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Management of Brain Metastasis in Melanoma Patients

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1. Introduction

The American Cancer Society estimates that 76,250 Americans will be diagnosed with malignant melanoma and 9,180 will die from the disease in 2012 [1]. The incidence is increasing both in the United States and worldwide [2]. Brain metastasis is a common problem in this population with 45-60% of those with metastatic melanoma developing brain metastases during the course of their illness [3]. Post-mortem studies demonstrate that brain lesions are present in 70-90% of patients who die of melanoma [3]. Development of brain metastases may have adverse impact both on a patient's prognosis and, if symptomatic, severe effects on quality-of-life (QOL) [4]. If left untreated, symptomatic brain lesions may be fatal within several weeks [3].

The literature pertaining to the treatment of brain metastasis from melanoma is scant when compared to brain metastases from more common solid tumors. In particular, brain metastases from non-small cell lung cancer (NSCLC) and breast cancer have been the subject of a larger number of investigative efforts. This chapter will extrapolate relevant results from other common solid tumors to the treatment of melanoma. In addition, systemic treatment approaches that may be useful in managing intracranial disease will be presented. Leptomeningeal involvement of the central nervous system, a less common form of central nervous system (CNS) invasion by melanoma, will not be discussed.

2. Treatment modalities

2.1. Surgery

Three randomized trials have investigated treatment of a single brain metastasis with whole brain radiation therapy (WBRT) alone or combined with surgical resection (Table 1) [5-7]. In

all three, overall survival (OS) was the primary endpoint. In one study, the addition of surgery to WBRT achieved better control at the target lesion site than did WBRT alone [7]. Two of the trials indicated a survival benefit conferred by surgical treatment when added to WBRT, compared to WBRT alone. Differences in the proportion of patients with NSCLC, percentages of patients with extracranial disease, treatment of patients with non-metastatic intracranial disease, and cross-over from one treatment arm to the other may explain why the study of Mintz and co-workers did not indicate a survival benefit [6]. Extent of extracranial disease status was a consistent predictor of survival.

Study	Centers (#)	Patients (#)	Disease Types # (%)	Median Survival	Recurrence/ Progression in CNS		Comments
					Treated Site	Distant	
Patchell *et al.*, 1990 [7]	1	48 25-S 23-R	37 NSCLC (77%) 3 Mel. (6%)	40 w-S 15 w-R P<0.01	20%-S 52%-R P<0.02	20%-S 13%-R P=0.52	37% of enrolled patients with metastatic disease at enrollment. Extracranial disease and older age predicted decreased survival in multivariate analysis.
Noordijk *et al.*, 1994 [5]	5	63 32-S 31-R	33 NSCLC (52%) 6 Mel. (10%)	10 m-S 6 m-R P=0.04	NR	NR	Survival benefit in those with stable extra-cranial disease (12 m-S vs. 7 m-R, p=0.02) and patients younger than 61 y (19 m-S vs. 9 m-R, p=0.003). No survival benefit for surgery in patients with progressive extracranial disease or age"/>60.
Mintz *et al.*, 1996 [6]	8	84 41-S 43-R	45 NSCLC (53%)	5.6 m-S 6.3 m-R P=0.24	NR	NR	45% of enrolled patients with metastatic disease at enrollment. Only extracranial disease status predicted survival in multivariate analysis.

KPS: Karnofsky performance status; Mel: Melanoma patients; NR: Not reported; NSCLC: Non-small cell lung cancer; OS: Overall survival; QOL: Quality of life; R: Refers to treatment arm receiving WBRT alone; S: Refers to treatment arm combining surgery and WBRT

Table 1. Randomized trials of surgical resection of a single brain metastasis combined with WBRT versus WBRT alone

Since these studies primarily enrolled patients with primary NSCLC or breast cancer, their applicability to melanoma is uncertain. No prospective trials of surgery for melanoma patients with brain metastases have been published to date. However, a number of large retrospective studies have been reported (Table 2) [8-13]. Surgical treatment is consistently reported as a factor strongly associated with prolonged survival over those treated with WBRT alone. Selection biases are inherent in retrospective studies. Indeed, two of the studies specifically identified factors predicting patient selection for more or less aggressive treatment and follow-up based on the presumed severity of CNS involvement [10, 12]. Given that these retrospective reports in melanoma concur with the randomized trials of surgical therapy in non-melanoma brain metastases, similar randomized trials of surgery for melanoma brain metastases are probably unnecessary.

Traditionally, surgical management of brain metastases was restricted to individuals with a single accessible lesion. Bindal and co-workers found that individuals with a variety of primary solid tumors (n=56; melanoma=25/45%) undergoing resection of 2-3 brain metastases had survival rates equivalent to those undergoing resection of a single lesion [14]. In patients with complete resection of all known lesions, median survival was 14 months, equivalent to that for patients treated surgically for a single CNS lesion. Patients who could not undergo complete resection of CNS disease demonstrated inferior median overall survival of 6 months. Thus, presence of multiple CNS metastases is not a contra-indication to surgical treatment, although the advent of stereotactic radiosurgery (SRS) has made this approach less common.

2.2. Stereotactic Radiosurgery (SRS)

Stereotactic radiosurgery (SRS) has become a major modality in the local treatment of brain metastases. When compared to conventional techniques, SRS allows for safe and effective dose escalation. This is achieved through use of multiple modulated beamlets from a variety of angles, allowing optimized conformality and avoidance of normal tissues. SRS is minimally or non-invasive and allows targeting multiple CNS lesions including those that may be surgically accessible. Treatment is often performed on an outpatient basis and over a short time duration. Retreatment of the same or of new lesions is possible.

The Radiation Therapy Oncology Group (RTOG) conducted a large randomized study of SRS combined with WBRT (n=164) versus WBRT alone (n=167) (Table 3) [15]. The study enrolled patients with a variety of tumor types, although NSCLC patients comprised the largest proportion. The addition of SRS to WBRT resulted in a survival benefit for patients with a single brain lesion (6.5 months for combination therapy versus 4.9 months for WBRT alone, p=0.0393), but not for patients with multiple lesions (5.8 months for combination therapy versus 6.7 months for WBRT alone, p=0.9776) or all patients combined (6.5 months for the combination versus 5.7 months for WBRT alone, p=0.1356). At 6 months, SRS-treated patients required lower doses of corticosteroids and were more likely to discontinue steroid use altogether (52% in SRS+WBRT decreased their dose compared to 33% in the WBRT only group, p<0.0158). Patients receiving SRS also were more likely to improve their performance status (13% improved vs. 4% improved in WBRT group, p=0.0331). Local control of targeted tumors was better with SRS. Disease control at distant sites within the brain was equivalent.

Study	Dates, Patient Source Population, Institution	Melanoma Patients Studied and Treatment	Median Survival	CNS Recurrence Rates Based on Therapy Received	QOL
Raizer *et al.,* 2008 [13]	1991-2001 All metastatic melanoma patients (n=1114) at a single center	355 total 12 S/R +SRS 20 S + SRS 58 S/R 20 R + SRS 36 S 26 SRS 100 R 83 Supp.	Surgery (9 m) vs. no surgery (4 m), p<0.0001 R 4.0 m Supp. 2.0 m	NR	NR
Fife *et al.,* 2004 [12]	1985-2000 All patients with brain metastasis from melanoma (n=1137) at a single center	686 total 158 S/R 47 S 236 R 210 Supp.	All pts. 4.1 m S/R 8.9 m S 8.7 m R 3.4 m Supp. 2.1 m S= S/R, p=0.21 S or S/R >R > Supp., p<0.001	NR	NR
Buchsbaum *et al.,* 2002 [10]	1984-1998 All brain metastasis patients (n=1154) at a single center	74 total 14 S/R 19 R + SRS 3 S/R + SRS 10 S or SRS 25 R 3 Supp.	All pts. 5.5m (S or SRS) + R 8.8 m S or SRS 4.8 m R 2.3 m Supp. 1.1 m (S or SRS) + R vs. other groups, p<0.0001 S/R =R + SRS, p=0.5128	49% Local + R 17% R 20% S or SRS	NR
Zacest *et al.,* 2002 [11]	1979-1999 All surgically treated melanoma patients with brain metastasis at a single center	147 total 9 S 102 S/R 33 S/R/C 3 S/C	All pts. 8.5 m	50% overall recurrence rate	Neurological symptoms after treatment: Resolved 52% Improved 26% Unchanged 9% N/A 13%
Wronski and Arbit, 2000 [9]	1974-1994	91 total 49 S/R	All pts. 6.7 m	56% S/R vs. 46% S, p=NR	NR

Study	Dates, Patient Source Population, Institution	Melanoma Patients Studied and Treatment	Median Survival	CNS Recurrence Rates Based on Therapy Received	QOL
	All surgically treated brain metastasis patients (n=702) at a single center	29 S 13 died within 62 d of surgery	S/R (9.5 m) vs. S (8.3 m), p=0.67		
Sampson et al., 1998 [8]	~1978-1998 All melanoma patients (n=6953) treated at a single center	524 total 87 S/R 52 S 180 R 205 C	Surgical therapy (NR) vs. R (120 d), p<0.0001 S/R (268 d) vs. S (195 d), p=0.9998 R (120 d) vs. C (39 d), p<0.0006	NR	No sig. difference in symptomatic results between patients treated with surgery and those treated with radiation (p=0.138)
Skibber et al., 1996 [53]	1979-1991 All surgically treated melanoma patients with a single brain metastasis at two centers. No active non-CNS metastases present.	34 total 22 S/R 12 S	S/R (18 m) vs. S(6 m), p=0.002	Overall CNS relapse rate: 30% S/R vs. 90% S, p=0.02	NR
Hagen et al., 1990 [54]	1972-1987 All surgically treated melanoma patients with a single brain metastasis at a single center	35 total 16 S 19 S/R	S (8.3 m) vs. S/R (6.4 m), p=NS	Median time to CNS relapse: S/R (26.6 m) vs. S (5.7 m), p<0.05	NR

C: Chemotherapy; Local Therapy: Treatment of CNS lesions with either surgery or stereotactic radiosurgery; KPS: Karnofsky performance status; NR: Not reported; NS: not significant; OS: Overall survival; QOL: Quality of life; R: Whole brain radiotherapy; S: Refers to treatment arm using surgery alone; Sig: Statistically significant; S/R: Surgery combined with whole brain radiotherapy; SRS: Stereotactic radiosurgery; Supp: Supportive care;

Table 2. Retrospective case series of surgery as treatment for brain metastasis in melanoma

A smaller study used the same design, but its primary endpoint was local disease control in patients with 2-4 brain lesions (Table 3) [16]. The study was halted at 60% of planned accrual due to meeting its primary endpoint (27 patients; 5 with melanoma). SRS-treated patients had significantly improved local disease control (p=0.0016). Median time-to-progression at SRS-treated sites was 6 months in patients treated with WBRT alone, versus 36 months in those

treated with SRS and WBRT (p=0.0005). Extracranial disease status was the major survival determinant in a *post hoc* analysis.

Only two relatively small, single-arm prospective studies of SRS in melanoma have been published. One of these studies enrolled 31 patients, including 14 (45%) with melanoma (Table 3) [17]. Patients received only SRS as CNS therapy. Overall intracranial failure rate was 50% at 6 months. About one-third of patients failed within the SRS-treated tumor volume. The second study enrolled 45 melanoma patients receiving SRS at one of two treatment centers (Table 3) [18]. Up to 6 metastases were treated. Use of WBRT in conjunction with this therapy was not reported. Median survival of all patients was 4.2 months. The local control rate with SRS was 86%, although the follow-up period was not defined. Follow-up imaging was available for only 71 out of 86 treated lesions.

Numerous retrospective studies have reported the results of SRS therapy in melanoma (Table 4) [19-41]. These are quite variable in design. While some studied melanoma patients exclusively, others enrolled patients with other tumor types. Several studies appear to include the same set of patients treated at a given institution during overlapping time periods (noted in Table 4). Treatment and follow-up plans were not pre-specified or standardized. Although all patients received SRS, they often received a wide array of other therapies, including immediate or delayed WBRT, concurrent or delayed surgery, and partial brain irradiation. Patients received SRS both as primary brain metastasis therapy and as salvage therapy after failure of prior treatment. Some patients received therapy for a single metastasis, while others were treated for multiple brain metastases. Several studies specifically identify selection bias in the treated population, with more aggressive therapy being reserved for patients with more severe CNS disease [37, 38]. Collectively, the study heterogeneity limits the conclusions that can be reached from these retrospective analyses.

Reported median survival of melanoma patients in these series ranged from 4.4 to 11.1 months. These values approximate ranges reported in patients with brain metastases from other primary tumor types, in which median survival is estimated to be 6.5 to 10.5 months [10, 42, 43]. Several factors predicted shorter survival in multiple studies: decreased performance status or its surrogate indicators, multiple CNS lesions, greater intracranial tumor volume, infratentorial lesion location, and active extracranial disease.

Some studies did not find that the initial number of lesions predicted survival [28, 29, 34, 37, 39]. This contradicts the results of the only randomized trial of SRS with survival as the primary endpoint, in which a survival benefit was observed only in patients with a single CNS lesion (OS was 6.5 months in patients with SRS+WRBT compared to 4.9 months in the WBRT group alone; p=0.0393) [15]. This may be due to inadequate statistical power in the retrospective studies, given the heterogeneity of the populations under study.

CNS disease control was reported in most of these retrospective studies as 1-year actuarial control rates. At SRS-treated sites, reported in most of the studies, this was 47-87%. One-year control at non-SRS treated sites was 24-57%. The overall CNS control at one year was only 24-38%.

Study	Study Design	Patient Numbers & Tumor Types	Treatment	Median Survival	CNS Recurrence
Andrews *et al.,* 2004 [15]	Randomized Multi-institution, cooperative group study 1996-2001 Primary endpoint: median survival	331 total 64% Lung 10% Breast 5% Melanoma 21% Other 1-3 CNS metastases	164 SRS+R 167 R	Overall 6.5 m S+R vs. 5.7 m R, p=0.14 Single met. 6.5 m SRS+R vs. 4.9 m R, p=0.39 Multiple met. 5.8 m SRS+R vs. 6.7 m R, p=0.98	Time to intra-cranial progression SRS+R=R, p=0.13 Local control at 1 yr 82% SRS+R vs. 71% R, p=0.01
Kondziolka *et al.,* 1999 [16]	Randomized Single institution Primary endpoint: local control at SRS-treated site	27 total: 44% Lung 19% Melanoma 15% Renal 15% Breast 7% Other 2-4 CNS metastases	13 SRS+R 14 R	11 m SRS+R vs. 7.5 m R, p=0.22.	Median time to CNS failure: Local: 36 m SRS+R vs. 6 m R, p=0.0005 Any: 34 m SRS+R vs. 5 m R, p=0.002
Manon *et al.,* 2005 [17]	Single-arm Multi-institution, cooperative group study 1998-2003 Primary endpoint: 3m and 6m intracranial progression rate	31 total 45% Melanoma 45% Renal 10% Sarcoma 1-3 CNS metastases	31 SRS	8.3 m	Intra-cranial Failure Rates 3 m: Any 25.8% SRS-treated 19.3% Outside SRS 16.2% 6 m: Any 48.3% SRS-treated 32.2% Outside SRS field32.2%
Friehs *et al.,* 1998 [18]	Single-arm Multi-institution 1998-2003 Primary endpoint: Overall survival	45 total 100% Mel. 1-6 CNS metastases	45 SRS	4.2 m	86% of SRS-treated tumors controlled at follow-up. 13 (29%) with known distant failure in CNS.

