Volumetric Response of Brain Oligometastatic Disease to Focal Hypofractionated Radiation Therapy

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Research Article

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Abstract

Background:

This study aimed to assess the volumetric response, morbidity and failure rates of hypofractionated radiation therapy (HFRT) for definitive focal management of brain oligometastatic disease.

Methods:

Patients managed with HFRT for unresected oligometastatic brain disease were entered into an ethics-approved database. HFRT was delivered using IMRT or VMAT with 30Gy or 25Gy in 5 fractions. Individual lesions had volumetric assessment performed at three timepoints. Primary endpoint was change of volume from baseline (GTV0) to one-month post-HFRT (GTV1); and to seven-months post-HFRT (GTV7). Secondary endpoints were local failure, survival, and rate of radiation necrosis.

Results:

One hundred and twenty-four patients with 233 lesions were managed with HFRT. Median follow-up was 23.5 months with thirty-two (25.8%) patients alive at censure. Median overall survival was 7.3 months, with 36.3% survival at 12 months, with superior survival predicted by GTV0 ($p=0.003$) and percentage volumetric response ($p<0.001$). Systemic therapy was delivered in 81.5% of cases.

At one-month post-HFRT 206 metastases (88.4%) were available for assessment; at seven-months post-HFRT this had reduced to 118 metastases (50.6%). Median metastasis volume at GTV0 was 1.6cm^3 (range: 0.1-19.1). At GTV1 and GTV7 this reduced to 0.7cm^3 ($p<0.001$) and 0.3cm^3 ($p<0.001$) respectively, correlating to percentage reductions of 54.9% and 83.3%. No significant predictors of volumetric response following HFRT were identified. Local failure was confirmed in 4.3% of lesions and radiation necrosis in 3.9%.

Conclusion:

HFRT is an effective method for oligometastatic disease in the brain to maximise initial volumetric response whilst minimising pseudoprogression and radiation necrosis.

Background

Brain metastasis (BM) is the most common intracranial complication of systemic cancer [1, 2]. Incidence of BM is increasing due to improved magnetic resonance imaging (MRI) surveillance and improved systemic therapy, increasing demand for BM management strategies [3, 4]. Improved intracranial control directly benefits quality-of-life, neurocognitive function and possibly overall survival (OS) [1]. Earlier detection also means management options need to balance durable intracranial control and treatment-related morbidity. Focal therapy of BM using stereotactic radiosurgery (SRS), with or without surgery, and

subsequent imaging surveillance is now established over whole brain radiation therapy (WBRT) to minimise morbidity [5–7].

Whilst SRS is historically the preferred radiation modality, there are concerns over potential morbidity with inflammatory complications such as early pseudoprogression or late radiation necrosis, especially with larger volume lesions or interactions with systemic therapies such as immunotherapy [8–9].

Hypofractionated radiotherapy (HFRT), utilising regimens of 3–5 fractions of focal have the potential, through smaller doses per fraction, minimises the risk of toxicity compared with single-fraction SRS, whilst permitting delivery of equivalent biologic doses [10]. A recent study of 289 patients comparing SRS and HFRT to unresected BMs found significantly improved local control (89% vs 80%, $p = 0.004$) and reduced radiation necrosis (9% vs 18%, $p = 0.01$) in the HFRT group [11].

To improve the evidence base of HFRT, this study aims to quantify the volumetric response and subsequent outcomes of unresected BM to HFRT, and thus assess the efficacy of this emerging radiation delivery technique to guide decision-making.

Methods

Patient selection

Patients diagnosed with unresected oligometastatic brain disease referred to the radiation oncology unit at two university teaching hospitals between January 2014 and July 2020 were entered into an ethics-approved prospective register. Oligometastatic brain disease was defined as 10 or fewer BMs [12]. Patients with lesions deemed unsuitable for neurosurgical resection by multidisciplinary team (MDT) consensus due to BM number, size, location or patient performance status were included in the cohort. Lesions previously managed with SRS or prior radiation therapy were excluded from analysis, however some included patients had received radiotherapy previously for prior BMs and were still eligible for inclusion. Patients who received WBRT at any point in their treatment course were excluded from this study. All lesions in each patient received a uniform modality and dose of radiotherapy, hence small lesions < 10mm were treated with HFRT rather than SRS if there was a concurrent larger lesion being treated.

