Journal of
Brain Tumors & Neurooncology

Harris et al., J Brain Tumors Neurooncol 2016, 1:3
DOI: 10.4172/2475-3203.1000110

Research Article Open Access

Low Rate of Subsequent Whole Brain Radiotherapy Following a Policy of Local Therapy with MRI Surveillance for Central Nervous System Oligometastases

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Received date: Jul 06, 2016; **Accepted date:** Aug 09, 2016; **Published date:** Aug 16, 2016

Abstract

Background: Palliative Whole Brain Radiotherapy (WBRT) for cerebral metastases has potential morbidity and in large randomized studies has not shown a clear survival benefit. This study audits the outcome of patients with cerebral oligometastatic disease (which we defined as 1-4 lesions on MRI) who were managed with an active policy avoiding WBRT utilising local therapies and MRI surveillance.

Methods: A clinical audit was performed of 31 patients with cerebral oligometastases referred for radiation therapy at the Northern Sydney Cancer Centre between July 2009 and December 2012. Patients were offered management with a programme of local therapy (neurosurgery, stereotactic radiosurgery or intensity modulated radiotherapy, or combined modality therapy) followed by protocol based MRI surveillance. Systemic therapy was delivered as indicated for extra-cranial disease. Data on patient, tumour and treatment factors was collected using a prospective database.

Results: Median follow-up for surviving patients is 23 months. Compliance with MRI surveillance was good (87%). 21 patients had CNS progression, of which 12 were detected by MRI surveillance without symptoms. Median CNS progression free survival was 11 months (95% CI: 4.9 - 17.1 months). Only 5 patients (16%) received WBRT at relapse. 16 patients died during follow-up with a median survival of 20 months (95% CI: 10.6 – 29.4 months), with cause of death attributable to CNS disease in 6 patients.

Conclusion: WBRT Avoidance with MRI surveillance is an acceptable management policy after local therapy for patients diagnosed with cerebral oligometastases. In our study, the rate of CNS progression was acceptable, it was not associated with increased mortality due to uncontrolled CNS disease and WBRT was avoided in the majority of these patients.

Keywords: Radiation therapy; Whole brain; Oligometastases

Introduction

The presentation of cerebral oligometastatic disease (generally considered as 1-4 lesions on MRI imaging, as demonstrated in Figure 1) is associated with a better prognosis than more numerous brain metastases and may reflect a favourable natural history [1-3]. This may produce a longer interval before subsequent CNS lesions; however patients may live to experience the late morbidity of interventions such as Whole Brain Radiation Therapy (WBRT).

Fortunately, recent developments in clinical practice have increased treatment options available to patients with CNS metastases. Improved accessible imaging with 3T MRI, reduced morbidity from salvage craniotomy or stereotactic radio-surgery and improved systemic therapies permit a more conservative initial approach to management of cerebral oligometastases without potential compromise of survival.

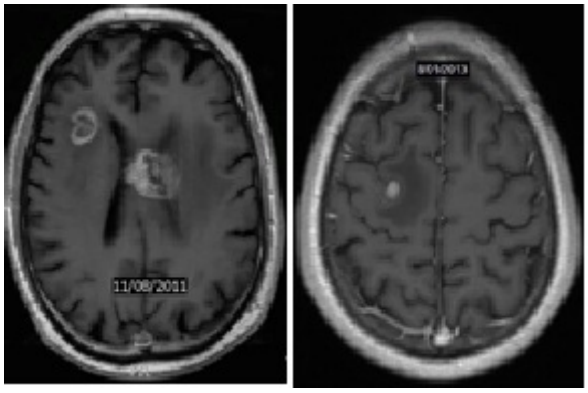

Figure 1: MRI demonstrating CNS oligometastases in two different patients

Whilst patients may be reassured by the clinical trials that report no survival benefit of WBRT after initial local therapy, there is uncertainty regarding the impact of relapse, and subsequent risk of functional deterioration from salvage interventions [4]. This study aims to audit the impact of a policy of WBRT avoidance utilizing MRI surveillance on subsequent functional outcomes in patients.

