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Future directions in treatment of brain metastases

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Abstract

Background: Brain metastases affect up to 30% of patients with cancer. Management of brain metastases continues to evolve with ever increasing focus on cognitive preservation and quality of life. This manuscript reviews current state of brain metastases management and discusses various treatment controversies with focus on future clinical trials. Stereotactic radiosurgery (SRS) and whole-brain radiotherapy (WBRT) are discussed in context of multiple (4+ brain metastases) as well as new approaches combining radiation and targeted agents. A brief discussion of modified WBRT approaches, including hippocampal-avoidance WBRT (HA-WBRT) is included as well as a section on recently presented results of Radiation Therapy Oncology Group (RTOG) 0614, a randomized, double-blind, placebo-controlled trial of menantine for prevention of neurocognitive injury after WBRT.

Methods: A search of selected studies relevant to management of brain metastases was performed in PubMed as well as in various published meeting abstracts. This data was collated and analyzed in context of contemporary management and future clinical trial plans. This data is presented in tabular form and discussed extensively in the text.

Results: The published data demonstrate continued evolution of clinical trials and management strategies designed to minimize and/or prevent cognitive decline following radiation therapy management of brain metastases. Hippocampal avoidance whole-brain radiation therapy (HA-WBRT) and radiosurgery treatments for multiple brain metastases are discussed along with preliminary results of RTOG 0614, a trial of memantine therapy to prevent cognitive decline following WBRT. Trial results appear to support the use of memantine for prevention of cognitive decline.

Conclusions: Different management strategies for multiple brain metastases (>4 brain metastases) are currently being evaluated in prospective clinical trials to minimize the likelihood of cognitive decline following WBRT.

Key Words: Brain metastases, review, radiosurgery, targeted therapy, treatments, whole-brain radiation therapy

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INTRODUCTION

Brain metastases affect up to 30% of patients with cancer.[56] A 2002 population-based study in the Netherlands found that 8.5% of cancer patients developed brain metastases.[65] This latter study showed that the 5-year cumulative incidence of brain metastases was approximately 16%, 10%, 7%, 5%, and 1% for patients with lung cancer, renal cell cancer, melanoma, breast cancer, and colorectal carcinoma, respectively. These incidence estimates for specific pathologies can be applied to estimates of new cancer cases in the United States for 2010 to yield an estimate of approximately 60,000-70,000 yearly cases of brain metastases.[34] However, if autopsy-based incidence figures are used, the expected number of cases of brain metastases may be as high as 170,000 per year.[35] Barnholz-Sloan *et al.*[9] calculated the population-based incidence of brain metastases within the Metropolitan Detroit Cancer Surveillance System. In this cohort, 16,210 patients were found to have brain metastases, representing 9.6% of all lung, melanoma, breast, renal, and colorectal cancer patients diagnosed from 1973 to 2001.[9]

More than 80% of brain metastases are detected after the primary tumor has been diagnosed (metachronous metastases) and less frequently, they are the first manifestation of disease or are diagnosed at the same time as the primary tumor (synchronous metastases). The median time from diagnosis of the primary tumor to the onset of neurologic symptoms is approximately 12 months, ranging from 3 months in the setting of lung adenocarcinoma to 53 months in breast cancer.[64] Brain metastases are symptomatic at some point in 67% of patients.[76]

Some types of primary cancer have a predilection for spread to the central nervous system. However, the reported percentage of cases of each primary type that metastasizes to the brain varies considerably. Lassman and De Angelis[43] reviewed nine studies and found the following variation in reported percentages of patients developing brain metastases for specific primary histologies: 18-64% (lung cancer), 2-21% (breast cancer), 2-12% (colorectal cancer), 4-16% (melanoma), 1-8% (kidney), 1-10% (thyroid), and 1-18% (unknown primary). The overall rate of brain metastases was 6-24% in five cited studies.

Cancer patients with brain metastases present with significant neurologic, cognitive, and emotional difficulties. Diagnosis of brain metastases was traditionally considered to represent end-stage disease and indicative of a turning point from curative treatment to palliative management. Fortunately, progress in systemic therapy is enabling patients with cancer to live longer after diagnosis of brain metastases, which has focused attention on the long-term sequelae of treatment of central nervous system (CNS) disease, such as somnolence, fatigue, depression, and complaints of "mental slowness" and "memory problems." Secondary effects related to neurocognition have come under scrutiny because of physician and patient desires to enhance quality of life (QoL) during and after cancer therapy.[49] Current trials and those being planned primarily focus on identifying the best treatment approaches for patients with multiple (>4 brain metastases, arbitrarily defined) and treatment approaches that can either prevent, minimize, or treat cognitive sequelae associated with brain metastases treatments. These topics will be briefly discussed below.

