review

Radiation therapy for melanoma brain metastases: a systematic review

John F. Thompson[1,2,3], Gabrielle J. Williams[1,2], Angela M. Hong[1,2,4]

[1] Melanoma Institute Australia, The University of Sydney, North Sydney, NSW, Australia

[2] Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia

[3] Royal Prince Alfred Hospital, Sydney, NSW, Australia

[4] Chris O'Brien Lifehouse, Sydney, NSW, Australia

Background. Radiation therapy (RT) for melanoma brain metastases, delivered either as whole brain radiation therapy (WBRT) or as stereotactic radiosurgery (SRS), is an established component of treatment for this condition. However, evidence allowing comparison of the outcomes, advantages and disadvantages of the two RT modalities is scant, with very few randomised controlled trials having been conducted. This has led to considerable uncertainty and inconsistent guideline recommendations. The present systematic review identified 112 studies reporting outcomes for patients with melanoma brain metastases treated with RT. Three were randomised controlled trials but only one was of sufficient size to be considered informative. Most of the evidence was from non-randomised studies, either specific treatment series or disease cohorts. Criteria for determining treatment choice were reported in only 32 studies and the quality of these studies was variable. From the time of diagnosis of brain metastasis, the median survival after WBRT alone was 3.5 months (IQR 2.4–4.0 months) and for SRS alone it was 7.5 months (IQR 6.7–9.0 months). Overall patient survival increased over time (pre-1989 to 2015) but this was not apparent within specific treatment groups.

Conclusions. These survival estimates provide a baseline for determining the incremental benefits of recently introduced systemic treatments using targeted therapy or immunotherapy for melanoma brain metastases.

Key words: radiation therapy; stereotactic radiosurgery; melanoma; brain metastases

Introduction

Brain metastases are common in patients with advanced-stage melanoma, with a 20%–30% incidence in the first year after diagnosis of Stage IV disease, a 30%–40% incidence by 3-years, and an incidence of up to 73% in autopsy series.[1-3] For patients with untreated, symptomatic brain metastases, the reported average survival times range from several weeks to a few months.[4,5] Patients who have melanoma brain metastases have a worse progno-sis than patients who have brain metastases from other solid tumours.[6]

The two main radiation therapy (RT) techniques used to treat melanoma brain metastases are whole brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS). WBRT has largely fallen out of favour in recent times due to its apparently limited benefits while SRS has gained favour, especially as modern imaging has enabled earlier identification of smaller lesions before they become symptomatic.

Other treatment options for melanoma brain metastases include surgery and systemic therapy. Newer systemic therapies with immune checkpoint inhibitors and BRAF-targeted agents have shown considerable benefit in patients with metastatic melanoma[7-9] and evidence is accumulating that they can effectively treat brain metastases.[10,11] Combinations of surgery, RT and systemic therapy are now often used, sometimes sequentially, sometimes concurrently. Many contemporary clinical management guidelines suggest multidisciplinary advice tailored for individual patients, given the complexity of treatment options and sequencing.[12-15] Surgery can provide rapid symptomatic relief and may be the treatment of choice for single or few[2-3] lesions or larger symptomatic metastases in surgically-accessible sites. SRS can be an alternative to surgical resection as a local therapy in patients with smaller metastases, multiple lesions or surgically-inaccessible ones.[16-18] Although WBRT was a common treatment in the past, it is used much less frequently today[19,20], and is often reserved for patients whose brain metastases progress during systemic therapy and who are not suitable for further surgery or SRS.[21,22]

The evidence base for assessing the efficacy of RT to treat melanoma brain metastases has been weak because few well-designed randomised controlled trials have been conducted. Clinical practice guidelines have therefore been based largely on low-level evidence or consensus opinion and, as a result, recommendations vary considerably. Guidelines in the USA[23] suggest that some patients should receive systemic therapy as their sole initial treatment modality with no need for brain-directed local therapy unless there is intracranial progression, and advise that many patients will require a combined modality approach. European guidelines[24] recommend combination immunotherapy or targeted therapy as the preferred initial option and their consensus-based recommendations are to treat melanoma brain metastases with SRS, but with surgery when SRS is not possible, restricting WBRT to patients without systemic therapy or local therapy options. Australian guidelines[13] provide a practice point that concurs with European opinion about the use of systemic drug therapy and suggest that this be considered as first-line treatment in asymptomatic patients; the evidence-based recommendation, however, is for SRS to be considered in patients with single or few brain metastases, while WBRT may be used for palliation. Another practice point states that surgical resection of brain metastases is recommended for metastases >1 cm in diameter in non-eloquent areas or for symptomatic metastases.

The aim of this systematic review was to analyse the results of all published studies documenting the results of RT, without systemic immunotherapy or targeted therapy, as treatment for melanoma brain metastases. The review was prompted by the need to provide a benchmark for assessing the outcomes of upfront systemic therapy for patients with melanoma brain metastases.

Materials and methods

Terms covering melanoma, brain metastases and RT (WBRT or SRS) were used in the search strategy of Medline (1947 – 24 September 2020), Embase (1947 – 25 September 2020), the Cochrane Database of systematic reviews and the Cochrane Central Trials Registry (to 30 September 2020). Full details and results are provided in Supplementary Table 1. No language restrictions were used. Included studies were those reporting outcomes in patients with melanoma brain metastases treated with RT. Studies reporting patients with a mixture of cancer types including melanoma were excluded, as were studies of melanoma in which not all patients had brain metastases. Single case reports were also excluded, as were studies in which all patients received a combination of radiation and some form of contemporary systemic therapy (immune checkpoint inhibitors, BRAF –directed targeted therapies) without a radiation-only cohort. Non-contemporary systemic immunotherapies included interferon, interleukin, BCG vaccine, and non-contemporary systemic chemotherapies included temolozolmide, fotemustine, dacarbazine, razoxane, cisplatin and lomustine.

Complete search results were imported into Endnote, duplicates were removed and references were coded for inclusion/exclusion with reasons. Those included in the review had their data extracted by one author (GW). Reference lists of identified studies and review articles were examined to identify additional studies. Extracted data included article identifiers, design features, inclusion criteria, method of diagnosis, patient characteristics, treatment details, follow-up duration, deaths, adverse events, survival data and details of recurrences or new intracranial lesions. Quality assessment was performed using a specific tool for cohort studies[25] and the Cochrane collaboration risk of bias assessment for randomised controlled trials (RCTs).[26]

Descriptive statistics were generated using SPSS v25[27] with medians and interquartile ranges (IQR),

TABLE 1. Studies of radiation treatment in patients with melanoma brain metastases

Reference	Year	Country	Treated years	Total patients	Prospective data	Design	Surgery	WBRT	SRS LA	SRS GK	Non-contemp
Carella[50]	1980	US	1971–NS	60	×	Treatment cohort	✓	✓			✓
Katz[51]	1981	US	1971–1980	63	×	Treatment cohort	✓	✓			
Vlock[52]	1982	US	1970–1980	46	×	Treatment cohort	✓	✓			✓
Byrne[43]	1983	US	1978–1980	80	×	Treatment cohort	✓	✓			
Stridsklev[53]	1984	Norway	1973–1980	39	×	Treatment cohort		✓			✓
Choi (A)[54]	1985	US	1972–1977	194	×	Treatment cohort	✓	✓			✓
Choi (B)[55]	1985	US	1972–1977	59	×	Treatment cohort	✓	✓			
Ziegler[56]	1986	US	1972–1984	72	×	Treatment cohort	✓	✓			
Rate[44]	1988	US	1980–1987	77	×	Treatment cohort	✓	✓			✓
Hagen[57]	1990	US	1972–1987	35	×	Treatment cohort	✓	✓			
Stevens[38]	1992	Australia	1982–1990	129	×	Treatment cohort	✓	✓			
Somaza[58]	1993	US	1988–1992	23	×	Treatment cohort		✓		✓	✓
Willner[59]	1995	Germany	1985–1993	30	×	Disease cohort	✓	✓			✓
Isokangas[40]	1996	Finland	1980–1994	60	×	Treatment cohort	✓	✓			✓
Skibber[60]	1996	US	1979–1991	34	×	Treatment cohort	✓	✓			
Gieger[36]	1997	US	1992–1994	12	×	Treatment cohort	✓	✓	✓		
Gupta[61]	1997	UK	1991–1996	31	×	Treatment cohort	✓	✓			
Grob[62]	1998	France	1993–1996	35	×	Treatment cohort	✓			✓	✓
Sampson[63]	1998	US	past 20 years	670	×	Disease cohort	✓	✓			
Seung[64]	1998	US	1991–1995	55	×	Treatment cohort		✓		✓	
Lavine[65]	1999	US	1994–1997	45	×	Treatment cohort	✓	✓		✓	
Kontsadoulakis[66]	2000	US	1970–1992	136	×	Disease cohort	✓	✓			✓
Ellerhorst[67]	2001	US	1992–1995	87	×	Treatment cohort	✓	✓			
Buchsbaum[68]	2002	US	1994–1998	74	×	Disease cohort	✓	✓	✓	✓	
Gonzalez-Martinez[69]	2002	US	1996–NS	24	×	Treatment cohort		✓		✓	✓
Mingione[70]	2002	US	1989–1999	45	×	Treatment cohort	✓	✓		✓	✓
Noel[71]	2002	France	1994–2001	25	×	Treatment cohort			✓		
Yu[72]	2002	US	1994–1999	122	×	Treatment cohort		✓		✓	
Zacest[73]	2002	Australia	1979–1999	147	×	Treatment cohort	✓	✓			✓
Harrison[74]	2003	US	1990–1997	65	×	Treatment cohort	✓	✓			
Conill[75]	2004	Spain	1997–2002	26	×	Treatment cohort		✓			✓

Reference	Year	Country	Treated years	Total patients	Prospective data	Design	Surgery	WBRT	SRS LA	SRS GK	Non-contemp
Fife[37]	2004	Australia	1985–2000 (also 1952–1984)	686 (+ 451)	✗	Disease cohort	✓	✓			
Meier[76]	2004	Switzerland	1966–2002	100	✗	Disease cohort	✓	✓	✓	✓	✓
Morris[77]	2004	UK	1998–2003	102	✗	Treatment cohort	✓	✓	?	?	✓
Radbill[78]	2004	US	1996–2001	51	✗	Treatment cohort	✓	✓		✓	
Selek[79]	2004	US	1991–2001	103	✗	Treatment cohort	✓	✓	✓		
Stone[80]	2004	US	1989–1999	83	✗	Disease cohort	✓	✓		✓	
Koc[81]	2005	US	1999–2003	26	✗	Treatment cohort				✓	✓
Panagiotou[82]	2005	Greece	1986–2001	64	✗	Disease cohort	✓	✓			✓
Rhomberg[83]	2005	Austria	1982–2002	19	✗	Treatment cohort		✓			✓
Christopoulou[84]	2006	UK	1998–2004	29	✗	Treatment cohort	✓	✓		✓	
Gaudy-Marquesta[85]	2006	France	1997–2003	106	✗	Treatment cohort				✓	✓
Conill[86]	2007	Spain	1997–2004	37	✗	Treatment cohort		✓			✓
Mathieu[87]	2007	US	1987–2005	245	✗	Treatment cohort	✓	✓		✓	
Samlowski[32]	2007	US	1999–2004	44	✗	Treatment cohort	✓	✓	✓		✓
Raizer[5]	2008	US	1991–2001	355	✗	Disease cohort	✓	✓	?	?	✓
Redmond[88]	2008	US	1998–2007	59	✗	Treatment cohort	✓	✓		✓	
Carrubba[89]	2009	US	2002–2007	37	✗	Disease cohort	✓	✓	?	?	
Ahmad[90]	2010	UK	2001–2009	65	✗	Treatment cohort	✓	✓			
Rades[91]	2010	Germany	1989–2008	51	✗	Treatment cohort		✓			
Schild[92]	2010	US	NS	7 (+ 53)	Y+N	Treatment cohort		✓			✓
Staudt[93]	2010	Germany	1986–2003	265	✗	Disease cohort	✓	✓	✓		✓
Davies[34]	2011	US	1986–2004	330	✗	Disease cohort	✓	✓	?	?	
Eigentler[94]	2011	Germany	1986–2007	672	✗	Disease cohort	✓	✓	?	?	✓
Liew[95]	2011	US	1987–2008	333	✗	Treatment cohort		✓		✓	
Skeie[96]	2011	Norway	1996–2006	77	✗	Treatment cohort	✓	✓		✓	
Zakrzewski[97]	2011	US	2002–2008	89	✗	Disease cohort	✓		?	?	✓
Bernard[98]	2012	US	2004–2010	54	✗	Treatment cohort	✓		✓		
Hauswald[33]	2012	Germany	2000–2011	87	✗	Treatment cohort	✓	✓	?	?	
Knisely[35]	2012	US	2002–2010	77	✗	Treatment cohort		✓		✓	✓
Koay[99]	2012	US	2005–2011	296	✗	Disease cohort	✓	✓	?	?	✓
Lo[100]	2012	US	2000–2007	28	✗	Treatment cohort		✓		✓	✓
Salvati[101]	2012	Italy	1997–2007	84	✗	Treatment cohort	✓	✓	?	?	

