Radiation therapy for melanoma brain metastases: a systematic review

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SUPPLEMENTARY TABLE 1. Search strategy

		Medline (24 Sep 2020)	**Embase (25 Sep 2020)**	**Cochrane Central register of Controlled trials (30 Sep 2020)**
1	Exp melanoma/ or melanoma.mp	134454	213839	5915
2	Exp brain neoplasms/ or brain metastases.mp	155412	194442	3142
3	1 and 2	3627	8978	219
4	Radiation therapy.mp. or Exp Radiotherapy/	231086	635595	14589
5	Exp Radiosurgery/ or stereo tactic radiosurgery.mp	15766	73230	217
6	Gamma knife	5015	9987	170
7	SRS.mp	13689	16066	1004
8	Whole rain radiotherapy.mp	1898	5032	494
9	Whole brain radiation.mp	1458	2642	233
10	WBRT	1731	3620	516
11	4 -10/or	244191	684450	15869
12	3 and 11	876	2992	83
13	Limit 12 to “therapy (maximises sensitivity)?”	Not Applied	1452	Not Applied

SUPPLEMENTARY TABLE 2A. Risk of bias assessment for the three included randomized controlled trials

First Author	Year	Random sequence generation	Allocation concealment	Blinding of patients and personnel	Blinding of outcome assessors	Incomplete outcome data (attrition bias)(loss to follow-up)	Selective reporting (reporting bias)	Other bias
Gupta[1]	2016	Unclear	Low	Low	Low	Low	Low	High
Hauswald[2]	2019	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Hong[3]	2019	Unclear	Low	High	Low	Low	Low	Low

SUPPLEMENTARY TABLE 2B. Quality assessment for non-randomised, cohort studies

First author	Year	Verification of lesions as melanoma	Treatment decision described?	Representative	Ascertainment of treatment and outcomes	Outcome influence inclusion	Treatment groups comparable?	Assessment of outcome (medical records/imaging)	Duration of follow up sufficient for outcomes?	Completeness of follow-up
Carella[4]	1980	✓✓	NS	✓✓	✓	×	NS	✓/NS	NS	✓
Katz[5]	1981	✓	NS	✓✓	✓	×	NS	✓/NS	NS	✓
Vlock[6]	1982	NS	NS	✓✓	✓	×	✓	✓/NS	NS	✓
Byrne[7]	1983	✓	NS	✓✓	✓	×	NS	✓/NS	NS	✓✓
Stridsklev[8]	1984	✓	NS	✓	✓	×	NS	✓/NS	NS	✓✓
Choi (A)[9]	1985	✓	NS	✓✓	✓	×	NS	✓/NS	NS	✓✓
Choi (B)[10]	1985	NS	NS	✓✓	✓	×	NS	✓/NS	NS	✓✓
Ziegler [11]	1986	✓	NS	✓	✓	×	×	✓/NS	NS	✓✓
Rate[12]	1988	✓	✓	✓✓	✓	×	NS	✓/NS	NS	✓✓
Hagen[13]	1990	✓	NS	✓✓	✓	×	✓	✓/✓	✓✓	NS
Stevens[14]	1992	✓	✓	✓✓	✓	×	×	✓/NS	✓✓	✓
Somaza[15]	1993	✓	NS	✓	✓	×	NS	✓/✓	✓✓	✓✓
Willner[16]	1995	✓	NS	✓✓	✓	×	NS	✓/NS	NS	✓✓
Isokangas[17]	1996	✓	✓	✓✓	✓	×	✓	✓/NS	✓✓	NS
Skibber[18]	1996	✓✓	NS	✓✓	✓	×	✓	✓/✓	NS	✓✓
Gieger[19]	1997	NS	✓	✓	✓	×	NS	✓/✓	✓	✓✓
Gupta[20]	1997	✓	NS	✓	✓	×	NS	✓/✓	NS	NS
Grob[21]	1998	NS	✓	✓	✓	×	NS	✓/✓	NS	✓✓
Sampson[22]	1998	✓	NS	✓✓	✓	×	NS	✓/NS	NS	✓✓