Primary systemic therapy was preferentially used for patients with EGFR-mutated non-small cell lung cancer (NSCLC) using tyrosine kinase targeted therapies, and metastatic melanoma using BRAF-targeted therapies or immunotherapy; however HFRT was used for large volume BMs or at time of BM progression in these cancers.

Baseline characteristics

Baseline information collected included patient demographics; primary tumour histology, presence of extracranial disease and prior systemic therapy; date of initial BM diagnosis and ECOG performance status at BM intervention.

Concurrent systemic therapy was defined as chemotherapy, immunotherapy, targeted therapy or a combination of these started within one month of commencement of HFRT.

HFRT Protocol

Patients were immobilised in either an Orfit mask or a frameless Brainlab cranial mask fixation system and computed tomography (CT) images were acquired with slice thickness of 1mm. The diagnostic gadolinium-enhanced MRI was fused within the treatment planning system and rigid registration undertaken. Image fusion accuracy was assessed by comparing both normal tissue structures and metastases on CT with the MRI-defined structures.

HFRT was delivered using an intensity-modulated radiation therapy (IMRT) or a volumetric-modulated arc therapy (VMAT) technique on a 6MV linear accelerator. The standard dose fractionation prescription was 30Gy in 5 fractions delivered in three fractions per week. An integrated boost approach to 25Gy was utilised to optimise the dose wash around the high dose region, with 30Gy dosed to the 100% isodose and delivered to the gadolinium enhanced lesion on MRI (GTV) expanded by 2mm (PTV30); and 25Gy delivered to that volume with an additional 3mm margin (PTV25). Alternative regimens of 25Gy in 5 fractions or 21Gy in 3 fractions were utilised in target-overlapped dose-limiting structures or poor patient performance status. Dosage to the optic chiasm and brainstem were limited to 20Gy and 25Gy respectively. Image guidance for each fraction involved cone beam CT.

Volumetric Assessment

Individual BM volumetric assessment (in cm³) was recorded at three timepoints: baseline pre-HFRT (GTV0); at one-month following HFRT (GTV1); and six-to-eight months post-HFRT (GTV7). This involved delineating the gadolinium-enhanced lesion within the radiation oncology planning system or in the diagnostic imaging PACS system. These time frames were selected as fixed points for post-treatment MRI surveillance, with patients receiving follow-up scans every three months after their initial one-month review. In the event of clinical deterioration interval imaging was recommended to exclude the presence of progressive disease or treatment related morbidity.

Study endpoints

The primary endpoints were median change in individual BM volume from GTV0 at one- and seven-months post-HFRT (GTV1 and GTV7). Volume reduction was calculated as a percentage of GTV0, with a negative value indicative of an increase in size. Secondary endpoints assessed were subsequent local failure, OS, cause of death and rate of radiation necrosis.

Any enhancement was assessed by consensus of the neuro-oncology MDT at time of occurrence, and classed into pseudoprogression, radiation necrosis or local failure after referral for sophisticated MRI and positron emission tomography. Local failure was defined as progressive increase in BM volume on two sequential MRI scans without reduction in volume in subsequent scans, deemed not to be due to the effects of radiotherapy. If death occurred from an extracranial cause before subsequent MRI could show resolution, the event was recorded as unconfirmed. Local control in other patients was defined as alive

without progression or absence of progression on last MRI or CT scan imaging prior to death. The toxicity outcomes recorded from treatment included either pseudoprogression (acute) or radiation necrosis (late), as above.

Statistical analysis

Descriptive statistics illustrated the baseline features of the study cohort, tumour characteristics and the type of treatments received by patients. GTV0 was compared on a per-lesion basis to the post-treatment timepoints using a paired-sample t-test. Factors impacting change in BM volume at one- and seven-months post-HFRT were determined through linear regression modelling. Survival curves for study outcomes were generated using Kaplan-Meier analysis of total patient BM bulk data. The log-rank test evaluated univariate, and Cox regression analysis with stepwise variable selection evaluated independent predictors of survival and progression. A p-value of < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Version 26.

