

Radiation therapy for melanoma brain metastases: a systematic review

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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 melanoma⁷⁻⁹ 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 few²⁻³ 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 USA²³ 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 guidelines²⁴ 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 guidelines¹³ 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 me-

tastases >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 studies²⁵ and the Cochrane collaboration risk of bias assessment for randomised controlled trials (RCTs).²⁶

Descriptive statistics were generated using SPSS v25²⁷ 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 | | Non-contemp |
|---------------------------------|------|-----------|---------------|----------------|------------------|------------------|---------|------|-----|----|-------------|
| | | | | | | | | | LA | GK | |
| Carella ⁵⁰ | 1980 | US | 1971–NS | 60 | x | Treatment cohort | ✓ | ✓ | | | ✓ |
| Katz ⁵¹ | 1981 | US | 1971–1980 | 63 | x | Treatment cohort | ✓ | ✓ | | | |
| Vlock ⁵² | 1982 | US | 1970–1980 | 46 | x | Treatment cohort | ✓ | ✓ | | | ✓ |
| Byrne ⁴³ | 1983 | US | 1978–1980 | 80 | x | Treatment cohort | ✓ | ✓ | | | |
| Stridskleiv ⁵³ | 1984 | Norway | 1973–1980 | 39 | x | Treatment cohort | | ✓ | | | ✓ |
| Choi (A) ⁵⁴ | 1985 | US | 1972–1977 | 194 | x | Treatment cohort | ✓ | ✓ | | | ✓ |
| Choi (B) ⁵⁵ | 1985 | US | 1972–1977 | 59 | x | Treatment cohort | ✓ | ✓ | | | |
| Ziegler ⁵⁶ | 1986 | US | 1972–1984 | 72 | x | Treatment cohort | ✓ | ✓ | | | |
| Rate ⁴⁴ | 1988 | US | 1980–1987 | 77 | x | Treatment cohort | ✓ | ✓ | | | ✓ |
| Hagen ⁵⁷ | 1990 | US | 1972–1987 | 35 | x | Treatment cohort | ✓ | ✓ | | | |
| Stevens ³⁸ | 1992 | Australia | 1982–1990 | 129 | x | Treatment cohort | ✓ | ✓ | | | |
| Somaza ⁵⁸ | 1993 | US | 1988–1992 | 23 | x | Treatment cohort | | ✓ | | ✓ | ✓ |
| Willner ⁵⁹ | 1995 | Germany | 1985–1993 | 30 | x | Disease cohort | ✓ | ✓ | | | ✓ |
| Isokangas ⁴⁰ | 1996 | Finland | 1980–1994 | 60 | x | Treatment cohort | ✓ | ✓ | | | ✓ |
| Skibber ⁶⁰ | 1996 | US | 1979–1991 | 34 | x | Treatment cohort | ✓ | ✓ | | | |
| Gieger ³⁶ | 1997 | US | 1992–1994 | 12 | x | Treatment cohort | ✓ | ✓ | ✓ | | |
| Gupta ⁶¹ | 1997 | UK | 1991–1996 | 31 | x | Treatment cohort | ✓ | ✓ | | | |
| Grob ⁶² | 1998 | France | 1993–1996 | 35 | x | Treatment cohort | ✓ | | | ✓ | ✓ |
| Sampson ⁶³ | 1998 | US | past 20 years | 670 | x | Disease cohort | ✓ | ✓ | | | |
| Seung ⁶⁴ | 1998 | US | 1991–1995 | 55 | x | Treatment cohort | | ✓ | | ✓ | |
| Lavine ⁶⁵ | 1999 | US | 1994–1997 | 45 | x | Treatment cohort | ✓ | ✓ | | ✓ | |
| Kontsadoulakis ⁶⁶ | 2000 | US | 1970–1992 | 136 | x | Disease cohort | ✓ | ✓ | | | ✓ |
| Ellerhorst ⁶⁷ | 2001 | US | 1992–1995 | 87 | x | Treatment cohort | ✓ | ✓ | | | |
| Buchsbaum ⁶⁸ | 2002 | US | 1994–1998 | 74 | x | Disease cohort | ✓ | ✓ | ✓ | ✓ | |
| Gonzalez-Martinez ⁶⁹ | 2002 | US | 1996–NS | 24 | x | Treatment cohort | | ✓ | | ✓ | ✓ |
| Mingione ⁷⁰ | 2002 | US | 1989–1999 | 45 | x | Treatment cohort | ✓ | ✓ | | ✓ | ✓ |
| Noel ⁷¹ | 2002 | France | 1994–2001 | 25 | x | Treatment cohort | | | ✓ | | |
| Yu ⁷² | 2002 | US | 1994–1999 | 122 | x | Treatment cohort | | ✓ | | ✓ | |
| Zacest ⁷³ | 2002 | Australia | 1979–1999 | 147 | x | Treatment cohort | ✓ | ✓ | | | ✓ |
| Harrison ⁷⁴ | 2003 | US | 1990–1997 | 65 | x | Treatment cohort | ✓ | ✓ | | | |
| Conill ⁷⁵ | 2004 | Spain | 1997–2002 | 26 | x | Treatment cohort | | ✓ | | | ✓ |

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

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

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

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.

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

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 patients²⁹ but were not reported for the trial of 7 patients.²⁸ The largest trial³⁰ 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.

