Brain Metastases

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Abstract

Brain metastases (BM) cause significant morbidity and mortality, with profound personal and societal impact. Historically, surgery and whole-brain radiotherapy (WBRT) were the mainstays of management. WBRT alone has been shown to have limited role for durable local control, and there are concerns regarding its impact on quality of life (QoL) and neurocognitive function. Advances in systemic therapeutics have afforded improved control of extracranial disease and paved the way for improved survival outcomes. In parallel, the overarching goals of BM management are to provide durable intracranial control and good QoL, with minimal long-term toxicities, and, if possible, to prolong survival. However, there remain significant controversies within the oncology community about how these goals should be achieved. Herein, we will review various management strategies, including the role of stereotactic radiosurgery (SRS) and methods to mitigate long-term toxicity of WBRT.

1 Introduction

BM are the most commonly encountered intracranial malignancy within the radiation oncology clinic. It is estimated that up to 40% of cancer patients (Nussbaum et al. 1996) will develop BM in their lifetime. Certain cancer primaries have a predilection to seed the brain, accounting for up to 80% of BM – these include primary lung, melanoma, breast, and renal cell cancers (Barnholtz-Sloan et al. 2004).

In the United States alone, there are an estimated 170,000–200,000 new cases of BM reported each year (Fox et al. 2011). Furthermore, the incidence of BM is expected to increase over time (Smedby et al. 2009). This is likely for a few reasons:

1. The onset of the silver oncologic tsunami: an aging population, buttressed by a rising incidence of cancer in those above 65 years (Chapman et al. 2015)
2. Improved systemic therapeutics which provide extracranial disease control, but fail to address BM
3. Improved diagnostic capabilities, including thin-slice magnetic resonance imaging (MRI) with volumetric reconstruction, to detect smaller lesions in asymptomatic patients
4. Improved reporting of cases, through better access to healthcare and early referrals

BM, unfortunately, carry a high mortality rate with the median survival historically being below 4 months (m) (DiStefano et al. 1979). As a result, the detection of BM has been the cue for many to assume a fatalistic approach, withholding aggressive treatment in a patient who is believed to have a poor outcome regardless. The routine use of WBRT has been the mainstay, and the potential treatment-related toxicities largely dismissed.

In more recent years, advances in neurosurgery, neuroimaging, systemic therapeutics, and radiation therapy have afforded longer survival in some patients, especially those with good performance status and prognostic factors (Sperduto et al. 2012). For example, the 1-year survival for patients treated between 1983 and 1989 was 15%, compared to 34% for patients treated between 2005 and 2009 (Nieder et al. 2011). As a result, there has been heightened concern about the routine use of WBRT and its attendant long-term (and often irreversible) toxicities. This has led to considerable dissonance within the oncology circle regarding the appropriate management of BM – especially with society's increasing focus of neurocognition and QoL. Consequently, in the absence of strong evidence, many centers have adopted SRS alone, as the preferred treatment option, in patients with multiple BM (Sneed et al. 1999; Hasegawa et al. 2003).

This chapter sets out to review the evolving literature and seminal trials that have shaped the

landscape in the management of BM. In particular, we will place emphasis on neurocognitive function and ways to mitigate late toxicities.

2 History and Evolution

2.1 WBRT

Prior to the advent of WBRT, survival of patients with BM was typically 1–2 m with corticosteroids alone (Vecht et al. 1994; Wolfson et al. 1994). Although steroids produced temporary symptom relief, invariably all patients died secondary to intracranial disease progression.

WBRT came to the forefront as the recommended treatment after the seminal publication by Chao in 1954 (Chao et al. 1954). In their publication, they suggested doses of 30–40 Gy achieved symptomatic relief in 24 of the 38 patients (63%), with about half living slightly over 3 months. Interestingly, WBRT has never been evaluated, until recently, in a randomized clinical trial against supportive care alone. However, its wide reach, ease of administration, and relatively low cost have made it the de facto treatment for patients with BM.

Much focus, primarily through RTOG, was placed on comparing various dose-fractionation schedules of WBRT (Harwood and Simson 1977; Kurtz et al. 1981; Borgelt et al. 1980, 1981; Chatani et al. 1986; Haie-Meder et al. 1993; Murray et al. 1997). Unfortunately, there was no survival benefit seen among the various tested regimens. Moreover, 27–54% of patient continued to die from neurological death (presumably from intracranial progression) despite having undergone WBRT (Borgelt et al. 1980).

The lack of a dose-response for survival can be attributed to two reasons:

1. The brain parenchyma is a radiosensitive structure, and the tested doses were mostly subtherapeutic for durable disease control (i.e., intracranial failure).
2. Patients succumbed to uncontrolled systemic disease instead. (i.e., extracranial failure).

In any case, these studies reiterated the fact that WBRT provides excellent palliation to patients with BM, with approximately 60% achieving relief of symptoms (such as headache, motor function, impaired mentation) by the end of week 2 (Borgelt et al. 1980).

2.2 SRS

SRS has emerged as an optimal form of focal therapy to treat BM. The characteristics of BM, namely, spherical shape, well-demarcated margin, and absence of normal brain parenchyma inside the tumor volume, lend themselves well for SRS. The ability to deposit an ablative dose in a focused manner while avoiding collateral damage to brain parenchyma has made it a valuable tool. Moreover, the large ablative doses utilized allow for superior control rates possibly through endothelial damage (Garcia-Barros et al. 2003) and immune-mediated mechanisms (Burnette et al. 2011; Lee et al. 2009).

The first report of SRS dated back to 1950, by a Swedish neurosurgeon (Dr Lars Leksell) (Leksell 1951). Subsequently in 1987, Sturm reported on the use of linear accelerator-based SRS techniques (Sturm et al. 1987). The RTOG 90-05 phase I dose-escalation study (Shaw et al. 2000) set the stage for the maximum-tolerated dose, which was determined by lesion size, and is still being followed today. In the modern setting, SRS platforms have become ubiquitous, and there have been multiple commercial options to deliver SRS. These include Gamma Knife (Elekta AB, Stockholm, Sweden), CyberKnife (Accuray Inc., Sunnyvale, USA), Novalis (Brainlab AG, Germany), TomoTherapy (Accuray Inc., Sunnyvale, USA), and Proton therapy.

SRS has allowed for a paradigm shift in the way BM are managed. This is evidenced by the exponential increase in its use in the twenty-first century (Halasz et al. 2013). The main advantages of SRS over WBRT are the sparing of most of the brain parenchyma, its single-session outpatient delivery facilitating minimal downtime, patient convenience, and ability to commence systemic therapy sooner. In addition, there remains an option to repeat the procedure to additional lesions that may surface subsequently, obviating the need for WBRT.

3 How Should We Treat Patients with Limited BM?

In patients who are expected to survive longer, sustained intracranial control becomes essential to prevent demise from local progression (i.e., neurological death). Historically, WBRT alone, as mentioned earlier, had been the mainstay treatment. However, it is unlikely to provide sustained control. Response of BM to WBRT is related to lesion size, underlying histology and dose. Nieder et al. (1997) demonstrated that complete radiological remission to WBRT differed by histology – 37% for small-cell carcinoma, 35% for breast cancer, 25% for squamous cancer, and 14% for non-breast adenocarcinoma. The size of the underlying lesion significantly influenced response rate (52% for lesions below 0.5 cc and 0% for lesions above 10 cc). A second study by Nieder et al.(1998) showed that partial remission rates improved with increasing biological effective dose; however, we are limited by the whole-organ radiation tolerance.

Taken together, the above studies suggest that long-term control of gross BM is unlikely with WBRT alone. A case in point of the suboptimal control would be the dismal 1-year control rates (0–14%) from the randomized controlled trials (RCT) performed by Kondziolka et al. (1999) and Patchell et al. (1990). This is concordant even in more recent trials with regular MRI surveillance, such as RTOG 0933, which reported the median progression-free survival to be 5.9 m (95% CI 4.7–8.4 m)

3.1 Surgery + WBRT Versus WBRT Alone

Intuitively, surgical resection of bulky BM provides immediate and effective palliation of symptomatic mass effect. Moreover, it can also provide histological confirmation of the diagnosis when it has not yet been established. However, there was equipoise in the benefits of addition of surgery to WBRT. To date, three RCTs have been conducted on the premise that improved local control would result in improved overall survival. Notably, all three trials only included patients with single BM.

Patchell et al. conducted a single-center randomized trial ($n = 48$), investigating the survival benefit of surgical excision plus WBRT versus WBRT alone (36 Gy in 12 fractions) (Patchell et al. 1990). All patients had good performance status (KPS > 70), and only a third (37.5%) had extracranial disease. The investigators reported a significant survival benefit with surgery (median survival 40 vs 15 weeks, $P < 0.01$). Moreover, patients treated with surgery maintained functional independence for a longer period (38 vs 8 weeks, $P < 0.005$).

Noordijk et al. conducted a similar multicenter randomized trial ($n = 66$), except that WBRT was delivered bi-daily (40 Gy in 20 fractions, over 2 weeks) (Noordijk et al. 1994). A survival benefit was, once again, demonstrated with the addition of surgery (10 vs 6 m, $p = 0.04$). However, subgroup analysis showed that the survival difference was present only in the patients (70%) with inactive extracranial disease (12 vs 7 m, $P = 0.02$; 5 m in the group with progressive extracranial disease irrespective of treatment arm).

Mintz et al. reported their trial ($n = 84$), which had similar study arms (Mintz et al. 1996). 30 Gy of WBRT was delivered over 10 fractions. Unlike the above 2 trials, this trial included a larger proportion of patients (45%) with extracranial disease and a sizeable portion (21.4%) who were of KPS 50–60. This was a negative trial, as they failed to find a survival benefit with surgery (5.6 vs 6.3 m, $P = 0.24$). Extracranial disease was reported to be a significant prognostic factor for mortality.

From the above studies, it is clear that patient selection remains important and survival gains may be diminished in patients with active extracranial disease or poor performance status.

3.2 SRS + WBRT Vs WBRT Alone

Trialists investigated whether similar benefits may be seen in patients treated with SRS, instead of surgical excision. A number of RCTs have addressed this question. Notably, they allowed up

to 4 lesions (which was chosen arbitrarily) and addressed varying endpoints.