Results

Demographic data

Between January 2014 and July 2020 124 patients with 233 unresected lesions were managed with HFRT and entered into the ethics-approved database. Patient demographic data is detailed in Table 1. Median age was 69.3 years (range 35.1–93.9 years). Lung was the commonest primary tumour site (43.5%). The median time from initial BM diagnosis to HFRT was 1.0 months (range 0.0-54.2 months).

Patient treatments and outcomes

The treatment and outcome data of the 124 included patients is presented in Table 2. Concurrent systemic therapy was delivered in 81.5% of patients. Following upfront therapy, patients were most commonly managed with supportive care alone (n = 74, 59.7%). The median percentage volume change per patient at the two follow-up timepoints were 48.5% (range – 304.4–100.0%) and 80.6% (range – 328.6–100.0%) respectively.

Median follow-up time was 23.5 months. Thirty-two (25.8%) patients were alive at the date of data censor. The median OS of the cohort was 7.3 months (Fig. 1), with 12-month survival being 36.3%. Of the deceased patients, twenty-one (16.9%) died of purely intracranial disease, and seven (5.6%) died of both intracranial and extracranial disease. The remaining 64 patients (51.6%) died from extracranial disease (44.4%) or other causes (7.3%).

Median total BM volume per patient was 3.4cm³ (range 0.1-48.2cm³) pre-HFRT, which fell significantly to 1.6cm³ after one month (range 0.0-45.8cm³, 48.5% reduction, p < 0.001) and 0.7cm³ (range 0.0-24.6cm³, 80.6% reduction, p < 0.001) after seven months (Fig. 2a).

Local failure was confirmed in only eight patients (6.5%), however, in sixteen (12.9%) patients it was impossible to determine whether local failure had occurred due to rapid decline from advanced extracranial disease without any further brain imaging. Seven (5.6%) patients experienced a radiation necrosis event (Table 2).

Individual lesion treatments and outcomes

The characteristics of the 233 lesions managed with HFRT are detailed in Table 3. The most common neuroanatomical sites were the frontal lobe (n = 60, 25.8%), cerebellum (n = 48, 20.6%) and the parietal lobe (n = 42, 18.0%). The 30Gy HFRT prescription was used for 88.8% of the lesions. The median biologically effective dose for an α/β of 12 (BED_{12}) was 45Gy.

At one-month post-HFRT, 206 metastases (88.4%) were available for assessment; and at seven-months post HFRT this had reduced to 118 metastases (50.6%).

Median individual BM volume pre-HFRT (GTV0) of the cohort was 1.6cm³ (range: 0.1-19.1cm³). Median GTV1 and GTV7 were 0.7cm³ (range: 0.0-35.1cm³, 54.9% reduction) and 0.3cm³ (range: 0.0-23.8cm³, 83.3% reduction). The median volumes at both GTV1 and GTV7 timepoints were significantly smaller than GTV0 median volume ($p < 0.001$ and $p < 0.001$ respectively) (Fig. 2b).

Thirty-four (14.6%) metastases had a volume increase $> 0.1\text{cm}^3$ from baseline at one-month post-HFRT, and subsequently ten of these (4.3%) were classified as events of pseudoprogression, and 15 (6.4%) died and could not be assessed further. Ten (4.3%) lesions which did not experience initial volume expansion were found to progress between the one- and seven-month scans. Failure was confirmed in a total of ten (4.3%) lesions and radiation necrosis in nine (3.9%), resulting in a local control rate of 95.7%. Among lesions stated to have achieved local control were 24 (10.3%) metastases defined as unconfirmed.

Factors associated with volumetric endpoints

Univariate linear regression of various factors including age at diagnosis, GTV0, primary tumour histology, radiation dose and concurrent systemic therapy showed no significant predictors of degree of volumetric response following HFRT on an individual metastasis or per-patient basis (Appendix A). Specifically, the total and individual GTV0 was not significantly associated with volumetric response at one month ($p = 0.948$, $p = 0.821$ respectively).