KPS: Karnofsky performance status; Mel: Melanoma; Met: Metastasis/metastases; MMSE: Mini-Mental Status Examination; NR: Not reported; QOL: Quality of life; R: Whole brain radiotherapy; SRS+R: Stereotactic radiosurgery combined with whole brain radiotherapy; SRS: Stereotactic radiosurgery

Table 3. Prospective trials of stereotactic radiosurgery as treatment for brain metastases in melanoma

Study	Study Design	Patient Numbers & Tumor Types	Treatment	Median Survival	CNS Control Rates (1-yr actuarial unless otherwise stated)	Comments (Prognostic factors multivariate unless otherwise noted)
Liew et al., 2011 [31]	1987-2008 Single institution All patients with mel. receiving GK	344 total 100% mel.	163 SRS 118 SRS+R 63 SRS + other	5.6 m after SRS 8.3 m from diagnosis of brain met	SRS treated sites 63% Distant 33%	R not sig. for survival or recurrence. Population may overlap with that of Mori et al., 1998 and Somoza et al., 1993.
Hara et al., 2009 [27]	1999-2005 Single institution All pts. receiving Cyberknife therapy for mel. or renal cancer	62 total 44 mel. 18 renal	33 SRS 17 SRS sal. 5 SRS+R 7 SRS + Surg.	8.3 m 5.6 m for mel.	SRS-treated sites 87% Local and distant 38%	
Powell et al., 2008 [34]	1998-2007 Single institution All patients receiving GK	76 total 50 mel. 23 renal 3 sarcoma	39 SRS 37 SRS+R	5.1 m Histology does not predict outcome	SRS-treated sites 78% Distant 37% Local and distant 26%	Local control higher for renal than mel . (94% vs. 63%, p=0.001)
Redmond et al., 2008 [36]	1998-2006 Single institution All mel. pts. receiving GK	59 total 100% mel.	32 SRS 27 SRS+R	4.4 m	NR	Timing between SRS and R undefined.
Samlowski et al., 2007 [37]	1999-2004 Single institution All mel. patients receiving LA-SRS	44 total 100% mel.	19 SRS 4 SRS +partial R 14 SRS+R 16% SRS with salvage R	11.1 m from brain metastasis diagnosis 48% 1-yr survival 18% 2-yr survival	SRS-treated sites 47%	Patients receiving SRS+R had a higher mean number of presented metastases (3.8) than those receiving salvage R after SRS failure (1.6). 22 (50%) treated with surgery at some point. Multiple lesions treated in 22 (50%).
Christopoulou et al., 2006 [22]	1998-2004 Single institution All mel. patients receiving GK	29 total 100% mel.	All SRS 4 with prior R 2 with prior surg.	5.7 m	NR	
Gaudy-Marqueste et al., 2006 [23]	1997-2003 Single institution All mel. patients receiving GK	106 total 100% mel.	106 SRS	5.1 m 13% 1-yr survival	SRS-treated sites 69%	No patients received planned R
Chang et al., 2005 [20]	1991-2002 Single Institution	189 total 103 mel. 77 renal	130 SRS 16 SRS + R 43 SRS sal.	7.5 m	For mel. SRS-treated sites 47%	Inadequate patients treated with R to assess effects.

Study	Study Design	Patient Numbers & Tumor Types	Treatment	Median Survival	CNS Control Rates (1-yr actuarial unless otherwise stated)	Comments (Prognostic factors multivariate unless otherwise noted)
	All patients with mel., renal cancer or sarcoma receiving SRS as therapy	9 sarcoma		24% 1-y survival for mel.	Distant 24%	
Koc et al., 2005 [29]	1999-2003 Single institution All mel. patients receiving GK as initial therapy	26 total 100% mel.	12 SRS 14 SRS+R	6 m 25% 1-yr survival	NR	
Radbill et al., 2004 [35]	1996-2001 Single institution All mel. patients receiving GK	64 total 100% mel.	32 SRS 13 SRS sal. 8 SRS+R 8 SRS+surg. 2 SRS + R + surg. 1 NR	26 wk Single CNS met. (77 wk) vs. multiple (20 wk), p=0.003	SRS-treated sites 56% Distant 25%	Adjuvant R did not decrease distant failure, although small population receiving it.
Selek et al., 2004 [38]	1991-2001 Single institution All mel. patients receiving LA-SRS	103 total 100% mel.	61 SRS 12 SRS + R 30 SRS sal.	Overall 6.7 m SRS 7.5 m SRS+R 3.7 m SRS sal. 5.4 m 25% 1-y survival	SRS-treated sites 48% SRS alone 60% SRS+R 0% SRS sal. 5% Distant 24% SRS alone 18% SRS+R 0% SRS sal. 51%	Patients with more aggressive disease were more likely to receive R after SRS.
Herfarth et al., 2003 [28]	1986-2000 Two institutions All mel. patients treated with LA-SRS	64 total 100% mel.	All SRS	10.6 m	SRS-treated sites 81% Lesions ≥2 cm (64%) vs. <2 cm (88%), p=0.05 Distant CNS control NR	
Brown et al., 2002 [19]	1990-2000 Single institution All patients with mel., renal cancer or sarcoma receiving SRS.	41 total 23 mel. 16 renal 2 sarcoma	20 SRS 4 R with SRS sal. 8 Surg. with SRS sal. 9 SRS + surg.	14.2 m No difference in survival SRS+R vs. SRS, p=0.54	6 m CNS control SRS-treated sites: SRS+R (100%) vs. SRS (85%), p=0.02 Distant: SRS+R (91%) vs. SRS (35%), p=0.004	
Gonzalez-Martinez et al., 2002 [25]	1996-2002 Single institution All mel. patients receiving GK	24 total 100% mel.	10 SRS 14 SRS+R	5.5 m	NR	

Study	Study Design	Patient Numbers & Tumor Types	Treatment	Median Survival	CNS Control Rates (1-yr actuarial unless otherwise stated)	Comments (Prognostic factors multivariate unless otherwise noted)
Mingione *et al.,* 2002 [32]	1989-1999 Single institution All mel. patients receiving GK	45 total 100% mel.	29 SRS 16 SRS+R	10.4 m 31% 1-yr survival	NR	Adjuvant R had no impact on survival or CNS recurrence rate.
Yu *et al.,* 2002 [41]	1994-1999 Single institution All mel. patients receiving GK	122 total 100% mel.	83 SRS 12 SRS + R 10 SRS/R >1.5 m before SRS 17 SRS/R >1.5 m after SRS	7 m 26% 1-yr survival	SRS-treated sites 84% Distant 57%	Population may overlap with that of Lavine et al., 1999 and Chen et al., 1999.
Chen *et al.,* 1999 [21]	1994-1999 Single institution All patients receiving GK	199 total 88 mel. 40 NSCLC 5 SCLC 12 Renal 12 Breast 9 Colon 24 Other	199 SRS	8.5 m 7 m for mel.	89% of lesions with follow-up "controlled for the lifetime of the patient"	Use of R reported, but not defined. Population may overlap with that of Yu et al., 2002 and Lavine et al., 1999. Follow-up available for only 69% of lesions.
Lavine *et al.,* 1999 [30]	1994-1997 Single institution All mel. patients receiving GK	45 total 100% mel.	43 SRS. 2 SRS + R	8 m	3 m CNS control SRS-treated sites 97% Distant 81%	Population may overlap with that of Yu et al., 1999 and Chen et al., 1999. Other therapies in addition to SRS depending on clinical condition. Only 2 (4%) received SRS+R
Grob *et al.,* 1998 [26]	1993-1996 Single institution All mel. patients receiving GK	35 total 100% mel.	35 SRS	7 m	Actuarial control rate of evaluable, treated lesions: 3 m 98% 6 m 100% 9 m 95% 12 m 87% Distant CNS control not reported	
Mori *et al.,* 1998 [33]	1988-1996 Single institution All mel. patients receiving GK	60 total 100% mel.	12 SRS 36 SRS+R 12 SRS sal.	7 m median survival 21% 1-yr survival	Control in 46 pts. receiving SRS +/-R: SRS-treated sites: Overall 85%	Population may overlap with that of Mathieu et al., 2007 and Somoza et al., 1993.

Study	Study Design	Patient Numbers & Tumor Types	Treatment	Median Survival	CNS Control Rates (1-yr actuarial unless otherwise stated)	Comments (Prognostic factors multivariate unless otherwise noted)
					SRS+R 80% SRS 100% SRS sal. 86% Distant: Overall 70% SRS+R 77% SRS 56% SRS sal. 57%	
Seung et al., 1998 [39]	1991-1995 Single institution (UCSF) All melanoma patients receiving GK	55 total 100% melanoma	28 SRS 11 SRS+ R 16 SRS sal.	35 wk	SRS-treated sites 77% Distant 36% Entire CNS 24%	
Gieger et al., 1997 [24]	1992-1994 Single institution All mel. patients receiving LA-SRS	12 total 100% mel.	1 SRS 10 SRS+R 1 SRS sal.	8 m 36% 1-y survival	At least 6 patients with at least one SRS-treated lesions progressing. At least 3 (25%) developing new distant CNS lesions	Imaging follow-up not consistent.
Somoza et al., 1993 [40]	1988-1992 Single institution All mel. patients receiving GK	23 total 100% mel.	19 SRS + R 4 SRS with R 3-12 m later	7 m 26% 1-y survival	NR	Population may overlap with that of Mathieu et al., 2007 and Mori et al., 1998.

CNS: Central nervous system; GK: Gamma knife-based stereotactic radiosurgery; KPS: Karnofsky performance status; LA-SRS: Linear accelerator-based stereotactic radiosurgery; Mel: Melanoma; Met: Metastasis/metastases; NR: Not reported; QOL: Quality of life; Partial R: Partial brain irradiation; R: Whole brain radiotherapy; RPA: Recursive Partitioning Analysis; Sig: Statistically significant; SIR: Score Index for Radiosurgery; SRS: Stereotactic radiosurgery; SRS+R: Stereotactic radiosurgery combined with whole brain radiotherapy; SRS sal: Stereotactic radiosurgery salvage after failure of prior therapy; SRS+Surg: Combination therapy of stereotactic radiosurgery and conventional surgical resection; Surg: Surgical resection

Table 4. Retrospective studies of stereotactic radiosurgery for brain metastasis in melanoma

2.3. Comparative benefit of SRS versus surgery

The relative benefit of SRS versus surgery has not been tested in randomized clinical trials to date. One small randomized trial indirectly addressed this question, although not specifically for melanoma (Table 5) [44]. Sixty-four subjects with a single, surgically accessible brain lesion were randomly assigned to surgical excision and adjuvant WBRT or to SRS alone. A direct comparison of surgery and SRS is not possible due to the inclusion of adjuvant WBRT for all surgical patients and its omission in SRS-treated patients. Nine (14%) of the subjects had

melanoma. No difference in overall survival was observed (9.5 months for surgery versus 10.3 months for SRS, p=0.8). A statistically non-significant improvement in local tumor control favored SRS (82% for surgery plus WBRT versus 97% for SRS, p=0.06). The one-year recurrence rate at distant CNS sites was significantly higher in the group receiving SRS alone (3% for surgery plus WBRT versus 26% for SRS alone, p<0.05). Thus, this study perhaps served to highlight the risks of omitting adjuvant treatment, rather than the relative merits of SRS versus surgery.

Two retrospective studies compared SRS to surgery [45, 46]. Melanoma patients were in the minority in both studies. O'Neill and co-workers analyzed patients seen from 1991-1999 at the Mayo Clinic who underwent either SRS or surgery for a solitary brain metastasis [45]. Eligible patients were candidates for either procedure: all had solitary lesions measuring less than 35 mm (maximum size conventionally treated with SRS), none of the lesions were surgically inaccessible, and none required immediate surgical decompression. Ninety-seven patients met these criteria, of whom only seven were melanoma patients. Seventy-four were treated surgically and twenty-three were treated with SRS. Although not achieving statistical signif-icance, more SRS-treated patients received WBRT (96% SRS vs. 82% surgery, p=0.172). The treatment groups differed at baseline in performance status (worse in the SRS group, p=0.0016). Overall survival was similar between the two groups and was predicted by age, performance status, and systemic extracranial disease status rather than the type of brain metastasis treatment. Similar proportions of patients had CNS recurrence (29% SRS versus 30% surgery), but patients receiving surgery were more likely to have local recurrence at treated sites (58% of recurrences in 19 patients vs. 0% out of 6 recurrences in SRS-treated patients, p=0.02). Although this study suggests that local recurrences are more common after surgery, the retrospective nature of the study and the small number of patients limits its applicability.

In contrast, another single institution, retrospective study from a similar time period (1991-1994) suggested that SRS led to higher local recurrence rates than surgery [46]. Thirty-one patients were treated with SRS and sixty-two with surgery for brain metastases. Twenty-one patients (23%) had melanoma. Patients were matched with regard to histology, extracranial disease status, performance status, time from initial diagnosis to CNS metastasis, number of CNS metastases, age, and gender. Patients in the two groups were equally likely to have received WBRT. Patients receiving surgical treatment survived significantly longer than those treated with SRS (16.4 months surgery vs. 7.5 months SRS, p=0.0018). This improvement in survival was attributable to decreased rates of death from neurological causes in the surgical group (19% surgery vs. 50% SRS, p=0.037); deaths due to systemic disease were equivalent (p=0.28). Surgery yielded lower local tumor recurrence rates than SRS (8.1% surgery vs. 38.7% SRS). There was no statistically significant different in distant CNS recurrence rates between the two groups.

This retrospective study is subject to the biases inherent in such an undertaking. The authors matched patients for a variety of known relevant parameters, but the differences in local control may reflect the use of older SRS technology, high quality neurosurgical treatment at the referral center where the study was undertaken, or a combination of both. These discrep-

ancies might explain the differences in results when contrasted with the results of the two other studies described [44, 45].

Collectively these studies do not indicate whether surgery or SRS is superior. There are no easily detectable differences in local control rates. Logistic differences therefore are important in selecting therapy. Unless a clinical situation arises in which surgery provides clear superiority (e.g. rapid control of symptomatic lesions; histological diagnosis), SRS will likely be the predominant modality employed to treat macroscopic melanoma lesions in the CNS.