The first of these trials, from the University of Pittsburgh (Kondziolka et al. 1999), randomized 27 patients who were KPS > 70 and had 2–4 metastases (below 2.5 cm) to WBRT alone (30 Gy in 12 fractions) or WBRT plus SRS (16 Gy). This trial was stopped early, as there was significant local failure without SRS (local failure 100% vs 8%). There was no difference in overall survival (OS) (7.5 vs 11 m $P = 0.22$), but it was possibly due to the lack of power. Once again, extent of extracranial disease emerged as a significant prognostic factor for survival.

Chougule et al. conducted a single-institution RCT (Chougule et al. 2000) for patients with 1–3 metastases and tumor volume below 30 cc. They were randomized to WBRT alone (30 Gy in 10 fractions) or WBRT plus SRS 20 Gy. Although published only in abstract form, local control was improved with SRS (91 vs 62%).

The strongest evidence for this strategy comes from the multi-institutional, RTOG 95-08 trial (Andrews et al. 2004) ($n = 331$). Patients with 1–3 metastases were randomly allocated to WBRT alone (37.5 Gy in 15 fractions) or WBRT followed by SRS boost. The SRS dose followed findings from the RTOG 9005 trial: 24 Gy up to 2 cm, 18 Gy for 2–3 cm, and 15 Gy for 3–4 cm. The primary outcome, OS, was not different between the 2 arms (6.5 vs 5.7 m, $P = 0.13$). However, subgroup analysis suggested that patients with single BM ($P = 0.04$) and/or age < 50 ($P = 0.04$), non-small-cell histology ($P = 0.05$), and RPA class 1 ($P = 0.05$) have a survival advantage with the addition of SRS. Local control rates, as expected, were improved with SRS boost ($P = 0.01$). However, the multiple unplanned subgroup analysis has been criticized as it increases the type 1 error rate. A secondary analysis (Sperduto et al. 2014), post-stratified by GPA, was performed ($N = 252$). Overall, the primary conclusion was not different from the earlier study. However, subset analysis revealed survival improvement (median survival SRS + WBRT 21 m vs 10.3 m WBRT alone, $P = 0.05$), only in good prognostic patients (GPA 3.5–4).

The above trials categorically proved that local control was improved with the addition of SRS to WBRT. For the purist who does not believe in subgroup analysis, none of the trials showed any improvement in survival with the addition of SRS.

3.3 Surgery Alone Vs Surgery + WBRT

The question of whether one could use focal therapy alone for BM was addressed in a number of clinical trials, focusing on outcomes including survival, neurocognitive function, and QoL. The key findings are summarized in Table 1.

Patchell et al. (1998) conducted the seminal RCT to determine if adjuvant WBRT is beneficial after excision of a single BM. Ninety-five patients with single BM were randomized to WBRT (50.4 Gy in 28 fractions) or observation after surgical resection. The primary endpoint of this trial was intracranial recurrence. WBRT group had reduced intracranial recurrence compared to observation (18 vs 70%, $P < 0.001$). Both local and distant recurrences were reduced by WBRT (10 vs 46%, $P < 0.001$; 14 vs 37%, $P < 0.01$). Although WBRT reduced neurological death, OS was not different. This trial proved that surgery alone for single BM is suboptimal and WBRT can reduce the risk of intracranial failure.

3.4 SRS Alone Vs SRS + WBRT

An early retrospective study addressing this question was published by Pirzkall and colleagues (1998). They performed a retrospective comparison of 236 patients (158 of whom received SRS alone 20 Gy, 78 received SRS 15 Gy followed by WBRT). The OS was not significantly different between both groups; however, for patients without extracranial disease, median survival was improved with WBRT (15.4 vs 8.3 m, $P = 0.08$). There was also a suggestion that higher doses of SRS resulted in improved outcomes. This study is often quoted as the basis to routinely offer WBRT in addition to

Table 1 Randomized Controlled Trials investigating surgery or SRS alone compared to surgery or SRS + WBRT

Author (year)	*N*	Median follow-up	Included patients	Primary endpoint	Local failure	Distant brain failure	Salvage therapy	Survival	Functional outcomes
Surgery vs surgery + WBRT									
Patchell et al. (1998)	95	43 weeks	Single BM KPS ≥ 70	Brain tumor recurrence	10 vs 46% ($P < 0.001$)	14 vs 37% ($P < 0.01$)	NR	48 vs 43 weeks ($P = 0.39$)	NR
Kocher et al. (2011)	160	40 m	1–3 BM ECOG 0–2 Stable systemic disease or asymptomatic synchronous primary	Duration of functional independence (ECOG ≥ 2)	27 vs 59% ($P < 0.001$)	23 vs 42% ($P = 0.008$)	16 vs 51%	10.9 vs 10.7 months ($P = 0.89$)	HRQOL better in observation arm
SRS alone vs SRS + WBRT									
Aoyama et al. (2006)	132	7.8 m	1–4 BM (<3 cm) KPS ≥ 70	OS	88.7 vs 72.5% ($P = 0.002$)	41.5 vs 63.7% ($P = 0.003$)	15 vs 43% ($P < 0.001$)	1 year actuarial survival 38.5% vs 28.4% (SRS alone) ($P = 0.42$)	No difference in MMSE or neurological functional preservation
Chang et al. (2009)	58	9.5 m	1–3 BM RPA 1–2 KPS ≥ 70	Neurocognitive function, measured by HVLT-R total recall at 4 m	67 vs 100% ($P = 0.012$)	45 vs 73% ($P = 0.02$)	0 vs 27%	1 year survival 21 vs 63% (SRS alone) ($P = 0.003$)	HVLT-R total recall mean posterior probability of decline 24 vs 52%
Kocher et al. (2011)	199	40 m	As above	Duration of functional independence (ECOG ≤ 2)	19 vs 31% ($P = 0.04$)	33 vs 48% ($P = 0.023$)	16 vs 51%	10.9 vs 10.7 months ($P = 0.89$)	HRQOL better in observation arm
Brown et al. (2016a)	213	7.2 m	1–3 BM (<3 cm)	Decline in >1SD , at 3 months, from baseline of any 6 cognitive tests	18.4 vs 7.4% at 6 m ($P = 0.034$)	11.6 vs 35.4% at 6 m ($P < 0.0001$)	7.8 vs 32.4% ($P < 0.001$)	Median OS 7.4 vs 10.4 m (SRS alone) (HR 1.02, $P = 0.92$)	Decline in cognition more in WBRT group (31 vs 8%, $P = 0.007$)

SRS. However, this study has several shortcomings, besides its retrospective nature. Patients from this study were treated between 1984 and 1997, when effective systemic therapy was likely unavailable. This is evidenced by the relatively short OS of the entire group (5.5 m). Secondly, the study design allowed either CT or MRI surveillance. As a result, early salvage may not have been instituted in patients who underwent CT surveillance, resulting in a survival difference.

Subsequently, a few prospective trials were conducted to address this question.

Aoyama reported the trial conducted by JROSG 99–1 (Aoyama et al. 2006), for which the primary outcome was OS. Investigators had planned to randomize 178 patients to detect a 30% difference in median survival time with a power of 80%. However, after interim analysis of 122 patients, the trial was terminated early as it was deemed unlikely to detect a difference in survival, and the outcome changed to brain tumor recurrence rate. In the end, 132 patients, with 1–4 lesions, were randomized to SRS alone or SRS plus WBRT (30 Gy in 10 fractions). SRS dose depended on tumor size (22–25 Gy for up to 2 cm, 18–20 Gy for 2–3 cm, dose reduced by 30% in WBRT group). Fifty percent of patients were above 65 years, and up to 50% had active extracranial disease (primary or metastasis). The 1-year survival rate was not different between the 2 arms (38.5 vs 28.4%, $P = 0.42$). As expected, the brain tumor recurrence rate was less with WBRT (46.8 vs 76.4%, $P < 0.001$). As a consequence, the SRS alone group required more salvage procedures (43 vs 15%, $P < 0.001$). However, this did not translate to a significant difference in systemic ($P = 0.53$) and neurological ($P = 0.99$) functional preservation. Unlike the Patchell trial, and despite the higher brain tumor recurrence rates, neurologic death was not reduced with WBRT (22.8 vs 19.3%, $P = 0.64$). The actuarial 12 m local control rates were significantly higher with WBRT (88.7 vs 72.5%, $P = 0.002$). This may be in part attributed to the advantages of fractionation in overcoming radiation resistance.

Neurocognitive testing (not a secondary endpoint) was performed optionally using Mini-Mental State Examination (MMSE) (Aoyama et al. 2007). Of the 82 patients with MMSE scores >27, or whose scores improved to >27 after treatment, there was no difference in the preservation of MMSE rate (log-rank $P = 0.73$ and 0.79, respectively). The average duration before MMSE deterioration was longer in the WBRT group (16.5 m vs 7.6 m, $P = 0.05$). The authors suggested that this difference may be due to the preventive effect on brain tumor recurrence from WBRT. These data also showed that for patients treated with SRS alone, deterioration in MMSE scores from intracranial relapses returned to baseline after salvage therapy compared to treatment-induced deterioration in MMSE score after WBRT plus SRS, which was refractory to medical and other interventions. However, no strong conclusions can be drawn from this. Firstly, the number of remaining patients was exceedingly small (i.e., in total 21 patients at 12 m, 10 patients at 24 m). Secondly, MMSE is a relatively crude and insensitive instrument to detect any change in neurocognitive function. Thirdly, patients for whom no follow-up MMSEs were available were excluded, introducing bias from incomplete outcome data.

A secondary analysis of this trial was published in 2015 (Aoyama et al. 2015). Eighty-eight patients with non-small-cell lung cancer (NSCLC) were post-stratified by disease-specific GPA (ds-GPA), to reduce bias pertaining to underlying histology. Authors report an improvement in survival with the addition of WBRT, for patient with better prognosis (ds-GPA 2.5–4). In this group of 47 patients, median survival was 16.7 m versus 10.6 m ($p = 0.04$). No difference in survival was seen for the group with poorer prognostic scores (DS-GPA 0.5–2), HR 1.05 (95% CI 0.55–1.99). Advocates of routine WBRT would cite this study as evidence that WBRT should be offered to patients with a better prognostic score. Others would argue that irreversible long-term toxicities are most likely in this group of potential long survivors, and hence WBRT should be avoided. Once again, it has to be noted that this is a post hoc analysis based on a small subgroup of patients and is subject to bias.