Younger age at diagnosis (HR = 0.93, $p = 0.006$) was associated with lesion local failure on individual logistical regression on a per-lesion basis (Appendix B), but no other factors were identified. Median GTV0 of lesions which locally failed was 4.6cm³ (range 0.9-5.4cm³), not significantly different to the remainder of the cohort ($p = 0.401$). There were no factors identified for development of radiation necrosis (Appendix B). Specifically, the median GTV0 of metastases which developed radiation necrosis was 2.1cm³ (range 0.7-6.0cm³), not significantly different to the remainder of the cohort ($p = 0.249$).

Factors associated with overall survival

The factors associated with OS are detailed in Table 4. On multivariate Cox regression analysis, factors independently associated with improved OS were smaller initial tumour volume (HR = 2.59, $p = 0.003$); volume reduction of > 50% at one-month post-HFRT (HR = 3.33, $p = 0.005$); volume reduction > 80% at seven-months post-HFRT (HR = 0.32, $p < 0.001$) and the use of a combination of more than one modality of systemic therapy concurrently with HFRT (HR = 0.43, $p = 0.035$).

Discussion

This study demonstrates that use of HFRT in the management of unresected oligometastatic disease of the brain confers an early and durable volume reduction, without significant risk of adverse events such as radiation necrosis. As there is minimal data to demonstrate the actuarial volume response following HFRT in unresected BM, this study assists in decision-making when considering SRS or HFRT for a larger-volume lesion. Among the 233 metastases included, the median pre-HFRT volume was 1.6cm^3 (range 0.1- 19.1cm^3), which significantly fell to 0.7cm^3 (48.5% reduction from baseline) one-month post-HFRT, and fell further in another six months to 0.3cm^3 (80.6% reduction from baseline). On linear regression, no patient, treatment or tumour factors were correlated with an inferior volume response, demonstrating that HFRT is equally effective at achieving a volumetric response for most BMs, irrespective of their initial size, site or histology. This differs from published SRS data which describes differing outcomes depending on the histopathological primary [13, 14].

The volumetric response greater than 80% to HFRT in this study is at least equivalent to published volumetric responses with SRS. Sharpton et al. found a 64% reduction in median volume after three months and no subsequent volume response was documented [14]. An analysis of 91 lesions treated with SRS alone by Diao et al. showed that the 60% volume reduction from baseline achieved one-month post-SRS diminished to a 43% reduction after 6 months [9]. Only in the SRS and immunotherapy arm of this study was a volume response rate of 80% achieved. In this current study only one-third of the cohort was managed with immunotherapy and the use of systemic therapy was not associated with improved volumetric response highlighting its potential as a neuro-oncological therapy [15].

Rates of transient pseudoprogression appear to be lower in HFRT compared to SRS, with this study finding that only 4.3% of patients experienced initial volume expansion which resolved by the seven months post-HFRT assessment. Pseudoprogression following SRS is postulated to be due to the opening of the blood-brain barrier and ingress of leukocytes to the treatment site, and is believed to reflect the high-fraction dose of radiation to the target lesion [8]. Cohorts treated with SRS experienced higher rates of pseudoprogression: the Bergen Criteria definition study of 348 SRS-treated metastases reported pseudoprogression rates of 14% [8]. Furthermore, Sparacia et al. found pseudoprogression in 28% of 54 lesions treated with SRS which resolved at 12 weeks [16]. Minimising pseudoprogression reduces symptom load and reduces anxiety of patients in whom there may be uncertainty over relapse. Oncologists may also need to delay or alter systemic therapy approaches, or increase corticosteroid requirements, which may impact on extracranial disease control [8, 17].