Reference	Year	Country	Treated years	Total patients	Prospective data	Design	Surgery	WBRT	SRS LA	SRS GK	Non-contemp
Mathew[102]	2013	US	2008–2011	58	×	Treatment cohort				✓	✓
Miller[103]	2013	Germany	2000–2010	34	×	Treatment cohort	✓			✓	✓
Partl[31]	2013	Austria	1988–2009	87	×	Treatment cohort	✓	✓	?	?	
Silk[41]	2013	US	2005–2012	70	×	Treatment cohort		✓	?	?	✓
Zukauskaite[104]	2013	Denmark	1995–2009	80	×	Treatment cohort	✓	✓	?	?	✓
Dyer[105]	2014	US	2000–2010	147	×	Treatment cohort		✓	✓		✓
Marcus[106]	2014	US	1998–2010	135	×	Treatment cohort	✓	✓	?	?	✓
Neal[107]	2014	US	2000–2009	129	×	Treatment cohort	✓	✓		✓	✓
Rades[108]	2014	Germany	2000–2013	54	×	Treatment cohort			✓	✓	
Vecchio[109]	2014	Italy	1994–2010	115	×	Disease cohort	✓	✓	?	?	✓
Christ[110]	2015	US	2005–2011	103	×	Treatment cohort	✓	✓	✓		✓
Frakes[111]	2015	US	2008–2012	28	×	Treatment cohort		✓	✓		
Hauswald[112]	2015	Germany	1990–2011	84	×	Treatment cohort	✓	✓	✓		✓
Ivanov[113]	2015	Russia	2009–2013	95	×	Treatment cohort	✓	✓		✓	
Ly[114]	2015	US	2009–2012	52	×	Treatment cohort	✓		✓		
Ostheimer[115]	2015	Germany	1992–2011	100	×	Treatment cohort	✓	✓	?	?	✓
Gallaher[116]	2016	US	since 2006	19	×	Treatment cohort		✓		✓	
Gupta[29]	2016	UK	NS	18	Yes	RCT		✓			✓
Patel[117]	2016	US	2007–2014 (abstract says 2005–2013)	87	×	Treatment cohort			✓		✓
Rades[118]	2016	Germany	2000–2015	23	×	Treatment cohort		✓			
Szyszka-Chare[39]	2016	Poland	1985–2012	110	×	Disease cohort	✓	✓	?	?	✓
Wolf[119]	2016	US	2012–2015	80	×	Treatment cohort	✓	✓		✓	✓
Acharya[120]	2017	US	2006–2016	72	×	Treatment cohort		✓		✓	✓
All[121]	2017	US	2008–2016	58	×	Treatment cohort			?	?	
Feng[122]	2017	US	2007–2014	87	×	Treatment cohort	✓	✓	✓	✓	✓
Kaidar-Person[123]	2017	US	2007–2015	58	×	Treatment cohort		✓	✓		✓
Minniti[124]	2017	Italy	2008–2015	120	×	Treatment cohort	✓		✓		✓
Patel[125]	2017	US	2009–2013	54	×	Treatment cohort	✓		✓		✓
Pessina[126]	2017	Italy	2011–2015	53	×	Treatment cohort	✓		?	?	
Sperduto[127]	2017	US	2006–2013	823/481	×	Disease cohort	✓	✓	?	?	
Xu[128]	2017	US	2010–2014	65	×	Treatment cohort	✓	✓		✓	✓
Diao(A)[129]	2018	US	2006–2015	72	×	Treatment cohort				✓	✓

Reference	Year	Country	Treated years	Total patients	Prospective data	Design	Surgery	WBRT	SRS LA	SRS GK	Non-contemp
Diao(B) [130]	2018	US	2006–2015	91	✕	Treatment cohort				✓	✓
Fang[131]	2018	US	2005–2011	235	✕	Disease cohort	✓	✓	?	?	✓
Gabani[132]	2018	US	2011–2013	1104	✕	Treatment cohort		✓	?	?	✓
Kano[133]	2018	US	1988–2012	422	✕	Treatment cohort	✓	✓		✓	✓
Kotecha[134]	2018	US	1987–2014	366	✕	Disease cohort	✓	✓	✓	✓	✓
Ladwa[135]	2018	Australia	2009–2016	142	✕	Disease cohort	✓	✓	?	?	
Matsunaga[136]	2018	Japan	1991–2015	177	✕	Treatment cohort	✓	✓		✓	✓
Tio[137]	2018	Australia	2011–2014	355	✕	Disease cohort	✓	✓	?	?	✓
Zubatkina[138]	2018	Russia	2009–2014	78	✕	Treatment cohort	✓	✓		✓	
Hauswald[28]	2019	Germany	2013–2017	7	Yes	RCT		✓			
Hong[30]	2019	Australia	2009–2017	215	Yes	RCT	✓	✓	?	?	✓
Jardim[139]	2019	Australia	2015–2017	43	✕	Treatment cohort	✓	✓		✓	✓
Mastorakos[140]	2019	US	2011–2015	198	✕	Treatment cohort	✓	✓		✓	✓
Phillips[42]	2019	Canada	2000–2018	277	NS	Disease cohort		✓	?	?	
Tjong[141]	2019	Canada	2008–2017	97	✕	Treatment cohort	✓	✓	?	?	
McHugh[142]	2020	New Zealand	2005–2017	110	✕	Treatment cohort	✓	✓	?	?	✓
Pomeranz-Krumme[143]	2020	US	2010–2018	25	✕	Treatment cohort	✓	✓	✓	✓	✓

GK = Gamma Knife methods; Non-contemp = non-contemporary systemic therapy; LA = linear accelerator; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy stereotactic radiosurgery

Results

Search results

Search results and exclusions are shown in Figure 1. There were 142 publications between 1980–2020, 112 of which were unique studies or were the primary publication of a series of publications, and 30 were duplicates or non-primary publications (Table 1.) Seven studies were published only as abstracts. 57.1% (64/112) of the publications were from the USA, 30.4% from Europe, and 11.6% from other countries. Sample sizes ranged from 7–1304 patients (median 77). While our focus

as data were not normally distributed. Medians were tested for difference using the non-parametric median test, Fisher's exact (2-sided). When three or more studies reported the same outcome for the same treatment group, data were pooled and analysed.

was on RT, most articles (96/112) included patients who had received a variety of other therapies for their brain metastases. Surgery was reported in 79 studies, WBRT in 95 studies, SRS in 84 studies and 64 reports included subsets of patients who received some form of systemic therapy as well as RT. Outcomes for the subsets of patients treated with both RT and any form of contemporary systemic therapy were not analysed. Amongst studies reporting the use of SRS, five reported using both linear accelerator and Gamma Knife methods, 32 used Gamma Knife only, 18 used linear accelerator only and 29 did not report which was used.

Only three studies were prospectively-conducted RCTs; the remainder were retrospective studies of patient cohorts of specific treatment/s (n = 85) or cohorts of patients treated for melanoma brain metastases (n = 24). A comparison of outcomes for different treatment regimens was reported in 97 studies, while 15 studies were non-comparative, reporting outcome data for a single treatment group.

Risk of bias assessment

Details of the risk of bias assessment for each study are provided in Supplementary Table 2 and summarised in Figure 2. Of the three RCTs, none reported how their randomisation sequence was generated but all reported complete outcome data and clinically-relevant outcomes. Two of the three trials[28,29] were closed early due to poor accrual and had sample sizes of 7 and 18, greatly limiting the reliability of their results. Baseline characteristics for the different treatment arms were reported and similar for the trial of 18 patients[29] but were not reported for the trial of 7 patients.[28] The largest trial[30] had 215 patients, and while not stratifying for previous treatments, randomisation was effective as previous treatments were well balanced between the two study arms, as were baseline characteristics. This trial provided the most reliable data for identifying the effects of adjuvant WBRT in conjunction with surgery and/or SRS for patients with 1–3 brain metastases.

For the 109 cohort studies, selection bias was a significant concern, as 77 studies (71%) did not provide information specifying how a treatment choice was made. Sixteen studies reported that there were no significant differences in patient characteristics such as age, number of brain metastases and tumour volume between treatment groups, while 11 studies reported significant differences between patients treated using different modalities. The remaining 82 studies did not report similarities or differences in patient characteristics, although in 21 studies the patient characteristics were provided. Fifty-six studies did not report if or how the diagnosis of melanoma brain metastases was verified; this may have resulted in misclassification of disease, although this is probably a relatively inconsequential source of bias.

Many studies reported analyses of one treatment without considering prior and subsequent forms of treatment (e.g. SRS preceded by surgical resection). Our analysis was based on grouping data based on all treatments received for brain metastases.

Treatment decisions

Five studies (651 patients) included only asymptomatic patients, nine studies (532 patients) included only symptomatic patients, 30 studies (5906 patients) had a mixture of asymptomatic and symptomatic patients and 57 studies (5452 patients) did not report this detail.
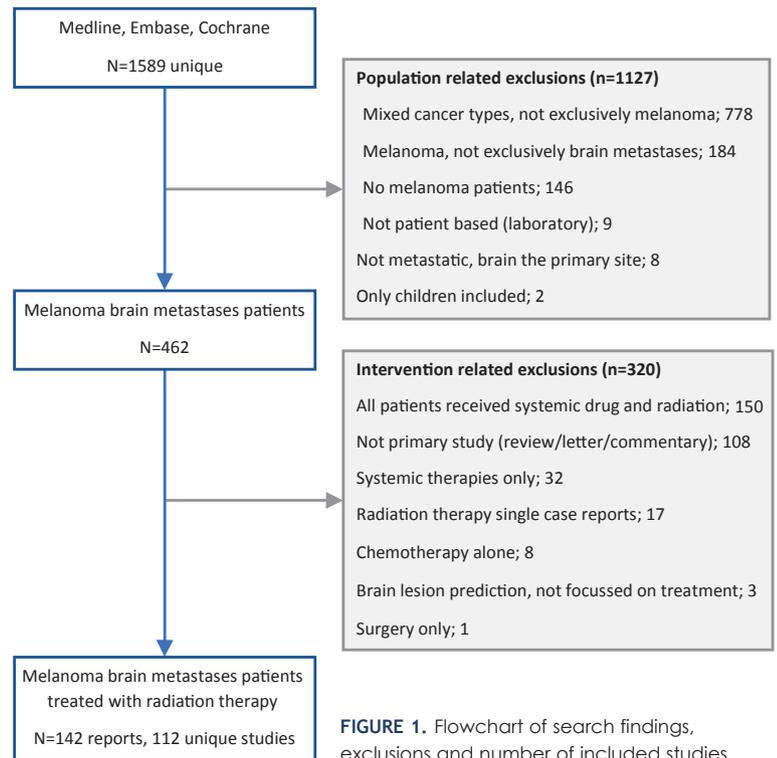
FIGURE 1. Flowchart of search findings, exclusions and number of included studies.