The EORTC conducted a prospective phase III trial (22952–26,001) (Kocher et al. 2011) comparing the addition of WBRT (30 Gy in 10 fractions) after initial surgery or SRS for patients with up to 3 BM, stable systemic disease, and asymptomatic primary. In total, 359 patients (199 SRS, 160 surgery) were included. The primary endpoint of the trial was time to deterioration of performance status (WHO ECOG >2), and the secondary endpoints included intracranial relapse, PFS and OS, and QoL. Patients with progressive systemic disease were excluded, but restaging scans were not mandated. There was no difference in the median time to deterioration of PS (10 m with observation vs 9.5 m with WBRT, HR = 0.96, $P = 0.71$). There was also no difference in OS (10.9 m vs 10.7 m, HR = 0.98, $P = 0.89$). As anticipated, WBRT reduced intracranial progression at initial sites, as well as distant intracranial sites. However, impact on local progression was more pronounced in the surgical group (59–27%, $P < 0.01$; SRS group 31–19%, $P = 0.04$). There were fewer deaths from intracranial progression in the WBRT arm (44 vs 28%). The lack in difference in OS has been criticized, due to the possible influence of extracranial progression and the absence of systematic restaging scans prior to randomization. However, in support of the trial findings, it has to be noted that the incidence rates of extracranial progression were not different in both arms (63% vs 65%, $P = 0.73$).

QoL results were assessed systematically by EORTC C30 and Brain Tumor Module, with a ≥10 point drop from baseline being considered clinically relevant (Soffietti et al. 2013). Understandably, compliance rates were low at the end of the first year (45%). Overall, patients on the observation arm had improved health-related QOL (HRQOL) scores compared to patients who underwent adjuvant WBRT.

Self-reported HRQOL (compared to a formal battery of neurocognitive tests) is not as sensitive for neurocognitive function per se; nevertheless, HRQOL is an increasingly important endpoint for patients and physicians alike. However, the high noncompliance rate affects the validity of these findings. It is interesting to note that although WBRT reduced intracranial progression, this did not translate into improved HRQOL for the patients. This is likely due to the early detection of asymptomatic relapses and the use of effective salvage therapy.

Chang et al. conducted a single-institution RCT comparing SRS ± WBRT (30 Gy in 12 fractions), for which the primary endpoint was neurocognitive function. This was assessed methodically by Hopkins Verbal Learning Test-Revised (HVLT-R) total recall at 4 months post-treatment (Chang et al. 2009). The trial was stopped early, after 58 patients were randomized as there was a 96% probability that patients undergoing WBRT were significantly more likely to show a decline in learning and memory function. As one would expect, a larger proportion of patients who underwent WBRT were free of CNS recurrence at 1 year (73 vs 27%, $P = 0.0003$). Although this trial was not powered to detect any survival differences, the median survival was worse in the arm undergoing WBRT (5.7 vs 15.2 m). This reason for this survival difference remains unclear, although the WBRT group had a slightly higher incidence of visceral disease (18 vs 7% liver metastasis, 18 vs 10% adrenal metastasis). Critics of this trial also point out that neurocognitive outcomes were measured at a single, and relatively early, time point; therefore, recovery of neurocognitive function after 4 months may not be reflected (Onodera et al. 2014).

Findings from the above trial were corroborated by the NCCTG N0574 (Alliance) trial (Brown et al. 2016a). The highlight of this trial is that it addressed neurocognition (via healthcare staff-administered battery of cognitive tests) and QoL at multiple time points. Two hundred thirteen patients (68% lung primary), with 1–3 BM (50% single lesion), were enrolled from 34 institutions. Patients in the SRS alone received 24 Gy (for lesions less than 2 cm) or 20 Gy (for lesions 2–2.9 cm). Patients in the combined modality arm received WBRT 30 Gy in 12 fractions with SRS 22 Gy (up to 2 cm) or 18 Gy (2–2.9 cm). The primary outcome of this trial was determined if the cognitive progression 3 months post SRS was worse with WBRT. This was defined as a drop by

>1 standard deviation from baseline, in any of the 6 cognitive tests. In keeping with previous studies, WBRT decreased intracranial progression (6 m progression rate 35.4% vs 11.6%, $P < 0.0001$), but did not impact OS (median 10.4 m SRS alone, 7.4 m WBRT + SRS, HR 1.02 $P = 0.92$). Despite having less intracranial progression, there was significantly more cognitive decline at 3 months in the WBRT arm (91.7% vs 63.5%, $p = 0.007$). Interestingly, this difference persisted at 6 months (97.9% vs 77.8%, $P = 0.03$). The specific domains which seemed to be affected include immediate recall (30 vs 8%), delayed recall (51 vs 20%), and verbal fluency (19 vs 2%). There were also significantly worse QoL measures with WBRT, which is in keeping with the EORTC trial findings.

The above studies have provided evidence required for a change in practice. The American Society for Radiation Oncology (ASTRO) has come out strongly to make a recommendation not to routinely add WBRT to SRS, for patients with limited BM, in their Choosing Wisely Campaign (http://www.choosingwisely.org/astro-releases-second-list/). The National Comprehensive Cancer Network (NCCN) has recently revised its guidelines to include SRS alone in this group of patients, for which the upper limit of BM number was left unspecified.

For patients undergoing the SRS alone approach, all trials have indicated that they have a higher incidence of salvage therapy. Therefore, close monitoring, with regular surveillance MRI, is critical. Based on the Aoyama series (Aoyama et al. 2006), only 16% of patients were symptomatic for their recurrences, and early salvage did not result in a difference in neurologic deterioration or death between the 2 arms. In contrast, neurological deficits may not recover fully if detected late. For example, the retrospective single-institution study by Regine et al. (2002) showed that 70% of patients developed symptomatic recurrences (after SRS alone), and this was associated with a 50% neurologic deficit progression-free survival at 1 year. As such, one may interpret that withholding WBRT without close surveillance (and early salvage) does more harm than WBRT itself.

3.5 Surgery vs. SRS

High-quality evidence comparing the two modalities is lacking. Empirically, most practitioners would favor surgery to establish histological diagnosis or obtain a rapid reduction in intracranial pressure. On the other hand, SRS has distinct advantages such as ability to address lesions within eloquent areas, outpatient delivery with minimal downtime, potentially lower costs, and avoidance of surgical and anesthetic risk.

Bindal et al. (1996) reported a retrospective matched comparison between surgical resection and SRS (2:1 matching, 93 patients). Interestingly, the group that underwent surgical resection had twice the median survival (16.4 vs 7.5 m, $P = 0.0016$); and treatment received was a significant factor in multivariate analysis. Local recurrence rates were lower with surgery (21 vs 8%), and the surgical group has a lower chance of death through neurological progression (50 vs 19%). According to the authors, the difference in the two groups was not attributable to the use of WBRT, which was similar in both groups. Although intriguing, the retrospective nature of this study and the lack of matching for tumor size suggest that these results should be interpreted with caution. Moreover, the radiosurgery doses used in these patients were lower than those used in the RTOG studies, which may account for the higher rates of local progression.

On the contrary, Rades et al. (2009) suggested that 1-year OS was improved with the use of SRS + WBRT compared to surgery + WBRT (56 vs 47% $P = 0.034$), for patients with 1–3 BM. Local control rates were also superior in the SRS arm (82 vs 66%, $P = 0.006$).

Owing to the retrospective nature of the above studies (although matching was performed for key factors), patient selection bias may have led to confounding of the results. Unfortunately, there is a dearth of prospective studies addressing the above question.

Muacevic et al. (Muacevic et al. 2008) reported the results of their RCT comparing microsurgery + WBRT (40 Gy) to SRS for patients with single BM (<3 cm). The study was closed prematurely due to poor accrual. At final

analysis, there were 33 patients in the surgical arm and 31 patients in the SRS arm. There were no significant differences in survival, neurological death rate, or freedom from local recurrences between the 2 arms. The SRS alone arm had higher distant recurrences ($P = 0.04$), but this difference was not significant after adjustment for salvage SRS ($P = 0.4$). The conclusions drawn from this trial are limited, due to the lack of statistical power.

Similarly, Roos and colleagues (2011) attempted to conduct a randomized non-inferiority trial to determine whether SRS + WBRT was as effective as surgery + WBRT in patients with solitary BM. However, this trial faced slow accrual which was closed prematurely. Twenty-one patients were analyzed, and the estimated median survival in the SRS arm was 6.2 m compared to 2.8 m (HR 0.53, 95% CI 0.2–1.43, $P = 0.2$). Like the above trial, the lack of statistical power precludes any valid conclusion being made.

3.6 Cavity SRS as an Alternative to WBRT or Observation

Investigators realized that local recurrences continued to be a significant problem after surgical resection of BM (Patchell et al. 1998; Kocher et al. 2011). WBRT was able to reduce local recurrences, but failed to impact OS. Pioneering work for resection cavity SRS was performed by the Stanford group, which suggested that SRS to the resection bed were able to provide similar local control rates without causing the dreaded long-term toxicities. For example, they had retrospectively reported the outcomes of 72 patients (76 cavities) whom underwent SRS (median marginal dose 18.6 Gy) with the resection cavity volume ranging from 0.1–66.8 cm^3 (mean 9.8cm^3) (Soltys et al. 2008). Actuarial control rate at 12 months was 79%, which was comparable to historical WBRT series (80–90%) and superior to observation alone (54%). Surprisingly, the group with the least conformal plan had the best control rates, suggesting that marginal misses through delineation errors, or local tumor infiltration, may be contributory.