Factor	Description	Patient Number (n =31)
Patient Age	Median	62 yrs
Primary Tumour Pathology	Breast	7
	NSCLC	6
	Renal	5
	Melanoma	5
	Colorectal	5
	Others	3
Time from Initial Diagnosis to CNS metastasis	Median	20 months
Extra-cranial Disease	Nil	4
	Asymptomatic	17
	Symptomatic	10
ECOG Performance Status	0	27
	1	12
	3-Feb	4
RTOG Neurologic Function Score	0	19
	1	10
	4-Feb	2
Number of CNS Metastases	1	22
	2	4
	3	2
	4	3

Table 1: Baseline characteristics and treatment details (n=31)

Materials and Methods

All patients diagnosed with cerebral oligometastases referred to radiation therapy at the Northern Sydney Cancer Centre are entered into an ethics approved prospective database. Eligible patients were identified from a single clinician's practice as those offered local therapy and MRI surveillance or WBRT between 1st July 2009 and 31st December 2012. All known cerebral metastatic lesions had to be treated prior to commencement of MRI surveillance. Treatment Protocol for WBRT avoidance involved initial local management of the oligometastases by craniotomy and resection; stereotactic radiosurgery and surgical cavity RT to those resected lesions greater than 30 mm or with gross residual disease post resection. A baseline MRI was performed at one month post local treatment and decision for WBRT avoidance made at that review. MRI surveillance then involved 3 monthly MRI for Year 1 and 2 followed by 4 monthly for Years 3, 4, 5.

Baseline characteristics

Initial patient and tumour details were recorded, specifically patient age, RTOG Neurologic Function Status, ECOG Performance status, primary tumour site, extent of extracranial disease, and presence of extracranial symptoms (Table 1). Initial CNS treatment was detailed including time from initial diagnosis, use of craniotomy, local field RT dose and fractionation.

MRI Analysis at baseline and follow-up was conducted in the same radiology unit with the same group of reporting neuro-radiologists. All MRI sequences including T1-weighted gadolinium enhanced images at 0.8 mm slice thickness were used for initial and follow-up assessment.

Local therapy details

The referral pathway for opinion regarding radiation therapy varied as to the clinical presentation. Generally surgery was utilised for patients with newly diagnosed metastatic disease or symptomatic mass lesions. Other patients with known disseminated malignancy, low bulk and asymptomatic disease were managed without surgical intervention.

Intensity Modulated Radiation Therapy (IMRT) was utilised for treatment to the surgical cavity postoperatively and involved a fractionated course with a dose of 25-30 Gy in 5 fractions delivered to the cavity wall and any residual enhancing tissue. For unresected lesions<2.5 cm stereotactic radiosurgery was utilised with a dose of 18-20 Gy single fraction delivered to the 80% isodose covering the lesion. For unresected lesions>2.5 cm fractionated IMRT was utilised with a dose of 30 Gy in 5 fractions.

No systemic therapy was utilised with the intent of managing the cerebral metastatic disease.

Study outcomes

Outcomes included the presence of CNS progression, either with radiological or symptomatic relapse; compliance with MRI surveillance protocol, subsequent use of WBRT and death. The cause of death was noted, specifically whether the death was related to neurological deterioration or extracranial disease.

Statistical considerations

The primary study endpoint was survival time in months without WBRT calculated from the time of initial local therapy. Secondary endpoints included overall survival; CNS progression free survival; WBRT use and neurological progression free survival, calculated in months from time of initial local therapy. Survival curves were generated using Kaplan and Meier method. Univariate predictors of survival duration were evaluated using log-rank comparisons. All reported p values are two-tailed. Statistical significance was defined as $p<0.05$ in all cases. STATA version12, (StataCorp, Texas, USA) was used for statistical analysis.