WHOLE-BRAIN RADIATION THERAPY

Almost half a century ago, in the absence of any effective therapy or brain imaging tools, the majority of patients with brain metastases presented with significant neurologic symptoms or increase in intracranial pressure and symptoms consequential to this. Although no contemporary studies of observation alone exist, older data suggest that these patients in general could be expected to live approximately a month, and the use of steroids to relieve edema and mass effect could lengthen survival to about 2 months.[14] A series of clinical trials, primarily led by Radiation Therapy Oncology Group (RTOG) in the 1960s, suggested that the use of whole-brain radiotherapy (WBRT) could lengthen median survival to about 4 months, and a considerable amount of clinical research effort was directed toward testing various dose-fractionation schemes, none of which was found to be superior to any other scheme. This lack of a dose-effect relationship was explained on the basis of two factors: The dose of WBRT was always subtherapeutic, given the inherent sensitivity of the brain to late radiation toxicity, and therefore, almost half of all patients continued to succumb to intracranial disease progression; and ineffective systemic therapies resulted in absence of extracranial disease control, which resulted in the demise of the other half of this group of patients. This observation was not surprising, given that almost half of all patients with brain metastases have lung cancer as the underlying disease, which was effectively untreatable with chemotherapy until the advent of the platinoids. Consequently, WBRT became the modality of choice, and although various schedules are in use, the schedules of 30 Gy in 10 fractions and 37.5 Gy in 15 fractions are most commonly used and balance the need to deliver modest dose of radiotherapy in a short period of time.[14,15] However, no modern trial compared the best supportive care with WBRT. The Medical Research Council has recently initiated a large randomized trial of corticosteroids/best supportive care alone compared with the same treatment plus WBRT in patients with primary nonsmall cell lung cancer and brain metastases.[21]

WBRT provides effective symptom relief in the majority of cases.[22] Although symptom response rates after WBRT vary, complete or partial responses have been documented in 43-64% of patients as early as week 2 in randomized controlled studies conducted by RTOG.[14,31,39,52] Recently, various groups have reported responses in the same range–in 38% of patients after 30 Gy WBRT;[2] symptomatic relief after ≥25 Gy in 66%, allowing corticosteroid dose reduction;[74] and radiographic responses in comparable proportions of patients.[55] WBRT-induced tumor reductions correlated with better survival and cognitive function preservation in a cohort of 135 patients from a phase III trial of WBRT with a sensitizing agent motexafin gadolinium.[44] Previous RTOG data suggest that patients with controlled brain metastases after WBRT tend to experience stable mini-mental status examination (MMSE) scores, whereas those with uncontrolled lesions experienced an average decrease of 6 point at 3 months.[63] Of the survivors at 6 months from the WBRT arm of the randomized RTOG radiosurgery trial, 40% experienced improvement in mental status, and 45% experienced a decreased need for corticosteroids.[1]

Although the median survival of 4 months has become a widely quoted statistic, and for the most part remains true even today, there is clear recognition that not all patients with brain metastases have equivalently poor survival outcome, and a small but significant minority live for a longer period of time. The most commonly used prognostic system is the RTOG Recursive Partitioning Analysis (RPA) classification.[27] Gaspar *et al.*[27] performed RPA to generate regression prognostic trees of 1200 patients from three consecutive RTOG trials conducted between 1979 and 1993, which tested several different WBRT fractionation schemes and radiation sensitizers. This classification scheme stratifies patients on the basis of three prognostic categories (RPA classes 1, 2, and 3, with a higher class indicating a worse prognosis) according to age at diagnosis, absence or presence of extracranial metastases, Karnofsky performance status (KPS) score, and status of the primary cancer. On the basis of this analysis, the median survival of patients with brain metastases ranges from 2.3 to 7.1 months, prompting the debate regarding whether the patients in at least the best-prognosis category should or should not be treated with more aggressive therapies to control intracranial disease. At the core of the debate was the recognition that WBRT produced only a modest rate of intracranial disease control and that, too, for a limited duration. For example, Nieder *et al.*[54] have shown that, with WBRT to 30 Gy, few lesions larger than 1 cm^3 are locally controlled after one year. In 1990, Patchell *et al.*[59] reported on a seminal trial, randomly assigning patients with a single brain metastasis and KPS ≥70 to WBRT with biopsy versus surgical resection, and although relatively small (N = 48), this trial changed practice because patients with a single brain metastasis experienced improved survival (median survival, 40 vs. 15 weeks for resection vs. biopsy), superior local control (80% vs. 48%), and lengthening of functional independence as defined by the maintenance of KPS greater than 70 (38 vs. 8 weeks). The clear lesson from this trial was that there are indeed some patients with brain metastases for whom enhanced intracranial disease control translates into a survival and QoL advantage. In part to better identify the cohort with improved prognosis, a more recent analysis (and more relevant to contemporary clinical practice) of the RTOG database of brain metastases led to the development of a revised prognostic scale – graded prognostic assessment (GPA).[71] Although analysis of the RTOG RPA database showed the status of the primary cancer to be prognostic, the RTOG GPA analysis showed the number of metastatic lesions (one, two, or three, or more than three) to be prognostic. Neither system suggested that the type of primary tumor influences outcomes when all brain metastases patients were analyzed in aggregate, however, when stratified by primary histology, marked survival differences emerged leading to the creation of diagnosis-specific GPA (DS-GPA) [Table 1].[72] Unfortunately, even the DS-GPA (and other prognostic indexes) do not consider the specific molecular biology of various tumors (e.g., patients with melanoma tumors bearing the BRAF V600E mutation tend to respond to therapy better and live longer than those without the mutation).[26] In general, patients with KPS >70 and limited (or stable) systemic disease tend to live longer with up to 30% survival being reported at one year.[66]