Seung[23]	1998	NS	✓	✓	✓	×	NS	✓/NS	✓✓	✓✓
Lavine[24]	1999	NS	✓✓	×	✓	×	NS	✓/✓	✓✓	✓✓
Kontsadoulakis[25]	2000	✓	NS	✓✓	✓	×	NS	✓/NS	✓✓	NS
Ellerhorst[26]	2001	✓✓	NS	✓✓	✓	×	NS	✓/✓	NS	✓
Buchsbaum[27]	2002	✓	NS	✓✓	✓	×	×	✓/NS	NS	NS
Gonzalez-Martinez[28]	2002	✓	✓	✓	✓	×	NS	✓/✓	✓	✓✓
Mingione[29]	2002	✓	NS	✓	✓	×	NS	✓/✓	✓✓	✓✓
Noel[30]	2002	NS	NS	✓	✓	×	NS	✓/NS	✓✓	✓✓
Yu[31]	2002	NS	✓	✓	✓	×	✓	✓/✓	NS	✓
Zacest[32]	2002	✓✓	✓✓	✓	✓	×	NS	✓/✓	✓	✓
Harrison[33]	2003	✓	NS	✓✓	✓	×	NA	✓/NS	NS	✓✓
Conill[34]	2004	NS	NS	✓✓	□	×	NS	✓/NS	NS	NS
Fife[35]	2004	NS	✓✓	✓✓	✓	×	NS	✓/NS	NS	✓✓
Meier[36]	2004	✓	NS	✓✓	✓	×	NS	✓/NS	NS	✓✓
Morris[37]	2004	✓	NS	✓	✓	×	NA	✓/✓	NS	✓
Radbill[38]	2004	✓	NS	✓	✓	×	NS	✓/✓	✓	NS
Selek[39]	2004	✓	NS	✓	✓	×	Ns	✓/✓	NS	✓✓
Stone[40]	2004	NS	NS	✓✓	✓	×	×	✓/NS	NS	NS
Koc[41]	2005	✓	NS	✓	✓	×	NS	✓/✓	✓	✓✓
Panagiotou[42]	2005	✓	NS	✓✓	✓	×	×	✓/✓	NS	✓✓
Rhomberg[43,44]	2005	✓	NS	✓✓	✓	×	✓	✓/✓	NS	✓✓
Christopoulou	2006	NS	NS	?	✓	×	NS	✓/✓	NS	✓✓
Gaudy-Marquesta[45]	2006	NS	✓✓	×	✓	×	NS	✓/✓	NS	✓✓
Conill[46]	2007	✓	NS	✓✓	✓	×	NS	✓/✓	NS	NS
Mathieu[47]	2007	✓	NS	✓	✓	×	NS	✓/✓	✓	✓
Samlowski[48]	2007	✓	✓	✓	✓	×	NS	✓/✓	✓✓	✓✓
Raizer[49]	2008	✓	NS	✓✓	✓	×	NS	✓/NS	✓✓	✓✓
Redmond[50]	2008	NS	NS	✓	✓	×	NS	✓/✓	✓	✓
Carrubba[51]	2009	NS	✓	✓	✓	×	×	✓/NS	✓✓	✓✓
Ahmad[52]	2010	NS	NS	✓✓	✓	×	NS	✓/NS	NS	NS
Rades[53]	2010	✓	NS	✓	✓	×	✓	✓/✓	NS	NS
Schild[54]	2010	✓	NS	✓	✓	×	×	✓/✓	NS	✓✓
Staudt[55]	2010	✓	✓✓	✓✓	✓	×	NS	✓/✓	NS	✓
Davies[56]	2011	✓	✓✓	✓	✓	×	NS	✓/NS	NS	✓✓
Eigentler [57]	2011	✓	✓	✓	✓	×	NS	✓/✓	NS	✓
Liew[58]	2011	✓	NS	✓	✓	×	NS	✓/✓	NS	✓✓
Skeie[59]	2011	✓	✓✓	✓	✓	×	NS	✓/✓	NS	✓✓