Results

32 patients with advanced malignancy and diagnosed with CNS oligometastases were entered into the database from 1st July 2009 to 31st December 2012. 31 patients elected to be managed with WBRT

avoidance and entered the department protocol. One patient declined the protocol and was managed with WBRT. The median age at diagnosis was 62 years. Tumour Primary Sites included Breast (7), Lung (6), Renal (5), Melanoma (5), Colorectal (5) and others (3). Extracranial disease was present in 27 patients, of which 17 were asymptomatic at initial presentation with cerebral disease. The median time from initial diagnosis to CNS disease was 20 months, but 7 patients had cerebral disease at initial diagnosis.

23 patients were managed with initial craniotomy and resection of a metastatic deposit. Subsequently 6 patients proceeded to adjuvant surgical bed IMRT postoperatively. 9 patients received definitive RT to unresected metastatic lesions with 8 patients receiving SRS and 1 patient receiving IMRT. At time of analysis on 1st September 2013, 16 of 31 patients had died with a median follow-up of 15 months. For surviving patients the median follow-up was 23 months. The compliance with MRI surveillance was good with only 4 patients not attending for regular imaging, though all surviving patients had MRI in the 4 months prior to analysis. No grade 3 or 4 late toxicity arising from local therapy was reported in the study cohort.

Factor	Description	Patient Number (n = 31)
Number of Metastases at CNS Progression	0	10
	1	11
	2	5
	>5	5
Intracranial Site of Relapse in relation to Initial Site of CNS Metastasis	Nil	10
	Initial Site Only	3
	Distant Site Only	13
	Combined	5
Salvage Treatment	No relapse	10
	Surgery	6
	SRS	7
	WBRT	5
	Nil	3
RTOG Neurologic Function Score at last Follow-up	0	16
	1	7
	4-Feb	8
Principal Cause of Death	Nil	15
	CNS Disease	6
	Extracranial	9
	Other	1

Table 2: Details of CNS progression and salvage treatment (n=31).

CNS progression

21 patients had CNS Progression of which 12 were detected by MRI surveillance in absence of symptoms. Details of CNS Progression are outlined in Table 2. The relapses were at initial site (3), distant site (13) and combined sites (5) in the CNS. 11 of 21 initial relapses involved one metastasis at relapse; and five patients were diagnosed with >5 lesions. The CNS progression free survival as shown in Figure 2 was 11 months (95% CI: 4.9 - 17.1 months). Of the 9 patients who presented with symptoms at relapse between MRI imaging, 4 of these patients were non-compliant with MRI surveillance.

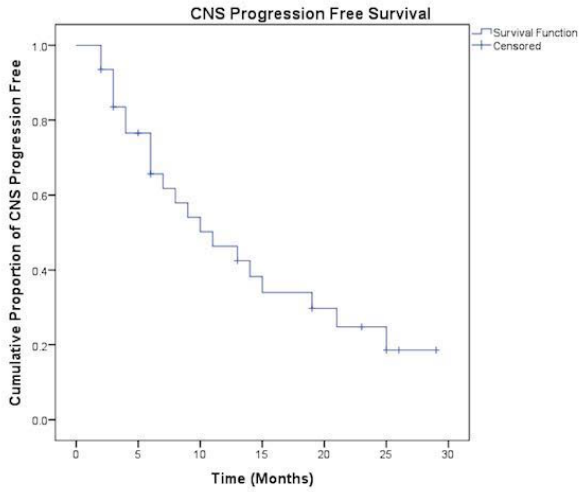

Figure 2: CNS progression free survival. The median CNS progression free survival was 11 months (95% CI: 4.9 - 17.1 months).

Only 5 patients (16%) were subsequently managed with WBRT at relapse. Two other patients were offered WBRT but declined electing for best supportive care alone. Of the 7 patients recommended for WBRT, 5 were at time of first relapse and the other 2 patients at second relapse. All 7 of these patients have subsequently died, with 5 related to CNS death.

No patients were offered new systemic therapy as a result of initial CNS progression. Neurological deterioration was noted in only 8 patients as assessed by a reduction in the RTOG Neurologic Function Score. The estimated median neurological progression free survival was 35 months (95% CI: 27.8 – 43.0 months); and neurological progression free survival at 24 months was 60%.