Those who favor inclusion of initial WBRT highlight the evidence that demonstrates improved local control and distant tumor control with concurrent administration of WBRT [Table 2]. They also argue that increased CNS tumor burden and failure of local and regional control contribute to cognitive decline and that the increased need for salvage therapy in patients not treated with upfront WBRT adversely affects QoL. Conversely, opponents of this strategy argue that improved CNS tumor control does not appear to increase overall survival time, and that routine use of initial WBRT limits therapeutic options at

Table 1: Median survival stratified by primary tumor diagnosis for patients with newly diagnosed brain metastases, according to DS-GPA database[71]

Primary diagnosis	Medial survival (months)	95% CI
Nonsmall cell lung cancer (NSCLC)	7.00	6.53-7.50
Small cell lung cancer (SCLC)	4.90	4.30-6.20
Melanoma	6.74	5.90-7.57
Renal cell carcinoma	9.63	7.66-10.91
Breast cancer (all subtypes)	11.93	9.69-12.85
Gastrointestinal cancer	5.36	4.30-6.30
Not-specified	6.37	5.22-7.49

Table 2: Studies comparing SRS plus WBRT with SRS alone

Study	Modality	Patients	Median survival (months)	1-year survival (%)	1-year freedom from CNS recurrence (%)	1-year local control (%)	1-year distant control (%)	Neurocognitive assessment
Chang[17]	SRS only	30	15.2	63.0	27.0	67.0	45.0	HVLT-R
	SRS+WBRT	28	5.7	21.0	73.0	100	73.0	(+ others)
Aoyama[3,4]	SRS only	67	8.0	28.4	23.6	72.5	36.3	MMSE
	SRS+WBRT	65	7.5	38.5	53.2	88.7	58.5	
Sneed[25]	SRS only	268	8.2	38.0	NR	NR	NR	None
	SRS+WBRT	301	8.6	35.0	NR	NR	NR	
Andrews[1]	WBRT	164	6.5	NR	NR	71.0	NR	None
	WBRT+SRS	167	5.7	NR	NR	82.0	NR	
Regine[63]	SRS only	36	9.0	36.0	53.0	61.1	75.0	None
Kocher[37]	SRS only	100	10.7	41.8	16.0	84.0	22.0	None
	SRS+WBRT	99	10.9	44.4	26.2	73.7	52.0	
Serizawa[66]	SRS only	778	8.6	NR	NR	89.5	54.3	None

A significant value of $P>0.05$ was used unless otherwise specified, NR: Not reported, MMSE: Folstein Mini-mental Status Evaluation, HVLT-R: Hopkins Verbal Learning Test–Revised

the time of recurrence. Additionally, the limited available evidence suggests that upfront WBRT might adversely affect neurocognition, late toxicity that patients wish to avoid. There remains considerable interest but scant data regarding neurocognitive effects. Acute side effects of WBRT include common effects (occurring in >50% of patients) such as alopecia, fatigue, and scalp erythema and less common effects (occurring in <20% of patients) such as otitis externa, impaired sense of taste, nausea, and headache. Early delayed and late side effects from WBRT may include tanning of the scalp, alopecia, hearing loss, neurocognitive decline, behavioral changes, somnolence syndrome, and radiation necrosis.

SRS VERSUS WBRT FOR >4 BRAIN METASTASES

In 1989, Lindquist *et al.*[45] reported the first case of stereotactic radiosurgery (SRS) for brain metastasis, in a patient treated for a cerebral hypernephroma. By the mid-1990s numerous reports of SRS alone or following WBRT had been published, and strong opinions developed regarding selection criteria for patients treated with WBRT, SRS, or both. Some practitioners adopted formulaic recommendations based on tumor size, KPS, age, status of extracranial disease, and number of brain metastases while giving no formulaic weight to potential brain toxicity.[24] Others used KPS together with a strict cut-off limit on the number of brain metastases that could be treated with SRS. Yet others adopted a less rigid approach that allows SRS for almost any number of targets, depending in a flexible manner on tumor location, degree of edema, likelihood of clinical complications, etc., Ideally, one might have hoped that published guidelines and editorials based mainly on interpretations of Phase III studies dealing with 1-4 brain metastases would lead to unanimity among experts regarding treatment recommendations for 1-4 brain metastases, and, by extrapolation, recommendations for patients with >4 brain metastases. For >4 brain metastases, WBRT remains the standard of care for some physicians despite the lack of randomized trials comparing WBRT to SRS, despite the relative lack of detailed outcome data for WBRT (other than overall survival and clinical response), and despite the small but favorable literature on SRS for multiple metastases.