Seven of the 95 studies provided specific criteria for choosing WBRT in their patients; four stated that it was used for multiple brain metastases[31-34], three reported its use for progression of brain metastases[31,35,36], one its use for single, large metastases[36] and one its use for symptomatic metastases.[37]

Nineteen studies reported criteria for choosing SRS. Twelve stated that it was used for small metastases, often <30mm in diameter, nine required good performance status as measured by Karnofsky performance score (KPS), with four of these using a cut-off of KPS ≥ 70. Seven studies used SRS for a small number of brain metastases (usually 1–3). Five studies used SRS when metastases were inaccessible for surgery, four used it in for multiple metastases, but only one specified a number (≤ 9), and three stated that it was used for asymptomatic lesions. Other infrequently used criteria were; expected survival > 3 months, non-life threatening lesions, high risk for surgery, including proximity to the brain stem or optic nerve. A single study[32] reported criteria for using a combination of SRS and WBRT, stating that this was used for ≥ 5 lesions.

Fourteen studies provided criteria for surgery; a single metastasis (5 studies), few or <3 metastases
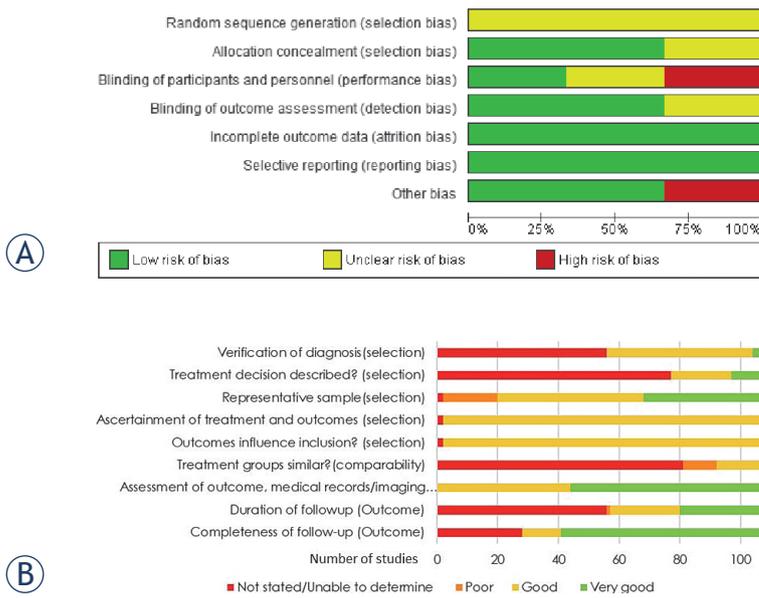
FIGURE 2. **(A)** Risk of bias assessments for randomised controlled trials evaluating radiation therapies in patients with melanoma brain metastases. **(B)** Quality assessment of cohort studies of patients with melanoma brain metastases treated with radiation therapy.

(2 studies), accessible metastases (8 studies), symptomatic metastases (4 studies), stable extracranial disease (4 studies), good KPS (1 study), life expectancy > 3 months (1 study), and 2–3 brain metastases if one was life-threatening (2 studies).

Treatment groupings

Many treatment groupings that included RT were reported but outcomes were not reported for all groups. Given the limited amount of data for clearly-defined treatment groups, we re-grouped data into two additional treatment options; (i) patients treated with WBRT and any of SRS, surgery or non-contemporary systemic therapy, and (ii) patients treated with SRS and any of WBRT, surgery, or non-contemporary systemic therapy.

Patient characteristics within treatment groups

Patient characteristics within different treatment groups are summarised in Table 2. For all treatment types, there was a predominance of males. Patients treated with WBRT alone were somewhat younger than those receiving SRS and patients undergoing WBRT were less likely to have a single brain metastasis. While the data were sparse, there was considerable overlap in patient characteristics

across different treatment modalities, indicating that the choice of treatment was not consistently determined by age, presence of symptoms, number of metastases or control of primary disease.

Median survival

Ninety-six studies reported median survival for all patients or subsets of patients and there were 49 different treatment groupings.

Within-study comparisons were possible for six treatment groupings (Table 3.). Eleven studies reported median survival for patients treated with WBRT alone or with WBRT and surgery. The median survival in the WBRT alone group was 4.0 months (IQR 3.0–4.0 months), significantly less than for those treated with surgery and WBRT (11.0 months, IQR 8.8–11.8 months) (p = 0.002). Expressing these findings as a median difference between treatments, patients who had WBRT and surgery had a 5.4 month (IQR 4.6–8.0 months) longer survival compared with those treated with WBRT alone. In this group of 11 studies, three reported using surgery in patients with a single brain metastasis[37-39], and two studies reported features for treatment with WBRT, this being good performance status alone in one study[40] and multiple lesions, good performance and symptoms in the second study.[37] Significant differences in median survival were also apparent between WBRT alone and surgery alone (6.0 months longer for surgery) and median survival for patients treated with WBRT plus SRS was 3.4 months longer than with WBRT alone. In the five studies with groups treated with WBRT alone or surgery alone, three reported that surgery was used for a single or few brain metastases[34,37,38] and WBRT was used for patients with more than one brain metastasis (1 study)[38] and for patients with good performance status (1 study[37]). None of the four studies reporting patients treated with WBRT alone or WBRT+SRS described features leading to these treatment choices. There were no significant differences in median survival between WBRT alone and SRS alone, or between WBRT alone and WBRT with chemotherapy, or SRS alone compared to WBRT with SRS.

Summarised findings for median survival in all studies are detailed in Table 3 and for other groupings in Supplementary Table 4. The group treated with WBRT alone had the shortest survival; 3.5 months (IQR 2.4–4.0 months). For the group treated with surgery and WBRT, the median survival was 11.0 months (IQR 7.8–12.0 months). Adding chemotherapy to WBRT appeared to provide lit-

TABLE 2. Patient characteristics within treatment group for the 51 studies that reported baseline characteristics

Treatment group		Age in years	Proportion of patients			
			Males	Asymptomatic	With single brain metastasis	With controlled primary disease
WBRT alone	Median	53.0	63.8%	i11.5%, i32.2%	26.6%	29.0%
	IQR	49.0–55.8	42.5–73.7 %	NA	18.5–48.6%	13.9–47.8%
	N studies(pts)	10 (295)	13 (496)	2 (85)	7 (339)	10 (329)
SRS alone	Median	60.2	66.7%	66.8%	54.8%	32.2%
	IQR	56.25–62.25	54.0–76.3%	59.65–78.79%	41.19–61.22	26.16–36.32%
	N studies(pts)	9 (444)	12 (822)	4 (359)	9 (706)	8 (669)
WBRT and any of SRS, surgery, chemotherapy, non-contemp	Median	53.0	63.4%	-	51.7%	45.9%
	IQR	47.00–58.75	51.64–73.88%	-	40.72–72.91%	30.18–68.06%
	N studies(pts)	5 (243)	6 (266)	0	4 (223)	6 (262)
SRS and any of; surgery, WBRT, chemotherapy, non-contemp	Median	56.9	59.1%	65.4%	38.8%	24.0%
	IQR	52.5 – 59.25	54.82 – 68.04%	51.28 – 66.38%	30.11 – 51.74%	17.56 – 39.70%
	N studies(pts)	17 (1127)	20 (1838)	5 (953)	16 (1697)	16 (1660)

GK = Gamma Knife methods; non-contemp = non-contemporary systemic therapy; i = individual study data; IQR = interquartile range; NA = not applicable; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy stereotactic radiosurgery

tle benefit, with six studies of 137 patients reporting a median survival of 4.3 months (IQR 2.8–6.0 months) (Supplementary Table 4). The compiled grouping of WBRT with any of SRS, surgery, or non-contemporary systemic therapy had a median survival of 7.2 months (IQR 4.6–9.4 months) across 47 studies with 2230 patients.

Median survival after SRS treatment alone was reported in eight studies, giving a median survival of 7.5 months (IQR 6.7–9.0 months). The median survival for patients treated with Gamma Knife SRS (5 studies, 208 patients) was 7.0 months (IQR 5.6–7.8 months) and for the three studies (980 patients) that did not report which SRS technology was used the median survival was 8.8 months. Eighteen studies reported using linear accelerator SRS but none reported the median survival for patients treated with SRS alone. Adding non-contemporary systemic therapy to SRS treatment did not improve the median survival (7.9 months, IQR 6.1–9.9 months) but the addition of surgery was associated with an increase in median survival of around 5 months (13.0 months, IQR 9.4, 13.5 months). Compiled grouping of SRS with any of WBRT, surgery, or non-contemporary systemic therapy gave a median survival of 8.0 months (IQR 6.2–10.9 months) over 42 studies involving 2702 patients.

In the only completed RCT in patients with melanoma brain metastases[30], median survival in the group treated with adjuvant WBRT after definitive local treatment of 1–3 metastases was 16.5 months (95% CI 13–24 months) compared to 13.0 months (95% CI 10–19 months) for those that did not receive adjuvant WBRT (p=0.86).

No studies reported median survival within treatment groups separately for asymptomatic and symptomatic patients. For the 5 studies that included only asymptomatic patients, there were no common treatment groups. In 4 studies of 89 symptomatic patients, the median survival for the treatment group WBRT with surgery was 9.2 months (IQR 5.4–12.8 months) and for WBRT with any other treatment; 5 months (IQR 2.5–10.0 months, 7 studies of 245 patients).

Median survival in different time periods

Median survival over time was explored by grouping the data into three time periods based on the first year of patient recruitment within each study (Table 4). Eighty-one studies reported median survival for their whole cohort irrespective of treatment, and these showed increasing survival over the years. There were significant differences in median survival between the pre-1989 group compared with the 1990–2002 (p = 0.017) and 2003–2015 groups (p = 0.002) and also between the groups first treated in 1990–2002 compared with 2003–2015 (p = 0.021).

Median survival within treatment groups over the three time periods showed a trend toward slightly increased survival in more recent years, but none of the differences was statistically significant.