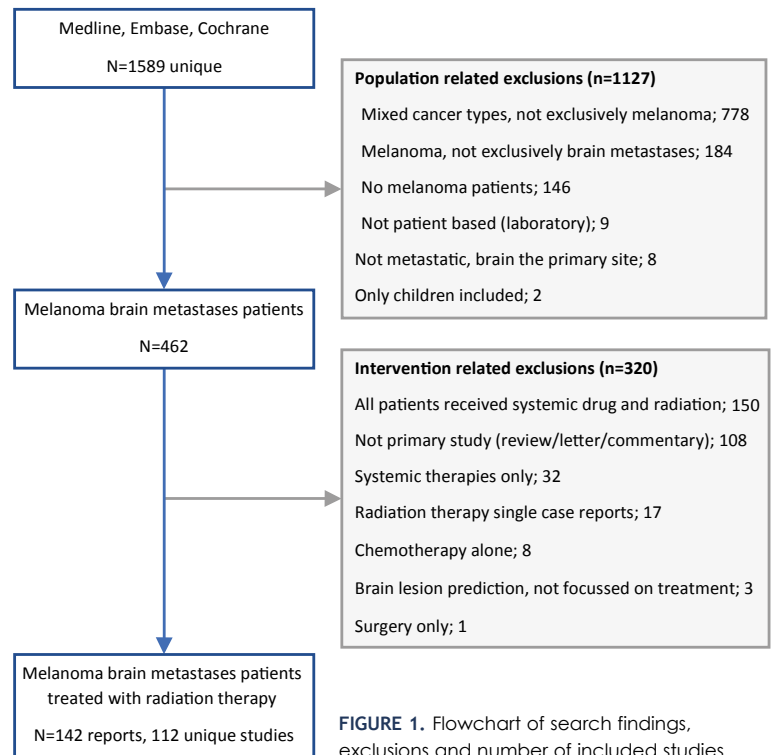


FIGURE 1. Flowchart of search findings, exclusions and number of included studies.

Seven of the 95 studies provided specific criteria for choosing WBRT in their patients; four stated that it was used for multiple brain metastases³¹⁻³⁴, three reported its use for progression of brain metastases^{31,35,36}, one its use for single, large metastases³⁶ 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 study³² 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

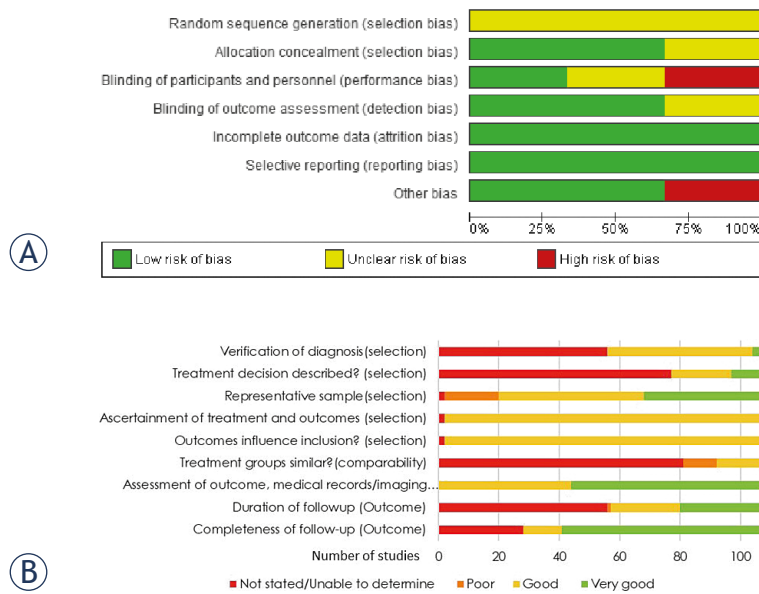


FIGURE 2. (A) Risk of bias assessments for randomised controlled trials evaluating radiation therapies in patients with melanoma brain metastases. **(B)** Quality assessment of cohort studies of patients with melanoma brain metastases treated with radiation therapy.

(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 study⁴⁰ 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 study³⁷). 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% | <i>i</i> 1.5%, <i>i</i> 32.2% | 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

the 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 metastases³⁰, 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 | - | Gr3 tox; 3/39 (1 study) |
| | Surgery | 5 (234) | 9.8 (7.6, 16.5) | 0 | - | 0 | - | 0 | - | |
| 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 | - | Hemorrhage; 4/56 lesions (1 study) (SRS-GK) |
| | SRS | 3 (980) | 8.8 (7.2, 11.4) | 0 | - | 0 | - | 0 | - | |
| All studies | SRS | 8 (1188) | 7.5 (6.7, 9.0) | 6 (330) | 35.5 (20.8, 47.8) | 4 (260) | 76.0 (62.8, 88.5) | 0 | - | |
| | | | | | | | | | | |
| SRS Type | SRS-GK | 5 (208) | 7.0 (5.6, 7.8) | 1 (83) | i26.0 | 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 | | | | | | | | | | |
| All studies | SRS+Chemo | 1 (23) | i6.5 | 0 | - | 0 | - | 0 | - | Hemorrhage; 1/106 pt (1 study), 4/56 lesions (1 study). Radiation necrosis; 1/106 pts (1 study) |
| | SRS+/- Chemo | 7 (580) | 7.9 (6.1, 9.9) | 2 (358) | i13.2, i27.9 | 1 (106) | i69.0 | 1 (106) | i12.0 | |
| 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) Leukopenia Gr1-2; 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 RCT³⁰, 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 RCT³⁰, 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 study⁴⁴ reported better survival in the single metastasis group (16 weeks) compared to the multiple metastases group (12 weeks) while the other study⁴³ 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 these³⁰ 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 di-

versity 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.

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