A follow-on study was published by Choi et al. (2012). Outcomes of patients treated with resection cavity SRS, with or without a 2 mm margin, were reported retrospectively. One hundred twelve patients (120 cavities) had a 12-month cumulative local failure rate of 9.5% and distant failure rate of 54%. The addition of a 2 mm margin decreased local failure rates from 16% to 3% ($P = 0.042$), without causing more toxicities (3 vs 8%, $P = 0.27$).

A phase II prospective study was conducted at MSKCC (Brennan et al. 2014). Forty-nine patients (50 lesions) with 1–2 BM were enrolled. Forty lesions received postoperative SRS with a median dose of 18 Gy. The cumulative local failure at 12 months was 22%, and regional failure was 44%. Compared to deep brain lesions <3 cm, superficial lesions ≥3 cm had a high local failure rate at 53.3% at 12 months.

Although this is a promising and novel approach, one should be cautious before universal adoption. Two phase III trials were presented at the 2016 ASTRO annual meeting. The first is a prospective randomized trial, from MD Anderson Cancer Center, comparing cavity SRS to observation for completely resected BM (Rao et al. 2016). The primary objective of this trial was local tumor control. One hundred twenty-eight were randomized (63 SRS, 65 observation) with a median follow-up of 13 m. As one would expect, the local control at 12 months was improved with SRS (72 vs 45%, HR 0.46 95% CI 0.25–0.85, $P = 0.01$). However, there was no difference in distant BM (HR 0.79, 95% CI 0.5–1.24, $P = 0.29$) or overall survival (HR 1.22 95% CI 0.79–1.87, $P = 0.37$). The incidence of leptomeningeal dissemination was similar in both arms (HR 1.4, 95% CI 0.6–3.4, $P = 0.46$). The second is NCCTG N107C/RTOG 12-70 trial, which is a multicenter RCT comparing postsurgical SRS to WBRT, where one of four (or fewer) lesions has been resected (Brown et al. 2016b). The primary endpoints are OS and cognitive-deterioration free survival. One hundred ninety-four patients were randomized with a median follow-up of 18.7 m. OS was not different between the 2 arms (11.5 vs 11.8 m, HR 0.93 95% CI 0.66–1.3, $P = 0.65$). However, the arm

SRS had an improved cognitive-deterioration free survival (3.3 vs 2.8 m, HR 2.05, 95% CI 1.51–2.77, $P < 0.0001$). WBRT significantly improved overall intracranial control, compared to SRS alone, but was associated with more toxicities.

4 Does Number Really Matter?

The definition of patients with limited BM has been sought with controversy. The majority of phase III trials (Aoyama et al. 2006; Kocher et al. 2011; Chang et al. 2009; Brown et al. 2016a) only included patients with one to three or four BM. The upper limit of limited BM was set rather arbitrarily for technical reasons. Early trials utilized SRS planning software which lacked sophistication to calculate integral dose from overlapping plans, creating a safety concern for multiple lesions. Moreover, SRS for multiple lesions would have taken prohibitively long using older SRS platforms. Thankfully, modern day equipment (such as flattening filter-free linear accelerators) and planning systems are able to execute the planned treatment efficiently. Guidelines from major societies based their recommendations on level 1 evidence and consequently have only recommended SRS for up to four lesions (Tsao et al. 2012a; Kocher et al. 2014).

Knisely et al. (2010) published the results of a survey done on 149 physicians, from San Francisco and Sendai, practicing SRS. Surprisingly, 55% of respondents from San Francisco would consider treating ≥5 lesions with SRS, and this was even more pronounced for the respondents from Sendai (83% would consider treating ≥5 lesions). As such, it was clear that there was no consensus on the number of BM that is considered suitable for SRS. The question really is, whether BM number alone is a harbinger of worse prognosis?

Karlsson et al. (2009) reported a large multi-institutional retrospective study of 2448 Gamma Knife treatments administered between 1975 and 2007. The survival in patients with a single BM was longer than that of patients with multiple BM (7.5 vs 6.1 m, $P < 0.0001$). However, this difference was lost when adjusted for controlled primary disease. Moreover, there was no difference in survival between patients with 2, 3–4, 5–8, or >8 BM. The use of WBRT did not impact survival (7.4 m with WBRT, 7.0 m without, $P = 0.43$).

Yonsei University group have published their experience with SRS alone for multiple BM ($N = 323$). Patients were divided into four groups based on the number of BM (group 1, 1–5; group 2, 6–10; group 3, 11–15; and group 4, >15 lesions). 2/3 of patients belonged to group 1. Surprisingly, there was no difference in OS between the 4 groups (log-rank $P = 0.554$). However, the probability and time to developing new BM was highest in group 4 ($P = 0.014$).

The best evidence regarding the impact on BM number comes from a recent report from Yamamoto et al. (2014). A large multi-institutional prospective observational study (JLGK0901) was performed to investigate whether SRS (sans WBRT), as the initial treatment, for patients with 5–10 BM was non-inferior compared to 2–4 BM, with respect to OS. Patients with KPS 70 or higher, from 23 centers in Japan, with 1–10 BM were eligible (largest tumor <10 mL, <3 cm in longest diameter; total cumulative volume < 15 mL). Tumors smaller than 4 mL were irradiated to 22 Gy, whereas tumor 4–10 mL received 20 Gy. Of the 1194 patients enrolled, median OS was 13.9 m in 455 patients with one tumor, 10.8 m in 531 patients with 2–4 tumors, and 10.8 m in 208 patients with 5–10 tumors. OS did not differ between the latter two groups (HR 0.97 95% CI 0.81–1.18). This was lower than the prespecified non-inferiority margin of 1.3 ($P < 0.0001$). In terms of treatment-related toxicity, there was no significant difference between the groups (9% in both groups $P = 0.89$). As expected similar to other WBRT avoidance studies, there was a relatively high incidence of new BM (58%), which highlights the crucial importance of regular and systematic surveillance with MRI scans. In toto 9% of patients required salvage WBRT, and this did not differ between groups ($P = 0.48$).

The above study provides the largest body of evidence that BM number alone should not be

used as a strict cutoff. However, there are some limitations which we need to acknowledge.

Firstly, this was not a randomized study, and therefore imbalances in the treatment arms are likely to have confounded outcome. For example, more patients with 5–10 BM had received systemic therapy compared to 2–4 BM. Secondly, robust neurocognitive assessment was not performed in this study.

To date, WBRT is still favored by many practitioners when there are 5 or more brain metastases as there are no completed RCTs supporting the use of focal therapy alone. However, SRS alone is regarded as maybe appropriate for patients with multiple metastases but small volume disease. According to National Comprehensive Cancer Network (NCCN) guidelines, SRS alone in patients with more than 3 metastases is still regarded as a good option if they have good performance status and low overall intracranial tumor volume.

A recently completed multi-institution propensity-matched retrospective study (Halasz et al. 2016) comparing SRS alone to WBRT alone suggests that survival is improved with SRS (adjusted HR 0.58, 95% CI 0.38–0.87) for patients with <4 metastases. This should be interpreted as hypothesis generating and should be confirmed by a randomized clinical trial.

The North American Gamma Knife Consortium NAGKC12–01 (NCT01731704) planned to conduct a RCT comparing WBRT 30 Gy in 10 fractions to SRS alone in patients with >5 BM. Unfortunately, this trial was closed prematurely.

Many reports have suggested that the patient's prognosis is influenced more by tumor volume, rather than absolute number. The earliest report came out of University of Pittsburgh (Bhatnagar et al. 2006), where outcomes of patients with ≥4 BM were published. In multivariate analysis of the 205 included patients, total treatment volume (sum of the volume of all treated BM) turned out to be significant for OS ($P = 0.002$), whereas the number of intracranial metastasis was not ($P = 0.33$). This study provided a hypothesis-generating concept to be explored further.

Likhacheva et al. (2013) and colleagues corroborated this finding in their report. Total tumor volume > 2 cm^3 was a significant predictor of OS (HR 1.98, $P < 0.001$) and local control (HR 4.56). However, the number of BM was not predictive for distant brain failure, local control, nor OS.

From the above reports, it was not clear if total BM volume should be considered as a continuous variable or best used as a categorical variable ($2cm^3$). Baschnagel et al. (2013) attempted to answer this question in their publication, assessing outcomes of 251 patients. The HR of total BM volume (continuous variable) on multivariate cox regression analysis was 1.04 (1.00–1.08, $P = 0.046$). When BM volume was dichotomized to above or below $2cm^3$, HR was 1.5 (1.1–1.93, $P = 0.008$). The number of BM, like in previous reports, was not a significant predictor of OS (HR 1.06 95% CI 0.99–1.13, $P = 0.098$).

One may conclude that the absolute number of BM is an arbitrary cutoff, which is often used, in SRS trials and guidelines. The definition of limited BM is under a state of flux, and focal therapy (with or without WBRT) may be offered to patients with good prognoses.

5 Is There Still a Need for Routine "Adjuvant" WBRT in the Modern Era?

There have been two main theories about the development of BM. The micrometastatic theory suggests that there is no entity such as a solitary BM. Microscopic deposits exist, which are undetectable on imaging, and the routine use of "adjuvant" WBRT enables control of these deposits. The reseeding theory suggests that new BM are deposited, over time, from active extracranial disease. In this scenario, routine "WBRT" adds toxicity without providing benefit.

The previously discussed trials (Aoyama et al. 2006; Kocher et al. 2011; Chang et al. 2009) have provided level 1 evidence that the addition of WBRT improves control of BM (i.e., compartmental control), but had little impact on survival. Meta-analysis is particularly useful tool to pool results of trials, which individually may have been underpowered to detect a survival difference. Two meta-analyses reiterated the effect of

improved compartmental control (by reducing distant and local brain recurrences) (Soon et al. 2014; Tsao et al. 2012b); but neither detected a survival improvement. Sahgal and colleagues went one step further, to conduct an individual patient data meta-analysis (Sahgal et al. 2015) of phase III trials (Aoyama et al. 2006; Kocher et al. 2011; Chang et al. 2009). Three hundred sixty-four patients (with KPS > 70) were included, where 51% were treated with SRS alone and 49% treated with SRS and WBRT. Age was found to be a significant effect modifier for survival (P = 0.04), in favor of SRS alone for patients below 50 years. Within this group, the hazard ratio was death which was incrementally reduced with younger age. No such differences were noted in the group over 50 years. Local control was improved, with WBRT, across both age groups. However, age was once again a significant effect modifier for distant brain failure (P = 0.043). WBRT reduced the risk of distant brain failure in the older group, with incremental benefits seen with increasing age. The authors hypothesized that exposing patients below 50 to the adverse effects of WBRT, without having therapeutic gain, may explain the differences noted in survival. However, this provocative hypothesis requires further validation. It is to be noted that that patients below 50 only made up 19% of the pooled cohort. In addition, there was a higher proportion of patients in this group who had extracranial metastasis (58 vs 68%). Although the total number of deaths was larger in the WBRT group (84% vs 71%), the neurological deaths were lower (22 vs 39%). This may suggest that these patients were perishing due to progressive systemic disease.