One-year survival

Fifty-six studies reported 1-year survival for all patients or subsets of patients (Table 3). Pooled

TABLE 3. Pooled outcome results for studies of radiation treatments

Treatment	Groups	Median survival		1-year survival rate, %		1-year local control rate		6-mo new brain lesion rate		Serious adverse events
		Studies (Patients)	Months (IQR)	Studies (Patients)	% (IQR)	Studies (Patients)	% (IQR)	Studies (Patients)	% (IQR)	
WBRT vs. WBRT + Surgery										
Non-random, comparative	WBRT	11 (980)	4.0 (3.0, 4.0)	0	-	0	-	0	-	Not reported
	WBRT+Surg	11 (439)	11.0 (8.8,11.8)	0	-	0	-	0	-	
All studies	WBRT	26 (2185)	3.5 (2.4, 4.0)	7 (189)	9.0 (0.0, 22.5)	1 (74)	5.5 (0.0, 12.0)	0	-	Post-op death; 2% (1 study), Hemorrhage; 3/72 lesions (1 Study)
	WBRT+Surg	16 (619)	11.0 (7.8, 12.0)	1 (19)	i41.0	0		0	-	
WBRT vs. Surgery										
Non-random, comparative	WBRT	5 (699)	3.9 (3.6, 5.0)	0	-	0	-	0	-	-
	Surgery	5 (234)	9.8 (7.6, 16.5)	0	-	0	-	0	-	Gr3 tox; 3/39 (1 study)
All studies	Surgery	9 (359)	8.7 (6.2, 10.4)	1 (16)	i36.0	0	-	0	-	Post-op death; 2% (1 Study)
WBRT vs. SRS										
Non-random, comparative	WBRT	3 (931)	4.1 (3.2, 5.6)	0	-	0	-	0	-	-
	SRS	3 (980)	8.8 (7.2, 11.4)	0	-	0	-	0	-	Hemorrhage; 4/56 lesions (1 study) (SRS-GK)
All studies	SRS	8 (1188)	7.5 (6.7, 9.0)	6 (330)	35.5 (20.8, 47.8) i26.0	4 (260)	76.0 (62.8, 88.5)	0	-	
SRS Type	SRS-GK	5 (208)	7.0 (5.6, 7.8)	1 (83)	-	0	-	0	-	
	SRS-LA	0	-	0	-	0	-	0	-	
	SRS-NS	3 (980)	8.8 (7.2, 11.4)	0	-	0	-	0	-	
WBRT vs. WBRT + Chemotherapy										
Non-random, comparative	WBRT	4 (148)	2.5 (1.0, 4.2)	0	-	0	-	0	-	Gr3 tox; 3/39 (1 study)
	WBRT +Chemo	4 (62)	5.5 (4.0, 6.0)	1 (7)	i0.0	0	-	0	-	
All studies	WBRT+Chemo	6 (137)	4.3 (2.8, 6.0)	2 (15)	i0.0, i37.0	0	-	0	-	Leukopenia; 2/8 (1 study), Toxicity; 9/14 (1 study)
SRS vs. WBRT+SRS										
Non-random, comparative	SRS	5 (881)	7.0 (6.0, 8.1)	1 (83)	i26.0	0	-	0	-	Swelling requiring surgical decompression; 3/77 pts (1 study)
	WBRT+SRS	5 (344)	6.5 (5.7, 6.5)	1 (39)	i23.0	0	-	0	-	
All studies	WBRT+SRS	12 (516)	7.0 (6.0, 8.0)	3 (58)	36.0 (29.5, 37.0)	0	-	0	-	-
WBRT vs. WBRT+SRS										
Non-random, comparative	WBRT	4 (337)	3.6 (2.7, 5.0)	1 (59)	i10.0	0	-	0	-	-
	WBRT+SRS	4 (197)	7.4 (6.5, 10.7)	1 (8)	i38.0	0	-	0	-	-
SRS+ Chemotherapy										
Al studies	SRS+Chemo	1 (23)	i6.5	0	-	0	-	0	-	-
	SRS+/- Chemo	7 (580)	7.9 (6.1, 9.9)	2 (358)	i13.2, i27.9	1 (106)	i69.0	1 (106)	i12.0	Hemorrhage; 1/106 pt (1 study), 4/56 lesions (1 study). Radiation necrosis; 1/106 pts (1 study)
SRS + Surgery										
All studies	SRS+Surg	4 (200)	13 (9.4, 13.5)	1 (60)	i58.0	1 (34)	i52.0	1 (34)	i32.0	Hemorrhage; 18% (1 study)
WBRT+ other treatments										
All studies	WBRT and any of surgery, SRS, non-contemp	47 (2230)	7.2 (4.6, 9.4)	19 (827)	21.4 (13.6, 37.0)	5 (208)	1.0 (0.0, 16.0)	8 (986)	46.5 (39.8, 55.5)	WBRT specific; Deaths;6/194 (1 study), headache; 12/26 (1 study), Toxicity > Gr3; 3/7 (1 study) LeukopeniaGr1-2; 2/9 (1 study) Hemorrhage; 1/20 (1 study)
SRS+ other treatments										
All studies	SRS and any of surgery, WBRT, non-contemp	42 (2702)	8.0 (6.2, 10.9)	35 (2644)	31.0 (25.0, 39.0)	16 (1043)	69.0 (60.0, 82.0)	10 (1261)	49.0 (42.0, 56.0)	SRS specific; Hemorrhage; 14% (4 studies, 441 patients) Radiation necrosis; 6.6% (4 studies, 241 patients Seizure-edema-death; 1/55 (1 study) Complications; 6/106 (1 study)

Chemo = chemotherapy; GK = Gamma Knife methods; Gr = grade; i = individual study data; IQR = interquartile range; LA = linear accelerator; non-contemp = non contemporary systemic therapy; SRS = stereotactic radiosurgery; Surg = surgery; WBRT = whole brain radiation therapy

TABLE 4. Median survival within treatment groups and grouped by the first year of patient recruitment

First year of recruitment	Pre–1989			1990–2002			2003–2015			Not reported		
	No. of studies	Median survival	IQR	No. of studies	Median survival	IQR	No. of studies	Median survival	IQR	No. of studies	Median survival	IQR
All patients	25	4.8	3.25–8.05	33	6.0	4.35–8.00	22	9.2	6.90–11.43	1	i3.0	NA
WBRT alone	17	3.6	2.49–4.0	7	2.5	2.3–4.0	6	4.2	2.75–4.80	3	4.3	3.40–6.40
SRS alone	2	i6.4, i7.7		4	7.3	5.78–7.88	2	i10.0, i11.9		0		
WBRT and any of surgery, SRS, non-contemporary systemic therapy	43	7.4	4.00–9.20	23	7.3	5.50–10.00	4	8.0	5.73–10.50	2	i3.6, i4.3	
SRS and any of surgery, WBRT, non-contemporary systemic therapy	17	8.3	5.90–9.65	29	7.9	5.85–10.04	18	9.0	6.90–13.00	0		

i = individual study data; IQR = interquartile range; NA = not applicable; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy

data from 7 studies of 189 patients treated with WBRT alone gave a 1-year survival rate of 9.0% (IQR 0.0–22.5%) while for SRS alone the 1-year survival was 35.5% (IQR 20.8–47.8%, p = 0.041) in six studies of 330 patients. In the compiled grouping of WBRT with or without any other therapy, the 1-year survival was 21.4% (IQR 13.6%–37.0%). For the SRS grouping with or without any other therapy (WBRT, surgery, non-contemporary systemic therapy), the 1-year survival was 31.0% (IQR 25.0–39.0%) across 35 studies of 2644 patients. In the only completed RCT[30], 1-year survival in the group treated with adjuvant WBRT was 58.4% (95%CI 49.6%–68.9%) compared with 54% (95%CI 45.3%–64.3%, p = 0.89) for those treated without WBRT.

Local control

Most studies defined local control as a reduction in metastasis size or stability of metastasis size, as determined by follow-up imaging. Fifty-three studies reported local control data, 21 without a defined time frame and for almost all it was reported for the total patient group, not separately for different treatment groupings. The 1-year local control rate was highest for those treated with SRS; 76% (IQR 62.8%–88.5%). The 1-year local control rate after WBRT was 5.5% (IQR 0.0%–12.0%, 1 study, 74 patients). For the 550 patients in 11 studies that treated patients with any combination of WBRT, SRS, surgery and non-contemporary systemic therapy, the 1-year local control rate was 68.0% (IQR 66.072.0%). There was no difference in the 1-year local control rate between Gamma Knife SRS and linear accelerator-based SRS (69% *vs.* 72.0%).

New brain lesions

Thirty-six studies reported rates of new brain lesions developing during the follow-up period. For the 23 studies that reported new brain lesions at 6-months the median rate was 44% (IQR 32.0%–53.0%) and at 12-months 67% (IQR 62.3%–71.5%, 14 studies). Three studies (189 patients) reported a 6-month new brain lesion rate in patients treated with WBRT and other treatment, giving a median rate of 39% (IQR 34.0%–44.5%) and for SRS and other treatment a rate of 47% (IQR 34.5%–55.5%, 11 studies, 1306 patients). At 12 months, the RCT of patients with 1–3 brain metastases reported a new brain lesion rate of 42% in the adjuvant WBRT group and 50.5% in those who did not receive adjuvant WBRT (p = 0.22). For patients treated with SRS, the proportion who developed a new brain lesion by 12 months was 67% (IQR 57.0%–75.0%; 11 studies, 1278 patients).

Neurologic deaths

Neurologic death was reported in 40 studies but only 11 reported this for a defined treatment group. The definition of neurologic death was variable. Only one study provided a definition that combined an objective measurement with radiological and clinical neurologic changes.[41] Other studies used brain lesion progression and/or recurrence (18 studies), brain hemorrhage alone (4 studies), neurologic dysfunction alone (4 studies) or other features (3 studies) as criteria for designating a death as neurologic. The reported proportion of patients with a neurologic cause of death ranged from 0% to 90%. Three studies reported the propor-

tion of patients treated with WBRT with or without surgery who experienced neurologic death (0%, 24%, 83%). Two studies reported neurologic deaths for patients treated with WBRT alone (14%, 88%), two studies reported on SRS alone (41%, 90%), two studies reported neurologic deaths in those treated with SRS and WBRT (50%, 58%) and two studies reported neurologic death in patients treated with WBRT with or without systemic therapy (57%, 75%). Re-grouping the data into SRS with any other treatment (6 studies), gave a median neurologic death rate of 53% (IQR 44.8%–69.4%), while for WBRT and any other treatment (10 studies), the median was 50% (IQR 19.3%–62.3%).

Effect of number of brain metastases on survival

Seventy-six studies assessed whether the number of brain metastases present at diagnosis impacted survival, with 58 reporting significantly improved survival for patients with single lesions while 18 reported no impact. In the RCT[30], the number of brain metastases (1 *vs.* 2–3) did not influence overall survival. Only three studies reported these data within specific treatment groups.[42-44] Two studies[43,44] reported survival in patients treated with WBRT alone comparing those with one metastasis to those with ≥ 2 brain metastases; one study[44] reported better survival in the single metastasis group (16 weeks) compared to the multiple metastases group (12 weeks) while the other study[43] did not (9 weeks for a single metastases and 11 weeks for multiple metastases).

Adverse effects of radiation therapy

Adverse effects of RT were reported in 41 studies, but only 17 reported events within treatment groups and these were primarily studies that included systemic therapy. Radiation necrosis (with various radiological and/or pathological definitions) was reported in 13 studies, 11 of which focussed on SRS. The median rate was 8.1% (IQR 3.4%–22.2%). In the four studies using Gamma Knife SRS, the median radiation necrosis rate was 3.4% (IQR 0.47%–5.49%) and for the 4 studies using linear accelerator SRS it was 22.2% (IQR 15.59%–25.66%). Two studies reported this for WBRT, with rates of 1.9% and 3.6%. Eight studies reported intracranial haemorrhage in their patients, with seven studies focussed on SRS, giving a median rate of 14.7% (IQR 0.94–18.8%). Three studies using Gamma Knife SRS reported brain haemorrhage rates with a median rate of 18.8% (IQR 9.86–24.01%) and two studies used linear accelerator SRS, with brain haemorrhage rates of 15% and 16%. Other reported adverse effects included headaches, seizures, skin reactions, fatigue, nausea, alopecia and confusion but because data were sparse and pooled analysis was not possible.

Discussion

For unbiased comparisons of an intervention, prospective randomised controlled trials are required. Although RT has long been used in the management of patients with melanoma brain metastases, there have been only three randomised trials of RT for this condition, and only one of these[30] recruited sufficient patients for meaningful analysis. However, a large number of non-randomised studies (n = 109) have published outcomes for patients with melanoma brain metastases treated with various RT regimens. The number of patients in each study varied, but most (86%) had fewer than 200 patients and medians of 20–30 for different treatment groups. This low number of patients per treatment group reduces the precision of estimates of survival duration within each study but when pooled over many studies, greater precision can be achieved. These non-randomised studies were of variable quality with multiple study design features poorly reported, hindering our understanding of how patients were selected for the studies and how representative they were. Over the 40-year period encompassed by this review there was a consistent trend towards improvement in the median survival of patients with melanoma brain metastases. This is likely due to earlier diagnosis of small brain metastases using newer imaging technologies, as well as a general improvement in treatment. However, we were unable to demonstrate an improvement in median survival within treatment groups over time, possibly due to a paucity of data for individual treatment groups.