2.4. Adjuvant Whole Brain Radiotherapy (WBRT)

Adjuvant therapy of the CNS is that which is administered in conjunction with definitive local therapy (surgery or SRS) of radiologically evident tumors to treat co-existing micrometastatic disease. This is distinguished from prophylactic cranial irradiation (PCI). PCI is administered in patients with systemic cancer after responses to systemic therapy, and has proven benefit in several conditions, such as small cell lung cancer (SCLC) [47, 48]. In melanoma, PCI has not been adequately assessed to recommend. Adjuvant CNS therapy has traditionally relied on WBRT. Although new systemic agents with proven anti-melanoma activity and CNS penetration may come to be used for this purpose as well, such use is experimental at present. Adjuvant WBRT is a controversial topic in metastatic brain tumor management, primarily due to questions of efficacy and of neurocognitive toxicity.

Three factors must be considered in determining whether or not to use adjuvant WBRT: (a) the effectiveness of WBRT in preventing emergence of new brain tumors; (b) the adverse effects of WBRT; and (c) the competing adverse effect of foregoing WBRT, namely an increased rate of CNS tumor progression. As new systemic therapies are proposed for this purpose, the same considerations apply. The relevant adverse effects relate to deterioration of neurocognitive function (NCF) and QOL, which could result from either WBRT itself or from progressive brain tumors. It is in balancing these factors that a rational decision regarding the use, or non-use, of adjuvant WBRT can be made.

2.4.1. Randomized trials of adjuvant WBRT in solid tumor patients

Despite the frequency of brain metastasis in melanoma patients, no prospective trials have been conducted to assess adjuvant WBRT in this population. Data from the treatment of brain metastases focusing on other tumor types must be reviewed to come to any conclusions (Table 5). Five randomized trials of adjuvant WBRT have been reported. Four of these are multi-institutional efforts, reflecting the difficulty in conducting this type of study [49-52]. A fifth study, discussed earlier, compared outcome in patients with a single brain metastasis treated with surgery and WBRT or with SRS alone [44]. The majority of patients in all of the studies were those with NSCLC primary tumors. Relatively few melanoma patients were enrolled.

Only one study used intracranial recurrence rate as the planned primary endpoint [52]. Ninety-five patients were enrolled after surgical resection of an isolated brain metastasis. Sixty percent had NSCLC. Forty-nine patients were randomized to receive adjuvant WBRT (50.4 Gy administered as 28-1.8 Gy fractions). The remaining forty-six patients were observed. Only

Study	Evaluable Patients (#)	Disease types #	Primary Endpoint	Median Survival	Recurrence/Progression in CNS		Comments
					S/SRS-site	Distant	
Patchell et al., 1998 [52]	95 total 49 S+R 46 S	57 NSCLC 9 Breast 29 Other	CNS recurrence rate	S+R (48 wk) vs. S (43 wk), p=0.39	10% S+R 46% S P<0.001	14% S+R 37% S P<0.01	Single brain metastasis. Overall CNS recurrence rate (primary endpoint) significantly less in R-treated patients (18% S+R vs. 70% S, p<0.001). Decreased rate of neurological cause of death in group receiving R (14% S +R vs. 44% S, p=0.003)
Aoyama et al., 2006 [49]	132 total 65 SRS+R 67 SRS	88 NSCLC 9 Breast 11 GI 10 Renal 14 Other	OS	SRS+R (7.5m) vs. SRS (8 .0 m), p=0.42	1-y rate 11% SRS +R 38% SRS P=0.002	1-y rate 42% SRS+R 64% SRS P=0.003	1-4 brain metastases. Overall CNS recurrence rate at 1-y: 47% SRS+R 76% SRS P<0.001 Salvage treatment required: 15% SRS+R 43% SRS P<0.001
Muacevic et al., 2008 [44]	64 total 31 SRS 33 S+R	22 NSCLC 10 GU 11 Breast 9 Mel. 4 GI 8 Other	OS	9.5 m S+R 10.3 m SRS P=0.8	1-y rate 3% SRS 18% S+R P=0.06	1-y rate 26% SRS 3% S+R P=0.04	Single, surgically accessible brain metastasis. Study stopped early due to poor accrual.
Chang EL et al., 2009 [50]	58 28 SRS+R 30 SRS	32 NSCLC 8 Breast 7 Mel. 4 Renal 7 Other	HVLT at 4 m vs. baseline	SRS+R (5.7 m) vs. SRS (15.2m), p=0.003	1-y rate 0% SRS+R 33% SRS P=0.01	1-y rate 27% SRS+R 55% SRS P=0.02	Up to 3 brain metastases. Decline in function at 4 m (primary endpoint): 48% SRS+R 24% SRS P=0.04 Study accrual stopped early due to achieving primary endpoint.
Kocher et al., 2011 [51]	359 total SRS 100 SRS+R 99 S 79 S+R 81	190 NSCLC 29 Renal 42 Breast 18 Mel. 30 Colon 50 Other	Duration of functional independence (measured as deterioration of WHO PS to >2)	WBRT (10.7 m) vs. No WBRT (10.9 m), p=0.89	2-y rate S – 59% S+R – 27% (p < 0.001) SRS – 31% SRS+R – 19% (p = 0.040)	2-y rate S – 42% S+R – 23% (p = 0.008) SRS – 48% SRS+R – 33% (p = 0.023)	1-3 brain metastasis eligible. Either stable extracranial disease for 3 months or no extracranial metastases. Median Survival with WHO PS ≤2 (primary endpoint) 9.5m WBRT vs. 10.0 m no WBRT, p=0.709 Overall rate of CNS progression at 6 and 24 m: 15.2% and 31.4% WBRT vs. 39.7 and 54% no WBRT, p<0.0001 Neurological cause of death 25% WBRT vs. 43% no WBRT, p=NR

Table 5. Randomized trials of adjuvant WBRT with surgery or stereotactic radiosurgery for brain metastases

one patient in each group had melanoma. The CNS recurrence rate was 18% (9/49) in those receiving adjuvant WBRT. This contrasted sharply with a 70% (32/46) CNS recurrence rate in the observation group (p<0.001). The median time-to-CNS recurrence was markedly prolonged in those receiving adjuvant WBRT (220 weeks versus 26 weeks observation, p<0.001) due to decreased recurrence rates both at resection sites (10% WBRT versus 46% observation, p<0.001) and at distant sites within the brain (14% WBRT versus 37% observation, p<0.01). There was no difference in median survival (49 weeks WBRT versus 43 weeks observation, p=0.39) or in maintenance of independent function (maintenance of KPS >60%). A decreased rate of neurologic cause of death was evident in the WBRT-treated group (14% WBRT versus 44% observation, p=0.003), although the determination of this was less objective than determination of intracranial recurrence by imaging.

Another randomized trial tested adjuvant WBRT (30 Gy in 10 fractions) in conjunction with SRS [49]. The study enrolled 132 patients with one-to-four metastases measuring less than 3 cm in maximal dimension. Sixty-five patients received SRS and WBRT; sixty-seven received SRS alone. Two-thirds of those enrolled had NSCLC. The majority of the remainder had breast, colon or renal primary sites. The primary endpoint was overall survival. The researchers initially estimated that 89 evaluable patients per group would be required to detect a 30% difference in median survival time. A planned interim analysis, performed after 122 patients enrolled, led to early study termination. Four-to-five-fold more patients would have been required to detect a significant difference in the primary endpoint.

Although underpowered to detect a survival advantage, a number of secondary endpoints yielded significant results. CNS progression at 1 year was 47% in the combination therapy group and 76% in the SRS monotherapy group (p<0.001). WBRT improved control at one year for both SRS-treated sites (89% WBRT versus 72% without, p=0.002) and distant CNS sites (58% WBRT versus 36% without, p=0.003). No differences were observed in median survival, neurological cause of death, and acute or late neurological toxicity. Rates of systemic functional preservation (assessed by KPS), neurological preservation, and neurocognitive preservation (assessed by the Mini-Mental Status Examination, MMSE) were also not different.

A third trial randomized patients with 1-3 brain metastases to either SRS or SRS combined with adjuvant WBRT (30 Gy in 12 fractions) [50]. A novel endpoint for the study was chosen: change in performance on the Hopkins Verbal Learning Test-Revised (HVLT) at 4 months after primary therapy. The majority of enrolled patients were those with NSCLC primary tumors (55%), with melanoma in the minority (12%). The study was stopped early after accrual of 58 patients (28 SRS+WBRT, 30 SRS) due to its achieving the primary endpoint. Patients treated with the combination demonstrated a 52% decline in HVLT score at 4 months, versus a 24% decline in those receiving SRS only (p=0.04). This difference persisted at 6 months. Significant differences in performance on a panel of other neurocognitive tests were not detected. The study was stopped early and may have therefore been underpowered to detect other important differences in outcome. Decreased HVLT performance occurred despite decreased rates of CNS progression at one year in the combination therapy group (SRS-treated sites: 0% SRS +WBRT vs. 33% SRS, p=0.01; distant CNS: 27% vs. 55%, p=0.02). The authors also reported

improved survival in the group treated with SRS alone (5.7 months SRS+WBRT vs. 15.2 months SRS, p=0.003).

Patients who were treated only with SRS required salvage therapy for intracranial progression in 87% of cases. Ten (33%) of the patients treated with SRS alone required craniotomy, ten (33%) received salvage WBRT and six (20%) received salvage SRS. In the group treated with SRS and adjuvant WBRT, two patients (7%) received salvage WBRT, and three (11%) progressed intracranially, but received no salvage therapy.

This study provides convincing evidence that the addition of adjuvant WBRT to SRS therapy for brain metastases impairs HVLT performance. This occurs despite a decreased rate of intracranial progression in those receiving WBRT. Salvage therapy for intracranial progression was required in the majority of patients treated with SRS alone, including salvage craniotomy in one-third of the patients. The clinical significance of HVLT deterioration due to adjuvant WBRT, vis a vis that of frequently needed salvage therapy for CNS disease was not addressed.

A fourth randomized trial assessing adjuvant WBRT enrolled patients with 1-3 brain metastases and stable or absent extracranial disease [51]. The majority of patients had NSCLC (53%); only 5% were melanoma patients. Patients received SRS or surgery as primary therapy and were then randomized to receive adjuvant WBRT (30 Gy in 10 fractions) or no additional therapy. The composite primary endpoint was median overall survival in patients with KPS of 0-2. In the intent-to-treat analysis, 180 patients were assigned to receive WBRT and 179 to observation. At the end of the study, per protocol, 164 patients received WBRT and 166 patients were on observation. Analysis was by intention-to-treat.

No differences were detected in the primary endpoint of survival with functional independence (9.5 months WBRT versus 10.0 months observation, p=0.709) or median overall survival (10.7 months WBRT versus 10.9 months observation, p=0.891). Intracranial recurrence rates were markedly suppressed by adjuvant WBRT. Overall intracranial progression occurred in 48% of WBRT-treated patients and in 78% of the observation group (p<0.001). This translated to improved progression-free survival (PFS) in the WBRT-treated group (4.6 months vs. 3.4 months observation, p=0.002). Two years after surgery, WBRT reduced the probability of relapse at intial site from 59% (observation) to 27% (p<0.001) and at distant CNS sites from 42% (observation) to 23% (p=0.008). Similarly, after SRS, WBRT reduced the probability of relapse at SRS-treated site from 31% (observation) to 19% (p=0.040) and at distant CNS sites from 48% (observation) to 33% (p=0.023). Neurological cause of death was suppressed by adjuvant WBRT (28% WBRT versus 44% observation; p<0.002). Extracranial disease progression rates at 24 months were identical (65% WBRT and 63% observation, p=0.73).

All four randomized trials showed decreased intracranial recurrence rates when adjuvant WBRT was administered, both at the site of treatment and at distant sites within the brain. Similar effects from adjuvant WBRT on distant CNS recurrence were reported by the trial of Muacevic and co-workers, in which patients were randomized to surgery with adjuvant WBRT versus SRS alone, discussed above [44]. The impact on the reduction in distant CNS recurrence with the use of adjuvant WBRT is likely from the eradication of subclinical microscopic disease present at the time of brain metastasis diagnosis. The effect of WBRT on CNS seeding from

uncontrolled extracranial disease is unclear, but likely has a lesser effect. If seeding from extracranial disease was a dominant mechanism leading to CNS failure, adjuvant WBRT would not be predicted to decrease its occurrence.

No trial to date evaluating the omission of adjuvant WBRT after local therapy has demonstrated a survival benefit to WBRT. The study by Chang and co-workers indicated that the use of adjuvant WBRT after local therapy might be associated with a decrement in survival. It is difficult to draw firm conclusions about these data, as the study was stopped early, was not powered to detect a survival benefit, and contradicted the survival results of the other four larger randomized studies presented above. This includes the study by Aoyama and co-workers [50], which evaluated overall survival as its primary endpoint and was unable to detect a survival difference between its treatment arms, without a marked increase in sample size to over 800. The study by Kocher and co-workers demonstrated an improvement in PFS associated with adjuvant WBRT [51]. This study excluded patients with uncontrolled or progressive primary disease, mitigating extracranial disease burden as a competing risk for death

The studies presented here represent the best assessment of the efficacy of adjuvant WBRT therapy in treatment of solid tumor brain metastases. This therapy is clearly able to decrease intracranial recurrence rates, both at locally treated and distant sites within the CNS. The effect of this therapy on survival and the relative benefits versus the cognitive effects of the therapy are less clear. Melanoma patients formed a small fraction of the patients enrolled in these trials and one might therefore question whether these results even apply in the melanoma setting. To do so requires examination of the rather imperfect retrospective dataset regarding adjuvant WBRT specifically in melanoma.

2.4.2. Adjuvant WBRT in melanoma patients

The randomized studies discussed above primarily enrolled patients diagnosed with NSCLC. There have been no prospective studies evaluating the role of adjuvant WBRT specifically in the melanoma patient population. Many retrospective studies have been reported; unsurprisingly, these have indicated that adjuvant WBRT confers no survival benefit (see Tables 2, 4) [8-10, 12, 19, 29, 31, 32, 34, 35, 38, 39, 41, 53]. Since most melanoma patients with brain lesions present with active extracranial disease, any potential survival benefit due to adjuvant WBRT after local CNS therapy is probably undermined: extracranial disease serves as a competing cause of death, diluting any study's statistical power.

It is difficult to make firm conclusions based on the numerous melanoma case series on whether adjuvant WBRT actually decreases the rate of intracranial recurrence after local therapy. Selection and ascertainment biases are major concerns. Patients with clinically advanced disease are often selected for more aggressive therapy. Groups receiving aggressive therapy are likely to undergo more frequent and detailed surveillance for recurrence.

Several retrospective studies identify such biases. In the study of Buchsbaum and co-workers a paradoxically *higher* rate of CNS recurrence (49%) was identified in patients having received combined local CNS lesion therapy and adjuvant WBRT versus local therapy alone (20%) [10].

Follow-up scans were more frequent in the combined therapy group, possibly explaining the increased detection of progression and therefore higher documented recurrence rates. Samlowski and co-workers indicated that patients having received combined SRS and adjuvant WBRT had a higher mean number of CNS lesions at presentation than those selected for SRS alone [37]. Not surprisingly, more aggressive upfront therapy is apparently administered to patients with a greater initial disease burden.