Some physicians recommend WBRT for >4 brain metastases, whereas others recommend SRS alone. This controversy is related to the controversy surrounding treatment of ≤4 brain metastases. Physicians who favor combined therapy (SRS+WBRT) for ≤4 metastases cite the widely accepted Phase III finding that brain control with combined therapy is significantly better than with SRS alone or WBRT alone.[4,17,37,38] Physicians who favor SRS alone cite the Phase III finding that risk of neurocognitive deficit is doubled with the addition of WBRT to SRS.[17] Whether SRS is used alone or combined with WBRT, these studies lend strong support for SRS, at least as a component of management; they lend little support for WBRT alone for patients meeting Phase III selection criteria. This suggests that SRS is underutilized.[30]

Most physicians recognize that WBRT for brain metastases provides improved survival and symptom relief compared with observation or corticosteroids even if the degree of benefit relative to number of brain metastases is not known. Nevertheless, given the lack of Phase III outcomes data supporting WBRT alone as the best currently available alternative for ≤4 brain metastases, it seems counterintuitive to blindly favor WBRT alone as the best currently available alternative for >4 brain metastases. Those who favor WBRT over SRS argue (1) that WBRT prevents some of the distant brain metastases that would otherwise develop after SRS alone;[4] (2) that brain recurrences after initial SRS alone are associated with a high rate of clinical neurological deficits;[62] (3) that there are methodological flaws[47] associated with the

Phase III finding that SRS-alone patients fare better than SRS+WBRT patients on Hopkins verbal learning tests;[4] and (4) that salvage therapy, widely known to be more frequently required in SRS-alone patients, could be less effective than initial therapy.

Physicians who favor SRS alone have several counter arguments: (1) they cite the Phase III findings of Chang[17] that although the addition of WBRT decreases distant brain failure compared with SRS alone, the addition of WBRT doubles the risk for significant verbal learning and memory deficits at 4 months; (2) they argue that the finding of Ayoma *et al.*[3] that the addition of WBRT to SRS leads to a significantly longer time to MMSE decline is based on the flawed assumption[50] that MMSE is an adequate measure of neurocognitive function changes related to radiation, and they further note that posttherapy leukoencephalopathy was seen on MRI in some patients in the combined arm and in no patients in the SRS-alone arm;[3] (3) they question Dr. Regine's conclusion that brain recurrences after SRS alone are associated with a high rate of neurologic deficits[62] since his reported rate of serious neurologic complications affecting language, memory, cranial nerve, gait, and motor function is far higher than that reported by other authors, which may reflect unfortunate target selection; (4) they believe the acknowledged brain control advantages of SRS+WBRT are not outweighed by the acknowledged side effects of WBRT[48,69,73] side effects, which have motivated proponents of WBRT to develop IMRT-based hippocampal-sparing WBRT techniques for multiple metastases;[28,61] and (5) they argue that salvage SRS, although needed more frequently in patients treated initially with SRS alone rather than with combined therapy, is safe, efficient, and effective, even for >4 brain metastases.[46] It is further argued that the four metastasis limit for SRS techniques is a historical relic reflecting technological and practical limitations of early SRS technology, limitations which have since been overcome.

Given the state of this controversy, the majority of patients in our own catchment area prefer SRS alone for >4 metastases to avoid hair loss and to minimize fears of WBRT-related neurocognitive deficits, and because they prefer a one-day rather than a multi-week procedure. Additionally, SRS patients (and their physicians) often express the desire to minimize interruptions in systemic therapy, leading them to prefer SRS treatment. For many physicians who favor SRS alone for 1-4 brain metastases, the recommendation for SRS for >4 brain metastases seems reasonable, especially when they are committed to obtaining frequent follow-up exams and providing salvage therapy as needed, as they do for patients with ≤4 metastases. That recommendation has been supported by the development of commercial radiosurgery apparatus that is capable of treating a large number of brain metastases, so that physicians using currently available apparatus are faced with few technical limitations in the number of lesions that can be treated with SRS. Our own clinical experience suggests that treating a large number of lesions is safe. Nevertheless, physicians should be mindful that normal tissue dose increases with number of tumors treated with SRS, and that normal tissue dose is apparatus-dependent.[46]

There are now several trials that directly compare SRS and WBRT in patients with 4+ brain metastases: (1) A University of California, San Francico (UCSF)-led multi-institutional trial evaluating neurocognitive outcomes in patients with 5+ brain metastases treated with SRS or WBRT (ClinicalTrials.gov identifier: NCT01731704) and (2) MD Anderson phase III trials comparing SRS versus WBRT in patients with 1-10 brain metastases from melanoma and nonmelanoma primary cancers (ClinicalTrials.gov identifiers: NCT01644591 and NCT01592968). These trials should inform about cognitive outcomes related to brain irradiation and to compare the relative effectives of two different approaches to brain metastases treatment.