Within-study comparisons were possible for only six treatment groupings. These analyses demonstrated significantly longer median survival times for patients who were treated with surgery alone (+6 months), WBRT and surgery (+7 months) and WBRT and SRS (+4 months) compared to those treated with WBRT alone (4 months). The better survival after surgery or SRS than after WBRT is almost certainly due mainly to selection issues since patients with fewer lesions, better performance status and a lower burden of extracranial disease were more likely to receive surgery or SRS and these fea-

tures are associated with improved survival. The benefit of within-study comparisons is the presence of a "control" group in the same study, meaning that treatment decisions, management and outcome assessment were likely to be more consistent than comparisons with studies performed at different institutions and at different times.

Many treatment groups were not represented in the within-study comparisons and were therefore reviewed across studies to provide estimates of median and 1-year survival rates for major treatment groupings. Patients treated with WBRT alone had a median survival of only 3.5 months, while those treated with SRS had a median survival of 7.5 months. Data were somewhat limited but suggest that linear accelerator-based SRS resulted in similar local control rates as Gamma Knife-based SRS. This is a reassuring finding as there is no randomised comparison of different SRS techniques for brain metastases. The combination of surgical removal of the lesion/s and WBRT was associated with substantially improved median survival, apparently adding 7.5 months of life, with median survival 11.0 months. These across-study median survival estimates are reassuringly consistent with the within-study findings. These findings, however, conflict with those of the randomised controlled trial that showed no survival gain and no improvement in intracranial control or performance status with adjuvant WBRT after adequate local treatment of 1–3 brain metastases.[30] This may be because about one third of the patients in the RCT also received SRS, which may have enhanced survival and limits our ability to compare their outcomes with those of patients treated with WBRT and surgery but no SRS.

Median survival for patients treated with surgery and SRS also showed benefit (+5.5 months), with a median survival of 13 months. Again, this is likely attributable to selection of patients with fewer metastases for surgery and SRS. Importantly, the data confirmed a lack of any survival benefit from the addition of non-contemporary systemic chemotherapy or non-contemporary forms of immunotherapy.

Limitations

Risk of bias assessment for these studies showed that many of the non-randomised studies included patients who were treated without explanation of how treatment choices were made. In the 30% of studies that did report treatment selection criteria there was considerable variation, reflecting the diversity of clinical practice between and even within individual centres and over the 40-year study period. This selection bias limited our ability to apply results to specific patient groups as we could not be sure in many instances which types of patients received particular treatments. Also, important prognostic factors such as performance status and extent of extracranial disease were rarely reported within treatment groups. Compiling the rather limited patient characteristics data for the different treatment groups showed that there was considerable overlap in the types of patients receiving WBRT and SRS. There was a degree of consistency in offering surgery to patients with a single or few brain metastases, as almost half of the studies that reported criteria for surgery stated this. However, it was not possible to determine survival outcomes for patients who underwent surgery for a single brain metastasis followed by RT as this was not reported. Most studies that analysed the effect on survival of having a single versus multiple brain metastases, irrespective of other treatments, reported improved survival with a single metastasis. This suggests that patients who undergo surgery have a greater likelihood of increased survival at baseline. A valid comparison of different RT modalities should consider or control for factors that have a major impact on survival, an issue not possible to evaluate using the current evidence.

Further difficulties arose in relation to the multitude of different outcomes reported that could not be easily combined. For example, median, 6-month, 1 and 2-year survival rates were often reported but recurrence/regrowth at a treated site versus new lesions at new sites were often not clearly specified within treatment groups or time frames. Similarly, the definitions of neurologic death varied between studies. Only one study provided a robust, measurable definition of this while others relied on less precise features. Definitions of radiation necrosis were also variable, provided in only eight studies, each of which was different; three relied solely on various imaging features, one solely on clinical signs of bleeding and four on combined imaging features and clinical signs. Radiation necrosis and neurologic death are important endpoints being measured in current clinical trials and an assurance of similar definitions and measurements will greatly aid interpretation of these outcomes across studies. A possible solution to the diverse and variably-defined outcomes in studies would be for clinicians, researchers and patients to agree on a minimum required and consistently-defined outcome reporting set, as has been done for other diseases

such as rheumatoid arthritis, ulcerative colitis, and lung cancer.[45-47] Researchers have developed a process for selecting outcomes of interest to clinicians and patients, and deciding how these can be implemented in their respective settings.[48,49] A similar strategy for future studies of patients with melanoma brain metastases would be feasible.

Few studies reported whether the treatments resulted in relief of symptoms for symptomatic patients. Australian guidelines suggest that WBRT may be considered in a palliative setting for relief of symptoms, and there are many anecdotal reports of its value in this situation, but we found little reported evidence to support the effectiveness of this option.

Use of treatment groupings was a substantial limitation to interpretation, as many studies grouped together patients who received different treatment combinations. Ideally more uniform treatment groups should be used but this would require studies of much greater size to achieve adequate numbers within each group.

Conclusions

One randomised trial and many observational studies have reported survival outcomes for patients treated with RT for melanoma brain metastases. WBRT alone and SRS alone resulted in median survival times of about 4 and 8 months respectively. For patients who were selected to have surgery in addition to RT, there was a 5–7-month improvement in survival, however, this likely reflects the tendency to select patients with a better baseline prognosis relative to patients not offered surgery. While most studies included in this review were not optimal for determining the efficacy of an intervention, they provide the only evidence currently available. Given the improved efficacy of newer systemic therapies in the treatment of metastatic melanoma, RT alone today has a diminished role in the management of melanoma brain metastases, and large-scale trials or cohort studies of RT alone would be considered unethical. Therefore, this systematic review of the various forms of RT with or without surgery provides baseline estimates for measuring the incremental benefits of contemporary systemic therapies over RT with or without surgery in the treatment of patients with melanoma brain metastases.

Acknowledgments

References

1. de la Monte SD, Moore GW, Hutchins GM. Patterned distribution of metastases from malignant melanoma in humans. *Cancer Res* 1983; **43:** 3427-33. PMID: 6850649

2. Amer MH, Al-Sarraf M, Baker LH, Vaitkevicius VK. Malignant melanoma and central nervous system metastases. Incidence, diagnosis, treatment and survival. *Cancer* 1978; **42:** 660-8. doi: 10.1002/1097-0142(197808)42:2<660::AID-CNCR2820420237>3.0.CO;2-E

3. Zhang D, Wang Z, Shang D, Yu J, Yuan S. Incidence and prognosis of brain metastases in cutaneous melanoma patients: a population-based study. *Melanoma Res* 2019; **29:** 77-84. doi: 10.1097/CMR.0000000000000538

4. Chukwueke U, Batchelor T, Brastianos P. Management of brain metastases in patients with melanoma. *J Oncol Practice* 2016; **12:** 536-42. doi: 10.1200/JOP.2016.011882

5. Raizer JJ, Hwu WJ, Panageas KS, Wilton A, Baldwin DE, Bailey E, et al. Brain and leptomeningeal metastases from cutaneous melanoma: survival outcomes based on clinical features. *Neuro Oncol* 2008; **10:** 199-207. doi: 10.1215/15228517-2007-058

6. Winston K, Walsh J, Fischer E. Results of operative treatment of intracranial metastatic tumors. *Cancer* 1980; **45:** 2639-45. doi: 10.1002/1097-0142(19800515)45:10<2639::AID-CNCR2820451025>3.0.CO;2-O

7. Pasquali S, Hadjinicolaou AV, Chiarion Sileni V, Rossi CR, Mocellin S. Systemic treatments for metastatic cutaneous melanoma. *Cochrane Database Syst Rev* 2018; **2:** CD011123. doi: 10.1002/14651858.CD011123.pub2

8. Hao C, Tian J, Liu H, Li F, Niu H, Zhu B. Efficacy and safety of anti-PD-1 and anti-PD-1 combined with anti-CTLA-4 immunotherapy to advanced melanoma: a systematic review and meta-analysis of randomized controlled trials. *Medicine* 2017; **96:** e7325. doi: 10.1097/MD.0000000000007325

9. Dequen P, Lorigan P, Jansen JP, van Baardewijk M, Ouwens MJ, Kotapati S. Systematic review and network meta-analysis of overall survival comparing 3 mg/kg ipilimumab with alternative therapies in the management of pretreated patients with unresectable stage III or IV melanoma. *Oncologist* 2012; **17:** 1376-85. doi: 10.1634/theoncologist.2011-0427

10. Rulli E, Legramandi L, Salvati L, Mandala M. The impact of targeted therapies and immunotherapy in melanoma brain metastases: a systematic review and meta-analysis. *Cancer* 2019; **125:** 3776-89. doi: 10.1002/cncr.32375

11. van Opijnen MP, Dirven L, Coremans IEM, Taphoorn MJB, Kapiteijn EHW. The impact of current treatment modalities on the outcomes of patients with melanoma brain metastases: a systematic review. *Int J Cancer* 2020; **146:** 1479-89. doi: 10.1002/ijc.32696

12. Coit DG, Thompson JA, Albertini MR, Barker C, Carson III WE, Contreras C, et al. Cutaneous melanoma, version 2.2019, NCCN clinical practice guidelines in oncology. *Natl Compr Canc Netw* 2019; **17:** e1. doi: 10.6004/jnccn.2019.0018

13. Long GS, Shivalingam B, Carlino M, Hong, A, Atkinson, V, Kefford, R, et al. Summary of recommendations and practice points: treatment approaches to brain metastases for patients with melanoma. Sydney: Cancer Council Australia; 2019 [updated 2019 Mar 7]; [cited 2021 Jan 28]. Available at: https://wiki.cancer.org.au/australia/Guidelines:Melanoma/Summary_of_treatment_approaches_to_brain_metastases

14. Michielin O, Van Akkooi A, Ascierto P, Dummer R, Keilholz U. Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2019; **30:** 1884-901. doi: 10.1093/annonc/mdz411

15. Hong AM, Waldstein C, Shivalingam B, Carlino MS, Atkinson V, Kefford RF, et al. Management of melanoma brain metastases: evidence-based clinical practice guidelines by Cancer Council Australia. *Eur J Cancer* 2021; **142:** 10-7. doi: 10.1016/j.ejca.2020.10.013

16. Tsao MN, Lloyd NS, Wong RK, Rakovitch E, Chow E, Laperriere N. Radiotherapeutic management of brain metastases: a systematic review and meta-analysis. *Cancer Treat Rev* 2005; **31:** 256-73. doi: 10.1016/j.ctrv.2005.04.007

17. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 2004; **363:** 1665-72. doi: 10.1016/S0140-6736(04)16250-8

18. Chen JC, Petrovich Z, O'Day S, Morton D, Essner R, Giannotta SL, et al. Stereotactic radiosurgery in the treatment of metastatic disease to the brain. *Neurosurgery* 2000; **47:** 268-81. doi: 10.1097/00006123-200008000-00003

19. Brastianos HC, Nguyen P, Sahgal A, Eisenhauer EA, Baetz T, Hanna TP. Association of innovations in radiotherapy and systemic treatments with clinical outcomes in patients with melanoma brain metastasis from 2007 to 2016. *JAMA Netw Open* 2020; **3:** e208204. doi: 10.1001/jamanetworkopen.2020.8204

20. Barbour AB, Jacobs CD, Williamson H, Floyd SR, Suneja G, Torok JA, et al. Radiation therapy practice patterns for brain metastases in the United States in the stereotactic radiosurgery era. *Adv Radiat Oncol* 2020; **5:** 43-52. doi: 10.1016/j.adro.2019.07.012

21. Sandler KA, Shaverdian N, Cook RR, Kishan AU, King CR, Yang I, et al. Treatment trends for patients with brain metastases: does practice reflect the data? *Cancer* 2017; **123:** 2274-82. doi: 10.1002/cncr.30607