Survival aside, WBRT improves compartmental control, but will everyone benefit from it equally? Several groups have suggested a risk-stratified approach to answer this question. Rodrigues et al. (2014) performed recursive partitioning analysis to determine the risk of regional failure (RF) and constructed a clinical nomogram, for patients who had undergone SRS alone (n = 361). Low risk (<25% 1-year RF) were classified as patients with a solitary lesion and above 55 years, intermediate risk (25–40% RF) as patients below 55 years and solitary lesions or WHO PS > =1 and 2–3 lesions, and high risk (>40% RF) as patients with WHO PS = 0 and 2–3 lesions.

A similar study was performed at Wake Forest University (Ayala-Peacock et al. 2014). They analyzed 464 patients, over a 10-year period, treated with SRS alone. Progressive systemic disease, number of metastases, discovery of new metastases at time of SRS, and histology were significant factors predicting time to distant intracranial failure. Among the histological subtypes included, melanoma and HER2-negative breast cancer were deemed to be of higher risk, as compared to HER2-positive breast cancer.

Although these models require external validation, a tailored approach may be suitable for patients deemed to have a high risk of distant intracranial failure. However, even in the high-risk group, it remains controversial if adjuvant WBRT would improve survival outcomes compared to SRS alone with early salvage.

6 What Are the Factors Determining Neurocognitive Function?

Neurocognitive function (NCF) has been increasingly used as the primary outcome in phase III trials in the last decade for a few reasons. Firstly, it has been demonstrated that cognitive function predicts survival (Johnson et al. 2012; Armstrong et al. 2011). Secondly, neurocognitive decline precedes imaging progression (Meyers and Hess 2003). Thirdly, NCF is a critical determinant of QoL (Li et al. 2008; Giovagnoli et al. 2005), and typically a drop in NCF is a harbinger for a drop in QoL. Lastly, it is an outcome that both patients and physicians place emphasis on and enables patients to function within the community and society.

Despite the merits, WBRT has come under scrutiny due to the increasing number of reports about its potential long-term, and often irreversible, effects on NCF. The first of these reports by DeAngelis et al. (1989) reported an 11% rate (5 of 47) of dementia at 1-year post-WBRT in survivors

without brain recurrence. The true incidence of neurocognitive dysfunction was not clear from this publication. Arguably, the incidence may be lower as all five patients received large fraction sizes (>3 Gy) and radiosensitizing agents. On the contrary, this was a retrospective case-finding methodology, and it is likely that only the severe cases would have been picked up. More recently, diffuse radiological periventricular white-matter changes have been reported to occur more frequently with WBRT (71.5%) than SRS (6.7%, $P < 0.0001$) (Stokes et al. 2015). Progressive white-matter changes have been correlated to neurocognitive decline, although not in the setting of radiation injury (Defrancesco et al. 2013; Hulst et al. 2013).

To be objective, NCF decline, albeit being negatively linked to WBRT, is multifactorial. Medications (such as steroids, chemotherapy), underlying psychosocial issues (such as fatigue, anxiety, depression), location and volume of underlying BM, and baseline NCF are likely suspects influencing eventual NCF. It is, however, not clear which of these factors has a higher attributable risk to NCF.

6.1 Intracranial Control Is Important for Neurocognitive Function

Evidence for the above came from an RTOG trial (Meyers et al. 2004) examining the addition of motexafin gadolinium to WBRT in patients with BM. This was the first collaborative trial to systematically examine NCF. 90.5% of patients had impairment of one or more neurocognitive tests at baseline, reiterating the fact that BM itself causes impairment in cognition. They found that impairment correlated with brain tumor volume but not number of BM, and predicted survival. Needless to mention, patients with progressive disease on MRI at 2 months continued to have neurocognitive deterioration. Surprisingly, even patients with partial response continued to have deterioration in most of the neurocognitive domains (except trail A and B tests). This may suggest that in addition to intracranial control, other factors (including WBRT) may contribute to the declining NCF. One shortcoming of this trial is that it failed to report outcomes beyond 2 months.

Another publication stemming from the above trial (Li et al. 2007) evaluated NCF in long-term survivors from the control arm (WBRT alone). One hundred thirty-five patients were assessable at 2 months and were dichotomized into good and poor responders. Time to NCF deterioration was improved among good responders, with significance seen in executive function and fine motor skills (but not memory). The differential impact on the various neurocognitive domains suggests that WBRT may particularly impair hippocampal-related functions such as memory and learning. This report suggested that disease progression was the main contributor to neurological decline. However, one has to note that all patients received WBRT in this trial, and it does not categorically answer the question about the harms of WBRT.

The last piece of evidence in support of this notion was from RTOG 9104 trial (Regine et al. 2001). This trial compared accelerated hyperfractionation to a standard treatment WBRT (30 Gy in 10 fractions) in 445 patients, of which 359 had MMSE performed. At 2 months, MMSE dropped 0.6 for patients with radiologically controlled BM, compared to 1.9 to those with uncontrolled BM ($P = 0.47$). However, at 3 months this was 0.5–6.3 ($P = 0.02$). Although this gives credence to the argument that uncontrolled BM leads to a decline in MMSE, the authors did not elaborate how radiological response was classified nor if the assessors were blinded.

6.2 WBRT or Intracranial Control?

The take-home message from the above reports is that failure to adequately control macroscopic disease leads to local intracranial progression, which in turn negatively impacts NCF and survival as a result of neurologic death. What remains unclear is the relative contributions of neurocognitive decline, between WBRT and intracranial progression.

In order to de-convolute the two competing risks, it is imperative that the scenario where

there is no macroscopic disease at baseline (i.e., prophylactic cranial irradiation PCI) should be examined. Gregor et al. (1997) assessed the impact of PCI in patients with limited-stage small-cell lung cancer. The authors failed to find a difference (at 1 year) between the two groups (PCI and no PCI). The PCI group was more likely to have worse verbal memory and sustained attention, although statistical significance was not reported. It is hard to draw conclusions from this study, in the absence of statistical reporting. Moreover, a wide range of PCI doses were allowed (physician's discretion), including 8 Gy in 1 fraction (13%).

A more contemporary phase III trial is RTOG 0214 comparing PCI (30 Gy in 15 fractions) versus observation in patients with locally advanced NSCLC (Gore et al. 2011; Sun et al. 2011). The primary endpoint was OS, and the secondary endpoints included NCF and QoL (measured using HVLT, MMSE, and activities of daily living scale). This trial was underpowered, as only 356 of the targeted 1058 patients were accrued. As a result, there was no difference in OS (HR 1.03 95% CI 0.77–1.36). However, the 1-year rates of BM were significantly different at 7.7 vs 18% (P = 0.004). Intuitively, from the above arguments, one would expect the group with less BM to have improved NCF and QoL. There was no statistically significant difference in QoL between the two arms; however, there was a trend for greater decline in patient-reported cognitive functioning with PCI. There was also a greater decline in HVLT in immediate recall (P = 0.03) and delayed recall (P = 0.08) in the PCI arm at 1 year. Therefore, in the absence of intracranial progression, these differences may be attributed to the treatment, namely, WBRT, rendered.

7 Management of BM in Patients with Poor PS or Asymptomatic Patients

There is significant equipoise about how best to treat patients with BM with a poor PS (KPS <50). Options include supportive care (with corticosteroids) or WBRT. The use of SRS for patients with poor PS is more controversial, with no RCT including patients with KPS <70.

Nieder et al. (2013) performed a matched retrospective analysis, involving 113 patients (median KPS 60, 80% RPA 3). Forty-one patients received supportive care alone, 41 patients received WBRT 30 Gy in 10 fractions, and 31 patients received WBRT 20 Gy in 5 fractions. The median survival of all patients was 2 months. There was no significant difference between BSC and WBRT 20 Gy; however WBRT 30 Gy had a marginally longer survival compared to BSC (2.2 vs 1.7 months, P = 0.002). Further subgroup analysis revealed that the difference in survival was limited to a patient with primary small-cell lung cancer.

Based on historical series data, it is a common assumption that WBRT improves survival compared to BSC. There has been only one randomized trial (Horton et al., 1971) (in the pre-CT era) comparing WBRT to BSC. Forty-eight patients with the presumptive diagnosis of BM were randomized to steroids with or without WBRT 40 Gy. The addition of WBRT improved survival (14 vs 10 weeks, P not reported) and duration of remission. More recently, the QUARTZ trial set out to answer this question.

The QUARTZ trial is a randomized, non-inferiority, phase III trial comparing optimal supportive care (OSC) alone to WBRT (20 Gy in 5 fractions), in patients with inoperable BM from non-small-cell lung cancer. The primary endpoint is improvement in quality-adjusted life years (QALY). This trial initially suffered poor accrual and the interim data was released (Langley et al. 2013). Fortunately, the trial met its target accrual and mature results were published (Mulvenna et al. 2016). Notably, about 40% of the patients had KPS <70, and 80% had GPA score of 2 or less. Median survival was not different between the 2 arms (49 vs 51 days, HR 1.06 95% CI 0.9–1.26). QALY was also not different (46.4 vs 41.7 days). Median dose of dexamethasone was also similar between both arms (8 mg). Subgroup analysis suggested that younger patients and patients with better performance status and controlled systemic disease may benefit from WBRT. One must note the characteristics of the

included patients – a sizeable proportion of the patients were of poor performance status and all were unsuitable for surgery or SRS. As such, in patients with poor prognosis, supportive care is not much worse than WBRT in terms of survival, QoL, or QALY.