Another study reported that patients receiving SRS with WBRT had 0% 1-year actuarial control within the CNS versus 60% for those treated with SRS alone (p=0.0005), strongly suggesting selection bias [38]. Those patients with initially more advanced disease were more likely to be treated with the combined modality technique. Advanced disease was found as a strong predictor for poorer outcomes. Therefore local control rates were likely confounded by the level of disease burden at presentation and not necessarily by the choice of treatment modality.

Other studies indicate similar paradoxical results in patients treated with adjuvant WBRT. Wronski and Arbit reported an increased risk of CNS recurrence (56%) in patients treated with surgery and WBRT versus 46% in those treated with surgery alone [9]. Another study reported a 20% failure rate at SRS-treated sites in patients receiving adjuvant WBRT versus 0% in those treated with SRS alone [33]. Perhaps indicative of a possible beneficial effect from adjuvant WBRT, failure at distant sites within the CNS was only 23% in the combination therapy group versus 44% in those treated with SRS alone. Those failing at the local site after combined modality treatment had larger initial volumes of disease compared with those treated with SRS alone. The additional fractionated dose contributed from WBRT at the site of failure may not have adequately addressed the increased tumor burden initially present. This was likely a significant confounder in local control outcomes.

Several studies concluded that WBRT does not significantly impact CNS recurrence rates. In one study of 333 melanoma patients, WBRT before or after SRS did not alter the intracranial recurrence rates [31]. The same study also showed that patient survival was significantly shorter with WBRT (4.5 months) compared to SRS alone (6.4 months, p=0.05). Again, selection bias for patients with more lesions or more aggressive disease could explain this result. Radbill *et al.* reported that adjuvant WBRT did not decrease the rate of failure at non-SRS-treated sites in the CNS (p=0.13) [35]. However, the number of patients treated with adjuvant WBRT (13%) was potentially too small to detect a benefit. Mingione *et al.*, studying 45 melanoma patients, of whom 16 received adjuvant WBRT, concluded that WBRT had no impact on outcomes [32]. Yu *et al.* also found that adjuvant WBRT did not decrease distant CNS recurrence; this conclusion was again limited by the small proportion of WBRT-treated patients (32/122 patients; 32%) [41].

Three studies have suggested a benefit from WBRT in preventing CNS recurrence in the melanoma population. One retrospective study of 35 melanoma patients undergoing resection of a single brain metastasis at a single institution from 1972 to 1987 documented a CNS recurrence rate of 37% in those treated with adjuvant WBRT, versus 69% in those not receiving this therapy (Table 2) [53]. Median time to CNS relapse was 26.6 months in the group receiving adjuvant WBRT, as compared to 5.7 months in those not receiving such therapy (p<0.05). Survival was predicted by the extracranial disease status, rather than receipt of adjuvant

WBRT. Death due to neurological causes was more common in the group that did not receive WBRT (24% WBRT versus 85% observation, p<0.01).

Another study during approximately the same time period (1979-1991) examined adjuvant WBRT after surgery in patients with a solitary CNS metastasis from melanoma (Table 2) [54]. Patients had no active extracranial disease and underwent resection of a single metastasis. Of the 34 subjects, 22 received WBRT. Median survival was improved in the combination therapy group (18 months versus 6 months with surgery alone, p=0.002), but CNS relapse rates were similar (30% surgery+WBRT *vs.* 22% surgery only; p=0.65). This study evaluated a highly selected patient group. This study and that of Hagen also suffer from being older studies, with more limited CNS imaging capabilities [53]. Nevertheless, the results tend to echo those of Patchell's randomized trial, suggesting a decreased CNS recurrence rate in CNS melanoma patients treated with adjuvant WBRT after local therapy [52].

Another report reviewed a single institution's experience with SRS in the treatment of 41 patients with radioresistant tumors, including 23 with melanoma [19]. Adjuvant WBRT improved local control (100% control with SRS and WBRT versus 85% with SRS alone at 6 months) and distant brain failure rates (17% failure with SRS and WBRT versus 64% failure with SRS alone). As might be predicted, adjuvant WBRT did not affect overall survival.

In summary, retrospective case series in melanoma indicate that adjuvant WBRT does not convey an overall survival benefit. This is consistent with the results of the randomized trials of WBRT primarily conducted in non-melanoma brain metastases. It is therefore reasonable to conclude that the addition of adjuvant WBRT does not improve the overall survival of the majority of melanoma patients with brain metastases.

As regards the effect of adjuvant WBRT on the prevention of CNS recurrence in melanoma, this collection of retrospective studies provides conflicting data. Some have shown no effect, others have shown decreased intracranial recurrence rates with the addition of WBRT, and still others have indicated that WBRT is associated with increased recurrence rates. Biases in treatment selection and ascertainment are strong confounders in many of the studies.

An ongoing randomized phase 3 trial is currently accruing for the comparison of distant intracranial control with the addition of adjuvant WBRT to observation following surgery and/ or SRS in melanoma patients with 1-3 brain lesions (NCT01503827) [55]. Secondary endpoints will include the effects on OS, QOL, and NCF. This prospective, randomized, melanoma-specific trial will hopefully reconcile the contradictory observations reported in the retrospective studies discussed above. With improving systemic therapy, including agents able to penetrate the CNS at clinically relevant concentrations, even this randomized trial may not be able to answer its major questions about adjuvant WBRT in melanoma patient.

Salvage SRS: An alternative to WBRT?

An alternative strategy to managing CNS metastases involves the use of "salvage" SRS. After patients receive initial local therapy with SRS alone, WBRT is omitted to spare normal brain tissues from unnecessary radiation doses and avoid potential adverse neurocognitive effects. Patients undergo CNS imaging at planned intervals or if symptoms suggest progression. SRS is then used to treat new lesions.

This strategy has not yet been tested in a randomized trial for patients with brain metastases from melanoma. There are limited data that have included melanoma patients in the prospective evaluation of this treatment paradigm. For example, one prospective study assessed SRS as a single treatment modality in 41 patients with no more than 4 brain metastases [56]. Seven (16%) of the patients had melanoma primary tumors. Twenty-three of the enrolled patients (56%) experienced intracranial progression. Nine received salvage treatment with additional SRS and one with surgery and WBRT for persistent tumor. Eleven patients were treated with salvage WBRT due to an excessive number of new CNS lesions and two patients received non-radiotherapy palliative therapy. Intracranial recurrences were common in the absence of upfront WBRT; less than half of recurring patients (9/23) were eligible for salvage SRS therapy due to excessive number of new lesions, limited life expectancy or decreased performance status.

Data from a large, multi-institutional, retrospective study of 569 patients (16% with melanoma) support the feasibility of salvage SRS in replacement of upfront WBRT [57]. Of 268 patients treated initially with SRS alone, 98 received salvage therapy for CNS recurrence. Sixty-three (64%) of those needing salvage therapy received WBRT as part of the salvage regimen (which included SRS and/or surgery) and forty-seven (48%) received WBRT as the sole salvage therapy.

One retrospective study examined 45 patients (20 with melanoma, 44%) receiving SRS as salvage therapy [58]. Excellent local control at treated sites was achieved (92.4% at 52 weeks). Patients who received upfront WBRT were significantly less likely to require salvage therapy (p=0.008), although no survival benefit was reported.

A CNS metastasis management strategy in which SRS is used as sole initial therapy warrants continued evaluation, particularly for patients diagnosed with melanoma. The existing studies of this approach suggest that intracranial recurrence rates remain high with the omission of WBRT. Although salvage therapy with SRS may be planned initially, a large fraction of patients will require WBRT in the salvage setting to treat macroscopic recurrences, when WBRT is likely to be *least* effective

2.4.3. Neurocognitive effects of WBRT

A major argument against the use of adjuvant WBRT relates to its impact on NCF and higher executive neurologic functions, including learning, memory, calculation, and task planning. A variety of standardized neuropsychological tests measure global NCF, such as the MMSE. NCF impairment has a direct impact on overall QOL, affecting patients' ability to carry out activities of daily living, medical treatment compliance, and higher order planning and function [59].

One widely cited retrospective study examined patients treated at a single center for brain metastasis by either WBRT alone (n=370) or surgical metastectomy combined with WBRT (n=118) [60]. Radiation-associated dementia was reported at a rate of 1.9 (n=7) and 5.1% (n=5), respectively. Cases were defined as those patients treated for brain metastases with WBRT without evident CNS recurrence who subsequently developed "…a progressive dementing

illness." Neither baseline neurocognitive data information for the identified cases nor information regarding the source populations was provided. Among the 12 cases identified, a variety of radiation dose and fractionation schemes were employed. The authors suggested that the incidence of radiation-related leukoencephalopathy might have been underestimated due to lack of sensitive tools for identifying neurocognitive dysfunction. Baseline neurocognitive dysfunction in patients with primary or secondary brain malignancy, however, is present in as many as 90% of patients prior to treatment [61] due to the general debility of patients with metastatic cancer, the neurocognitive effects of systemic chemotherapy and supportive therapies, and the age of the patients. Thus, the results of this relatively old study do not provide a clear picture of neurocognitive dysfunction associated with radiotherapeutic treatment of brain metastases.

Fairly good evidence shows that radiation therapy of the brain leads to neurocognitive dysfunction, which in some cases can be severe. A variety of patient-related factors play a role in the development of risk for developing radiation-associated neurocognitive dysfunction. These include patient age (children or those more than 50 years of age), other therapies received (chemotherapy and/or anti-convulsants), and length of survival post radiation therapy (as seen in survivors diagnosed with more favorable and indolent diseases, e.g., low-grade glioma) [62-68]. Factors related to radiation therapy delivery include total dose received, dose per fraction, and amount of cerebral volume irradiated [68-71].

More rigorous prospective assessments suggest that the neurocognitive impact of WBRT may be modest. Data from the study of primary brain tumor patients, in which extracranial disease and its treatment are not factors, may be relevant. For example, one study examined the dose-dependency of radiotherapy-associated neurocognitive dysfunction in patients treated for primary brain tumors [71]. Neuropsychological testing was undertaken up to 12 months after completion of radiotherapy. No dysfunction was observed in patients receiving up to 30 Gy, a typical dose used for adjuvant WBRT. Fraction size was not reported.

Another setting to examine the effects of WBRT is in diseases for which PCI is of proven benefit, such as SCLC. In two large studies evaluating the role of PCI for good responders with SCLC, there was no difference in NCF between those randomized to receive WBRT or not (24 Gy in 12 fractions-36 Gy in 18 fractions) [47, 48]. In the study by Gregor *et al.*, both groups of patients demonstrated baseline neurocognitive impairment versus normal controls, likely reflecting effects of prior treatment. Among those without baseline impairment, impairment in cognitive test performance was evident at 6 months and 1 year, but no obvious differences were seen when comparing PCI-treated and –untreated patients. The authors did not, however, describe rigorous statistical assessment of the longitudinal neurocognitive testing data [48].

Another prospective, non-randomized study showed no difference in cognitive function after 30-40 Gy of radiation therapy with 2-34 months of follow-up [72]. Again, a high degree of pre-existing neurocognitive deficit was already present. This may have been attributable to chemotherapy given prior to radiation therapy.

A non-randomized, prospective study of PCI was undertaken in NSCLC patients [73]. Seventy-five patients received induction radiochemotherapy for locally advanced NSCLC. Forty-seven

received PCI (30 Gy over 3 weeks), while twenty-eight others did not. PCI reduced the overall rate of brain relapse from 54% to 13% at 3-4 years. In fifteen long-term survivors (10 PCI, 5 without PCI), no significant differences were noted in a battery of neuropsychological tests undertaken at a median of 47 (PCI) and 70 (no PCI) months.

A study recently presented short term follow-up of longitudinal NCF in patients having received PCI (small cell lung cancer; n=13), therapeutic cranial irradiation (TCI; brain meta-stases; n=16) or non-cranial irradiation (control: breast cancer; n=15) [74]. NCF was assessed prior to and during radiation treatment and 6-8 weeks after its completion. At 6-8 weeks after treatment, only verbal memory scores were lower in patients receiving cranial irradiation versus controls. Visual memory and attention were not affected. Pre-treatment verbal memory performance score was the major predictor of post-treatment outcome in univariate analysis, with a lesser contribution attributable to cranial irradiation. The data from this admittedly small study suggest that WBRT can have a negative impact on verbal memory, although other factors contributing to the baseline status seem dominant.

Aoyama and co-workers conducted a randomized trial of SRS with or without WBRT, discussed in detail above [75]. Baseline and follow-up MMSE scores were available for 110 and 92 of the 132 patients enrolled in the trial, respectively. Baseline MMSE scores were predicted by patient age, performance status, tumoral edema and total tumor volume, but not by the initial number of tumors.

Deterioration in MMSE occurred in equal proportions of each group (14/36 SRS + WBRT versus 12/46 SRS alone, p=0.21). Average time-to-deterioration was longer in the combined therapy group (13.6 months versus 6.8 months SRS alone, p=0.05). In the 14 members of the combined therapy group, the adjudged cause of deterioration was brain tumor progression in 3, toxic effects of radiotherapy in 5 and indeterminate in 6; in the group treated only with SRS, MMSE deterioration was due to brain tumor progression in 11 and indeterminate in 1 (combined vs. SRS, p<0.0001). The temporal trends in NCF between the two arms suggest that SRS-related cognitive decline may be associated with tumor recurrence, which may or may not be rever-sible with salvage therapy. Later dysfunction with WBRT is more variable in cause. Some may be attributable to CNS tumor recurrence, but other cases being attributable to late effects of radiation on normal brain tissue. Such treatment-associated damage would not be amenable to corrective therapy with further tumor-specific therapy.

The study of Chang and co-workers, discussed earlier, prospectively addressed NCF in the setting of adjuvant WBRT [50]. This study is notable in that the score on a specific neurocog-nitive test, HVLT, was the primary endpoint. Patients receiving adjuvant WBRT experienced greater rates of decline in their HVLT performance than those treated with SRS alone, despite decreased intracranial progression in the WBRT-treated patients.

The HVLT tests basic verbal learning capacity and is proposed as a screening test for mild dementia [76, 77]. The HVLT may have somewhat greater sensitivity for mild dementia than the MMSE, as well some logistical advantages [78]. In isolation, however, results from the HVLT must be judged cautiously, as it does not assess other more complex neurocognitive

functions [79]. In studies of patients with brain metastases, the test is part of a battery of administered tests intended to develop a general overview of neurocognitive function [80, 81].

In the Chang study, a battery of neurocognitive function tests was administered, along with HVLT. Differences in performance on these other tests were not different between the two groups. The authors cautioned that the wide confidence intervals in the results of non-HVLT tests did not exclude a difference between the two test groups, but they also did not demonstrate a specific difference between the groups.

Studies of the effects of brain radiotherapy presented here vary in quality. They do not however give a clear picture suggesting severe adverse consequences of brain radiotherapy. Adverse effects are certainly identified in several studies, although their clinical significance is not certain and its cause is not clearly attributable to CNS radiotherapy. Intuitively, radiation therapy in and of itself is not beneficial for the nervous system. In the setting of brain metastasis treatment, however, the adverse effects of radiation therapy must be balanced against those of CNS tumor recurrence.