On univariate analysis age, primary tumour pathology, time from initial diagnosis to CNS disease, number of metastases, presence of extra cranial disease and baseline neurologic function or performance status was all not associated with CNS Progression. Specifically the median time to CNS progression for initial solitary metastasis versus two-four lesions was 9 months and 14 months respectively. Similarly for patients presenting more than the median 20 months from initial diagnosis of primary tumour, the median time to CNS Progression was 8 months compared to 13 months for those presenting with less than 20 months duration.

Overall survival

The median overall survival of the study group was 20 months (95% CI: 10.6 - 29.4 months; Figure 3). The cause of death was attributable to CNS disease in 6 patients. Baseline Neurological Function was

associated with median survival (p=0.009); with a median survival in asymptomatic patients of 29 months (95%CI: 12.9 – 45.0 months) compared with 6 months (95%CI: 2.6 – 9.4 months) in those with initial neurological impairment.

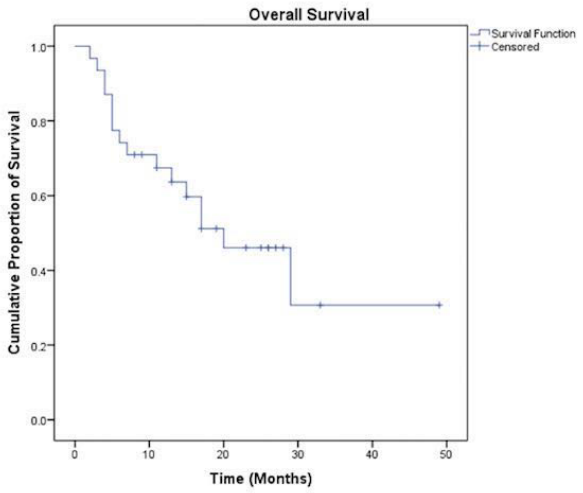

Figure 3: Overall Survival. The median overall survival of the study group was 20 months (95% CI: 10.6 - 29.4 months).

Discussion

Whole Brain Radiotherapy (WBRT) has traditionally served as the standard palliative treatment for brain metastases, and is generally associated with a median survival of 3 to 6 months [1-4]. Palliative WBRT reduces neurological deterioration associated with multiple or isolated unresectable brain metastases and associated cerebral oedema. It also reduced the relative risk of any intracranial disease progression by 53%, athough this did not translate to an improved survival or duration of functional independence [5]. WBRT is not without insignificant morbidity, including lethargy, poor body image, immune suppression, and the risk of long term neurocognitive impairment.

This clinical audit reviews the outcomes of patients with advanced malignancy and cerebral oligometastases who were managed with an active policy of WBRT avoidance with MRI surveillance, and provides preliminary data regarding overall survival time to CNS progression and CNS related death. Following local therapy with either surgery, SRS, IMRT or combined modality treatment, patients underwent a policy of close MRI surveillance imaging. The overall rate of CNS relapse was 67% with a CNS progression free survival of 11 months, which is comparable with results for the observation only arm following local therapy from the large EORTC 22952-26001 phase 3 randomised controlled trials. There was no apparent increase in mortality due to uncontrolled CNS disease with deferral of WBRT undertaken with close MRI surveillance.

Several recent developments in clinical practice including advancements in medical imaging and MRI detection of CNS metastases, improved systemic agents with better control of both extra cranial disease and agents which cross the blood-brain barrier, and increased access to salvage options including neurosurgery, Stereotactic Radiosurgery (SRS), Intensity-Modulated Radiotherapy (IMRT) and combined modality treatment, have increased treatment options available to patients with CNS metastases and seen an increase in median survival approaching 9 months and greater [6,7]. Choice of therapy must also consider impact of aggressive palliation on quality of life and financial cost.

