Brain metastases: treatment patterns and outcomes at Charlotte Maxeke Johannesburg Academic Hospital Radiation Oncology Department

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Declaration

I, Masana Ndleve, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in Radiation Oncology in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Candidate's signature

25/09/2020

Date

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I would like to extend my gratitude and appreciation to all who assisted me during the course of this research. All feedback and guidance were invaluable.

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Abstract

Title: Brain metastases treatment patterns and outcomes at Charlotte Maxeke Johannesburg Academic Hospital radiation oncology department.

Background: Improved therapies in cancer care have resulted in an increased incidence of patients with a diagnosis of brain metastases. Despite this, patient outcomes remain poor.

Aim: We reviewed treatment patterns and outcomes of patients with brain metastases following whole brain radiation therapy (WBRT)

Setting: Charlotte Maxeke Johannesburg Academic Hospital Department of Radiation Oncology, during the period 1 July 2016 - 30 June 2017

Methods: A retrospective record review of patients who received WBRT. Demographic and clinical data was collated in a data sheet and descriptive analysis performed using STATA Software 13 version. Survival analysis was done using Kaplan Meier method. All tests were considered statistically significant for $p<0.05$.

Results: A total of 89 patient records were reviewed of which 64 met the inclusion criteria. The mean age was 50.7 years, with a range of 24 to 76 years. Patients were predominantly female, (n= 51, 79.7%). The most common primary malignancies were breast (n=36, 56.3%) and lung (n=9, 14.1%). Only 2 (3.1%) cases were biopsy proven, with majority of cases being diagnosed radiographically by CT scan (n=60, 93.8%). MRI was done in only 8 (12.5%) patients. Over half of the cohort, (n=33, 51.6%) presented with headache, followed by motor weakness/gait disturbances in 31 (48.4%) patients. All patients received steroids at some point in their treatment. The most frequent radiation prescription dose given was 20Gy in 5 fractions; in 60 (93.8%) patients. Of these, 45 (70.3%) patients completed their radiation therapy. At 3 and 6 months follow up, 14 (77.8%) and 9 (81.8%) patients

respectively reported improvement in symptoms following treatment. A total of 45 (70.3%) deaths were registered at 1 year following WBRT. Forty one (64.1%) of these patients died within the first month following WBRT. Of these, 25 (39.1%) died within one week. The median survival of patients was 3.4 months. Patients in RPA class 3 predictably had the worst overall survival (p=0.0088). Whilst breast cancer patients had a worse overall survival than lung cancer patients, there was no statistically significant difference in survival functions for gender and age group.

Conclusion: WBRT may improve symptoms in patients treated for brain metastases, however the survival of majority of these patients remains poor in our clinical setting.

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List of abbreviations

BM	Brain metastases
CHBH	Chris Hani Baragwanath Hospital
CNS	Central Nervous System
CI	Confidence Interval
CT	Computed Tomography
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
ECOG	Eastern Co-operative Oncology Group Performance Status
GPA	Graded Prognostic Assessment
Gy	Gray
HJH	Helen Joseph Hospital
KPS	Karnofsky Performance Score
IMRT	Intensity-Modulated Radiotherapy
MRI	Magnetic Resonance Imaging
RPA	Recursive Partitioning Analysis
SRS	Stereotactic Radio Surgery
WBRT	Whole Brain Radiation Therapy

Chapter 1

Literature review

1.1 Introduction

Brain metastases (BM) are the most common intracranial tumours in adults (1). The incidence of patients with brain metastases is increasing due to better systemic therapies, which control the primary malignancy but don't cross the blood brain barrier well, therefore leaving the brain as a sanctuary site (2).

The management of brain metastases is complex and rapidly evolving with recent advances in treatment options. In most cases the outcome remains palliation of symptoms with the view to gain overall functional or rarely survival benefit. Reviewing the management and outcomes of patients with BM, enables us to improve and individualize care plans in our clinical setting (3).

1.2 Incidence

Prevalence and incidence data on BM is often lacking (4). Surveillance brain imaging is not always performed on neurologically asymptomatic cancer patients and autopsy studies are outdated, making it difficult to give an accurate account of the incidence of BM in cancer patients (5). The prevalence of BM in South Africa is not known because in the National Cancer Registry data of 2014, they are sometimes combined with central nervous system cancer statistics (6). Globally, approximately 20-40% of patients with malignancies will develop BM (6). The most common tumours to metastasize to the brain include lung, breast, melanoma, and renal cell carcinoma (7). Breast cancer is the most common cause of BM in women, however, overall lung cancer is the most common cause (5).