2.4.4. Neurocognitive effects of brain tumor progression

While little melanoma-specific data are available, the primary brain tumor literature reveals that there are significant negative cognitive effects from tumor progression. This literature is particularly useful, as cognitive deterioration in primary brain tumor patients is due entirely to incracranial disease and CNS treatment effects, as opposed to extracranial disease progression. Deterioration in MMSE was a strong predictor of impending intracranial tumor progression in a study of 1,244 glioma patients [82]. A change in MMSE score was seen even *prior* to radiographic progression. Decreased MMSE score also strongly correlated with performance status deterioration.

Another study in 445 brain metastasis patients (25 with melanoma) compared the drop in MMSE score before and after treatment with WBRT [83, 84]. The study was designed to assess the effect of the radiation fractionation schedules on survival, for which no effect was found. Tumor control was the primary factor in determining MMSE scores at 3 months. A 6.2 point drop (out of 30 possible) was seen in those with radiographic evidence of progression, compared to a 0.5 point drop in those with controlled tumors. In multivariate analysis, control of brain metastases was the only factor affecting MMSE score.

Another prospective brain metastasis study assessed a novel radiosensitizing agent combined with WBRT [85]. A detailed neurocognitive battery assessed NCF before and after therapy. Patients in the control arm, receiving WBRT alone, were subdivided into "good responders" (at least a 45% reduction in tumor size) and "poor responders" (less than a 45% reduction). Good responders had better NCF preservation rate, as well as a modest survival advantage (median survival 300 days versus 240 days; p=0.03).

These studies indicate that CNS tumor progression has adverse effects on neurocognitive status and QOL (reflected by performance status deterioration). While not melanoma-specific, there is no reason to believe that CNS progression of melanoma tumors would be

any less adverse. These adverse effects of tumor progression must be balanced against those of adjuvant WBRT.

2.4.5. WBRT in advanced CNS melanoma

In some patients, disease in the CNS cannot reasonably be controlled using local treatment of brain metastases with surgery or SRS. At some point, lesion number becomes excessive, or lesions are present in locations that are not amenable to local treatment. Alternatively, a patient's extracranial disease may be so extensive that it is likely to be life-limiting, and the goal of CNS disease treatment is primarily symptom palliation. WBRT is often used in this circumstance, with the twin goals of improving survival and providing symptoms palliation.

No randomized, prospective studies are available to quantitate the benefit of WBRT, especially when compared to supportive care alone. A number of large retrospective case series have examined the questions specifically of survival, although these suffer from heterogeneous patient populations. In the study of Sampson and co-workers, 205 melanoma patients with brain metastases received systemic palliative chemotherapy, with median OS of 39 days, versus 120 days among the 180 patients treated only with whole brain radiotherapy (p=0.0006) [8]. Receipt of radiotherapy treatment was statistically significant in the multivariate analysis of another large retrospective study, with radiotherapy demonstrating median OS of 3.6 months, versus 1.3 months for those treated with corticosteroids alone (HR=0.38; p<0.001). In the study of Raizer and co-workers, 83 patients received no specific therapy for brain metastases, vesus 100 receiving WBRT alone [13]. Median OS was 2.0 and 4.0 months, respectively. The statistical significance of this difference was not reported.

The study of Fife and co-workers examined patients treated at a single center in Australia in the 1952-2000 date range [12]. For the 1985-2000 cohort, 210 patients received supportive care, versus 236 receiving radiotherapy alone. Median OS was 2.1 and 3.4 months in these two groups; in multi-variate Cox regression analysis, radiotherapy was associated with a decreased hazard ratio for death (HR-0.851; p=0.111). This may not have achieved statistical significance due to the heterogeneity of the patients in these two groups. In addition to treatment modality, other significant factors associated with survival were the presence of concurrent metastases at diagnosis, older age, and a longer time from initial melanoma diagnosis.

An older retrospective study identified 60 melanoma patients with cerebral melanoma metastases that were enrolled in two Radiation Therapy Oncology Group (RTOG) studies [86]. The study sought to determine the effects of WBRT on performance status, neurologic function, and neurologic symptoms. In the analysis, this study demonstrated that WBRT provided improvement of neurologic symptoms (including headache, motor loss, convulsion) in 76% of patients. Median survival in this uncontrolled report was 10-14 weeks, although the baseline clinical characteristics of the study population were quite variable.

Another retrospective study identified 87 patients who had received WBRT, of whom 46 (53%) had 3 or more metastases [87]. The majority of patients were already receiving dexamethasone before initiating radiation, and therefore it was difficult to isolate the effects of WBRT, since CNS signs and symptoms can be alleviated by corticosteroid treatment. The fraction of patients

discontinuing corticosteroids due to symptom improvement served as a surrogate marker for palliative effects of WBRT. Upon completion of WBRT, 52% of all patients and 48% of symptomatic patients discontinued steroids. The same study demonstrated a small measurable response in tumor size following WBRT. Out of 87 patients, 65 had measurable disease at baseline; only 28 had at least one follow-up MRI scan to assess response. This may reflect a bias favoring follow-up scans being undertaken in those with responding disease. In these 28 patients at a median follow-up of 7 weeks, 75 tumors showed a median reduction in tumor size of 17%. The median OS of all patients evaluated in this study was 19 weeks. The median OS for patients who had undergone surgical resection prior to WBRT (22 patients) was 45 weeks, versus 16 weeks for those who did not undergo surgical resection (p<0.0001). Absence of extracranial disease (in 14 patients) was associated with higher median OS of 54 weeks, compared to 17 weeks in patients who had extracranial disease (p<0.0001).

Two prospective studies have combined WBRT with either temozolomide or fotemustine in melanoma patients with brain metastases [88, 89]. With temozolomide in a phase 2 study of 31 patients, only 3 (10%) demonstrated a response in the CNS, with median PFS in the CNS and OS of 2 and 6 months, respectively. In the phase 3 study of the combination with fotemustine, objective response rate (ORR) was 10% with median time-to-CNS-progression of 56 days and median OS of 105 days. These studies provide estimates of the clinical effect of WBRT, even though the relative contributions of WBRT and chemotherapy drug cannot be quantitated.

The use of WBRT in a patient with advanced CNS melanoma probably yields a modest survival benefit over supportive care alone. Symptom palliation is also probably a benefit of this therapy. There are many holes in the WBRT data set, many of which will never be answered definitively as melanoma treatment evolves. WBRT as a monotherapy has several signifcicant disadvantages, including its modest benefit at best, inability to undertake re-treatment, and lack of effect on extracranial disease. These limitations will likely be overcome only with the design of systemic therapy regimens, to be administered concurrently with, or in lieu of, WBRT.

2.5. Systemic therapy

Until the recent approvals in 2011 of ipilimumab [90, 91] and vemurafenib [92], no therapy tested in a randomized trial demonstrated an improvement in overall survival for metastatic melanoma patients. Dacarbazine had been the standard first-line systemic treatment since it was approved in the United States in 1975. Metastatic melanoma patients with intracranial or meningeal metastases were generally excluded from clinical trial participation for three reasons: 1) brain metastases were thought to portend a poor prognosis; 2) systemic therapies that were tested were not very effective in intracranial disease; and 3) it was presumed that most agents would not cross the blood-brain barrier. In this section, we will cover efforts to use chemotherapy, molecularly-targeted therapy, and immunotherapy for the management of melanoma brain metastases (Table 6) [88, 89, 93-99].

2.5.1. Chemotherapy

Several chemotherapeutic regimens failed to demonstrate benefit in melanoma brain metastasis, including regimens containing platinum-based compounds, dacarbazine, etoposide, and others [87, 100-109]. This may be largely due to the low efficacy of many of the tested agents in melanoma generally. It is probably unreasonable to expect agents with limited activity against extracranial disease to have activity in the CNS, with the added barrier of CNS penetration. Three chemotherapy agents with defined CNS activity in non-melanoma neoplastic settings, namely temozolomide, thalidomide, and fotemustine have been investigated in some detail in melanoma [110, 111].

Temozolomide is metabolized to the same active metabolite as dacarbazine. It is orally bioavailable and penetrates the blood-brain barrier at clinically significant concentrations [111]. The drug is approved for the treatment of primary brain tumors, confirming its clinically significant penetration of the CNS. Since temozolomide is as effective as dacarbazine in treatment of metastatic melanoma and yields similar patient survival [112], several clinical trials evaluated its efficacy in melanoma patients with brain metastases.

A multicenter, open label, single-arm phase 2 study aimed to determine the efficacy and safety (both as primary endpoints) of temozolomide in metastatic melanoma patients who had developed brain metastasis [93]. The study enrolled 151 patients, comprising of 117 chemotherapy-naïve and 34 previously treated. The clinical condition of the enrollees did not require immediate surgery or radiation therapy, justifying chemotherapy as the sole therapy.

For chemotherapy-naïve patients, eight patients (7%) achieved response, including one complete (CR) and seven partial responses (PR); 34 patients (29%) achieved stable disease (SD) in brain lesions for at least 4 weeks. Median OS was 3.5 months. In previously treated patients, 1 patient (3%) achieved PR, 6 (18%) had SD, and the median OS was 2.2 months. Notably, 25% of the chemotherapy-naïve and 21% of previously treated patients had extensive intracranial disease, defined as more than 4 radiologically evident brain lesions. The authors concluded that further evaluation was warranted, particularly in combination with other treatment modalities, but activity as a single agent in this setting was limited.

The combination of temozolomide and WBRT has been evaluated. A prospective phase 2 trial evaluated the combination in patients with CNS melanoma [88]. In 31 evaluable patients, temozolomide and WBRT combination yielded an overall ORR of 9.7%, comprising of one CR in the CNS lasting 4.5 months and two PR in the CNS lasting 2 months and 7 months. Although the combination of temozolomide and WBRT could be safely administered, its efficacy was limited.

Thalidomide, an anti-angiogenic agent crossing the blood-brain barrier, has been tested in combination with temozolomide to treat melanoma patients with brain metastases. In a phase 2 study, the combination of temozolomide and thalidomide was tested in chemotherapy-naïve patients [96]. The primary endpoint was ORR in the brain assessed every 8 weeks. Of the 26 patients treated, 16 patients were symptomatic and 25 had extracranial metastases. Treatment-associated toxicity, especially hemorrhage and thromboembolism was a problem: eleven patients discontinued treatment before completing one cycle of treatment due to intracranial

hemorrhage (n=7), pulmonary embolism (n=2), deep vein thrombosis (n=1), and grade 3 rash (n=1). Of 15 evaluable patients, 3 (12% of the intent-to-treat population) achieved CR or PR, while 7 patients had minor response or SD in the brain. Of the 10 patients who derived benefit, however, 5 patients progressed at extracranial sites. Overall OS was 5 months in all 26 patients, while it was 6 months in the 15 evaluable patients. Given the limited efficacy and the toxicity associated with the temozolomide/thalidomide combination, its use in melanoma is not warranted, outside the setting of a clinical trial.

Temozolomide has also been evaluated in the adjuvant setting. A multicenter phase 3 study compared temozolomide to dacarbazine in the time to develop CNS metastasis [94]. The study randomized 150 patients to receive either oral temozolomide or intravenous dacarbazine in combination with cisplatin and interleukin-2. Compared to dacarbazine, temozolomide reduced the 1-year CNS failure from 31.1% to 20.6%, but was not statistically significant (p=0.22). The median OS was not different between the two arms. Even though temozolomide penetrates the CNS, it did not delay incidence of CNS failure. Thus it appears that temozolomide may not be very effective in the adjuvant setting.

Fotemustine is a chloroethyl-nitrosurea approved in Europe for the treatment of metastatic melanoma. Fotemustine demonstrates high CNS penetration; its efficacy in melanoma patients with intracranial disease has been evaluated in three major studies. A French multicenter phase 2 study evaluated 153 metastatic melanoma patients for response to single-agent fotemustine [97]. Previously treated patients were allowed in the study. Since fotemustine crosses the blood brain barrier, patients with intracranial metastases were enrolled.

Out of the 153 evaluable patients, 36 (23.5%) had cerebral metastasis as the dominant disease site. In patients with cerebral metastases, the drug yielded an ORR of 25% in the CNS, similar to the 24.2% ORR observed in extracranial disease. The median OS of all patients was 85 weeks, but survival of the brain metastases patients was not reported. This study suggests that fotemustine has activity in melanoma, including CNS metastases. The magnitude of the benefit is similar in the CNS and at extracranial sites.

To confirm the observed activity, a phase 3 trial randomized 229 patients with metastatic melanoma to receive either fotemustine or dacarbazine [113]. Dacarbazine is a useful and interesting comparator in this study, as prior studies had failed to demonstrate any significant activity in the CNS [100, 102, 104]. This study enrolled patients with and without pre-existing brain metastases. Forty-three patients with brain metastases enrolled, of whom 22 received fotemustine, while 21 patients received dacarbazine.

Among all patients, fotemustine yielded an ORR of 15% versus dacarbazine's 7% (p=0.043). The authors reported a trend to improved survival among fotemustine-treated patients, with median OS of 7.3 months versus 5.6 months in the dacarbazine arm (p=0.067). In the brain metastases sub-group, fotemustine yielded a 6% ORR, while dacarbazine produced no responses. While myelosuppression was the most common adverse event observed in both arms, fotemustine-induced myelosuppression was more frequent and severe. In the fotemustine arm, 71% (vs. 14% with dacarbazine) of patients experienced neutropenia, and 51% (vs. 5% with dacarbazine) of patients experienced grade 3- 4 neutropenia. Similarly, thrombocy-

topenia was observed in 94% of patients receiving fotemustine (vs. 57% with dacarbazine) and grade 3- 4 occurred in 43% of patients (vs. 6% with dacarbazine).

The responses of patients who had brain metastases in this study were not as impressive as previously reported in the phase 2 study discussed above, although this might be expected in a more rigorous phase 3 study setting. Although not quite statistically significant, fotemustine delayed the median time-to-develop first brain metastasis among those without pre-existing brain lesions to 22.7 months, versus 7.2 months for patients treated with dacarbazine (p=0.059), suggesting that fotemustine might have activity as an adjuvant treatment after surgical management of CNS metastases. This has not been tested, as of 2012.

A multicenter phase 3 trial randomized 76 patients to receive fotemustine alone or in combination with WBRT in brain metastasis patients and sought to determine the cerebral response and time-to-cerebral-progression [89]. The primary endpoints of this study was to compare the CNS ORR (CR+PR), CNS control rate (CR+PR+SD), and the time to CNS progression. Compared to fotemustine alone, the combination did not significantly improve the ORR or the control rate. The addition of WBRT, however, delayed CNS progression; it was 49 days (range 11–539 days) in the fotemustine-only arm and 56 days (range 19–348 days) in patients treated with fotemustine and WBRT (Wilcoxon test, p=0.028). The combination did not, however, significantly improve the clinical CNS control rate (after 7 weeks) or OS. In regards to safety, myelosuppression was similar in both arms, but alopecia was much higher in the combination arm (40% compared to 2.6% in the fotemustine-only arm).