Local control rates in this study were greater than 90%, though noting that almost 13% of patients were unable to have response assessment. This is an accepted issue in reporting outcomes in advanced cancer complicated by BM where there are the competing risks of intracranial and extracranial disease [18]. Two retrospective comparative studies between HFRT and SRS have found that local control rates at 12 months for HFRT were 91% [11] and 70% [19], compared with 77% and 56% respectively with SRS, consistent with our study. Minniti et al. which reported 70% local control at 12 months delivered a dose of HFRT with median BED₁₂ of 47Gy [11], equivalent to the current study.

Despite international guidelines recommending SRS for limited BM in most clinical circumstances [20, 21], the biological advantages, efficacy and safety of hypofractionation of radiation doses is established [22, 23]. Compared with SRS, fractionation improves radiosensitisation through re-oxygenation of hypoxic malignant cells, augmenting tumour shrinkage through oxidative stress [24]. There is differing radiobiology between normal brain and tumour which can be optimised through HFRT over SRS. Since normal brain is a late-responder to radiation with a low α/β , and BM an early-responder with a high α/β , SRS is more likely than HFRT to damage normal tissue, leading to complications such as radiation necrosis [25]. A HFRT approach with VMAT or IMRT, although treating more surrounding normal brain, may limit the injury to that tissue by allowing maximal recovery time between fractions [26, 27]. In this study, radiation necrosis was reported in only 3.9% of metastases during the follow-up period. In Putz et al.'s comparison of HFRT (n = 98) and SRS (n = 92), a similar necrosis rate of 3.4% was found in the 12-months following HFRT to a median BED₁₂ of 52.4Gy [28]. Despite a lower median BED₁₂ of 41.0Gy being used for SRS, the rate of necrosis was significantly higher (14.8%, p = 0.045 on multivariate analysis). Rates of necrosis following HFRT are typically < 10% [11, 19, 28–30], whilst SRS has been associated with necrosis in over 20% of patients in two studies each over 250 metastases by Minniti et al. [11, 31].

Overall survival in this study was 7.3 months, equivalent to other studies of HFRT in unresected BM: a summary of six cohorts by Murai et al. totalling 363 patients demonstrated median OS post-HFRT of 3–15 months [32]. The survival of 7.3 months ought to be considered with the fact that initial management for many patients is resection followed by adjuvant cavity radiotherapy [33]. Only those with advanced extracranial disease, multiple lesions or co-morbidity are selected for non-operative management. Despite the range of benefits of HFRT over SRS, neither appear to confer superior survival, with several retrospective comparative studies of 90–190 patients finding no significant difference [19, 34–36], which may be due to the competing risk of extracranial disease on OS, but in this study, HFRT conferred a significant and consistent volumetric response which was independently predictive of superior OS.

Although the data demonstrate a role for HFRT in management of BM, the logistical impact on departmental workload should be considered, with the benefit of low rates of necrosis, pseudoprogression and local failure being balanced against more patient attendances being required for HFRT over SRS [37] and an increased dose of radiation to normal brain tissue, especially where multiple small-volume BMs are being treated, or multiple HFRT courses are required [38]. Improved planning software and delivery techniques may mitigate these risks through improved dosimetry. Additionally more

data is required to prove whether three- and five-fraction regimens provide equivalent outcomes, reducing the logistical impost.

The interpretations from this study are principally limited by the retrospective audit design, and the variability of extracranial disease influencing patient selection. There was extensive heterogeneity in choice of systemic therapy as patients were being managed by multiple medical oncologists for a range of primary subtypes during an era where immunotherapy and targeted therapies were evolving in clinical practice. Toxicity data is also limited with an absence of dexamethasone data, and diagnosis of late radiation necrosis being dependent upon timing of imaging and patient survival. Balancing these features is that all patients were treated uniformly with similar dosing regimens by only two radiation oncologists in units with established follow-up procedures.

Conclusion

Hypofractionated radiotherapy is an effective method for delivering high-dose radiation to oligometastatic brain disease, which maximises initial volumetric response whilst minimising pseudoprogression and radiation necrosis. Volumetric response, an independent predictor of survival, was demonstrated in metastases of all treated primary tumour pathology, sites in brain and tumour volumes. The data from this study should provide confidence in decision-making for advanced cancer patients with intracranial metastases.