As mentioned earlier, the use of SRS in poor PS patients is controversial. Sanghavi et al. (2001) published a large retrospective series (502 patients from 10 institutions) where both SRS and WBRT were used. Patients were stratified according to RPA, and survival was significantly different between groups (RPA 1 16.1 m vs RPA 2 10.3 m vs RPA III 8.7 m, $P < 0.001$). These results were significantly better compared to survival of historical cohorts treated with WBRT alone (7.1 vs 4.2 vs 2.3 m, $P < 0.05$). The conclusion from this study was that the survival benefit, from SRS, was not restricted to RPA class. However, one has to interpret this conclusion cautiously, as patient selection bias would have confounded the results of this retrospective series.

7.1 Asymptomatic Patients

The use of high-resolution fine-slice MRI technology has enabled us to detect BM prior to patients developing symptoms. The incidence of asymptomatic BM has been reported to be as high as 18% at diagnosis (Kim et al. 2005).

Most of the evidence in the management of asymptomatic BM comes from NSCLC. Kim et al. (2010) reported the outcome of 135 patients with newly diagnosed NSCLC and asymptomatic synchronous BM. Of these, 78 (57.8%) received upfront chemotherapy, 27 (20%) received WBRT followed by chemotherapy, and 24 (17.8%) received SRS followed by chemotherapy. There was no significant difference in OS among the three groups (13.9 vs 17.7 vs 22.4 m, $P = 0.86$). However, subgroup analysis of adenocarcinoma patients (110 patients) had significant survival gains with SRS (29.3 m) compared to WBRT (17.7 m, $P = 0.01$) or chemotherapy alone (14.6 m, $P = 0.04$). Of note, only about 11% of patients were treated with tyrosine kinase inhibitors, TKI (like gefitinib or erlotinib). This study did not report EGFR mutation status, and it is unclear if these results are applicable to that group.

This led to a phase III RCT (Lim et al. 2015) comparing SRS to observation in patients with asymptomatic BM (up to 4) from NSCLC. Unfortunately, the study closed early due to poor accrual. There were 49 patients in both arms, which was balanced for both GPA and EGFR mutation status (30%). There was no difference in OS between the SRS (14.6 m) and the observation group (15.3 m, $P = 0.418$). As expected, the intracranial local progression-free survival was prolonged in the SRS group (not reached vs 10.2 m, $P < 0.001$). Of interest, the overall response rate (ORR) in the upfront chemotherapy group was 37%. Although this study is underpowered, the lack of survival difference may also be attributed to the effective salvage therapy used in both groups.

8 What Is the Role of Systemic Therapy in Patients with BM?

Historically, systemic therapy has mainly been used as the upfront choice for highly chemosensitive malignancies (e.g., germ cell tumor, small-cell lung carcinoma). Emerging data from trials (such as the one above (Lim et al. 2015)) have offered the option for upfront chemotherapy in asymptomatic BM from NSCLC.

There are two main obstacles for the use of systemic therapy in BM: firstly, the intrinsic chemosensitivity of the lesion and, secondly, the blood-brain barrier permeability of the chemotherapy agent. Although BM cause variable amounts of blood-brain barrier breakdown, as evidenced by contrast enhancement on imaging, the concentration of these agents within the brain is unpredictable.

Conventional chemotherapy has not made much progress in phase III trials. For example, topotecan and carboplatin given in combination with WBRT failed to show a survival advantage over WBRT alone in patients with BM from NSCLC (Neuhaus et al. 2009; Guerrieri et al.

2004). Temozolomide and thalidomide for BM from melanoma failed to show any improvement (Krown et al. 2006).

However, targeted therapies (small-molecule inhibitors and monoclonal antibodies) have shown promise in the management of BM. When targeted agents are able to effectively control micrometastatic disease, the need for WBRT can potentially be obviated. For example, lapatinib has been shown to prevent new BM (Cameron et al. 2008) and is active against established BM (Lin et al. 2009; Bachelot et al. 2013). A meta-analysis by Soon et al. (Soon et al. 2015) indicates the response rate of tyrosine kinase inhibitors in EGFR-mutant patients with BM to be in the range of 83% (95% CI 76–91%). The use of dabrafenib (Long et al. 2012) and vemurafenib (Dummer et al. 2014) in BM from BRAF-mutant melanoma shows response rates ranging from 30% to 39%. However, sunitinib was reportedly ineffective against BM from renal cell carcinoma (Chevreau et al. 2014).

The combination of targeted therapy and radiation has been explored in many completed and ongoing trials. An early trial, which failed to accrue completely, was the RTOG 0320 trial (Sperduto et al. 2013). One hundred twenty-six patients with NSCLC primary and 1–3 BM were randomized into WBRT+ SRS, WBRT+ SRS + temozolomide, and WBRT + SRS + erlotinib. Temozolomide or erlotinib was offered in the adjuvant setting up to 6 months after the completion of radiation. The median survival between the groups was not significantly different likely due to the lack of power (13.4 m vs 6.3 m vs 6.1 m). Combination therapy has caused grade 3–5 toxicities to be significantly higher with systemic therapy.

Contrary to the findings of RTOG 0320, Welsh et al. (2013) found no significant added toxicity when erlotinib was added to WBRT in their single-arm phase II study. Moreover, the response rate was 86%, and patients had improved survival with combination therapy compared to historical controls.

The combination of SRS with targeted and immune systemic therapies has been increasingly utilized and reported. For instance, SRS has been combined with ipilimumab (anti-CTLA4) demonstrating to improve median survival from 4.9 to 21.3 m (Knisely et al. 2012). Anti-PD-1 agents with SRS have been shown to improve lesional response further, but its impact on survival is still unknown (Qian et al. 2016). For BRAF V600E-mutant patients, the combination of SRS and vemurafenib was potent with 75% patients responding and nearly half having a complete response (Narayana et al. 2013).

A comprehensive review of this topic is beyond the scope of this chapter. Although impressive response rates (mostly radiological) have been observed, further phase III trials are needed to see if this translates into improved survival as the only two phase III trials have failed to demonstrate any survival benefit with combination treatment (Sperduto et al. 2013; Lee et al. 2014). As radiation therapy is combined with targeted and immune systemic therapies that have shown activity in the brain, better synergy may be noted for improved survival benefit. However, increased toxicity may also be seen and combination treatment needs further study.

9 What Are the Ways to Mitigate WBRT Toxicity?

Investigators have spent much effort to evaluate methods that may reduce the long-term impact of WBRT, with particular attention to neurocognition and QoL.

Parallels were drawn between the pathophysiology of vascular dementia and changes seen post-WBRT. The vascular hypothesis of radiation damage implicates radiation-induced atherosclerosis and microangiopathy, which ultimately leads to small infarcts secondary to vascular insufficiency. The N-methyl-D-aspartate (NMDA) receptor is involved in learning and memory. Ischemia can induce excessive NMDA stimulation leading to excitotoxicity. It was hypothesized that agents that block the NMDA receptor may protect against further damage. Memantine, an NMDA receptor antagonist, was investigated in the RTOG 0614 trial (Brown et al. 2013). This double-blind, placebo-controlled

trial randomized 554 patients into WBRT (37.5 Gy in 15 fractions) with memantine (for 24 weeks) or placebo. Patients were assessed with a battery of neuropsychological tests including HVLT, COWA, and MMSE. The primary endpoint was preservation of cognitive function, particularly HVLT-R, at 24 weeks. Compliance on both arms was equally poor (only about 30% completed 24 weeks). Notably, only 149 were analyzed at 24 weeks as a majority had died (34%) and some withdrew consent (11%). There was a trend toward less decline in HVLT-R in the memantine arm (median decline of 0) compared to the placebo arm (median decline −0.9) at 24 weeks; however, this was not statistically significant (P = 0.059). Considering only 149 patients were available for analysis, this results in a mere 35% statistical power. Patients in the memantine arm had a longer time to cognitive decline (HR 0.78, 95% CI 0.62–0.99, P = 0.01) and lower probability of cognitive failure at 24 weeks (53.8 vs 64.9%).

Donepezil, a selective oral acetylcholinesterase inhibitor, increases acetylcholine signaling by slowing its synaptic degradation. Rapp et al. conducted a phase III placebo-controlled randomized trial (Rapp et al. 2015) investigating the role of donepezil (for 24 weeks) in patients who have undergone cranial irradiation. Overall, the composite scores did not vary between groups (P = 0.48). However, the donepezil group fared better in terms of memory, motor speed, and dexterity.

Besides pharmacology, the other approach to mitigate neurocognitive decline has been through hippocampal avoidance. Neural stem cells, located in the subgranular zone of the hippocampal dentate gyrus, have been associated with the formation of new memory. Radiation injury to these stem cells has been hypothesized to be the central cause of early cognitive decline. Hippocampal avoidance is a feasible strategy due to 2 reasons. Firstly, the incidence of perihippocampal BM has been reported to be low at 8.6%, based on retrospective data from 2 institutions involving 371 patients (Gondi et al. 2010a). Secondly, modern techniques, such as intensity-modulated radiotherapy, volumetric-modulated arc therapy, and helical tomotherapy, enable effective sparing of the subgranular zone of the hippocampus (Gondi et al. 2010b). This led to a single-arm phase II trial, RTOG 0933 (Gondi et al. 2014). This trial completed accrual faster than anticipated, despite the extensive credentialing required, suggesting the widespread interest to mitigate treatment-related toxicity. One hundred thirteen patients were treated with HA-WBRT 30 Gy in 10 fractions, and subjected to standardized cognitive function and QoL assessments. The primary endpoint was HVLT-R at 4 months. The mean relative decline in HVLT-R from baseline to 4 months was 7%, which was significantly lower than historical control ($P < 0.001$). These promising results have opened the door for ongoing phase III trials. For example, NRG CC001 is evaluating the combination of memantine to HA-WBRT. NRG CC003 is investigating the role of HA-WBRT for PCI in small-cell lung cancer.