WBRT FOR >4 BRAIN METASTASES

Until recently, most physicians accepted that WBRT represents the standard of care for patients with >4 brain metastases, and most would agree that WBRT is preferable to observation or corticosteroids. For over 50 years, innumerable such patients have received WBRT, and numerous Phase III trials have examined various WBRT outcomes with various dose/fractionation schemes but without regard to number of brain metastases. Surprisingly, there are few publications relating relative number of lesions to outcomes for patients with >4 tumors [Table 3]. Some information is available from Nieder *et al.*,[54] who studied 113 patients with a median of 6 (range 4-50) brain metastases treated with WBRT. They found that number of brain metastases had no appreciable influence on survival. Direct comparisons with SRS-alone series cannot be made, since there is no way to know if Nieder's patients might have met reasonable SRS selection criteria.

There are as yet no published Phase III data directly addressing the current controversy. Despite that, several professional medical organization have published consensus documents that include reference to management of >4 brain metastases. In addition, there are several published retrospective studies on SRS for multiple brain metastases, which relate overall survival and/or local or distant brain control and/or clinical or radiographic complications to number of brain metastases. There are few similar WBRT publications. Most consensus statements do not address more than >4 brain metastases, except tangentially or by implication.[11,36,68,70,77,78]

Table 3: The below authors analyzed the relationship of number of brain metastases to various outcomes. In most cases number of metastases was not a significant factor (p=ns). Variable numbers of patients in each series may have received WBRT or surgery before or after SRS. Selection criteria for SRS varied. Data from Caballero[16] are for salvage SRS after WBRT failure. Data from Nieder[54] are for WBRT without SRS

Author	Patients	Outcome	Number of mets (*P*=ns)	Number of mets (*P*<0.05)
Bhatnagar[13]	205	Survival	4-18	
		Local control	4-18	
Chang[18]	323	Survival	1->15	>15 worse
		Local control	1->15	than ≤15
		Progression-free survival	1-15	
		MRI changes	1->15	
Hunter[33]	64	Survival	5-10	
Serizawa[67]	1508	Survival	2-10	2-4 worse than 1
Serizawa[66]	778	Survival	1-10	
		Local control	1-10	
		Neurologic death-free survival	1-10	
		Functional survival	1-10	
Yamamoto[80]	1676	Survival	2-15	2 worse than 1
Caballero[16]	310	Survival	2-31	>1 worse than 1
Nieder[54]	113	Survival	4-50	

SRS FOR >4 BRAIN METASTASES

In 2006, Bhatnagar *et al.*[12] reported results of 205 patients treated with SRS for 4-18 (64% with >4) brain metastases, 17% of whom had SRS alone, 46% SRS+WBRT, and 38% SRS after WBRT failure. The median treatment volume was 6.8 cc (range 0.6-51.0 cc). Median overall survival was 8 months, time to progression or time to new brain metastases was 9 months, and local control was 71% and 49% at 1 and 2 years, respectively. Multivariate analysis showed that significant factors for overall survival included total treatment volume, age, RPA class, and marginal dose. The number of intracranial metastases was not significant (P = 0.333). For local control, total treatment volume was significant and the number of intracranial metastases was not significant. The authors propose that total treatment volume instead of (or together with) number of metastases should be a selection factor.

In 2010, Chang *et al.*[18] reported results of SRS for 323 patients treated with SRS, an unspecified number of whom received WBRT. Total treatment volumes were not specified. Patients were retrospectively placed into groups based on number of brain metastases, with 1-5, 6-10, 11-15, and >15 lesions in Groups 1-4, respectively. Median survivals were not significantly different at 10.0, 10.0, 13.0, and 8.0 months, respectively (P = 0.554). Local tumor control rates were not significantly different between the four groups. Median progression-free survivals were 9.0, 11.0, 8.0, and 6.0 months, and was significantly shorter for Group 4 (P = 0.03), as was distant brain progression (P = 0.014). Follow-up radiologic changes did not differ significantly between the groups (7.9%, 10.3%, 11.8%, and 3.0%, respectively). The authors conclude that SRS is a reasonable treatment for patients with multiple brain metastases, even for >15 lesions.