Abbreviations

BED – biologically effective dose

BM – brain metastasis

GTV – gross tumour volume

HFRT – hypofractionated radiotherapy

OS – overall survival

PTV – planning target volume

SRS – stereotactic radiosurgery

VMAT - volumetric modulated arc therapy

WBRT – whole-brain radiotherapy

Declarations

Ethics approval and consent to participate: Ethics approval (ref: LNR/15/HAWKE/355) granted by Research and Ethics Governance Information System of New South Wales. Participants were consented at time of consult for inclusion in the prospective database of BM patients managed with definitive HFRT. Patients were provided with an information leaflet on the project and outcomes to ensure informed consent prior to giving consent.

Consent for publication: Participants were made aware through the information leaflet that the aim of the research was publication, and all included patients consented to these terms.

Availability of data and materials: The data that support the findings of this study are available from Royal North Shore Hospital Department of Radiation Oncology, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Royal North Shore Hospital Department of Radiation Oncology.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: ARW conducted the literature search, collected patient data, performed statistical analysis and prepared and proofed the manuscript. DTJ designed the study, effected patient treatment, collected patient data, edited and proofed the manuscript. JA effected patient treatment, collected patient data and proofed the manuscript. MFB created the database, obtained ethics approval, designed the study, effected patient treatment, collected patient data, prepared, edited and proofed the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1

Demographic data of the 124 cohort patients. ECOG=European Collaborative Oncology Group performance status score.

Patient Characteristics	N = 124
Age (years)	
Median (range)	69.3 (35.1–93.9)
Gender (%)	
Male	64 (51.6)
Female	60 (48.4)
Primary tumour location – Number (%)	
Lung – Non-Small Cell	50 (40.3)
Lung – Small Cell	4 (3.2)
Melanoma	21 (16.9)
Breast	15 (12.1)
Colorectal	8 (6.5)
Oesophageal	2 (1.6)
Renal	8 (6.5)
Others/Unknown Primary	16 (12.9)
Time from CNS metastasis to radiotherapy (months)	
Median (range)	1.0 (0.0-54.2)
Extracranial disease	
Nil	6 (4.8)
Asymptomatic	51 (41.1)
Symptomatic	67 (54.1)
ECOG performance status – Number (%)	
0	9 (7.3)
1	47 (37.9)
2	46 (37.1)
3	21 (16.9)
4	1 (0.8)

Table 2

Summary of treatments and volumetric outcomes of the 124 included patients. HFRT=hypofractionated radiotherapy, SRS=stereotactic radiosurgery, VMAT=volumetric modulated arc therapy, WBRT=whole-brain radiotherapy. *A negative value for volume reduction indicates volume expansion.

Patient Treatments and Outcomes	N = 124
Number of metastases per patient at diagnosis	
Median (range)	1 (1–7)
HFRT dose - Number (%)	
30Gy/5	106 (85.5)
25Gy/5	9 (7.3)
21Gy/3	7 (5.6)
Other	2 (1.6)
Prior management – Number (%)	
Nil Prior Management	75 (60.5)
Surgery	26 (21.0)
Systemic Therapy	11 (8.9)
Distant Site SRS	3 (2.4)
Combination	9 (7.3)
Concurrent systemic therapy – Number (%)	
Nil	23 (18.5)
Chemotherapy Alone	39 (31.5)
Targeted Therapy Alone	12 (9.7)
Immunotherapy Alone	16 (12.9)
Immunotherapy + Chemotherapy	19 (15.3)
Immunotherapy + Targeted Therapy	10 (8.1)
Chemotherapy + Targeted Therapy	5 (4.0)
Volume at time of diagnosis	
Median volume (range) (cm ³)	3.4 (0.1, 48.2)
Volume one-month post-HFRT	