2.5.2. Targeted agents

Approximately 40 to 50% of all melanomas harbor a mutation in *BRAF* [114]. Notably, 95% of *BRAF* mutations are at the valine in the amino acid position 600, and over 90% of these are substitutions to aspartic acid (depicted as V600E). *In vitro*, the V600E mutation causes a 500-fold increase in the activity of B-Raf kinase; its expression is sufficient to cause tumor formation by normal melanocytes injected into nude mice [114].

Vemurafenib, a small molecule inhibitor of the V600E-mutant, was approved in the United States in 2011 for the treatment of metastatic melanoma in patients harboring the V600E mutation [92]. Clinical trials leading up to its approval excluded patients who had active intracranial disease. Thus, the efficacy of vemurafenib is not well studied in patients with pre-existing intracranial disease.

A single-arm, open-label, pilot study was conducted in metastatic melanoma patients with the V600E mutation and unresectable brain metastases, who failed previous treatments of temozolomide and/or WBRT. Four patients, with extensive disease (3 to 10+ brain metastases), were enrolled. At the time of the abstract presentation, the staging reports for two of the four patients were available. The first patient had a confirmed PR in both intracranial and extracranial lesions, while the second patient had minor responses in intracranial and extracranial metastases. Although very limited data, vemurafenib exhibits preliminary evidence of activity in melanoma patients with brain metastases who failed prior therapy [115]. Additional studies are in progress to demonstrate efficacy of vemurafenib in melanoma patients with intracranial

disease. For example, NCT01378975 is an open-label single-arm phase 2 study enrolling metastatic melanoma patients with BRAF V600 and measurable brain metastases (symptomatic or asymptomatic). Patients are enrolled regardless of prior systemic treatment history for brain metastases (except for previous treatment with BRAF or MEK inhibitors). The high response rate of patients harboring V600E mutations in melanoma (~50% vs. ~5% for dacarbazine) suggests that vemurafenib, and potentially other BRAF-targeted therapies, might be useful in post-surgical/SRS adjuvant therapy as an alternative to WBRT. This hypothesis should be tested, especially if CNS activity is confirmed.

Dabrafenib is another potent and selective BRAF V600E inhibitor that inhibits growth of B-Raf mutant melanoma and mutant B-Raf colorectal xenografts in mice [116]. In a phase 1 study, 184 patients with metatastic melanoma, untreated brain metastases, or other solid tumors received dabrafenib [117]. Only three patients with wildtype B-Raf were evaluated, with no evidence of benefit; such patients were subsequently excluded. The study included 156 metastatic melanoma patients, of whom 10 had pre-existing brain metastases. For patients with intracranial disease due to melanoma, 9 out of the 10 patients had reductions in the size of their brain lesions as well as their extracranial disease, with 4 of them achieving complete resolution of the CNS lesions.

A phase 2 study specifically assessing the response to dabrafenib in melanoma patients with intracranial disease harboring a V600E or V600K mutation was recently published [98]. The study enrolled 172 patients, of whom 89 patients had not received previous local treatment for brain metastases (cohort A) and 83 patients who progressed following previous local treatment (cohort B). In cohort A, the overall intracranial response rate (OIRR), which is the primary endpoint of this study, was 39.2% (29/74) in patients with the V600E mutation and 6.7% (1/15) in patients with the V600K mutation. In cohort B, the OIRR was 30.8% (20/65) in patients with the V600E mutation and 22.2% (4/18) in patients harboring the V600K mutation. These data suggest clinical activity in melanoma brain metastases patients harboring the V600E mutation and some activity in V600K patients, whether or not they received prior therapy for their brain metastases.

Given the limited activity of agents available up to this time, such as temozolomide, findings of CNS activity may not require formal confirmation in a phase 3 randomized trial. It is difficult to imagine what the comparator agent of such a trial would be. However, a study of the combination of either WBRT or SRS with concurrent B-Raf inhibitors (vemurafenib or dabrafenib) or with B-Raf inhibitors following radiotherapy would be important in the development of optimal therapy for patients with CNS metastases of melanoma.

2.5.3. Immunotherapy of melanoma in the central nervous system

Following the success, and subsequent FDA approval, of ipilimumab in the management of metastatic melanoma [90, 91], several anecdotal case reports highlighted the activity of ipilimumab in melanoma patients with brain metastases [118, 119]. For example, a retrospective analysis assessing the activity of ipilimumab in melanoma patients with brain metastasis who were enrolled in a phase 2 trial [120] identified 12 patients, of whom 2 achieved PR and

3 had SD in brain metastases. The median OS of all 12 patients was 14 months (range was 2.7 to 56.4 months).

Another retrospective study evaluated the outcome of 77 patients who underwent radiosurgery between 2002 and 2010 for melanoma brain metastases, of whom 27 (35%) received ipilimumab [121]. Ipilimumab–treated patients displayed a median OS of 21.3 months, versus 4.9 months for those not treated with ipilimumab. Even when adjusted for performance status, ipilimumab treatment was associated with a higher survival probability (HR 0.48, p=0.03). The median survival of ipilimumab-treated patients with poor prognosis (11/27 patients), who had Diagnosis-Specific Graded Prognostic Assessment (DS-GPA; discussed in more detail below) score of 0-2 was 15.7 months, while those with better prognosis (16/27 patients), DS-GPA score of 3-4 had a median survival of 25.2 months. The survival of patients who received ipilimumab was similar whether they received ipilimumab before or after developing brain metastases.

To determine the efficacy of ipilimumab prospectively, Margolin and colleagues designed a phase 2 study to assess the activity of ipilimumab in melanoma patients with brain metastasis [99]. The study segregated patients into two cohorts; cohort A included 51 patients who were neurologically asymptomatic, while cohort B included 21 patients with symptoms requiring corticosteroids, which continued during the course of the study, if necessary. The overall ORR in cohort A was 18% (9/51) and 5% (1/21) in cohort B. When assessing response in brain lesions alone, the ORR in cohort A was 24% (12/51) and 10% (2/21) in cohort B. The ORR of extracranial disease was similar in each group to the intracranial response: ORR was 27% (14/51) and 5% (1/21) in cohorts A and B, respectively. The median OS was 7 months for cohort A and 3.7 months in cohort B. Since the study did not specifically address the cause of deaths for patients enrolled in the study, it is not clear whether the variation in OS between the two cohorts was due to progression of intracranial or extracranial disease, or additional complications associated with symptomatic intracranial disease.

A number of observations can be made from the results of this study: a) the response of brain lesions was similar to responses in extracranial metastases; and b) patients with asymptomatic intracranial disease, not on corticosteroid treatment, tended to respond better. The authors of the study present two hypotheses that may explain the difference in response between the two cohorts: i) as suggested by survival data, patients with symptomatic intracranial disease requiring corticosteroids have inherently poorer prognosis; or ii) corticosteroids may potentially interfere with the effector lymphocyte activation induced by ipilimumab. The authors did contend that corticosteroid use with ipilimumab did not entirely abrogate its efficacy.

A single-arm phase 2 study conducted in seven Italian centers assessed the combination of ipilimumab and fotemustine in patients with metastatic melanoma, including patients with asymptomatic brain metastases [95]. The open-label, single-arm phase 2 study enrolled 86 metastatic melanoma patients, of whom 20 had brain metastases at baseline. The overall study population disease control rate (defined as immune-related CR, PR, or SD) was 46.5% (40/86 patients). Similarly, ten of the brain metastasis patients (50%) achieved disease control. This

study provides preliminary evidence that the combination of ipilimumab and fotemustine is active in patients with metastatic melanoma, including those with intracranial disease. To confirm the activity of the combination, a randomized phase 3 trial is planned and will compare the activity of the combination versus fotemustine alone in patients with advanced melanoma and brain metastases (NIBIT-M2; CA184-192).

Study	Treatment	Evaluable Patients	Primary Endpoint	Response	Median Survival	Comments
Agarwala et al., 2004 [93]	TMZ	151 total 117 treatment naive 35 pts prior CTx	ORR in brain and toxicity	No prior CTx: ORR 7% SD 29% Prior CTx: PR 3% SD 18%	Treatment Naïve: 3.5m Prior CTx: 2.2m	
Margolin et al., 2002 [88]	TMZ and WBRT	31 pts	ORR	CNS ORR 10% (1 CR and 2 PR)	PFS 2m OS 6m	
Hwu et al., 2005 [96]	TMZ + Thalidomide	26 pts 16 symptomatic 25 extensive extracranial mets	ORR in CNS	15 evaluable pts 3 CR or PR (12% by intent-to-treat)	OS 5m OS 6m (for evaluable pts)	15 pts completed ≥ 1 cycle. 11 discontinued before completing 1 cycle: 7 for intracranial hemorrhage, 2 for pulmonary embolism, 1 deep vein thrombosis, and 1 for Grade 3 rash
Chiarion-Sileni et al., 2011 [94]	CTI (TMZ + Cisplatin + IL2) vs. CDI (DTIC + Cisplatin + IL2) Phase 3	150 pts 118 evaluable (57 in CTI and 61 in CDI)	Time to CNS mets	CNS failure: CTI - 24/57 pts CDI 34/61 pts P = 0.22 1y CNS failure rate CTI – 21% CDI – 31%	PFS CTI – 4.1m CDI – 3.9m P=0.90 OS CTI – 8.4m CDI – 8.7m 1y OS CTI – 31% CDI – 42%	
Jacquillat et al., 1990 [97]	Fotemustine	153 evaluable pts; 36 (23.5%) had CNS disease	ORR	ORR 25% CNS	NR for CNS pts.	The overall ORR in all pts was 24%
Mornex et al., 2003 [89]	Arm A: Fotemustine vs. Arm B: Fotemustine + WBRT Phase 3	76 pts Arm A: 39 pts Arm B: 37 pts	CNS ORR on day 50 CNS Control Rate (CR+PR +SD) on day 50	ORR 7.4% (arm A) 10.0% (arm B) P = 0.73 Control Rate 30% (arm A) 47% (arm B)	OS 86 days (arm A) 105 days (arm B). P = 0.561	

Study	Treatment	Evaluable Patients	Primary Endpoint	Response	Median Survival	Comments
			Time to objective CNS progression	$P = 0.19$ Time to CNS progression 49 days (arm A) 56 days (arm B) $P = 0.028$		
Long et al., 2012 [98]	Dabrafenib	172 pts Cohort A: no prior CNS therapy, 89 pts Cohort B: Prior CNS therapy, 83 pts	OIRR	Cohort A V600E 39% V600K 6.7% Cohort B V600E 31% V600K 22%	At 6 months, Cohort A: 27% Cohort B: 41%	Study limited to V600E and V600K BRAF mutated melanoma
Margolin et al., 2012 [99]	Ipilimumab	72 pts 51 Cohort A (no CNS symptoms) 21 Cohort B (CNS symptoms requiring corticosteroids) Phase 2	DCR (CR, PR, SD) at 12 wks	DCR Cohort A 18% Cohort B 5% DCR in CNS Cohort A – 24% Cohort B – 10%	OS Cohort A 7m Cohort B 3.7m	
Di Giacoma et al., 2012 [95]	Fotemustine + Ipilimumab	86 pts total 20 CNS disease at baseline	Immune-related DCR (CR, PR, SD) at 24 weeks	DCR Overall 46.5% CNS 50%	CNS PFS 4.5m CNS OS 13.4m At 1-yr, 54% of CNS pts alive	Out of the 10 brain responses 5 PR or SD 5 CR

CNS: Central Nervous System; CR: Complete response; CTx: Chemotherapy; DC: Disease control; DCR: Disease control rate; DTIC: Dacarbazine; NR: Not reported; OIRR: Overall intracranial response rate; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; SD: Stable disease; TMZ: Temozolomide; WBRT: Whole-brain radiation therapy

Table 6. Prospective trials of systemic therapy treatments for melanoma brain metastases

3. Risk stratification

Several systems estimate risk of recurrence and death in patients with brain metastases, including some with melanoma-specific data (Table 7). Recursive Partitioning Analysis (RPA) is one such system [122-124]. This combines age, performance status, and extracranial disease status to assign a class from I to III that estimates survival. Its original intention was to stratify

patients for enrollment in clinical trials. Its clinically available factors are useful to consider in a discussion of brain metastasis patients.

RPA's initial description included 1200 patients, 200 of whom were affected by melanoma. Histology and tissue of origin were significant prognostic factors, with melanoma being unfavorable. The validity of RPA has since been confirmed in the melanoma subgroup [10, 19, 35, 42, 43].

While originally intended for stratification of patients in radiation therapy trials, RPA class also stratifies risk in patients undergoing surgical metastectomy [125, 126]. In 2004, the RTOG study enrolled 333 patients between 1996 and 2001, of whom 167 were assigned to WBRT and SRS and 164 received WBRT alone [15]. Median survival was longer in patients with a single brain metastasis for patients receiving WBRT+SRS combination compared to patients who only received WBRT (6.5 months *vs.* 4.9 months, p=0.0393). This study shed light on a limitation of RPA: it does not take into account the number of brain metastases present.

The Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) was developed by retrospective analysis of 4,259 patients newly diagnosed with brain metastases [127]. In addition to the factors in RPA, it includes number of brain metastases and the underlying disease giving rise to brain metastases. In the melanoma subset, the analysis identified two significant prognostic factors: performance status (represented by KPS) and number of radiologically evident brain metastases. For KPS, a score of 90-100 is 2 points, 70-80 is 1 point, and less than 70 is 0 points. A single brain metastasis is 2 points, 2 to 3 metastasis is 1 point, and more than 3 metastases is 0 points. The DS-GPA score, calculated by adding the point values from a patient's KPS score and number of metastases, ranges from 0 (worst prognosis) to 4 (best prognosis). Median OS for melanoma patients ranges from 3.4 months (GS-GPA score of 0 to 1.0) to 13.2 months (GS-GPA score of 3.5 to 4.0).

Several other systems have been developed for use in specific sub-populations. The Basic Score for Brain Metastases (BS-BM) was developed by analyzing results from 110 SRS-treated patients [128]. The system generates a score based on KPS, control of primary tumor site, and extracranial disease status. Only 19 patients (17%) of the initial group of patients had melanoma. The system has not yet been studied in melanoma patients specifically and focuses on SRS treatment. Its applicability to other treatment modalities remains to be established.

The Score Index for Radiosurgery (SIR) was developed from the study of 65 SRS-treated patients with brain metastases from a variety of primary tumor types [129]. SIR derives a score from patient age, performance status, systemic disease status, maximum CNS lesion volume, and number of CNS lesions. In the population initially studied, SIR was more accurate in predicting survival than RPA. A retrospective study confirmed its utility in melanoma patients [38].

The Malignant Melanoma-Gamma Knife Radiosurgery score (MM-GKR) also assesses outcomes in metastatic melanoma patients treated with SRS [23]. Scoring is based on performance status, age, and CNS lesion location. The authors claim greater prognostic accuracy than with either RPA or SIR, particularly in identifying patients with an especially poor prognosis.

The Prognostic Index (PI) score estimates prognosis in patients treated with palliative WBRT [43]. Factors used in this system include number of extracranial metastatic sites, RPA class,

CNS disease progression prior to WBRT, and the presence of meningeal disease. This system is focused on those with extensive disease, not amenable to local therapy with SRS or surgery.