In 2011, Hunter *et al.*[33] focused on overall survival in 64 patients treated with SRS for ≥4 brain metastases, of whom 63% had received "prior WBRT" >1 month prior to SRS, 14% had received "concurrent WBRT" within 1 month of SRS, and 23% had received "no WBRT." The median number of lesions treated was 6 (range 5-10). The median total lesion volume was 4.1 cc (range 0.003-25.5 cc). The median overall survival was 7.5 months, and was significantly improved for KPS ≥80 compared with KPS ≤70 (P = 0.008). "Prior WBRT" patients had significantly improved survival compared with "concurrent WBRT" patients (P = 0.034). However, omitting WBRT showed no disadvantage, in that no significant survival differences were seen when comparing "no WBRT" with either "prior WBRT" or "concurrent WBRT." Median survival for ≤8 lesions (6.6 months) was not significantly different from that for ≥8 lesions (9.9 months). Local control, distant brain control, and radiographic changes were not addressed.

In 2010, Chang *et al.*[18] reported a series of 26 patients treated with SRS for ≥10 brain metastases (range 10-37), of whom 13 had failed prior WBRT, 5 had received SRS and concurrent WBRT, 2 had received WBRT for SRS failure, and 6 had received SRS alone. Overall survival was significantly longer for synchronous brain metastases compared with metachronous metastases, for KPS ≥80 compared with 70, for primary disease controlled compared with uncontrolled, and for ≥2 cycles of systemic chemotherapy compared with <2 cycles. Local control in a subset of 17 patients with 263 lesions was 79.5%. Radiation necrosis was observed in only one lesion (in a patient who had 19 target lesions and did not receive WBRT). The lesion had largely resolved at 38 months.

In 2010, Nath *et al.*[53] reported clinical results in 26 patients who received SRS for a median of 5 brain metastases (range 2-13), 23% of whom had received prior WBRT. Actuarial one-year survival was 38%. Actuarial one-year local control was 83%, with significantly improved local control at 6 months for lesion size ≤1.5 cm. Local control was not significantly affected by use of WBRT. Distant brain failures developed in seven patients and were salvaged in five patients with WBRT and in two patients with SRS.

In 2010, Serizawa *et al.*[67] analyzed results of SRS as sole treatment for 1508 patients who met the inclusion criteria of the otherwise unrelated Japanese multi-institutional trial JLGK0901 (a trial designed to assess noninferiority of SRS as sole treatment of 5-10 brain metastases compared with 2-4 brain metastases), including patients with 1-10 newly diagnosed brain metastases, largest tumor volume <10 cc, total brain metastases volume <15 cc, and no CSF dissemination, and excluding patients with KPS ≤70 due to extracranial disease. Patients were divided into three groups based on number of tumors: Group A (1 tumor), Group B (2-4 tumors), and Group C (5-10 tumors). Univariate analysis revealed mean survivals of 0.99 years for Group A, 0.68 years for Group B, and 0.62 years for Group C, and they were significantly different (A vs. B, P <0.0001; B vs. C, P = 0.0312). However, multivariate analysis showed significantly worse survival for Group B (2-4 tumors) compared with Group A (1 tumor), but no survival difference for Group B (2-4 tumors) compared with Group C (5-10 tumors). This analysis did not address local and distant brain control or complications.

In 2010, Serizawa *et al.*[66] published a somewhat different analysis than that discussed above, involving 778 similarly selected patients who were placed in five analysis groups according to number of tumors: Group A (1 tumor), B (2), C (3-4), D (5-6), and E (7-10). The median maximum tumor volume was 1.8 cc (range 0.1-9.9 cc) and the median total tumor volume was 2.8 cc (range 0.1-15.0). Extracranial disease was controlled in 84 patients and uncontrolled in 694 patients. Lesions were synchronous in 201 patents and metachronous in 577 patients. Mean survival times were in the range 0.83-0.59, but were not significantly different between any two groups. As expected, mean survival was significantly (P < 0.0001) related to RPA class: Class 1 (2.2 years) versus class 2 (0.7 years) versus class 3 (0.3 years). One-year neurological death-free survivals in Groups A-E were 96.8%, 95.5%, 84.7%, 91.2%, and 89.2%, respectively, with no significant differences between any two groups. One-year local control was significantly (P = 0.0001) related to tumor size: 98% (tiny) versus 92.3% (small) versus 77.9% (medium-sized). One-year distant brain control rates were 71.6%, 53.7%, 43.6%, 50.7%, and 66.3% for groups A-E, respectively. Significant differences were seen when comparing A and B, and also when comparing C and D. The authors concluded that the number of brain lesions treated with SRS alone did not influence overall survival, local control, neurological death-free survival, or functional survival.

In 2012, Yamamoto *et al.*[80] analyzed 1676 patients treated with SRS and made pairwise comparisons of actuarial survival based on 14 pairs of number of metastases treated (1 vs. 2, 2 vs. 3, 3 vs. 4….14 vs. 15), and found a significant difference in median survival only for the 1 versus 2 pair (P = 0.0002).