22. Waldstein C, Wang W, Lo S, Shivalingam B, Fogarty GB, Carlino MS, et al. Melanoma brain metastases: the outcome of whole brain radiation therapy in the era of effective systemic therapy. *Ther Radiol Oncol* 2021; **5:** 1-11. doi: 10.21037/tro-21-6

23. NCCN. NCCN Guidelines Version 3.2022 Melanoma: Cutaneous US2022. [cited 2022 Mar 15]. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

24. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Bastholt L, et al. European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment - Update 2019. *Eur J Cancer* 2020; **126:** 159-77. doi: 10.1016/j.ejca.2019.11.015

25. Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute. 2011. [cited 2022 Mar 14]. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm

26. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomsied trials. *BMJ* 2011; **343:** d5928. doi: 10.1136/bmj.d5928

27. IBM. Statistical Software for the Social Sciences (SPSS) version 25. Armonk, NY: IBM Corp; 2016.

28. Hauswald H, Bernhardt D, Krug D, Katayama S, Habl G, Lorenzo Bermejo J, et al. Whole-brain helical tomotherapy with integrated boost for brain metastases in patients with malignant melanoma - final results of the BRAIN-RT trial. *Cancer Manag Res* 2019; **11:** 4669-76. doi: 10.2147/CMAR.S204729

29. Gupta A, Roberts C, Tysoe F, Goff M, Nobes J, Lester J, et al. RADVAN: a randomised phase 2 trial of WBRT plus vandetanib for melanoma brain metastases - results and lessons learnt. *Br J Cancer* 2016; **115:** 1193-200. doi: 10.1038/bjc.2016.318

30. Hong AM, Fogarty GB, Dolven-Jacobsen K, Burmeister BH, Lo SN, Haydu LE, et al. Adjuvant whole-brain radiation therapy compared with observation after local treatment of melanoma brain metastases: a multicenter, randomized phase III trial. *J Clin Oncol* 2019; **37:** 3132-41. doi: 10.1200/JCO.19.01414

31. Partl R, Richtig E, Avian A, Berghold A, Kapp KS. Karnofsky performance status and lactate dehydrogenase predict the benefit of palliative whole-brain irradiation in patients with advanced intra-and extracranial metastases from malignant melanoma. *Int J Radiat Oncol Biol Phys* 2013; **85:** 662-6. doi: 10.1016/j.ijrobp.2012.06.009

32. Samlowski WE, Watson GA, Wang M, Rao G, Klimo Jr P, Boucher K, et al. Multimodality treatment of melanoma brain metastases incorporating stereotactic radiosurgery (SRS). *Cancer* 2007; **109:** 1855-62. doi: 10.1002/cncr.22605

33. Hauswald H, Dittmar JO, Habermehl D, Rieken S, Sterzing F, Debus J, et al. Efficacy and toxicity of whole brain radiotherapy in patients with multiple cerebral metastases from malignant melanoma. *Radiat Oncol* 2012; **7:** 130. doi: 10.1186/1748-717X-7-130

34. Davies MA, Liu P, McIntyre S, Kim KB, Papadopoulos N, Hwu WJ, et al. Prognostic factors for survival in melanoma patients with brain disease. *Cancer* 2011; **117:** 1687-96. doi: 10.1002/cncr.25634

35. Knisely JP, Yu JB, Flanigan J, Sznol M, Kluger HM, Chiang VL. Radiosurgery for melanoma brain metastases in the ipilimumab era and the possibility of longer survival. *J Neurosurg* 2012; **117:** 227-33. doi: 10.3171/2012.5.JNS111929

36. Gieger M, Wu JK, Ling MN, Wazer D, Tsai JS, Engler MJ. Response of intracranial melanoma metastases to stereotactic radiosurgery. *Radiat Oncol Investig* 1997; **5:** 72-80. doi: 10.1002/%28SICI%291520-6823%281997%295:2%3C72::AID-ROI5%3E3.0.CO;2-G

37. Fife K, Colman M, Stevens G, Firth I, Moon D, Shannon K, et al. Determinants of outcome in melanoma patients with cerebral metastases. *J Clin Oncol* 2004; **22:** 1293-300. doi: 10.1200/JCO.2004.08.140

38. Stevens G, Firth I, Coates A. Cerebral metastases from malignant melanoma. *Radiother Oncol* 1992; **23:** 185-91. doi: 10.1016/0167-8140(92)90329-S

39. Szyszka-Charewicz B. The effectiveness of brain metastases radiotherapy in patients with melanoma. *Nowotwory* 2016; **66:** 367-74. doi: 10.5603/NJO.2016.0066

40. Isokangas OP, Muhonen T, Kajanti M, Pyrhonen S. Radiation therapy of intracranial malignant melanoma. *Radiother Oncol* 1996; **38:** 139-44. doi: 10.1016/0167-8140(95)01691-0

41. Silk AW, Bassetti MF, West BT, Tsien CI, Lao CD. Ipilimumab and radiation therapy for melanoma brain metastases. *Cancer Med* 2013; **2:** 899-906. doi: 10.1002/cam4.140

42. Phillips WJ, Lo B, Ong M, Smith T, Song X. Clinical outcomes in patients with melanoma brain metastases at a tertiary cancer center. *J Clin Oncol* 2019; **37(Suppl 15):** e13586. [abstract]. doi: 10.1200/JCO.2019.37.15-suppl.e13586

43. Byrne TN, Cascino TL, Posner JB. Brain metastasis from melanoma. *J Neurooncol* 1983; **1:** 313-7. doi: 10.1007/BF00165714

44. Rate WR, Solin LJ, Turrisi AT. Palliative radiotherapy for metastatic malignant melanoma: brain metastases, bone metastases, and spinal cord compression. *Int J Radiat Oncol Biol Phys* 1988; **15:** 859-64. doi: 10.1016/0360-3016(88)90118-6

45. Cooney RM WB, Altman DG, Abreu MT, Travis SPL. Outcome measurement in clinical trials for ulcerative colitis: toward standardisation. *Trials* 2007; **8:** 17. doi: 10.1186/1745-6215-8-17

46. Mak KS, Van Bommel AC, Stowell C, Abrahm JL, Baker M, Baldotto CS, et al. Defining a standard set of patient-centred outcomes for lung cancer. *Eur Respir J* 2016; **48:** 852-60. doi: 10.1183/13993003.02049-2015

47. Tugwell P, Boers M, Brooks P, Simon LS, Strand V, Idzerda L. OMERACT: an international initiative to improve outcome measurement in rheumatology. *Trials* 2007; **8:** 38. doi: 10.1186/1745-6215-8-38

48. Tong A, Manns B, Wang AYM, Hemmelgarn B, Wheeler DC, Gill J, et al. Implementing core outcomes in kidney disease: report of the Standardized Outcomes in Nephrology (SONG) implementation workshop. *Kidney Int* 2018; **94:** 1053-68. doi: 10.1016/j.kint.2018.08.018

49. Tunis SR, Maxwell LJ, Graham ID, Shea BJ, Beaton DE, Bingham CO, et al. Engaging stakeholders and promoting uptake of OMERACT core outcome instrument sets. *J Rheumatol* 2017; **44:** 1551-9. doi: 10.3899/jrheum.161273

50. Carella RJ, Gelber R, Hendrickson F, Berry HC, Cooper JS. Value of radiation therapy in the management of patients with cerebral metastases from malignant melanoma: radiation therapy oncology group brain metastases study I and II. *Cancer* 1980; **45:** 679-83. doi: 10.1002/1097-0142(19800215)45:4<679::AID-CNCR2820450410>3.0.CO;2-J

51. Katz HR. The relative effectiveness of radiation therapy, corticosteroids, and surgery in the management of melanoma metastatic to the central nervous system. *Int J Radiat Oncol Biol Phys* 1981; **7:** 897-906. doi: 10.1016/0360-3016(81)90006-7

52. Vlock DR, Kirkwood JM, Leutzinger C, Kapp DS, Fischer JJ. High-dose fraction radiation therapy for intracranial metastases of malignant melanoma: a comparison with low-dose fraction therapy. *Cancer* 1982; **49:** 2289-94. doi: 10.1002/1097-0142(19820601)49:11<2289::AID-CNCR2820491115>3.0.CO;2-8

53. Stridsklev IC, Hagen S, Klepp O. Radiation therapy for brain metastases from malignant melanoma. *Acta Radiol Oncol* 1984; **23:** 231-5. doi: 10.3109/02841868409136017

54. Choi KN, Withers HR, Rotman M. Metastatic melanoma in brain. Rapid treatment or large dose fractions. *Cancer* 1985; **56:** 10-5. doi: 10.1002/1097-0142(19850701)56:1<10::AID-CNCR2820560103>3.0.CO;2-G

55. Choi KN, Withers HR, Rotman M. Intracranial metastases from melanoma. Clinical features and treatment by accelerated fractionation. *Cancer* 1985; **56:** 1-9. doi: 10.1002/1097-0142%2819850701%2956:1%3C1::AID-CNCR2820560102%3E3.0.CO;2-X

56. Ziegler JC, Cooper JS. Brain metastases from malignant melanoma: conventional vs. high-dose-per-fraction radiotherapy. *Int J Radiat Oncol Biol Phys* 1986; **12:** 1839-42. doi: 10.1016/0360-3016(86)90327-5

57. Hagen NA, Cirrincione C, Thaler HT, DeAngelis LM. The role of radiation therapy following resection of single brain metastasis from melanoma. *Neurology* 1990; **40:** 158-60. doi: 10.1212/WNL.40.1.158

58. Somaza S, Kondziolka D, Lunsford LD, Kirkwood JM, Flickinger JC. Stereotactic radiosurgery for cerebral metastatic melanoma. *J Neurosurg* 1993; **79:** 661-6. doi: 10.3171/jns.1993.79.5.0661

59. Willner J, Bohndorf W. [CNS metastases in malignant melanomas]. [German]. *Strahlenther Onkol* 1995; **171:** 165-73. PMID: 7709333

60. Skibber JM, Soong SJ, Austin L, Balch CM, Sawaya RE. Cranial irradiation after surgical excision of brain metastases in melanoma patients. *Ann Surg Oncol* 1996; **3:** 118-23. doi: 10.1007/BF02305789

61. Gupta G, Robertson AG, MacKie RM. Cerebral metastases of cutaneous melanoma. *Br J Cancer* 1997; **76:** 256-9. doi: 10.1038/bjc.1997.371

62. Grob JJ, Regis J, Laurans R, Delaunay M, Wolkenstein P, Paul K, et al. Radiosurgery without whole brain radiotherapy in melanoma brain metastases. *Eur J Cancer* 1998; **34:** 1187-92. doi: 10.1016/S0959-8049%2898%2900026-4

63. Sampson JH, Carter JH, Friedman AH, Seigler HF. Demographics, prognosis, and therapy in 702 patients with brain metastases from malignant melanoma. *J Neurosurg* 1998; **88:** 11-20. doi: 10.3171/jns.1998.88.1.0011

64. Seung SK, Sneed PK, McDermott MW, Shu HK, Leong SP, Chang S, et al. Gamma knife radiosurgery for malignant melanoma brain metastases. *Cancer J Sci Am* 1998; **4:** 103-9. PMID: 9532412

65. Lavine SD, Petrovich Z, Cohen-Gadol AA, Masri LS, Morton DL, O'Day SJ, et al. Gamma knife radiosurgery for metastatic melanoma: an analysis of survival, outcome, and complications. *Neurosurgery* 1999; **44:** 59-66. doi: 10.1097/00006123-199901000-00031

66. Konstadoulakis M, Messaris E, Zografos G, Androulakis G. Prognostic factors in malignant melanoma patients with solitary or multiple brain metastases: is there a role for surgery? *J Neurosurg Sci* 2000; **44:** 211-8. PMID: 11327290

67. Ellerhorst J, Strom E, Nardone E, McCutcheon I. Whole brain irradiation for patients with metastatic melanoma: a review of 87 cases. *Int J Radiat Oncol Biol Phys* 2001; **49:** 93-7. doi: 10.1016/S0360-3016(00)01355-9