Median survival times predicted by studies of brain metastasis patients generally are similar to those reported for melanoma patients with CNS involvement. With minor differences, the systems described utilize similar and easily available data to arrive at their risk estimations. RPA has probably been examined in the widest array of clinical trial settings. It also does not seem to be specific to a given treatment modality. Its components are fairly simple to derive from clinical parameters. It will therefore be used for further discussion.

System	Prognostic Factors	Prognostic Classification	Median OS (all tumor types)	Median OS (melanoma)	Comments	References
RPA	KPS, age, extra-cranial disease status, control of primary disease site	Class I: KPS≥70, age<65 y., controlled primary disease site, no extra-cranial disease Class II: Not Class I or III Class III: KPS<70	Class I: 7.1 m Class II: 4.2 m Class III: 2.3 m	Class I: 6.5-10.5 m Class II: 3.5-5.9 m Class III: 1.8-2.5 m	Validated for radiation therapy and surgery.	Gaspar *et al.,* 1997 [122] Gaspar *et al.,* 2000 [123] Buchsbaum *et al.,* 2002 [10] Lutterbach *et al.,* 2002 [124] Harrison *et al.,* 2003 [42] Morris *et al.,* 2004 [43] Radbill *et al.,* 2004 [35] Brown *et al.,* 2002 [19]
PI	Number of ECM, RPA class (see above), PD on imaging prior to WBRT, presence of LM	Index= Number of ECM sites + (2 x RPA class) + (2 if PD on pre-WBRT imaging) + (4 if LM present)	NR	Score 2-4 138 d 5-6 80 d 7-8 42 d 9-10 18 d 11+ 15 d	To determine outcome following palliative WBRT.	Morris et al., 2004 [43]
SIR	Age, KPS, extra-cranial disease status, volume of largest CNS lesion, number of CNS lesions	Factor 0 1 2 Age ≥60 51-59 ≤50 KPS ≤50 60-70 ≥70 Systemic disease status PD PR/SD CR or NED Largest Lesion Volume (cm³) "/>13 5-13 <5	Score 0-3 2.9 m 4-7 7 m 8-10 31 m	Score ≤6 4 m "/>6 7 m	Point values for individual factors are added to derive score. Intended for assessment of outcome after SRS.	Weltman *et al.,* 2000 [129] Selek *et al.,* 2004 [38]

System	Prognostic Factors	Prognostic Classification				Median OS (all tumor types)		Median OS (melanoma)		Comments	References
		# of CNS lesions	≥3	2	2						
MM-GKR	Age, KPS, Adverse CNS lesion locations (brainstem, posterior fossa, nuclei, cerebellum)	Factor	0	1	1.5 2	NR		Score		Intended for assessment of outcome after SRS.	Gaudy-Marqueste et al., 2006 [23]
		KPS	<80	-	- ≤80			0	7.1 m		
		Age	≤60	"/>60	- -			1-2	5 m		
		Adverse Location	No	-	Yes -			≥2.5	2.2 m		
BS-BM	KPS, control of primary tumor, presence of ECM	Factor	0		1	Score		NR		Not validated in melanoma, although study included 19 melanoma patients out of 110 total (17%). Score of 3 had OS not reaching median with 30 m of follow-up. Intended for assessment of outcome after SRS.	Lorenzoni et al., 2004 [128]
		KPS	50-70		"/>70	0	1.9 m				
		Primary tumor control	No		Yes	1	3.3 m				
						2	13.1 m				
						3	ND				
		ECM	Yes		No						
DS-GPA	RPA factors (KPS, age, extra-cranial disease status, control of primary disease site) and number of brain mets	Factor	0	1	2	0.0-1.0	3.4m	0.0-1.0	3.4m	In melanoma, only 2 significant prognostic factors: KPS (p<0.0001) and number of brain mets (p<0.0001)	Sperduto et al., 2010 [127]
		KPS	<70	70-80	90-100	1.5-2.5	6.4m	1.5-2.5	4.7m		
		# of brain mets	>3	2-3	1	3.0	11.6m	3.0	8.8m		
						3.5-4.0	14.8m	3.5-4.0	13.2m		

CNS: Central Nervous System; CR: Complete response; DS-GPA: Diagnosis-Specific Graded Prognostic Assessment; ECM: Extracranial metastases; KPS: Karnofsky performance status; LM: Leptomeningeal metastasis; MM-GKR: Malignant Melanoma-Gamma Knife Radiosurgery score; ND: Not defined; NED: No evidence of disease; NR: Not reported; OS: Overall survival; PD: Progressive disease; PI: Prognostic Index; PR: Partial Response; QOL: Quality of life; RPA: Recursive Partitioning Analysis; SD: Stable disease; SIR: Score Index for Radiosurgery

Table 7. Risk Stratification of Patients with Brain Metastases from Melanoma

An important caveat in discussing outcomes estimates derived using these risk stratification systems is that they all were first developed prior to 2011. Prior to that time, reliably effective and proven treatments for advanced melanoma were not available for general clinical use. Development of drugs with proven activity, such as ipilimumab and vemurafenib discussed above, are changing the outlook for melanoma patients. This includes patients with brain metastases. With these drugs, and more being developed with potentially even greater activity, the risk estimates of these systems will certainly change for the better. This is especially likely

to be the case in patients with very high risk/poor prognosis disease. Treatment recommendations for the brain metastasis problem in melanoma will therefore likely be very fluid over the next several years, as new treatment paradigms for melanoma evolve.

4. Therapy of CNS disease

4.1. Unfavorable/poor risk

By definition, RPA class III patients have a KPS less than 70%. Often, they have multi-focal brain metastases, active extracranial disease, or both. Historically, their life expectancy was very limited. The PI prognostic system, intended to assess prognosis in this group as described above, uses days rather than months as the unit of time for its estimates [43].

Conventionally, surgery or SRS would only be used judiciously with palliative intent and well-defined goals. WBRT may be undertaken for symptom palliation and a very modest survival benefit [8, 12, 86, 130-132]. The anticipated duration of survival played an important part in designing any treatment approach, as even therapy of several weeks duration could consume a significant proportion of a patient's remaining lifespan. The burden of coming to repeated treatments (as might be the case with palliative WBRT, frequently administered as 10 treatments over 2 weeks) may lead to a significant QOL decrement in patients with poor performance status. By definition, RPA class III patients have such a poor performance status.

Prior to the approval in the United States of ipilimumab and vemurafenib in 2011, systemic therapy played a minimal role in this group. Exceptions included steroid therapy for tumor-associated edema and anti-convulsants for seizures. The low performance status and CNS disease in these patients excluded them from virtually all clinical trials. Activity of systemic agents with CNS penetration, such as temozolmide and fotemustine, was limited, with an onset of action too slow to benefit most patients with melanoma who were in this category.

As of 2011, BRAF mutational status serves as an important factor in making treatment decisions. This may be especially important in patients with RPA class III melanoma with CNS involvement. The BRAF inhibitors vemurafenib and dabrafenib, discussed above, have rapid onset of action, high response rates, preliminary evidence of CNS activity, oral administration and manageable toxicity profiles. As of November 2012, vemurafenib is approved in the United States and Europe, and debrafanib's approval is pending. For patients possessing an appropriate BRAF mutation, treatment with one of these agents would be reasonable to consider, even with RPA class III. Of course, the patient must be aware that information about this drug in the brain metastasis population is presently very limited. Data regarding combinations with radiotherapy is also very limited at this time. While a clinical trial would be the preferred setting to treat these patients, use of BRAF inhibition therapy would be reasonable to offer to BRAF-mutant melanoma patients with brain metastases and RPA class III.

For patients in whom a targetable BRAF mutation is not present, fewer options are available. Ipilimumab, discussed above, has a relatively slow onset of action, taking 3-4 months in phase 3 trials to confer a survival benefit versus controls [90, 91], with an overall low response rate.

For someone with a poor performance status unlikely to live that long, ipilimumab is unlikely to provide benefit, despite preliminary evidence of CNS activity. For these patients, further developments in melanoma therapy are awaited. Pallitative WBRT likely remains the standard therapy for these patients.

One peculiar circumstance remains: some patients present with RPA class III advanced disease, including brain metastases and poor performance status, but their BRAF mutational status is unknown. Given their overall condition and location of disease, obtaining a tumor specimen to determine BRAF mutation status may not be possible. A wait of 1-2 weeks for results of mutational testing may consume a significant portion of their remaining lifespan. In such patients, standard care would be supportive, potentially with the addition of WBRT. Given a frequency of BRAF mutations targeted by presently available drugs of about 50% and the lack of other proven options, a therapeutic trial of BRAF inhibition is unlikely to cause significant harm, and might lead to dramatic benefit if the patient possesses an appropriate mutation. Again, before embarking on such a treatment course, the patient must be aware of the limitations of our current dataset.

4.2. Favorable/good risk

Patients of RPA class I have a relatively good prognosis and warrant an aggressive treatment approach. Such patients are young, have a good performance status, and no active extracranial disease. However, among patients with metastatic melanoma, true RPA class I patients are infrequently encountered, especially those completely lacking detectable extracranial disease.

The major treatment decision for these patients relates to local therapy of existing brain lesions (Figure 1). The goal would be to treat all evident CNS disease by some form of definitive therapy (surgery or SRS). Traditionally, surgery was favored in cases involving one surgically accessible lesion, and benefit was reported in surgeries targeting up to 3 lesions [14, 133]. Surgery is also especially useful in specific situations where SRS is less favorable, such as large lesion size (> 3cm) or symptomatology (for example, bleeding). Surgery also yields a specimen to confirm the diagnosis and analyze for targetable alterations in the tumor, such as BRAF mutations status. In patients lacking any other evident disease, these data can be very important and only obtainable from a surgically resected CNS specimen. Otherwise, SRS is emerging as the preferred local therapy, both for its simpler administration and possibly for better local control [44]. SRS may also be able to provide definitive treatment at sites inaccessible to surgery. Surgery and SRS are not mutually exclusive: both may be necessary to provide definitive treatment of all lesions in multi-focal metastatic CNS disease.

SRS has been a remarkable addition to our armamentarium for treatment of brain metastases. Previously, surgery was the only approach to definitive treatment. If more than 3 lesions were present, or they were located in surgically inaccessible locations, surgery could not be used with the intention of long-term control. SRS allows treatment of multiple lesions, in sites inaccessible to surgery. It also offers the possibility of re-treatment. At some point, presumably, the number of lesions exceeds the ability of SRS to control the disease. The exact number is not defined, but some have advocated SRS to control up to five CNS lesions [37]. Beyond this, it may be unreasonable to expect a local treatment modality like SRS to control what is clinically

widespread involvement in an organ system, even if limited to the CNS. Surgery and SRS may be able to control specific lesions that are symptomatic in such patients, but the overall treatment approach relies primarily on therapeutic WBRT and systemic therapy, discussed below under "Intermediate Risk."

In patients with RPA class I disease from melanoma, risk of failure in the CNS is high if treatment focuses solely on radiologically evident disease. This likely reflects the underlying biology, in which specific neurotropic sub-clones of melanoma develop that colonize the CNS, leading to brain metastases. Limiting treatment to surgery and/or SRS of only radiologically evident lesions ignores this biological reality. This observation is confirmed in the multiple randomized trials of adjuvant WBRT enrolling patients with multiple tumor types, including melanoma. Adjuvant WBRT decreases intracranial recurrence rates when combined with definitive local therapy. This effect is evident at both definitively treated macroscopic sites (treating residual contamination) and at distant sites within the CNS. At distant sites, adjuvant WBRT must accomplish this by either treating pre-existing radiologically undetectable micrometastatic disease or making the CNS less receptive to colonization from extracranial sites. The former is the more plausible biological explanation.

Approaches to address the problem of distant CNS recurrence have been discussed in detail earlier. Basically, these come down to either administering adjuvant WBRT up-front, or using an expectant management strategy, with regular imaging and re-treatment (primarily with SRS), at the time of CNS progression. Arguments against adjuvant WBRT include concern regarding its cognitive toxicity, its lack of clear survival benefit and inability to undertake re-treatment. As described earlier, cognitive effects of adjuvant WBRT, while not absent, are not unreasonable in the setting of CNS metastases, especially when balanced against the cognitive effects of tumor progression and those of re-treatment (as, for example, by SRS). Adjuvant WBRT is unlikely to be associated, in general, with an overall survival benefit overall due to extracranial disease as a competing cause of death. In the setting of RPA class I patients, who lack active extracranial disease, adjuvant WBRT may very well have a survival benefit [54, 134].

As noted above, the use of a salvage strategy, relying on SRS in the event of tumor progression, is associated with high rates of intracranial failure. The cognitive effects of such a strategy have not been assessed in detail, but the data regarding cognitive effects of allowing tumor progression have been reviewed and are clearly unfavorable. Whether the effects are better or worse than those due to adjuvant use of WBRT can only be answered by a randomized comparison of the two strategies.

We concede that the decision regarding use of adjuvant WBRT is not simple and clear-cut. To determine whether to recommend its use, the benefit of decreased intracranial progression rates must be balanced against its adverse effects. Overall, we believe that the published evidence generally supports the use of adjuvant WBRT in melanoma patients.

Systemic adjuvant therapy might be an alternative to adjuvant WBRT. Traditional cytotoxic therapy agents with known CNS activity, such as fotemustine or temozolomide, have not been shown clearly to impact the subsequent development of CNS disease in melanoma patients [113, 135]. In the setting of melanoma patients with CNS disease, their primary purpose was

to treat extracranial disease, an important prognostic factor once CNS disease was controlled. By definition, true RPA class I patients have no active extracranial disease.