In 2012, Caballero *et al.*[16] analyzed prognostic factors for survival in 310 patients treated with salvage SRS for new, progressive, or recurrent brain metastases after prior WBRT. The median number of brain metastases treated was 4 (range 1-31) and 53% of patients had 4-31 brain metastases treated. Patients treated with SRS for a single tumor had longer median survival than those treated for >1 tumor (12.0 vs. 7.9 months, P = 0.001), but among patients with multiple lesions treated there was no significant trend toward shorter survival with increasing number of brain metastases. The authors concluded that for multiple metastases, the median survival of 7.9 months made SRS a worthwhile therapy for patients who had failed or progressed after prior WBRT, and they found no evidence to support the use of a cutoff for number of brain metastases appropriate for salvage therapy.

To address this controversy, UCSF is conducting a single-arm prospective trial in patients with 1-10 brain metastases treated with SRS alone. This prospective study should be able to supplement similar ongoing studies from Japan in patients with multiple brain metastases and better inform about both oncologic and cognitive outcomes associated with initial SRS treatment as well as subsequent salvage therapies. To date, no SRS-only study prospectively addressed the issue of salvage SRS treatment in patients treated with upfront radiosurgery and the impact of this treatment paradigm on cognitive function.

MODIFIED WHOLE-BRAIN RADIOTHERAPY APPROACHES

To reduce cognitive injury of conventional WBRT, several groups are exploring modified WBRT approaches to treat multiple brain metastases. Proponents of these approaches argue that it is possible to retain benefits of whole-brain treatment while reducing its toxicity by reducing dose to specific brain regions. Perhaps the best know and most studied approach is hippocampal-avoidance WBRT (HA-WBRT).[28] In this approach, complex planning techniques are used to reduce dose to bilateral hippocampal structures while treating the rest of the brain. Hippocampal-dependent functions of learning, memory, and spatial information processing seem to be preferentially affected by radiation therapy.[5,6] It is argued that since <5% of brain metastases occur within 5 mm of the hippocampus, reducing dose to the hippocampus is safe and feasible.[75] The feasibility of this approach has been studied prospectively in a multi-institutional setting by the RTOG study 0933. The accrual to this study recently completed. Other similar approaches, based on the biological rationale that preservation of neural stem cell compartments in the brain will maintain brain plasticity and will lead to consequent preservation of cognitive function, have also been proposed but less extensively studied.[7,8]

Finally, some groups are investigating the feasibility of modified WBRT with simultaneous boost of gross brain metastases.[29,32]

All of these approaches seek to prevent or mitigate cognitive injury related to WBRT while preserving its oncologic benefits. To date, it is unclear if these approaches will lead to meaningful clinical outcomes. Some of the criticisms of the RTOG 0933 study are that it uses Hopkins Verbal Learning Test–Revised edition (HVLT-R) as its primary endpoint. While this measure has been previously validated in multiple studies, it is highly sensitive and but not very specific. In this trial, HVLT-R is given along with a "shopping" recall test (another word list learning test and a visual memory test) on the same day, prompting concerns that the two tests will interfere and cause problems with both tasks. Furthermore, compliance and completion of neurocognitive assessments in a multi-disciplinary setting has traditionally been quite low (<50%) for a variety of reasons. Nonetheless, this study (and other RTOG trials utilizing neurocognitive outcomes) will contribute to our understanding of disease- and treatment-related impacts on cognition and QoL.

SYSTEMIC AGENTS FOR BRAIN METASTASES

Reports of brain metastases response to systemic treatment with targeted agents[41] prompted development of clinical trials where these agents are used alone or in conjunction with radiation therapy (SRS and/or WBRT). Many find the combination of SRS (for treatment of gross brain disease) and targeted systemic agents an attractive strategy with the potential to reduce CNS recurrence, and therefore, the need for salvage radiation therapy. There are at least 19 open clinical trials recorded on ClinicalTrails.gov website exploring this approach. The RTOG has also embarked on a systematic approach to study targeted agents in this setting with trials that have the potential not only to inform about potential efficacy and toxicity of this approach, but will also enable more relevant and precise patient stratification/selection since many of these trials require *a priori* knowledge of various cytogenetic abnormalities within the treatment cohort. It is hoped that this data will also result in improved models for patient classification and prognostication.

PREVENTION OF COGNITIVE DYSFUNCTION

The pathophysiology of late radio therapy (RT) injury is dynamic, complex and a result of inter- and intracellular interactions between the vasculature and many of the parenchymal cell lines.[51] The vascular hypothesis of radiation-induced injury attributes accelerated atherosclerosis and mineralizing microangiopathy that result in vascular insufficiency and infarction to radiation injury and inflammation.[40] Taken together, the mechanisms of radiation-induced injury result in a picture similar to the small vessel disease seen with vascular dementia.[10] For this reason there is great interest in studying vascular dementia treatments to prevent or reduce radiation-induced cognitive injury. Additionally, because treatment of cognitive decline after radiation is limited, treatments ideally would be developed to prevent the detrimental cognitive effects of cerebral radiation.