1.3 Anatomy and Pathophysiology

The brain parenchyma is the most common site of metastatic disease. The calvarium, meninges (both dura and leptomeninges), brain structures such as the choroid plexus and pituitary gland are less common non-parenchymal sites. Mechanism of dural involvement is usually direct extension of overlying calvarial metastases. Carcinomatosis is the involvement of the leptomeninges by malignant cells spread through the cerebrospinal fluid (8).
Different malignancies have a predilection for metastasizing to different areas of the brain. Metastases from renal cell carcinoma, arising from highly vascularized kidney parenchyma, are more often found in the well vascularized choroid plexus of the lateral ventricle than in other parts of the brain. Breast tumours tend to commonly metastasize to the posterior fossa. Prostate carcinoma rarely metastasizes intra-cranially, whilst small cell lung tumours tend to be equally distributed in all areas of the brain (5, 9).

The mechanisms of tumour cell attachment and local progression of micrometastases in the brain are multifactorial (5). The expansion of the intracranial tumour mass with surrounding oedema results in intratumoral haemorrhage, obstructive hydrocephalus, or embolisation by the tumour cells (9). This results in various clinical neurological sequalae.

Lymphatic drainage is absent in the brain, thus arterial haematogenous spread is the most common mechanism of metastatic spread of tumour to the brain. Tumour clumping results from emboli growth at the gray-white mater junction of the brain where the diameter of blood vessels decreases. The most common neuroanatomic sites where BM occur are the cerebral hemispheres (80%), the cerebellum (15%), and the brainstem (up to 5%) (9) Figure 1.1). This distribution is proportional to the blood flow in each area.

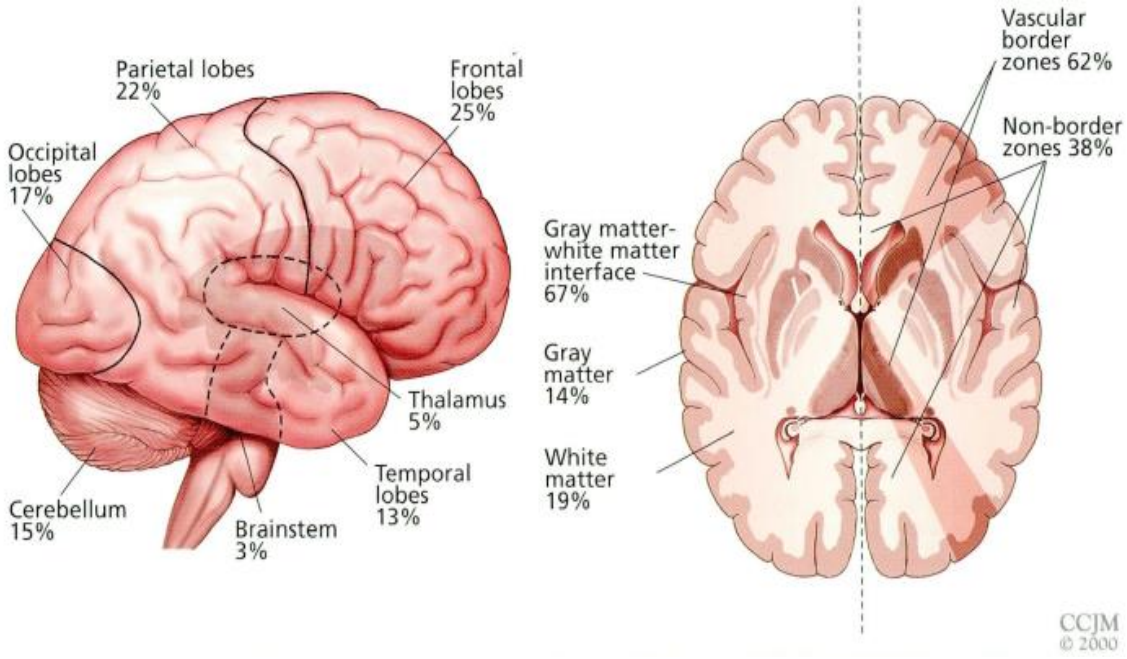

Figure 1.1: Distribution of brain metastases (10)

The discrepancy between a solitary brain metastasis and a single brain metastasis has treatment implications. A solitary brain metastasis is defined as the only known metastatic foci in the whole body which happens to be localized in the central nervous system (CNS). A single brain metastasis is defined as a single cerebral metastasis with or without the presence of other metastases in other organ systems (3).