Patient Treatments and Outcomes	N = 124
Number of patients alive – Number (%)	105 (84.6)
Median volume (range) (cm ³)	1.6 (0.0, 45.8)
Percent reduction - Median (range) (%)*	48.5 (-304.4, 100.0)
Volume seven-months post-HFRT	
Number of patients alive – Number (%)	67 (54.0)
Median volume (range) (cm ³)	0.7 (0.0, 24.6)
Percent reduction - Median (range) (%)*	80.6 (-328.6, 100.0)
Subsequent management – Number (%)	
Best Supportive Care	74 (59.7)
Surgery	5 (4.0)
SRS/VMAT	13 (10.5)
WBRT	10 (8.1)
Systemic Therapy	22 (17.7)
Outcome of treatment – Number (%)	
Radiation necrosis	7 (5.6)
Local failure	8 (6.5)
Unconfirmed	16 (12.9)
Cause of death – Number (%)	
Alive	32 (25.8)
Intracranial	21 (16.9)
Extracranial	55 (44.4)
Both	7 (5.6)
Other	9 (7.3)

Table 3

Summary of treatments and volumetric outcomes of the 233 individual metastasis. HFRT=hypofractionated radiotherapy. *A negative value for volume reduction indicates volume expansion. **Pseudoprogression.

Individual Lesions Treatments and Outcomes	N = 233
Location – Number (%)	
Frontal	60 (25.8)
Parietal	42 (18.0)
Temporal	39 (16.7)
Occipital	19 (8.2)
Brainstem	7 (3.0)
Cerebellum	48 (20.6)
Other	18 (7.7)
Radiation dose - Number (%)	
30Gy/5	208 (89.3)
25Gy/5	10 (4.3)
21Gy/3	12 (5.2)
Other	3 (1.3)
At time of diagnosis	
Number of metastases – Number (%)	233 (100.0)
Median volume (range) (cm ³)	1.6 (0.1, 19.1)
One-month post-HFRT	
Number of metastases – Number (%)	206 (88.4)
Median volume (range) (cm ³)	0.7 (0.0, 35.1)
Percent reduction - Median (range) (%)*	54.9 (-700.0, 100.0)
Volume increase – Number (%)	34 (14.6)
Seven-months post-HFRT	
Number of metastases – Number (%)	118 (50.6)
Median volume (range) (cm ³)	0.3 (0.0, 23.8)
Median volume (range) (cm ³)*	83.3 (-328.6, 100.0)

Individual Lesions Treatments and Outcomes	N = 233
Volume increase at one-month sustained – Number (%)	9 (3.9)
Volume increase at one-month transient – Number (%)**	10 (4.3)
Volume increase at one-month died – Number (%)	15 (6.4)
Outcome of treatment - Number (%)	
Radiation necrosis	9 (3.9)
Local failure	10 (4.3)
Unconfirmed	24 (10.3)

Table 4

Factors predictive of overall survival. BM=brain metastasis, GTV0=volume pre-HFRT, GTV0=volume at one-month post-HFRT, GTV7=volume at seven-months post-HFRT, HFRT=hypofractionated radiotherapy, MV=multivariate analysis with Cox regression, NSCLC=non-small cell lung cancer, OS=overall survival, SCLC=small-cell lung cancer, UV=univariate analysis with Log-rank test.

Factors associated with overall survival		n = 124			
	Median OS (months)	UV HR (95% CI)	UV p-value	MV HR (95% CI)	MV p-value
Sex (M/F)	6.3/11.1	1.44 (0.95–2.18)	0.083	-	-
Age at diagnosis (< 75/>75)	8.6/3.6	1.71 (1.09–2.69)	0.017	0.69 (0.33–1.46)	0.336
GTV0 (< 3.4cm ³ />3.4 cm ³)	11.1/6.9	1.56 (1.02–2.38)	0.038	2.59 (1.38–4.86)	0.003
GTV1 (< 3.0cm ³ />3.0 cm ³)	13.9/6.9	2.22 (1.44–3.69)	0.002	0.88 (0.34–2.28)	0.787
GTV7 (< 0.7cm ³ />0.7cm ³)	20.4/13.7	2.34 (1.35–4.78)	0.003	1.65 (0.51–5.36)	0.405
GTV1 reduction (< 50%/>50%)	6.9/14.7	0.61 (0.38–0.97)	0.034	3.33 (1.44–7.68)	0.005
GTV7 reduction (< 80%/>80%)	11.3/23.4	0.33 (0.17–0.62)	< 0.001	0.32 (0.17–0.61)	< 0.001
ECOG (0–1/2–4)	17.0/5.0	2.59 (1.68–4.00)	< 0.001	1.27 (0.65–2.49)	0.488
Melanoma primary (Y/N)	5.5/7.8	1.49 (0.88–2.49)	0.123	-	-
Colorectal primary (Y/N)	5.1/8.6	1.60 (0.82–3.09)	0.161	-	-
NSCLC primary (Y/N)	7.3/7.1	0.87 (0.57–1.32)	0.505	-	-
SCLC primary (Y/N)	6.4/7.8	1.11 (0.35–3.52)	0.863	-	-
Renal primary (Y/N)	8.6/7.0	0.63 (0.23–1.72)	0.362	-	-