Glutamate is the principle excitatory amino acid neurotransmitter in cortical and hippocampal neurons.[58] One of the receptors activated by glutamate is the N-methyl-D-aspartate (NMDA) receptor, which is involved in learning and memory.[23] Ischemia can induce excessive NMDA stimulation and lead to excitotoxicity, suggesting that agents that block pathologic stimulation of NMDA receptors may protect against further damage in patients with vascular dementia.[42] One such agent is memantine, an NMDA receptor antagonist. Memantine is a noncompetitive, low-affinity, open-channel blocker, that has been shown to be neuroprotective in preclinical models.[19,20,60] Additionally, two placebo-controlled phase III trials found memantine to be well-tolerated and effective in treatment for vascular dementia, especially for patients with small-vessel disease.[57,79] On these basis, RTOG launched a placebo-controlled, double-blind, randomized trial to evaluate the potential protective effect of memantine on neuro-cognitive function in patients receiving WBRT. The results of this study (RTOG 0614) were recently reported. On this trial, eligible adult patients with brain metastases were stratified by RPA class (I or II) and prior radiosurgery or surgical resection. Patients received WBRT (37.5 Gy in 15 fractions) and were randomized to receive placebo or memantine, 20 mg/day, within 3 days of initiating radiotherapy, for 24 weeks. Standardized tests of cognitive function were performed at baseline, 8, 16, 24, and 52 weeks. Between March 2008 and July 2010, 554 patients were accrued of which 508 were eligible. Patient and treatment characteristics were balanced between arms. Grade 3 or 4 toxicities and study compliance were similar between arms with only 32% of patients completing drug therapy per protocol mainly due to death, progressive disease, or noncompliance. Median follow-up for censored patients was 12.4 months. No differences in OS or PFS were seen between the arms.

The memantine arm had significantly longer time to cognitive decline (HR 0.78; 95% CI, 0.62-0.99; P = 0.02) and the probability of cognitive function preservation at 24 weeks was 30.6% in the memantine and 19.7% in the placebo arm (data presented at the 17th Annual Meeting of Society for Neuro-Oncology [SNO], Washington, DC). There was less decline on the HVLT-R Delayed Recall (HVLT-R DR) in the memantine arm (median decline of 0) compared with the placebo arm (median decline of 0.90) at 24 weeks

(P = 0.059) that was not statistically significant as 149 analyzable patients at 24 weeks resulted in only 35% statistical power for the primary endpoint. There was less decline on the HVLT-R Delayed Recognition in the memantine arm at 24 weeks (P = 0.0149) and the MMSE (P = 0.0093). Fewer patients receiving memantine experienced decline on Controlled Oral Word Association (COWA) at 8 weeks (2% vs. 13% deterioration; P = 0.0015). Linear regression models for the complete case date, revealed significant differences favoring the memantine arm for COWA at 8 (P = 0.008) and 16 weeks (P = 0.0041) and for Trail Making Test Part A and MMSE (P = 0.0137 and 0.0038, respectively) at 24 weeks. Using the imputed data, a significant difference was found for COWA scores at 8 weeks (P = 0.0103) favoring the memantine arm.

In summary, the addition of memantine during and after WBRT appears to result in better cognitive function over time; specifically delaying time to cognitive decline and reducing the rate of decline in memory, executive function, and processing speed. This needs to be considered in context – no statistically significant difference was seen in HVLT-R DR due to low study compliance. However, since the toxicity and tolerance of memantine is essentially equivalent to placebo, consideration of treatment with memantine for patients receiving WBRT to maintain cognitive function was highly recommended. Nonetheless, nearly 70% of patients still experienced cognitive deterioration by 6 months despite memantine therapy. For this reason, RTOG is working to develop future trials of preventive therapy in patients who are treated with WBRT.

CONCLUSIONS

Management of patients with brain metastases continues to evolve toward more patient- and disease-specific treatments. A *priori* knowledge of cytogenetic alterations in tumors is now being incorporated into therapeutic selection algorithms with treatments specific to a particular disease subtype. The level of stratification will parallel the expansion of our understanding of disease and various underlying cytogenetic mechanisms that drive carcinogenesis. Clinicians will have to embrace this complexity to provide truly personalized care. This increasing complexity and choice of therapies will undoubtedly create a need for trials of comparative effectiveness that will also have to consider impact of therapy on the patient and caregiver(s) as well as healthcare costs. Studies of posttreatment neurocognitive function and QoL are a step in the right direction since they directly relate to ability of the patient (and their caregivers) to participate in and to contribute to society. To date, there is relative paucity of comparative effectiveness research in oncology but this is expected to change with rising controls on healthcare expenditures.

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