The rationale for adjuvant WBRT following local therapies such as surgery, SRS or IMRT is to eliminate residual microscopic cancer cells at the site of resection as well as elsewhere within the brain, thereby reducing recurrence rates. Multiple retrospective series of surgery followed by focal RT to the tumour bed with a view to deferring WBRT have reported local control rates of approximately 75 to 95 per cent at one year and 60 to 80 per cent at two years [8-10]. There have been no prospective randomised controlled trials comparing postoperative WBRT with RT to the tumour bed, which may not mitigate the risk of recurrence elsewhere within the brain. Adjuvant WBRT following either surgery or SRS has been shown in three published randomised controlled trials to be associated with improved local and distant control, though there was no difference in overall survival and duration of functional independence [11-14]. With regard to toxicity, a randomised controlled trial of 58 patients was stopped early by its data monitoring committee after finding that patients receiving SRS and adjuvant WBRT were significantly more likely to show a decline in learning and memory function by 4 months compared to those who received SRS alone [14]. More recently, results from the randomised NCCTG N0575 trial evaluating 208 patients with or without WBRTs after SRS for 1-3 cerebral metastasis was presented at ASCO 2015, with the primary endpoint being cognitive progression [15]. The authors showed a statistically significant decline in cognitive function from baseline in the WBRT plus SRS group compared to SRS alone (88.0% vs 61.9%). Statistically significant deterioration was noted in both immediate and delayed recall as well as verbal fluency.

In this series, the CNS progression free survival of 11 months is acceptable with the understanding of available salvage options. The vast majority of patients with recurrence were asymptomatic, with progression identified on MRI only. Only 5 of the 21 patients with recurrence were offered WBRT at initial relapse, while 16 returned to MRI surveillance after further local therapy. The overall rate of subsequent WBRT (26%) was similar to the three randomised trials which demonstrated similar rates of WBRT use at relapse of 33%, 31% and 38% respectively [11-13]. Identification of early asymptomatic CNS relapse either locally or at a distant site within the brain may result in less morbid therapy, with the potential for ongoing close surveillance and deferral of further treatment until symptomatic. Salvage local therapy (with the potential for smaller surgical and radiotherapy volumes), or delivery of WBRT can then be instituted.

Similarly there was no apparent increase in mortality due to uncontrolled CNS disease with deferral of WBRT with close MRI surveillance. 14 of 31 patients were deceased at the time of analysis, with a median survival of 29 months. The cause of death was attributable to CNS progression in 6 patients (28%), a result which is once again comparable to the outcomes of a large randomised controlled trial in which patients received adjuvant WBRT following local therapy [13].

To date, patient performance status has been one of the major factors in guiding decision making [16]. Other important factors which may also influence treatment choices include number of brain metastases, extent of extracranial disease, and the histopathology of the primary tumour as a guide to radiosensitivity. A deferred WBRT approach might be particularly appropriate for patients with relatively radioresistant tumours (such as melanoma, sarcoma and renal cell

carcinoma) in whom the effectiveness of WBRT might be lower, or those patient with a good prognosis with respect to extracranial disease who may have a lower risk of developing further brain lesions and in whom the late neurocognitive effects of WBRT might reduce quality of life.

Clearly those patients eligible for such a program must be amenable to regular MRI surveillance and compliant with close follow-up. In the event of local recurrence or progression of intracranial disease, patients may be retreated while sparing patients the long-term toxicity of WBRT, with preservation of neurologic and neurocognitive function, and maximising quality of life.

The results from this small series supports other published data regarding a more conservative approach to the management of cerebral oligometastases by deferring treatment whole brain radiotherapy. This series provides data in regards to outcomes including overall survival, time to CNS progression, as well as toxicity and impact on quality of life. Potential limitations of our proposal for active MRI surveillance include access and affordability of imaging, and lack of a suitable alternative method of surveillance for those unable to tolerate an MRI (for example, presence of cardiac pacemakers, or severe claustrophobia).

Conclusion

WBRT avoidance with MRI surveillance is an acceptable management policy after local therapy for patients diagnosed with cerebral oligometastases. The rate of CNS progression is consistent with other published studies, predominantly detected by MRI prior to symptoms, and is not associated with an increased rate of death due to uncontrolled CNS disease. Use of WBRT is avoided in the majority of patients.

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