and oligoprogressive disease. *Rep Pract Oncol Radiother* (2021) 26:325–40. doi: 10.5603/RPOR.a2021.0055

31. Scorsetti M, Alongi F, Filippi AR, Pentimalli S, Navarria P, Clerici E, et al. Longterm local control achieved after hypofractionated stereotactic body radiotherapy for adrenal gland metastases: A retrospective analysis of 34 patients. *Acta Oncol* (2012) 51:618–23. doi: 10.3109/0284186X.2011.652738

32. Scouarnec C, Pasquier D, Luu J, le Tinier F, Lebellec L, Rault E, et al. Usefulness of stereotactic body radiation therapy for treatment of adrenal gland metastases. *Front Oncol* (2019) 9. doi: 10.3389/fonc.2019.00732

33. Shah MM, Isrow D, Fareed MM, Wen N, Ryu S, Ajlouni M, et al. Single institution experience treating adrenal metastases with stereotactic body radiation therapy. *J Cancer Res Ther* (2019) 15:S27–32. doi: 10.4103/jcrt.JCRT_655_16

34. Rudra S. Stereotactic body radiation therapy for curative treatment of adrenal metastases. (2013) 12:8. doi: 10.7785/tcrt.2012.500320

35. Toesca DAS, Koong AJ, von Eyben R, Koong AC, Chang DT. Stereotactic body radiation therapy for adrenal gland metastases: Outcomes and toxicity. *Adv Radiat Oncol* (2018) 3:621–9. doi: 10.1016/j.adro.2018.05.006

36. Torok J, Wegner RE, Burton SA, Heron DE. Stereotactic body radiation therapy for adrenal metastases: a retrospective review of a noninvasive therapeutic strategy. *Future Oncol* (2011) 7:145–51. doi: 10.2217/fon.10.165

37. van Vliet C, Dickhoff C, Bahce I, Engelsman AF, Hashemi SMS, Haasbeek CJA, et al. Treatment patterns for adrenal metastases using surgery and SABR during a 10year period. *Radiother Oncol* (2022) 170:165–8. doi: 10.1016/j.radonc.2022.02.023

38. Zhao X, Zhu X, Zhuang H, Guo X, Song Y, Ju X, et al. Clinical efficacy of Stereotactic Body Radiation Therapy (SBRT) for adrenal gland metastases: A multi-center retrospective study from China. *Sci Rep* (2020) 10:7836. doi: 10.1038/s41598-020-64770-2

39. Chen WC, Baal JD, Baal U, Pai J, Gottschalk A, Boreta L, et al. Stereotactic body radiation therapy of adrenal metastases: A pooled meta-analysis and systematic review of 39 studies with 1006 patients. *Int J Radiat OncologyBiologyPhys* (2020) 107:48–61. doi: 10.1016/j.ijrobp.2020.01.017

40. Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG, et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up †. *Ann Oncol* (2016) 27:v1-v27. doi: 10.1093/annonc/mdw326

41. Jayaraman P, Parikh F, Newton JM, Hanoteau A, Rivas C, Krupar R, et al. TGF- β 1 programmed myeloid-derived suppressor cells (MDSC) acquire immunestimulating and tumor killing activity capable of rejecting established tumors in combination with radiotherapy. *OncoImmunology* (2018) 7:e1490853. doi: 10.1080/ 2162402X.2018.1490853

42. Garcia-Barros M, Paris F, Cordon-Cardo C, Lyden D, Rafii S, Haimovitz-Friedman A, et al. Tumor response to radiotherapy regulated by endothelial cell apoptosis. *Science* (2003) 300:1155–9. doi: 10.1126/science.1082504

43. Denekamp J. Vascular endothelium as the vulnerable element in tumours. *Acta Radiol Oncol* (1984) 23:217–25. doi: 10.3109/02841868409136015

44. Song CW, Lee Y-J, Griffin RJ, Park I, Koonce NA, Hui S, et al. Indirect tumor cell death after high-dose hypofractionated irradiation: implications for stereotactic body radiation therapy and stereotactic radiation surgery. *Int J Radiat Oncol Biol Phys* (2015) 93:166–72. doi: 10.1016/j.ijrobp.2015.05.016

45. Kim M-S, Kim W, Park IH, Kim HJ, Lee E, Jung J-H, et al. Radiobiological mechanisms of stereotactic body radiation therapy and stereotactic radiation surgery. *Radiat Oncol J* (2015) 33:265. doi: 10.3857/roj.2015.33.4.265

46. Miljanic M, Montalvo S, Aliru M, Song T, Leon-Camarena M, Innella K, et al. The evolving interplay of SBRT and the immune system, along with future directions in the field. (2022) 10:. doi: 10.3390/cancers14184530

47. Kabiljo J, Harpain F, Carotta S, Bergmann M. Radiotherapy as a backbone for novel concepts in cancer immunotherapy. *Cancers (Basel)* (2019) 12:79. doi: 10.3390/ cancers12010079

48. Riboldi M, Orecchia R, Baroni G. Real-time tumour tracking in particle therapy: technological developments and future perspectives. *Lancet Oncol* (2012) 13:e383–391. doi: 10.1016/S1470-2045(12)70243-7

49. Zhang W, Oraiqat I, Litzenberg D, Chang K-W, Hadley S, Sunbul NB, et al. Realtime, volumetric imaging of radiation dose delivery deep into the liver during cancer treatment. *Nat Biotechnol* (2023) 41:1160–7. doi: 10.1038/s41587-022-01593-8

50. Nolan E, Bridgeman VL, Ombrato L, Karoutas A, Rabas N, Sewnath CAN, et al. Radiation exposure elicits a neutrophil-driven response in healthy lung tissue that enhances metastatic colonization. *Nat Cancer* (2022) 3:173–87. doi: 10.1038/s43018-022-00336-7

51. Carney DN, Mitchell JB. In vitro radiation and chemotherapy sensitivity of established cell. (1983) 43.

52. Katipally RR, Pitroda SP, Juloori A, Chmura SJ, Weichselbaum RR. The oligometastatic spectrum in the era of improved detection and modern systemic therapy. *Nat Rev Clin Oncol* (2022) 19:585–99. doi: 10.1038/s41571-022-00655-9

53. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, 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):2830–8. doi: 10.1200/JCO.20.00818

54. Bauml JM, Mick R, Ciunci C, Aggarwal C, Davis C, Evans T, et al. Pembrolizumab after completion of locally ablative therapy for oligometastatic nonsmall cell lung cancer: a phase 2 trial. *JAMA Oncol* (2019) 5(9):1283–90. doi: 10.1001/ jamaoncol.2019.1449

55. Mahabir R, Tanino M, Elmansuri A, Wang L, Kimura T, Itoh T, et al. Sustained elevation of Snail promotes glial-mesenchymal transition after irradiation in Malignant glioma. *Neuro Oncol* (2014) 16:671–85. doi: 10.1093/neuonc/not239