Factors associated with overall survival			n = 124		
Breast primary (Y/N)	13.5/7.0	0.70 (0.35–1.40)	0.316	-	-
Symptomatic extracranial disease (Y/N)	5.3/13.2	2.01 (1.32–3.06)	0.001	1.2 (0.58–2.56)	0.597
Neurosurgery prior to HFRT (Y/N)	13.2/6.7	0.55 (0.32–0.95)	0.030	0.66 (0.31–1.41)	0.287
Systemic therapy prior to HFRT (Y/N)	41.0/7.0	0.43 (0.18–0.99)	0.040	1.01 (0.25–4.10)	0.987
Number of BMs (< 1/>1)	8.6/6.0	1.42 (0.87–2.31)	0.158	-	-
Radiation dose 30Gy/5 (Y/N)	8.6/6.0	0.74 (0.34–1.60)	0.438	-	-
Systemic therapy concurrent with HFRT (Y/N)	8.6/3.5	0.49 (0.30–0.80)	0.003	1.73 (0.62–4.78)	0.293
Concurrent immunotherapy (Y/N)	8.6/6.9	0.74 (0.48–1.16)	0.191	-	-
Concurrent targeted therapy (Y/N)	17.2/6.7	0.50 (0.28–0.87)	0.012	0.65 (0.27–1.58)	0.339
Concurrent chemotherapy (Y/N)	9.0/5.5	0.80 (0.53–1.21)	0.281	-	-
Concurrent combination systemic therapy (Y/N)	14.1/6.4	0.50 (0.30–0.83)	0.006	0.43 (0.20–0.94)	0.035
Salvage neurosurgery (Y/N)	NR/6.9	0.13 (0.02–0.96)	0.019	0.37 (0.05–2.88)	0.341
Salvage systemic therapy (Y/N)	13.9/6.3	0.60 (0.35–1.05)	0.072	-	-
Salvage radiotherapy (Y/N)	9.0/7.1	1.04 (0.62–1.76)	0.871	-	-
Local Failure (Y/N)	2.5/8.6	2.15 (1.32–3.49)	0.001	1.19 (0.44–3.21)	0.729

Figures

Figure 1

Kaplan-Meier plot of survival of the cohort of 124 patients. Median overall survival is 7.3 months. Two-month, six-month and twelve-month survival is 79.8%, 50.0% and 36.3% respectively.

Figure 2

Change in volume a) of total tumour bulk per patient (N=124). Pre-HFRT volume is significantly greater than at one-month post-HFRT ($p < 0.001$, ****) and then seven-months post-HFRT ($p < 0.001$, ****). Volume at one-month is significantly greater than at seven-months post-HFRT ($p < 0.001$, ****). b) of each metastasis (N=233). Pre-HFRT volume is significantly greater than at one-month post-HFRT ($p < 0.001$, ****) and is significantly greater than seven-months post-HFRT ($p < 0.001$, ****). Volume at one-month and seven-

months post-HFRT are not significantly different to each other ($p=0.224$, n.s.). GTV0=volume pre-treatment, GTV1=volume at one-month post-HFRT, GTV7=volume at seven-months post-HFRT, HFRT=hypofractionated stereotactic radiotherapy.

Supplementary Files

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