1.4 Imaging

The differential diagnosis for any patient presenting with focal neurological deficits includes; infectious processes, cerebral infarction or other primary central nervous system (CNS) tumour (8). However, in a patient with a known malignancy, a clinician should have a high index of suspicion for BM.

The diagnostic imaging modality of choice used to detect BM is not computerized tomography (CT) scan, but magnetic resonance imaging (MRI) (11). Contrast enhancement is preferred in both imaging modalities for the detection of BM (12,13). Whilst MRI cannot unequivocally differentiate metastases from other lesions, certain radiological features favour the

diagnosis of BM. These include:

- A more spherical shaped lesion with clear demarcation from surrounding brain tissue
- Location of the tumour: as BM are often at grey-white mater junctions in watershed areas of the brain
- On T1 weighted MRI images after gadolinium contrast injection, BM are isointense or hypo intense
- Haemorrhagic BM can be hyperintense on T1
- The characteristic surrounding vasogenic oedema can be better visualized on T2 weighted images and FLAIR sequences
- BM can be single or multiple. Up to half the lesions are single with a third of diagnoses of BM made with the finding of multiple brain lesions (11,13)

Newer MRI techniques such as diffusion and perfusion imaging, MR spectroscopy and positron emission tomography (PET) tracers beyond traditionally used F18- fluorodeoxyglucose are being used and explored to provide physiologic and metabolic detail to add to standard MRI evaluation. These modalities are assisting in describing angiogenesis, perfusion, hypoxia, metabolite concentrations, cellularity and other critical features of malignancy (8).

In resource limited settings, MRI may not be readily accessible (14). The role of CT is then useful, particularly as a screening tool in patients with new onset neurologic symptoms. Unenhanced CT scan is capable of excluding acute life threatening sequalae of metastatic brain tumours which may require urgent neurosurgical intervention, such as mass effect, hydrocephalus or haemorrhage. An iodine contrast enhanced CT is required to comment on radiological features which support a diagnosis of BM, such as: the presence of multiple lesions (often underestimated on CT versus MRI), the localization of lesions at watershed areas (between the junction of grey and white mater) and the presence of circumscribed margins with surrounding vasogenic oedema (described as rim enhancing lesions) (8). CT is the modality of choice to display bony destruction, such as in calvarial metastases (8).

In unusual circumstances, such as uncharacteristic imaging features of BM, particularly in the setting of a patient with an unknown primary cancer diagnosis or a patient in remission, pathologic confirmation may be required for a definitive diagnosis of BM (15).

1.5 Symptoms

Neurologically asymptomatic patients with BM often go undiagnosed. The detection arises due to presentation with neurological signs or symptoms. These symptoms may range from non-specific to acute focal neurological deficits. The presentation is dependent on the size, number and location of the metastatic lesions. The most common symptom reported in patients with BM is that of headaches (49%). The history of headache on early morning wakening, is not pathognomonic but highly suggestive of BM especially in association with nausea and vomiting. Other signs and symptoms reported include focal weakness (30%), mental disturbances (32%), gait ataxia (21%), deficits of higher cortical functions such as comprehension, or speech difficulty (12%), visual (6%) and sensory disturbances (6%). Acute symptoms such as seizures (18%), suggest more extensive disease with either multiple metastases or leptomeningeal spread. An important and potentially fatal, initial complication is the sub- acute or acute rise in intracranial pressure due to obstructive hydrocephalus caused by metastases in the posterior fossa or brainstem (6).

The neurological status of a patient with BM is important as it assists in assessing symptoms experienced, as well as their effect on a patient's quality of life in terms of their physical, social and emotional well-being. The Karnofsky performance scale (KPS) and the Eastern Cooperative Oncology Group (ECOG) scales enable us to assess how patients care for themselves and carry out activities of daily living (16). These scales are often criticized due to their subjectivity and lack of reproducibility. In the clinical context however they remain important measures in predicting prognosis (17).

1.6 Whole Brain Radiation Technique

Whole brain radiation therapy (WBRT) is a non-invasive, radio therapeutic treatment modality historically used to bring about symptom relief in patients with BM (6). Without treatment or with best supportive care, patients' median survival was 1-2 months in previous trials. WBRT increased this by 3-6 months (18–20). These trials also showed that a clinical response was seen in 60– 90% of symptomatic patients following WBRT, with a median duration of improvement of 10–12 weeks. However, brain metastases were reported to be the cause of death in up to half of the patients. Thus no significant difference in survival outcomes, overall symptomatic response or duration of symptomatic response was seen in these trials (20).