Zakrzewski[60]	2011	NS	Ns	✓✓	✓	×	NS	✓/NS	✓✓	✓✓
Bernard[61]	2012	NS	NS	✓✓	✓	×	NS	✓/✓	✓	NS
Hauswald[62]	2012	NS	✓	✓	✓	×	NS	✓/✓	✓	✓✓
Knisely[63]	2012	NS	✓	✓	✓	×	NS	✓/✓	✓	✓✓
Koay[64]	2012	NS	NS	×	✓	×	NS	✓/NS	NS	NS
Lo[65]	2012	NS	NS	✓	✓	×	NS	✓/✓	✓	NS
Salvati[66]	2012	✓	✓✓	×	✓	×	NS	✓/✓	NS	✓✓
Mathew[67]	2013	NS	✓	×	✓	×	✓	✓/✓	✓	✓✓
Miller[68]	2013	NS	NS	✓	✓	×	NS	✓/✓	✓✓	✓✓
Partl[69]	2013	NS	✓	✓	✓	×	NS	✓/NS	NS	NS
Silk[70]	2013	NS	NS	×	✓	×	✓	✓/✓	✓✓	✓✓
Zukauskaite[71]	2013	✓	NS	✓✓	✓	×	NS	✓/NS	NS	NS
Dyer[72]	2014	Ns	NS	×	✓	×	NS	✓/✓	✓✓	✓✓
Marcus[73]	2014	NS	NS	✓	✓	×	NS	✓/NS	NS	✓✓
Neal[74]	2014	NS	NS	✓	✓	×	NS	✓/✓	✓	✓✓
Rades [75]	2014	NS	NS	✓	✓	×	✓	✓/NS	✓✓	NS
Vecchio[76]	2014	✓	✓	✓✓	✓	×	NS	✓/NS	NS	✓
Christ[77]	2015	✓	✓	NS	✓	×	NS	✓/✓	✓	✓
Frakes[78]	2015	✓	NS	✓	✓	×	NS	✓/✓	✓	✓✓
Hauswald[79]	2015	NS	NS	✓	✓	×	NA	✓/✓	✓	✓✓
Ivanov[80]	2015	✓	NS	✓✓	✓	×	NS	✓/✓	NS	NS
Ly[81]	2015	NS	NS	×	✓	×	NS	✓/✓	✓✓	NS
Ostheimer[82]	2015	✓	NS	✓✓	✓	×	NS	✓/✓	×	✓✓
Gallaher[83]	2016	NS	NS	×	✓	×	NS	✓/✓	✓✓	✓✓
Patel[84]	2016	NS	NS	×	✓	×	✓	✓/✓	✓	NS
Rades[85]	2016	NS	NS	✓	✓	×	✓	✓/NS	NS	NS
Szyszka-Chare[86]	2016	✓	✓	✓✓	✓	×	NS	✓/NS	NS	✓✓
Wolf[87]	2016	✓	NS	✓	✓	×	NS	✓/✓	NS	✓✓
Acharya[88]	2017	NS	NS	✓	✓	×	×	✓/✓	✓✓	✓✓
All[89]	2017	NS	NS	Unsure	✓	×	NS	✓/✓	NS	NS
Feng[90]	2017	NS	NS	✓	✓	×	NS	✓/✓	NS	NS
Kaidar-person[91]	2017	NS	NS	✓	✓	×	×	✓/✓	✓✓	✓✓
Minniti[92]	2017	NS	✓✓	✓	✓	×	✓	✓/✓	✓✓	✓✓
Patel[93]	2017	NS	NS	×	✓	×	✓	✓/✓	✓	NS
Pessina[94]	2017	NS	✓✓	×	✓	×	×	✓/✓	✓✓	✓✓
Sperduto[95]	2017	NS	NS	✓✓	✓	×	NS	✓/NS	NS	✓✓
Xu[96]	2017	✓	NS	×	✓	×	✓	✓/✓	NS	✓✓
Diao(A)[97]	2018	NS	NS	✓	✓	×	×	✓/✓	✓	NS