10 How should We Treat Patients with Leptomeningeal Dissemination?

Leptomeningeal (LM) dissemination occurs in approximately 5% of patients with cancer. LM is more common with lymphoma, leukemia, breast cancer, lung cancer and melanoma. The overall prognosis is very poor, with the average survival being 4–6 weeks without therapy (Grossman and Krabak 1999). Few advances have been made in the treatment of LM in the past several decades. The goals of treatment in patients with LM are to improve QoL, by slowing or reversing the neurological deficits. Prolonged survival may be occasionally seen with endocrine-receptor positive breast cancer. Factors that influence treatment choice include performance status, presence of fixed neurological deficit and systemic tumor burden. Patients deemed to be of good prognosis, based on the multifocal nature of LM, may benefit from chemotherapy (intravenous, or intracerebrospinal fluid (CSF)). Best supportive care, with corticosteroids, and/or radiotherapy (to

symptomatic sites) is usually recommended for patients with poor performance status and multiple fixed neurological deficits.

10.1 Chemotherapy

The majority of the systemic agents fail to achieve cytotoxic concentrations within the CSF. Exceptions include high-dose intravenous methotrexate, cytarabine and thiotepa. However, toxicity stemming for high doses, and possible intrinsic resistance of underlying malignancy, limits the widespread use of these agents. Intra-CSF chemotherapy (via lumbar puncture or Ommaya reservoir) may be used to address the entire neural axis while having minimal systemic toxicity. The main agents which can be given intrathecally include methotrexate, thiotepa, cytarabine, and liposomal cytarabine. There is no strong evidence regarding the choice of these agents, except in lymphomatous neoplasms where liposomal preparation of cytarabine was shown to have a higher response rate and improved KPS (Glantz et al. 1999a). In solid malignancies, depot cytarabine has been shown to have a comparable response rate to methotrexate and increasing time to neurological progression (Glantz et al. 1999b). However, before the administration of intrathecal chemotherapy, one must ensure the patency of CSF flow (by radionuclide cisternogram). CSF blockage hampers the uniform distribution and may lead to increased neurotoxicity, secondary to pooling of chemotherapeutic agents. On occasion, limited-field radiotherapy may be utilized to overcome areas of CSF obstruction. Intrathecal targeted agents such as trastuzumab targeted at HER2neu + for patients with breast cancer may have more promising results though limited data currently (Zagouri et al. 2013).

10.2 Radiotherapy

Intrathecal chemotherapy is limited by its penetrability into deep tissue and thus has limited efficacy for nodular or bulky lesions. As such, external beam radiotherapy has a role in palliating symptomatic sites and areas of bulky LM disease. Cranio-spinal irradiation is used infrequently, due to the lack of survival benefit (Hermann et al. 2001) and significant acute toxicities (such as myelosuppression, odynophagia, mucositis, and nausea).

Classically, WBRT in the setting of LM covers the reflections of the meninges. Particular attention is paid to the cribriform plate, reflections along the optic nerve, inferior extent of temporal meninges, and exit regions of cranial nerves III, IV, V, and VI. Classic teaching recommends that the inferior edge of the field be at the C2/C3 junction; however, this does not stem from strong evidence. This likely originated in the pre-CT planning era, where prophylactic cranial irradiation was used for acute lymphoblastic leukemia (Krepler et al. 1975).

11 How Should We Prognosticate Patients with BM?

Forecasting the survival of patients forms the basis of decision-making and helps to streamline treatment recommendations. Patients who are expected to have a limited survival are unlikely to benefit from overly aggressive management. Unfortunately, doctors have been notoriously poor at prognostication. A prospective cohort study by Christakis et al. (Christakis and Lamont 2000) showed that merely 20% of doctors were accurate (within 33% of actual survival). The same study showed that most predictions (63%) were overestimates (usually by 5 times).

Karnofsky performance status (KPS) is often used as a yardstick, to estimate patient's prognosis. This is rightfully so, as KPS has emerged as a significant factor predicting survival on many prognostic indices. However, there can be significant inter-assessor variability when determining a patient's KPS. For example, Hutchinson et al. (1979) reported an inter-rater agreement of only 29%. However, this may have been spuriously low as this study was performed in the emergency room on hemodialysis patients. Sorensen et al.

(Sorensen et al. 1993) performed a single-center study, involving 100 consecutive cancer patients, assessing the reliability of the ECOG scale. Only moderate agreement was found between the 3 observers (Kappa 0.44 95% CI 0.38–0.51). Fortunately, agreement with regard to allocation of patient's PS 0–2 versus 3–4 was high.

More relevant to this chapter, Kondziolka et al. (2014) performed an interesting prospective study. Data of 150 consecutive cancer patients with BM undergoing SRS were recorded (including histology, number of BM, extracranial disease status, age, KPS). Eighteen cancer specialists (neurosurgeon, radiation oncology, medical oncology) were asked to prognosticate the survival of these patients. In patients who died within 10 months of SRS (median survival 4.2 months), the predictions of neurosurgeons (8.7 m), radiation oncologists (8.3 m), and medical oncologists (7 m) were all overoptimistic. Of the 2700 predictions, 1226 (45%) were off by more than 6 months and 488 (18%) were off by more than 12 months.

Many models have been developed to aid clinicians in prognosticating survival of this group of patients. The earliest of these was the recursive partitioning analysis (RPA) model (Gaspar et al. 1997). This was based on 1200 patients, entered into 3 consecutive RTOG trials, from 1979 to 1993. This statistical method, based on 18 pretreatment characteristics and 3 treatment-related variables, provided 3 classes. RPA class I patients (median survival 7.1 months) were less than 65 years, had a KPS of at least 70, and had controlled primary tumor with the brain-only metastasis. RPA class III patients (median survival 2.3 months) had a KPS less than 70. RPA class II (median survival 4.2 months) consisted of all other patients who did not fit into the other classes. The strengths of the RPA classification are that it has been validated in a prospective trial (Gaspar et al. 2000) and that it was easy to use in the clinics. However, it does come with several limitations. Firstly, the vast majority of these patients have unresectable and/or multiple metastases. Secondly, all the patients included in this analysis received WBRT, and therefore the effect of focal therapy is not reflected. Thirdly, the trials were conducted prior to the advent of effective imaging modalities and systemic therapy, affecting its generalizability to the modern era. Moreover, majority of patients would fall into class II, which tends to be heterogeneous and does not provide discriminatory power.

The RTOG 95-08 trial (Andrews et al. 2004) reported a survival benefit with additional SRS (to WBRT) for patients with solitary BM, but not for 2 or 3 BM. As such, number of BM was thought to be an important prognostic factor, based on that trial. Moreover, the RPA classification required an estimation of systemic disease control, which can be highly varied due to interpretation bias and imaging modalities used.

The graded prognostic assessment (GPA) model ($n = 1960$, including 328 from the RTOG 9508 trial) was conceived to include number of lesions, in addition to age, KPS, and extracranial disease (binary format) (Sperduto et al. 2008). The sum of each of these four factors (scored 0, 0.5, or 1) will be utilized to classify patients into four groups (0–1, 1.5–2.5, 3, 3.5–4). The respective median survival was 2.6 m, 3.8 m, 6.9 m, and 11 months ($P < 0.0001$).

However, owing to the heterogeneous nature of BM patients, there was still equipoise regarding the optimal treatment. Clearly, primary tumor histology influences the behavior of the secondary intracranial lesions and treatment response. A more recent model, through a multi-institutional effort involving 4259 patients, has been formulated (Sperduto et al. 2010, 2012). The diagnosis-specific GPA (DS-GPA) evaluated patient outcomes by diagnosis and treatment rendered and correlated the GPA scores by diagnosis. Prognostic factors for survival were determined for each primary site, and only statistically significant ones were used to determine the DS-GPA score. NSCLC patients form the majority (44.3%), followed by breast (15.1%) and melanoma (11.3%). Table 2 lists the prognostic factors (by diagnosis group) as well as the estimated median survival. Outcomes were also influenced by treatment rendered. For example, in NSCLC, all treatments were considered superior to WBRT alone; in breast cancer, WBRT + SRS/surgery, surgery + SRS, or a combination of these is

Table 2 Diagnosis-Specific GPA

GPA scoring criteria								Median survival (m)
	0	0.5	1	1.5	2	3	4	
Non-small cell and small-cell lung cancer								
Age(y)	>60	50–60	<50					GPA 0 – 1 = 3 GPA 1.5 – 2 = 5.5 GPA 2.5 – 3 = 9.4 GPA 3.5 – 4 = 14.8
KPS	>70	70–80	90–100					
ECM	Present	–	Absent					
No. of BM	>3	2–3	1					
Melanoma								
KPS	<70		70 – 80		90–100			GPA 0 – 1 = 3.4 GPA 1.5 – 2 = 4.7 GPA 2.5 – 3 = 8.8 GPA 3.5 – 4 = 13.2
No. of BM	>3		2–3		1			
Breast cancer								
KPS	<50	60	70–80	90–100				GPA 0 – 1 = 3.4 GPA 1.5 – 2 = 7.7 GPA 2.5 – 3 = 15.1 GPA 3.5 – 4 = 25.3
Subtype	Basal		Luminal A	Her-2	Luminal B			
Age(y)	>=60	<60						
Renal Cell Carcinoma								
KPS	<70		70 – 80		90–100			GPA 0 – 1 = 3.3 GPA 1.5 – 2 = 7.3 GPA 2.5 – 3 = 11.3 GPA 3.5 – 4 = 14.8
No. of BM	>3		2–3		1			
GI Cancers								
KPS	<70		70		80	90	100	GPA 0 – 1 = 3.1 GPA 2 = 4.4 GPA 3 = 6.9 GPA 4 = 13.5

superior to WBRT alone (however, SRS alone was not statistically superior to WBRT). This model provides a more granular assessment of patient outcome and helps to refine decision-making in the clinics. This colossal multi-institutional effort has to be lauded; however, one has to keep in mind that this is based on retrospective data which is prone to patient selection bias.