68. Buchsbaum JC, Suh JH, Lee SY, Chidel MA, Greskovich JF, Barnett GH. Survival by radiation therapy oncology group recursive partitioning analysis class and treatment modality in patients with brain metastases from malignant melanoma: a retrospective study. *Cancer* 2002; **94:** 2265-72. doi: 10.1002/cncr.10426

69. Gonzalez-Martinez J, Hernandez L, Zamorano L, Sloan A, Levin K, Lo S, et al. Gamma knife radiosurgery for intracranial metastatic melanoma: a 6-year experience. *J Neurosurg* 2002; **97(Suppl. 5):** 494-8. doi: 10.3171/jns.2002.97.supplement_5.0494

70. Mingione V, Oliveira M, Prasad D, Steiner M, Steiner L. Gamma surgery for melanoma metastases in the brain. *J Neurosurg* 2002; **96:** 544-51. doi: 10.3171/jns.2002.96.3.0544

71. Noel G, Simon JM, Valery CA, Cornu P, Boisserie G, Ledu D, et al. Linac radiosurgery for brain metastasis of melanoma. *Stereotact Funct Neurosurg* 2002; **79:** 245-55. doi: 10.1159/000070838

72. Yu C, Chen JCT, Apuzzo MLJ, O'Day S, Giannotta SL, Weber JS, et al. Metastatic melanoma to the brain: prognostic factors after gamma knife radiosurgery. *Int J Radiat Oncol Biol Phys* 2002; **52:** 1277-87. doi: 10.1016/S0360-3016%2801%2902772-9

73. Zacest AC, Besser M, Stevens G, Thompson JF, McCarthy WH, Culjak G. Surgical management of cerebral metastases from melanoma: outcome in 147 patients treated at a single institution over two decades. *J Neurosurg* 2002; **96:** 552-8. doi: 10.3171/jns.2002.96.3.0552

74. Harrison BE, Johnson JL, Clough RW, Halperin EC. Selection of patients with melanoma brain metastases for aggressive treatment. *Am J Clin Oncol* 2003; **26:** 354-7. doi: 10.1097/00000421-200308000-00009

75. Conill C, Fernandez-Ibiza J, Malvehy J, Puig S, Sanchez M, Castel T. Temozolomide in patients with melanoma brain metastases treated with whole brain irradiation. *Med Clin (Barc)* 2004; **122:** 413-5. doi: 10.1016/s0025-7753(04)74256-6

76. Meier S, Baumert BG, Maier T, Wellis G, Burg G, Seifert B, et al. Survival and prognostic factors in patients with brain metastases from malignant melanoma. *Onkologie* 2004; **27:** 145-9. doi: 10.1159/000076903

77. Morris SL, Low SH, A'Hern RP, Eisen TG, Gore ME, Nutting CM, et al. A prognostic index that predicts outcome following palliative whole brain radiotherapy for patients with metastatic malignant melanoma. *Br J Cancer* 2004; **91:** 829-33. doi: 10.1038/sj.bjc.6602018

78. Radbill AE, Fiveash JF, Falkenberg ET, Guthrie BL, Young PE, Meleth S, et al. Initial treatment of melanoma brain metastases using gamma knife radiosurgery: an evaluation of efficacy and toxicity. *Cancer* 2004; **101:** 825-33. doi: 10.1002/cncr.20447

79. Selek U, Chang EL, Hassenbusch SJ, 3rd, Shiu AS, Lang FF, Allen P, et al. Stereotactic radiosurgical treatment in 103 patients for 153 cerebral melanoma metastases. *Int J Radiat Oncol Biol Phys* 2004; **59:** 1097-106. doi: 10.1016/j.ijrobp.2003.12.037

80. Stone A, Cooper J, Koenig KL, Golfinos JG, Oratz R. A comparison of survival rates for treatment of melanoma metastatic to the brain. *Cancer Invest* 2004; **22:** 492-7. doi: 10.1081/CNV-200026387

81. Koc M, McGregor J, Grecula J, Bauer CJ, Gupta N, Gahbauer RA. Gamma Knife radiosurgery for intracranial metastatic melanoma: an analysis of survival and prognostic factors. *J Neurooncol* 2005; **71:** 307-13. doi: 10.1007/s11060-004-2027-1

82. Panagiotou IE, Brountzos EN, Kelekis DA, Papathanasiou MA, Bafaloukos DI. Cerebral metastases of malignant melanoma: contemporary treatment modalities and survival outcome. *Neoplasma* 2005; **52:** 150-8. PMID: 15800714

83. Rhomberg W, Eiter H, Boehler F, Saely C, Strohal R. Combined razoxane and radiotherapy for melanoma brain metastases. a retrospective analysis. *J Neurooncol* 2005; **74:** 295-9. doi: 10.1007/s11060-004-7557-z

84. Christopoulou A, Retsas S, Kingsley D, Paddick I, Lindquist C. Integration of gamma knife surgery in the management of cerebral metastases from melanoma. *Melanoma Res* 2006; **16:** 51-7. doi: 10.1097/01.cmr.0000198451.26827.b2

85. Gaudy-Marqueste C, Regis JM, Muracciole X, Laurans R, Richard MA, Bonerandi JJ, et al. Gamma-Knife radiosurgery in the management of melanoma patients with brain metastases: a series of 106 patients without whole-brain radiotherapy. *Int J Radiat Oncol Biol Phys* 2006; **65:** 809-16. doi: 10.1016/j.ijrobp.2006.01.024

86. Conill C, Berenguer J, Vargas M, Lopez-Soriano A, Valduvieco I, Marruecos J, et al. Incidence of radiation-induced leukoencephalopathy after whole brain radiotherapy in patients with brain metastases. *Clin Transl Oncol* 2007; **9:** 590-5. doi: 10.1007/s12094-007-0108-2

87. Mathieu D, Kondziolka D, Cooper PB, Flickinger JC, Niranjan A, Agarwala S, et al. Gamma knife radiosurgery in the management of malignant melanoma brain metastases. *Neurosurgery* 2007; **60:** 471-81. doi: 10.1227/01.NEU.0000255342.10780.52

88. Redmond AJ, Diluna ML, Hebert R, Moliterno JA, Desai R, Knisely JP, et al. Gamma Knife surgery for the treatment of melanoma metastases: the effect of intratumoral hemorrhage on survival. *J Neurosurg* 2008; **109 (Suppl)**: 99-105. doi: 10.3171/JNS/2008/109/12/S16

89. Carrubba CJ, Vitaz TW. Factors affecting the outcome after treatment for metastatic melanoma to the brain. *Surg Neurol* 2009; **72**: 707-11. doi: 10.1016/j.surneu.2009.03.005

90. Ahmad S, Ricco A, Brown R, Hanlon A, Yang J, Feng J, et al. Single institutional experience of stereotactic radiosurgery alone for first brain metastatic event and salvage of second brain metastatic event in a community setting with review of the literature. *Front Oncol* 2017; **7**: 32. doi: 10.3389/fonc.2017.00032

91. Rades D, Heisterkamp C, Huttenlocher S, Bohlen G, Dunst J, Haatanen T, et al. Dose escalation of whole-brain radiotherapy for brain metastases from melanoma. *Int J Radiat Oncol Biol Phys* 2010; **77**: 537-41. doi: 10.1016/j.ijrobp.2009.05.001

92. Schild SE, Behl D, Markovic SN, Brown PD, Sande JR, Deming RL, et al. Brain metastases from melanoma: is there a role for concurrent temozolomide in addition to whole brain radiation therapy? *Am J Clin Oncol* 2010; **33**: 633-6. doi: 10.1097/COC.0b013e3181c4c54b

93. Staudt M, Lasithiotakis K, Leiter U, Meier F, Eigentler T, Bamberg M, et al. Determinants of survival in patients with brain metastases from cutaneous melanoma. *Br J Cancer* 2010; **102**: 1213-8. doi: 10.1038/sj.bjc.6605622

94. Eigentler TK, Figl A, Krex D, Mohr P, Mauch C, Rass K, et al. Number of metastases, serum lactate dehydrogenase level, and type of treatment are prognostic factors in patients with brain metastases of malignant melanoma. *Cancer* 2011; **117**: 1697-703. doi: 10.1002/cncr.25631

95. Liew DN, Kano H, Kondziolka D, Mathieu D, Niranjan A, Flickinger JC, et al. Outcome predictors of gamma knife surgery for melanoma brain metastases. Clinical article. *J Neurosurg* 2011; **114**: 769-79. doi: 10.3171/2010.5.JNS1014

96. Skeie BS, Skeie GO, Enger PO, Ganz JC, Heggdal JI, Ystevik B, et al. Gamma knife surgery in brain melanomas: absence of extracranial metastases and tumor volume strongest indicators of prolonged survival. *World Neurosurg* 2011; **75**: 684-91; discussion 598-603. doi: 10.1016/j.wneu.2010.12.054

97. Zakrzewski J, Geraghty LN, Rose AE, Christos PJ, Mazumdar M, Polsky D, et al. Clinical variables and primary tumor characteristics predictive of the development of melanoma brain metastases and post-brain metastases survival. *Cancer* 2011; **117**: 1711-20. doi: 10.1002/cncr.25643

98. Bernard ME, Wegner RE, Reineman K, Heron DE, Kirkwood J, Burton SA, et al. Linear accelerator based stereotactic radiosurgery for melanoma brain metastases. *J Cancer Res Ther* 2012; **8**: 215-21. doi: 10.4103/0973-1482.98973

99. Koay EJ, Bucheit AD, Jakob JA, Hyun ED, Settle SH, Brown PD, et al. Correlation of BRAF and NRAS mutation status with tumor characteristics and treatment outcomes in melanoma patients with brain metastasis. [abstract]. *J Clin Oncol* 2012; 30 **(15 Suppl 1)**. doi: 10.1200/jco.2012.30.15_suppl.8584

100. Lo SS, Radawski JD, Nelson A, Clarke JW, McGregor JM, Mayr NA, et al. Stereotactic radiosurgery with or without whole brain radiotherapy for patients with one to three melanoma brain metastases. *J Radiat Oncol* 2012; **1**: 73-9. doi: 10.1007/s13566-012-0006-2

101. Salvati M, Frati A, D'Elia A, Pescatori L, Piccirilli M, Pietrantonio A, et al. Single brain metastasis from melanoma: remarks on a series of 84 patients. *Neurosurg Rev* 2012; **35**: 211-8. doi: 10.1007/s10143-011-0348-z

102. Mathew M, Tam M, Ott PA, Pavlick AC, Rush SC, Donahue BR, et al. Ipilimumab in melanoma with limited brain metastases treated with stereotactic radiosurgery. *Melanoma Res* 2013; **23**: 191-5. doi: 10.1097/CMR.0b013e32835f3d90

103. Miller D, Zappala V, El Hindy N, Livingstone E, Schadendorf D, Sure U, et al. Intracerebral metastases of malignant melanoma and their recurrences--a clinical analysis. *Clin Neurol Neurosurg* 2013; **115**: 1721-8. doi: 10.1016/j.clineuro.2013.03.019

104. Zukauskaite R, Schmidt H, Asmussen JT, Hansen O, Bastholt L. Asymptomatic brain metastases in patients with cutaneous metastatic malignant melanoma. *Melanoma Res* 2013; **23**: 21-6. doi: 10.1097/CMR.0b013e32835ae915

105. Dyer MA, Arvold ND, Chen YH, Pinnell NE, Mitin T, Lee EQ, et al. The role of whole brain radiation therapy in the management of melanoma brain metastases. *Radiat Oncol* 2014; **9**: 143. doi: 10.1186/1748-717X-9-143

106. Marcus DM, Lowe M, Khan MK, Lawson DH, Crocker IR, Shelton JW, et al. Prognostic factors for overall survival after radiosurgery for brain metastases from melanoma. *Am J Clin Oncol* 2014; **37**: 580-4. doi: 10.1097/COC.0b013e318280d7be