Diao(B)[98]	2018	NS	NS	✓	✓	×	✓	✓/NS	✓	✓✓
Fang[99]	2018	NS	NS	×	✓	×	NS	✓/✓	✓✓	✓✓
Gabani[100]	2018	✓	✓	✓✓	✓	×	NS	✓/NS	✓	✓✓
Kano[101]	2018	NS	NS	✓	✓	×	NS	✓/NS	NS	✓✓
Kotecha[102]	2018	NS	✓	✓✓	✓	×	NS	✓/✓	✓	✓✓
Ladwa[103]	2018	NS	NS	✓✓	✓	×	NS	✓/NS	✓	✓✓
Matsunaga[104]	2018	NS	NS	✓	✓	×	NS	✓/✓	NS	✓✓
Tio[105]	2018	✓	NS	✓✓	✓	×	NS	✓/✓	✓✓	✓✓
Zubatkina[106]	2018	✓	NS	×	✓	×	NS	✓/✓	✓	✓✓
Jardim[107]	2019	NS	✓✓	✓	✓	×	NS	✓/✓	✓✓	NS
Mastorakos[108]	2019	NS	NS	×	✓	×	NS	✓/NS	✓✓	✓✓
Phillips[109]	2019	NS	NS	✓✓	✓	×	NS	✓/NS	NS	NS
Tjong[110]	2019	NS	NS	✓	✓	×	NS	✓/✓	✓✓	✓✓
McHugh[111]	2020	NS	NS	×	✓	×	NS	✓/NS	NS	NS
Pomeranz-Krummel[112]	2020	NS	✓	×	✓	×	NS	✓/NS	NS	✓✓

SUPPLEMENTARY TABLE 3. Infrequently reported outcomes and the number of studies reporting this outcome

Outcome reported	Number of studies reporting this outcome
Duration of progression free survival	8
Stable Disease	8
Progression of Disease	8
Survival analysis, Hazard Ratio (ie risk of death)	7
3 year survival rate	6
New brain metastases	6
Time to intracranial failure	6
Cavity recurrence	5
Some improvement	5
Partial response	4
Distant intracranial failure	4
Local failure rate	4
Intracranial failure within 12 mo	4
1 yr, no distant brain failure (%pts)	4
6 mo local control rate	4
5 year overall survival rate	4
Rate of progression free survival at 12 months	3
Complete Response, in treated lesion/s	3
Intracranial progression	3
Intracranial disease control rate	3
Recurrence/relapse in brain (n patients)	3
Time to Intracranial progression/new metastases	3
1 yr failure free survival, % of pts	3
Hazard Ratio for local failure	3
Intracranial response rate	3
Rate of progression free survival at 6 months	2
Disease progression	2
Brain progression free survival (median)	2
Number of patients with distant intracranial recurrence	2
6 month local failure rate	2
Hazard Ratio for distant control	2
9 month overall survival rate	1
18 month overall survival rate	1
Intracranial complete response	1
6 month Intracranial progression free survival	1
Cummulative intracranial failure	1
Patients with CNS/brain metastases progression	1
Gene expression data	1
Progression free survival rate at 6 mo	1
Global progression free survival rate at 9 mo	1
Complete Symptom improvement	1
Duration of response	1
Brain only relapse (N pts)	1
Rapid progression of extracranial disease	1
2 year patient based local control	1
Time to out of field CNS progression	1
Odds Ratio for neurologic death	1
Duration of extra-CNS progression free survival	1

SUPPLEMENTARY TABLE 4. Criteria for determining treatment type for patients with brain metastases undergoing radiation therapy, in papers that reported this detail