A nomogram for individualized estimation of survival based on 7 RTOG trials (n = 2367) (Barnholtz-Sloan et al. 2012). The rationale for this stemmed from the wide distribution of survival seen within each RPA class or DS-GPA score group. The nomogram provides survival estimates at median, 6 m and 12 m. Such a personalized tool is especially useful in the clinic for counselling patients on clinical outcomes and prognosis. However, this nomogram has yet to externally validated. Moreover, the data was derived from trials spanning many years (1979–2001), where effective systemic therapy and/or SRS may not have been utilized. As such, this may lead to an underestimate of survival of patients in the modern era.

12 Should We Consider the Cost-Effectiveness of Each Strategy?

Many policy makers and administrators have started to emphasize on value-based medicine. From a societal perspective, resources of spent on healthcare have to be seen in the context of quality-of-life years gained from a particular treatment. This is especially pertinent to patients with BM. A WBRT for-all strategy may be cheap and easy to implement, but the survival detriment (WBRT without surgery/SRS) in patients with limited BM has been categorically proven. SRS for patients with multiple BM will come under scrutiny, as there may be conflicts of interest stemming from the fee-for-service payment model. Furthermore, the costs incurred from the treatment and/or regular and frequent surveillance MRI, let alone salvage procedures, can be considerable. Do the benefits justify the costs? What is the threshold we are willing to pay for an additional of year of life? This may vary between countries and between perspectives (patient's perspective, payer's perspective, or societal perspective). Costs incurred may be indirect – i.e., additional time off-work or inability to be economically productive, increased care required, costs from frequent imaging, or costs from commuting to tertiary centers for healthcare. Comparing treatment cost alone, though this may vary widely, patients treated with SRS may be paying 2.2 more compared to those without (Halasz et al. 2013). Data from the 2008 non-Medicare charges indicate that a course of WBRT ranged from $9201 to 17,003; in contrast, SRS charges ranged from $40715 to 65,000 (Tsao et al. 2012c).

Cost-effective analysis (CEA) in the setting of BM has been very sparse. Research into this area is desperately needed, to form the basis of our fiscally prudent recommendations.

12.1 Surgical Resection vs SRS

Mehta et al. (1997) conducted a CEA comparing resection or SRS (with adjuvant WBRT), to WBRT alone for patients with single BM. Information was obtained from RCT, as well as multi-institutional retrospective data (1989–1994). Surgery was reported to be 1.8 times costlier than SRS. The SRS strategy was the most cost-effective: the average cost per week of survival being $310 for WBRT alone, $524 for surgery plus WBRT, and $270 for SRS plus WBRT. This study was one of the first evaluating cost-effectiveness in the context of radiation oncology. However, the cost derivation was from a retrospective review of single-institution billing data. Secondly, patient-related factors are likely to have been uncontrolled resulting in severe bias of outcomes, in favor of the surgery/SRS arms. Thirdly, the cost of follow-up and late complications was not considered for this study (presumably more in the surgery/SRS arms).

Similarly, Vuong et al. conducted 2 CEA comparing surgical resection to SRS (Vuong et al. 2012, 2013). One was based on a patient's perspective from a lower-income country (Vietnam), and the other based on the perspective from the German statutory health insurance system. In both settings, SRS was deemed to be more cost-effective than surgical resection.

12.2 SRS With or Without WBRT

The MD Anderson group performed a CEA (Lal et al. 2012), comparing SRS with or without adjuvant WBRT, from a healthcare institution perspective (based on the Chang trial (Chang et al. 2009)). The observation arm had a higher average cost ($119,000 compared to $74,000). This included costs from salvage therapy for recurrences, which was higher in this arm. However, as we know, the observation arm had a longer survival (1.64 life-years saved (LYS) versus 0.6 LYS). This equated to $41,783/QALY, for the observation arm. Even with sensitivity analysis, this strategy was more cost-effective, up to a willingness-to-pay threshold of $100,000/QALY.

Hall et al. conducted a CEA comparing SRS alone, SRS + WBRT, and surgery + SRS (Hall et al. 2014). Based on this retrospective study, there was no difference in OS (9.8, 7.4,

10.6 months). As before, the SRS alone required for salvage procedures. Despite that, the average cost per month of median survival favored the SRS alone strategy ($2412 (SRS), $3220 (SRS + WBRT), $4360 (surgery + SRS)).

Savitz et al. (2015) performed a base-case CEA comparing WBRT, SRS (with salvage), HA-WBRT, or a combination of these in a hypothetical cohort of patients (1–3 BM) expected to survive between 3 and 24 months. They reported that traditional treatments (WBRT, SRS alone) remained cost-effective for patients surviving between 3 and 6 months, whereas HA-WBRT and SRS + HA-WBRT became more cost-effective in longer survivors. This study demonstrates the cost-savings of mitigating late toxicity in potential long survivors.

It remains to be seen if SRS to multiple lesions (>4), compared to WBRT, is a cost-effective option and more studies are needed in this area.

13 What Is the Impact of Histology of Underlying BM?

Historically, majority of BM trials have not restricted participants to a specific primary tumor site. As a result, varying histologies have been placed into the same basket. These trials were understandably designed to maximize patient accrual. Moreover, WBRT doses were determined more by tolerance of normal brain parenchyma, rather than underlying histology. Typically, non-small-cell lung cancer patients make up to 50% of the trial participants, with the 2nd largest group either being breast cancer or melanoma.

Over the years, we are aware that the natural history of each disease is unique. Even within a particular histological group, there exists remarkable heterogeneity due to different molecular subtypes and their varying responsiveness to treatments. For example, a patient with a luminal B subtype breast cancer has a drastically improved prognosis compared to a patient with basal subtype (Sperduto et al. 2012). Moreover, the onslaught of targeted therapies has changed the landscape within the oncology clinic, especially for those with targetable driver mutations (e.g., gefitinib for EGFR-mutant lung cancer).

As such, we need to have a more granular assessment of patients presenting with BM. DS-GPA provides some evidence that the underlying histology influences prognosis (Sperduto et al. 2010). However, the heterogeneity of enrolled patients, and the lack of molecular subtypes, hampers the identification of prognostic factors.

As alluded to earlier, Nieder et al. (1997) have demonstrated the complete remission rates differed by underlying histology when WBRT was applied. Certain histological types are thought to be more "radioresistant" than others. The ECOG 6397 phase II trial (Manon et al. 2005) evaluated the utility of SRS alone in patients with 1–3 BM from renal cell carcinoma, melanoma, and sarcoma. These are traditionally thought to be more radioresistant. Doses were selected by tumor size and ranged from 15 to 24 Gy. The infield failure rate was 32.2%, at 6 months, which is relatively higher than other series (Flickinger et al. 1994). Chang et al. (2005) reported a retrospective series (n = 189) over a 10-year period. The 1-year freedom from progression was 64% for renal cell carcinoma, but much lower for melanoma (47%) and sarcoma (0%) patients.

Moving forward, we will need to design clinical trials with an enriched cohort of patients from selected histological groups, where molecular subtyping and driver mutation status is available. This will allow us to elucidate the true impact of BM-directed treatment for that particular histology.

14 Response Assessment and Follow-Up

There can be substantial variation in the interpretation of response for a patient with BM. Factors contributing to this variation include modality and frequency of assessment, the magnitude of change, and (lack of) ability to differentiate between tumor-related and treatment-related changes. Furthermore, patients treated with SRS

Table 3 Summary of recommendations by RANO-BM group

	Complete response	Partial response	Stable disease	Progressive disease
Target lesions	None	≥30% decrease in sum longest distance relative to baseline	<30% decrease relative to baseline but >20% increase in sum longest distance relative to nadir	≥20% increase in sum longest distance relative to nadir
Nontarget lesions	None	Stable or improved	Stable or improved	Unequivocal progressive disease
New lesion(s)[a]	None	None	None	Present
Corticosteroids	None	Stable or decreased	Stable or decreased	Not applicable[b]
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse
Requirement for response	All	All	All	Any of the above

[a]A new lesion is one that is not present on prior scans and is visible in minimum two projections. If a new lesion is equivocal, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. For immunotherapy-based approaches, new lesions alone do not define progression

[b]Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

or immunotherapy may experience pseudoprogression. Recently, the Response Assessment in Neuro-oncology Brain Metastases (RANO-BM) working group published their proposal (Lin et al. 2015). A summary of their recommendations are presented in Table 3.

For patients treated off-trial, especially with a SRS alone approach, regular and frequent imaging schedule should be followed. Although no guidelines exist, most practitioners obtain surveillance imaging every 3 months. As such, the physician and patient must ascertain that resources are available prior to adopting this strategy.

Conclusion

Few topics in radiation oncology have stirred more controversy and debate than the management of BM and the role of SRS and WBRT. Deeply etched opinions have influenced clinical practice, which at times cannot be justified based on the limited level 1 evidence. Neurocognitive detriment, which has been notoriously (and sometimes unfairly) linked to WBRT, has caused a paradigm shift within the oncology community.

Consistently, multiple RCTs have demonstrated reduced local and distant intracranial failure with WBRT, but no survival benefit (likely due to early and effective salvage) and decline in NCF and QoL. Subgroup or post hoc analyses have demonstrated a survival benefit (for SRS + WBRT) in certain groups, but these need further validation. Many cooperative groups have shifted their focus from prolonging survival to maintaining patient's physical and mental function, for as long as possible, as their primary goal.

SRS and WBRT should be viewed as complementary, rather than competition. It seems reasonable to offer SRS alone, with close surveillance, in high-functioning patients who are concerned about cognitive decline. In patients deemed to have a high risk of distant intracranial failure, adjuvant WBRT may be used sparingly. With the available technology, many have combined the best of both worlds with hippocampal-sparing WBRT with simultaneous integrated boost techniques (Bauman et al. 2007; Gutierrez et al. 2007; Hsu et al. 2010).

Effective targeted systemic agents continue to be evaluated, which tackle both intra- and extracranial disease, and may reduce the standing of radiation and surgery. Future research should be conducted in an enriched cohort of patients,

which should be histology-specific groups and include molecular subtyping (e.g., RTOG 1119). Cost-effectiveness outcomes should be integrated into these randomized trials.

Until that evidence is clear, we should align with the Hippocratic Oath of "primum non nocere."

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