107. Neal MT, Chan MD, Lucas Jr JT, Loganathan A, Dillingham C, Pan E, et al. Predictors of survival, neurologic death, local failure, and distant failure after gamma knife radiosurgery for melanoma brain metastases. *World Neurosurg* 2014; **82**: 1250-5. doi: 10.1016/j.wneu.2013.02.025

108. Rades D, Hornung D, Blanck O, Martens K, Khoa MT, Trang NT, et al. Stereotactic radiosurgery for newly diagnosed brain metastases: comparison of three dose levels. *Strahlenther Onkol* 2014; **190**: 786-91. doi: 10.1007/s00066-014-0625-1

109. Vecchio S, Spagnolo F, Merlo DF, Signori A, Acquati M, Pronzato P, et al. The treatment of melanoma brain metastases before the advent of targeted therapies: associations between therapeutic choice, clinical symptoms and outcome with survival. *Melanoma Res* 2014; **24**: 61-7. doi: 10.1097/CMR.0000000000000029

110. Christ SM, Mahadevan A, Floyd SR, Lam FC, Chen CC, Wong ET, et al. Stereotactic radiosurgery for brain metastases from malignant melanoma. *Surg Neurol Int* 2015; **6(Suppl 12)**: S355. doi: 10.4103/2152-7806.163315

111. Frakes JM, Figura NB, Ahmed KA, Juan TH, Patel N, Latifi K, et al. Potential role for LINAC-based stereotactic radiosurgery for the treatment of 5 or more radioresistant melanoma brain metastases. *J Neurosurg* 2015; **123**: 1261-7. doi: 10.3171/2014.12.JNS141919

112. Hauswald H, Stenke A, Debus J, Combs SE. Linear accelerator-based stereotactic radiosurgery in 140 brain metastases from malignant melanoma. *BMC Cancer* 2015; **15**: 537. doi: 10.1186/s12885-015-1517-1

113. Ivanov PI, Zubatkina IS, Tumarova DI, Andreev GI, Volkov NM. [Analysis of results of Gamma knife radiosurgery for patients with melanoma brain metastases]. [Russian]. *Voprosy onkologii* 2015; **61**: 586-91. doi: УДК616.5-616-831-006;615.47.616-072.7

114. Ly D, Bagshaw HP, Anker CJ, Tward JD, Grossmann KF, Jensen RL, et al. Local control after stereotactic radiosurgery for brain metastases in patients with melanoma with and without BRAF mutation and treatment. *J Neurosurg* 2015; **123**: 395-401. doi: 10.3171/2014.9.JNS141425

115. Ostheimer C, Bormann C, Fiedler E, Marsch W, Vordermark D. Malignant melanoma brain metastases: treatment results and prognostic factors - a single-center retrospective study. *Int J Oncol* 2015; **46**: 2439-48. doi: 10.3892/ijo.2015.2970

116. Gallaher IS, Watanabe Y, DeFor TE, Dusenbery KE, Lee CK, Hunt MA, et al. BRAF mutation is associated with improved local control of melanoma brain metastases treated with Gamma knife radiosurgery. *Front Oncol* 2016; **6**: 107. doi: 10.3389/fonc.2016.00107

117. Patel BG, Ahmed KA, Johnstone PA, Yu HH, Etame AB. Initial experience with combined BRAF and MEK inhibition with stereotactic radiosurgery for BRAF mutant melanoma brain metastases. *Melanoma Res* 2016; **26**: 382-6. doi: 10.1097/CMR.0000000000000250

118. Rades D, Sehmisch L, Bajrovic A, Janssen S, Schild SE. Comparison of 20x2 Gy and 12x3 Gy for whole-brain irradiation of multiple brain metastases from malignant melanoma. *In Vivo* 2016; **30**: 917-9. doi: 10.21873/invivo.11013

119. Wolf A, Zia S, Verma R, Pavlick A, Wilson M, Golfinos JG, et al. Impact on overall survival of the combination of BRAF inhibitors and stereotactic radiosurgery in patients with melanoma brain metastases. *J Neurooncol* 2016; **127**: 607-15. doi: 10.1007/s11060-016-2072-6

120. Acharya S, Mahmood M, Mullen D, Yang D, Tsien CI, Huang J, et al. Distant intracranial failure in melanoma brain metastases treated with stereotactic radiosurgery in the era of immunotherapy and targeted agents. *Adv Radiat Oncol* 2017; **2**: 572-80. doi: 10.1016/j.adro.2017.07.003

121. All S, Patel H, Keller A, Ramakrishna NR. Initial volumetric response and local control following stereotactic radiosurgery for melanoma brain metastases. *Int J Radiat Oncol Biol Phys* 2017; 99 **(2 Suppl 1)**: E62-3. doi: 10.1016/j.ijrobp.2017.06.739

122. Feng R, Oermann EK, Shrivastava R, Gold A, Collins BT, Kondziolka D, et al. Stereotactic radiosurgery for melanoma brain metastases: a comprehensive clinical case series. *World Neurosurg* 2017; **100**: 297-304. doi: 10.1016/j.wneu.2017.01.014

123. Kaidar-Person O, Zagar TM, Deal A, Moschos SJ, Ewend MG, Sasaki-Adams D, et al. The incidence of radiation necrosis following stereotactic radiotherapy for melanoma brain metastases: the potential impact of immunotherapy. *Anticancer Drugs* 2017; **28:** 669-75. doi: 10.1097/CAD.0000000000000497

124. Minniti G, Paolini S, D'Andrea G, Lanzetta G, Cicone F, Confaloni V, et al. Outcomes of postoperative stereotactic radiosurgery to the resection cavity versus stereotactic radiosurgery alone for melanoma brain metastases. *J Neurooncol* 2017; **132:** 455-62. doi: 10.1007/s11060-017-2394-z

125. Patel KR, Shoukat S, Oliver DE, Chowdhary M, Rizzo M, Lawson DH, et al. Ipilimumab and stereotactic radiosurgery versus stereotactic radiosurgery alone for newly diagnosed melanoma brain metastases. *Am J Clin Oncol* 2017; **40:** 444-50. doi: 10.1097/COC.0000000000000199

126. Pessina F, Navarria P, Tomatis S, Cozzi L, Franzese C, Di Guardo L, et al. Outcome evaluation of patients with limited brain metastasis from malignant melanoma, treated with surgery, radiation therapy, and targeted therapy. *World Neurosurg* 2017; **105:** 184-90. doi: 10.1016/j.wneu.2017.05.131

127. Sperduto PW, Jiang W, Brown PD, Braunstein S, Sneed P, Wattson DA, et al. The prognostic value of BRAF, C-KIT, and NRAS mutations in melanoma patients with brain metastases. *Int J Radiat Oncol Biol Phys* 2017; **98:** 1069-77. doi: 10.1016/j.ijrobp.2017.03.030

128. Xu Z, Lee CC, Ramesh A, Mueller AC, Schlesinger D, Cohen-Inbar O, et al. BRAF V600E mutation and BRAF kinase inhibitors in conjunction with stereotactic radiosurgery for intracranial melanoma metastases. *J Neurosurg* 2017; **126:** 726-34. doi: 10.3171/2016.2.JNS1633

129. Diao K, Bian SX, Routman DM, Yu C, Kim PE, Wagle NA, et al. Combination ipilimumab and radiosurgery for brain metastases: tumor, edema, and adverse radiation effects. *J Neurosurg* 2018; **129:** 1397-406. doi: 10.3171/2017.7.JNS171286

130. Diao K, Bian SX, Routman DM, Yu C, Ye JC, Wagle NA, et al. Stereotactic radiosurgery and ipilimumab for patients with melanoma brain metastases: clinical outcomes and toxicity. *J Neurooncol* 2018; **139:** 421-9. doi: 10.1007/s11060-018-2880-y

131. Fang P, Boehling NS, Koay EJ, Bucheit AD, Jakob JA, Settle SH, et al. Melanoma brain metastases harboring BRAF V600K or NRAS mutations are associated with an increased local failure rate following conventional therapy. *J Neurooncol* 2018; **137:** 67-75. doi: 10.1007/s11060-017-2695-2

132. Gabani P, Fischer-Valuck BW, Johanns TM, Hernandez-Aya LF, Keller JW, Rich KM, et al. Stereotactic radiosurgery and immunotherapy in melanoma brain metastases: patterns of care and treatment outcomes. *Radiother Oncol* 2018; **128:** 266-73. doi: 10.1016/j.radonc.2018.06.017

133. Kano H, Morales-Restrepo A, Iyer A, Weiner GM, Mousavi SH, Kirkwood JM, et al. Comparison of prognostic indices in patients who undergo melanoma brain metastasis radiosurgery. *J Neurosurg* 2018; **128:** 14-22. doi: 10.3171/2016.9.JNS161011

134. Kotecha R, Miller JA, Venur VA, Mohammadi AM, Chao ST, Suh JH, et al. Melanoma brain metastasis: the impact of stereotactic radiosurgery, BRAF mutational status, and targeted and/or immune-based therapies on treatment outcome. *J Neurosurg* 2018; **129:** 50-9. doi: 10.3171/2017.1.JNS162797

135. Ladwa R, Atkinson V. The changing paradigm of management in melanoma brain metastases. *Asia Pac J Clin Oncol* 2018; **14:** 453-8. doi: 10.1111/ajco.12998

136. Matsunaga S, Shuto T, Yamamoto M, Yomo S, Kondoh T, Kobayashi T, et al. Gamma Knife radiosurgery for metastatic brain tumors from malignant melanomas: a Japanese multi-institutional cooperative and retrospective cohort study (JLGK1501). *Stereotac Funct Neurosurg* 2018; **96:** 162-71. doi: 10.1159/000489948

137. Tio M, Wang X, Carlino MS, Shivalingam B, Fogarty GB, Guminski AD, et al. Survival and prognostic factors for patients with melanoma brain metastases in the era of modern systemic therapy. *Pigment Cell Melanoma Res* 2018; **31:** 509-15. doi: 10.1111/pcmr.12682

138. Zubatkina I, Ivanov P. Early imaging radioresponsiveness of melanoma brain metastases as a predictor of patient prognosis. *J Neurosurg* 2018; **129:** 354-65. doi: 10.3171/2017.1.JNS162075

139. Jardim A, Scott J, Drew Z, Foote MC, Sadasivan AP, Hall B, et al. Extent of surrounding edema does not correlate with acute complications after radiosurgery for melanoma brain metastases. *Neurooncol* 2019; **145:** 581-5. doi: 10.1007/s11060-019-03330-9

140. Mastorakos P, Xu Z, Yu J, Hess J, Qian J, Chatrath A, et al. BRAF V600 mutation and BRAF kinase inhibitors in conjunction with Stereotactic radiosurgery for intracranial melanoma metastases: a multicenter retrospective study. *Neurosurgery* 2019; **84:** 868-80. doi: 10.1093/neuros/nyy203

141. Tjong MC, Moraes FY, Shultz D. Intracranial control and radionecrosis in melanoma patients with brain metastases treated with stereotactic radiosurgery. *Radiother Oncol* 2019; **139(Suppl 1):** S59-60. doi: 10.1016/S0167-8140%2819%2933190-1

142. McHugh FA, Kow CY, Falkov A, Heppner P, Law A, Bok A, et al. Metastatic melanoma: surgical treatment of brain metastases - Analysis of 110 patients. *J Clin Neurosci* 2020; **73:** 144-9. doi: 10.1016/j.jocn.2019.12.063

143. Pomeranz Krummel DA, Nasti TH, Izar B, Press RH, Xu M, Lowder L, et al. Impact of sequencing radiation therapy and immune checkpoint inhibitors in the treatment of melanoma brain metastases. *Int J Radiat Oncol Biol Phys* 2020; **108:** 157-63. doi: 10.1016/j.ijrobp.2020.01.043