	Criteria for choosing treatment			
Author, year	**Surgery**	**WBRT**	**SRS**	**Generally**
Rate 1988[12]	Accessible location and appropriate medical condition	Dose based on physician decision		
Hagan 1990[13]				Physicians choice
Stevens 1992[14]	Based on patients general health, single brain lesion, little or no extracranial disease and neurosurgeons opinion			
Isokangas 1996[17]				Patients with poor general condition were not given WBRT
Gieger 1997[19]	Location of lesion, large sized lesions, significant symptoms, superficial lesions (ref is Black 1993). Single lesion > 30mm, primary tumour controlled or limited systemic disease, acceptable anaesthetic risk	Single lesions, > 30mm, with advanced primary tumour or systemic disease, poor anaesthetic risk (Coffey 1991)	Deep lesions, or with concurrent medical conditions such as bleeding diathesis (Black 1993). Single lesion <= 30mm	
Grob 1998[113]			≤ 3 lesions, max diameter < 30mm by MRI, no life threatening metastases, KPS ≥60	
Seung 1998[23]	NS	NS	< 3cm diameter, KPS ≥70	
Lavine 1999[24]	NS	NS	1-3 lesions, ≤35mm, KPS≥70	
Buchsbaum 2002[27]				Physician and patient discussion
Gonzalez-Martinez 2002[28]			KPS > 50, maximum lesions diameter ≤40mm	
Yu 2002[114]	Significant symptoms		Expected survival >3 months, KPS≥70, 1-3 lesions with no prior WBRT, or < 5 lesions with prior WBRT, max lesions dimaeter < 35mm	
Zacest 2002[32]	Single, surgically accessible cerebral metastasis and either stable or no extracranial metastases, or if more than 1 metastasis and 1 was imminently life threatening			
Fife 2004[35]	1 lesion, surgically accessible, with stable or absent extracranial disease, or when pt had 2-3 mets and 1 was considered life threatening	Reasonable performance status who had symptomatic brain lesions but not considered for surgery		
Radbill 2004[38]				Discussion by physician and patient
Panagiotou 2005[42]				Physicians choice
Gaudy-Marquesta 2006[45]			1-4 lesions seen on CT, KPS≥60, no immediately life threatening metastases, not < 5 mm from optic pathway,	
Samlowksi 2007[48]	Dominant symptomatic surgically accessible lesion	SRS+WBRT when ≥5 lesions	When < 5 lesions	

Carrubba 2009[51]				Age, tumour size, extent of systemic disease, comorbidities, number of lesions, presence of neurological deficit, presence of hemorrhage, hydrocephalus, mass effect and patient preference
Staudt 2010[55]	Few or single brain lesions, good KPS and surgically accessible		Surgically inaccessible lesions	
Davies 2011[56]	1-3 lesions	Diffuse metastases	1-3 lesions	
Eigentler 2011[57]	Number of lesions (not further specified)			
Skeie 2011[59]			If <3 lesions, maximum diameter 3.5cm, total vol < 20cm^3, no mass effect or signs of increased intracranial pressure, KPS≥70, expected survival > 3 mo	
Hauswald 2012[62]		When SRS isn't possible or >3 lesions are present		
Knisely 2012[63]		Salvage for rapid progression	Multiple lesions if performance is good	
Lo 2012[65]				Physicians choice
Salvati 2012[66]	Life expectancy > 3 months, systemic disease under control	Routine after surgery from 1997-2002. Rare after 2001	When lesions < 1 cm3 and KPS< 70	
Mathew 2013[67]			If ≤ 9 lesions	
Partl 2013[69]		For progression or multiple lesion presentation		
Marcus 2014[73]				At discretion of physician
Vecchio 2014[76]	When considered resectable			
Christ 2015[77]	Large lesion, symptomatic and accessible in non eloquent area	NA	Lesion < 3 cm, no neurological deficit	
Szyszka-Chare 2016[86]	single accessible BM		unresectable	
Minniti 2017[92]	surgery+SRS if large and or symptomatic BM		Lesion > 2 cm or located close to brainstem or optic pathway, or had multiple lesions, or were high risk for surgery or who refused surgery	
Pessina 2017[94]	Surgery+SRS if KPS≥70, controlled extracranial disease, single lesion with diameter ≥ 15mm or multiple lesions with mass effect and neurological deficits, uncontrolled by medical treatments		Single brain lesions <15mm, or multiple lesions ≤25 mm. Hypofractonated SRS alone if lesion > 25 mm in pts with KPS<70 and uncontrolled disease	
Kotecha 2018[102]				Number of lesions, KPs, size of lesions, neurological status, age, extent of primary tumour, extracranial progression and patient input
Jardim 2019[107]	Large or symptomatic brain lesion/s or when tissue sample required		Smaller, multiple, asymptomatic or surgically inaccessible lesions	
Pomeranz 2020[112]				Radiation therapy based on number of lesions as per local practices

SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy

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