Newly developed agents, such as vemurafenib and ipilimumab, may have a role defined in the future for adjuvant therapy in patients with RPA class I CNS disease from melanoma. They may be able to affect both CNS recurrence rates and progression of extracranial disease. However, data supporting such use is not available at present. Their use as adjuvant therapies in this population is not warranted, outside the setting of a clinical trial.
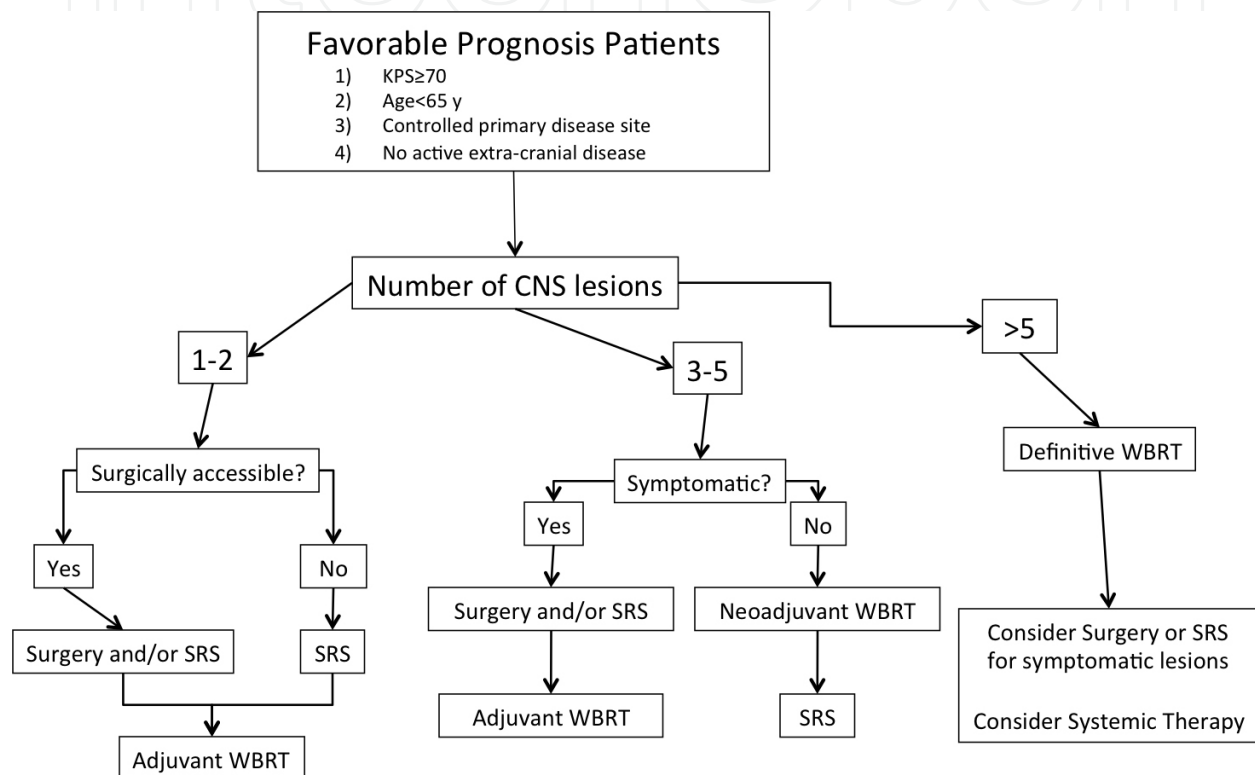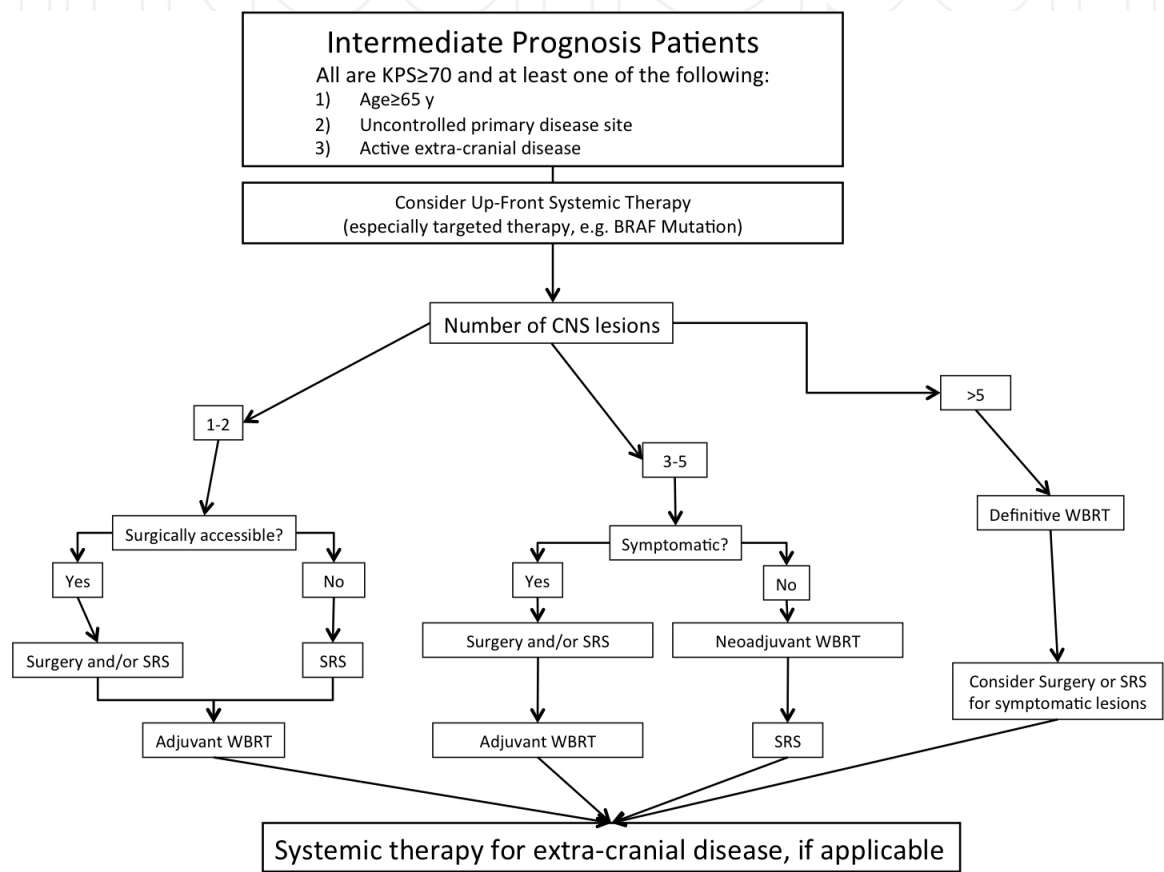

Figure 1. Treatment of melanoma patients with brain metastases with favorable risk profile, equivalent to RPA class I. In patients with more than one brain lesion who are to receive local therapy, it may be necessary to use both surgery and radiosurgery to treat all lesions. By definition, RPA class I patients have no active extracranial disease. Thus, systemic therapy is not indicated except in an experimental trial. CNS: central nervous system; KPS: Karnofsky performance status; RPA: Recursive Partitioning Analysis; SRS: stereotactic radiosurgery; WBRT: whole brain radiotherapy.

4.3. Intermediate risk

Treatment decisions in intermediate risk patients (equivalent to RPA class II) are probably most difficult of all (Figure 2). This relates to their variable clinical presentation. They have better performance status than those with unfavorable RPA class III. They are also of advanced age (according to RPA, anyone older than 65 years), have active extracranial disease, or both, conveying a negative prognosis relative to RPA class I. A logical way to divide this population is into those with CNS disease amenable to local definitive therapy and those with CNS disease too extensive for complete, definitive local therapy of all lesions.

Considerations regarding the use of adjuvant WBRT and the desirability for treatment in the context of a clinical trial are essentially the same as for favorable prognosis patients. The key differentiating question is whether local therapy of CNS lesions with surgery or SRS should be attempted at all. Several clinical situations argue against their use. Lesions may be inaccessible for surgery or too large for SRS or they may simply be too numerous. If definitive treatment of all CNS disease sites is possible, then it should be attempted. If CNS disease is not amenable to local therapy of all lesions, then treatment must rely on therapeutic WBRT and systemic therapy, with surgery or SRS reserved for large or symptomatic lesions.

Figure 2. Treatment of melanoma patients with brain metastases with intermediate prognosis, equivalent to RPA class II. In patients with more than one brain lesion who are to receive local therapy, it may be necessary to use both surgery and radiosurgery to treat all lesions. Patients with active extracranial disease should be considered for systemic therapy. While in the past, few active systemic agents were available, newer therapies might have relevance early in the treatment of intermediate prognosis patients. For example, BRAF inhibition with vemurafenib has rapid onset of control, high response rates, and even preliminary evidence of CNS activity. Thus, early use of systemic therapy might be able to impact both CNS disease and extracranial disease. Extracranial disease activity is a consistent adverse prognostic factor in intermediate patients, once CNS disease is controlled. CNS: central nervous system; KPS: Karnofsky performance status; RPA: Recursive Partitioning Analysis; SRS: stereotactic radiosurgery; WBRT: whole brain radiotherapy.

In RPA class II patients with CNS melanoma, active extracranial disease status is a key prognostic factor. Disease outside the CNS represents a competing cause of death. Before the approval in 2011-2012 of agents with proven anti-melanoma activity (such as vemurafenib and ipilimumab), systemic therapy of the CNS was limited to temozolomide or fotemustine (in

Europe). Although these drugs treated extracranial disease as well, they were not highly active in either the CNS or extracranial compartments, and did not demonstrate clear or dramatic survival benefits.

Systemic therapy of melanoma in RPA class II patients is appearing brighter than it has in the past. Clinical trials are opening which permit these patients to enroll, and highly active agents, with CNS activity moreover, such as vemurafenib are available non-experimentally for patients with BRAF mutations. For patients lacking BRAF mutations, treatment with ipilimumab is a reasonable consideration, due to its survival benefit in a phase 3 trial, which included patients with pre-existing, treated brain metastases [90]. Most of these patients will live long enough to derive benefit from ipilimumab. As new agents are developed, their use in RPA class II melanoma patients is justified, even without demonstrable CNS activity, due to the active extracranial disease present in most of this population as a competing cause of death.

5. Directions for the future

Brain metastasis is part of the natural history of metastatic melanoma. It is a common problem and has a major adverse impact on treatment outcomes and QOL. The bulk of melanoma-specific research consists of retrospective analyses and single-center studies. Prospectively validated, comprehensive treatment paradigms do not yet exist. The preceding discussion suggests some important research questions for the future.

Optimal use of SRS technology remains undefined. One question relates to the treatment of multiple lesions. The only major randomized trial of SRS in brain metastasis therapy demonstrated a survival benefit in the presence of only a single brain metastasis [15]. No prospective data support a survival benefit from SRS when more than one lesion is present; retrospective data from several sources indicate that multiple CNS lesions are associated with worse survival [22, 26, 35].

At some point, the absolute number of CNS lesions poses a barrier to effective SRS therapy. Some argue that the presence of multiple lesions (up to about 5) should not preclude therapy, based on results indicating that the number of CNS melanoma lesions did not predict subsequent survival [39, 136]. Whether some threshold number of lesions exists is an unanswered question appropriate for investigation.

SRS itself is a generic term for a rapidly evolving technology. The relevance of even recently published results to current treatment technologies may be questioned. What is unlikely to change is the local nature of SRS therapy: SRS treats the radiated region, but not that which is unradiated. As discussed extensively, concurrent micrometastatic disease is not addressed by SRS, as it is also not by surgery. The use of adjuvant therapy after local treatment with surgery or SRS lacks melanoma-specific prospective data. Five randomized trials, described above, indicate that adjuvant WBRT can decrease intracranial recurrence rates, both at sites treated with surgery/SRS and at untreated sites. The adverse neurocognitive effects of WBRT and the efficacy of this modality in the metastatic melanoma population are valid questions. As noted above, such a study is in progress (NCT01503827) [55].

An alternative to the use of adjuvant WBRT is a planned radiosurgical salvage strategy. This presumably minimizes exposure of the CNS to WBRT and its adverse effects. Little data is available regarding this treatment approach. A randomized clinical trial would be most helpful, in which patients are randomized to receive immediate adjuvant WBRT after SRS therapy or undergo planned SRS salvage treatments, with WBRT only when SRS is not possible. This study would provide data to balance the neurocognitive consequences of immediate WBRT with those due to an increased rate of later macroscopic CNS progression. Further, some estimate of the neurocognitive cost of SRS re-treatment would be obtained.

SRS itself is used for adjuvant purposes after surgical metastectomy to treat residual disease at the resection site. The efficacy of this has not been defined. Additionally, such therapy does not treat occult disease at other sites within the CNS. A randomized trial comparing the efficacy of adjuvant SRS to either no adjuvant therapy or to adjuvant WBRT would be appropriate.

Finally, and perhaps most significantly, systemic therapy of melanoma is evolving rapidly, and those advances will have a major impact on treatment of CNS disease. Even now, convincing preliminary evidence of CNS activity of these several new agents has been presented. Previously, melanoma patients with CNS disease were excluded from clinical trials in the belief that the blood-brain barrier posed to great a hurdle to clinical efficacy. This no longer appears to be a valid assumption. As new agents emerge, their activity in the CNS should either be addressed in CNS-specific trials, or patients with CNS melanoma should be considered similar to any other melanoma patient, so long as their CNS disease is minimally or asymptomatic.

Much of this review has focused on the controversy of adjuvant therapy in the CNS. Adjuvant WBRT is not an optimal solution to this problem. It does not prevent CNS re-seeding from extracranial sites and cannot be used repeatedly. Adverse cognitive effects of WBRT are clearly demonstrable, even if their clinical impact is arguable. Critically, adjuvant WBRT also does not address the problem of extracranial disease, a major prognostic factor. Optimal adjuvant therapy to address these limitations is likely to be systemic. The development of highly active agents with CNS penetration opens the possibility of their use in melanoma patients after definitive treatment of brain metastases.

Several prior studies can provide necessary baseline data regarding rates of CNS progression for sample size calculations [113, 135]. Neurocognitive effects must be a secondary endpoint in any study, as it cannot be assumed that systemic agents are devoid of adverse neurocognitive effects. For example, case reports of melanoma patients treated with fotemustine reported toxic leukoencephalopathy with progressive dementia in several patients, [137, 138].

6. Conclusions

Brain metastasis is a frequent and serious problem for melanoma patients. New technologies, such as SRS and agents, such as vemurafenib and ipilimumab, are expanding our ability to treat this condition. Melanoma-specific studies guiding optimal employment of new technologies are limited. Most information regarding CNS treatment in melanoma is extrapolated

from other conditions or is based on retrospective analyses from individual centers. Data from well-designed, prospective trials is lacking in many regards. This deficiency has been noted at least eight years previously by others [139]. At present, many of the same questions posed by those workers remain unanswered. Fortunately, melanoma treatment itself has not remained static, with new agents generating new questions regarding optimal treatment of the condition.

Well-designed, rigorous trials will allow our patients to receive the best and most cost-effective treatments available. Melanoma patients with brain metastases can look forward to a brighter future. We must, however, demand rigorous investigations to allow the best use possible of the arsenal being placed at our disposal to treat this challenging problem.

Abbreviations

BS-BM: Basic Score for Brain Metastases; CNS: Central Nervous System; CR: Complete Response; CT: Computed Tomography; DS-GPA: Diagnosis-Specific Graded Prognostic Assessment; Gy: Grey, unit of radiation dose; HVLT: Hopkin's Verbal Learning Test; KPS: Karnofsky Performance Status; MM-GKR: Malignant Melanoma-Gamma Knife Radiosurgery; MMSE: Mini-Mental Status Examination; MRI: Magnetic Resonance Imaging; NCF: Neuro-cognitive Function; NSCLC: Non Small Cell Lung Cancer; OIRR: Overall Intracranial Response Rate; ORR: Objective Response Rate; OS: Overall Survival; QOL: Quality-of-Life; PCI: Prophylactic Cranial Irradiation; PFS: Progression-Free Survival; PI: Prognostic Index; PR: Partial Response; RPA: Recursive Partitioning Analysis; RTOG: Radiation Therapy Oncology Group; SCLC: Small Cell Lung Cancer; SD: Stable Disease; SIR: Score Index for Radiosurgery; SRS: Stereotactic Radiosurgery; TCI: Therapeutic Cranial Irradiation; WBRT: Whole Brain Radiation Therapy

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