With increasing local and systemic treatment options for managing patients with BM, WBRT is now mainly used in patients with an unfavourable prognosis because of uncontrolled extracranial disease or in patients with multiple brain metastases or poor performance status (3). WBRT has also been used in the management of recurrent disease, as well as in an adjuvant setting following surgery or stereotactic radiosurgery in order to improve local control at the tumour site and destroy microscopic disease at distant intracranial sites (21).

The technique of WBRT entails treating the patient with opposed lateral beams with the patient's head immobilised supine in a mask or tape, in order to deliver the radiation to the brain. The treatment field usually encompasses the lower end of the foramen magnum inferiorly to C1 or C2, and a margin (flash) anteriorly, superiorly and posteriorly (Figure 1.2). Blocks may be used to shield organs at risk such as the orbit, nasopharynx, oropharynx, and throat (22). Short-term complications of WBRT include dermatitis, otitis media and externa, and alopecia whilst long term complications include neurocognitive decline, decrease in cerebellar function, cataracts and the possibility of blindness (18). The relatively short survival of a majority of these patients often negates the need to consider optimizing WBRT to

circumvent the late complications. However with more conformal techniques, the ability to reduce the dose to the bilateral hippocampi is possible. This provides the benefit of sparing the dose to the neuro-regenerative stem cells in the hippocampi, thereby limiting neurocognitive decline (23,24). These modern intensity modulated radiotherapy (IMRT) techniques have also been used to improve the tolerability of WBRT. An example of this is scalp sparing techniques which limit the toxicity of alopecia (20).

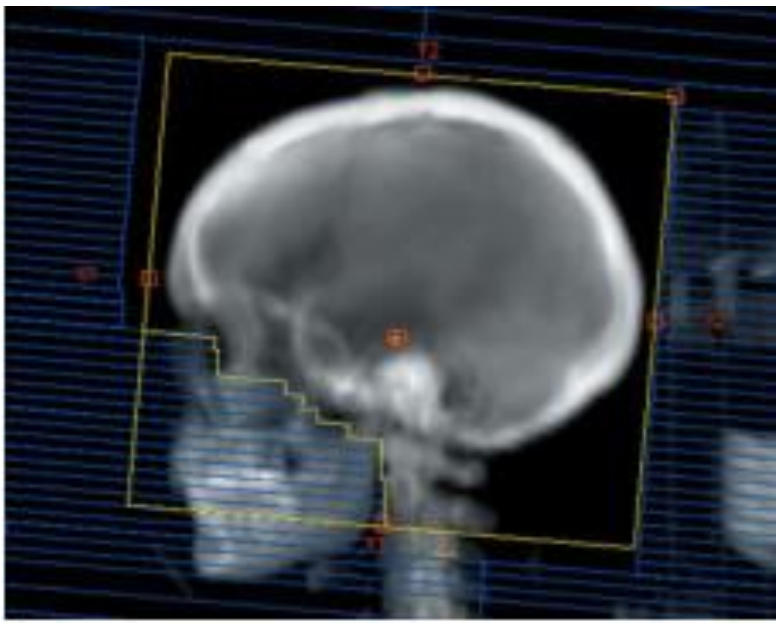

Figure 1.2: Whole Brain Radiation Treatment Field (24)

The optimal dose or fractionation schedule of WBRT is unknown. Systematic reviews have compared a regime of 30 Gy in 10 fractions, to ultra- rapid fractionated WBRT (10 Gy in one fraction, 12 Gy in two fractions, 15 Gy in two fractions over 3 days), or extended fractionation (50 Gy in 20 fractions or 54.4 at 1.6 Gy twice daily (19,20). A meta-analysis, failed to show a significant difference or survival benefit of dose escalation or altered WBRT dose schedules compared to standard doses of 30 Gy in 10 fractions or 20 Gy in 5 fractions (6). In clinical practice, acceptable fractionation schedules include 4 Gy × 5, 3 Gy × 10 being most common, with 2.5 Gy × 15, and 2 Gy × 20 also described.

1.7 Prognostic Indices and Survival

Prognostic indices are essential in guiding goals of therapy. The estimated overall survival of a patient guides management principles, preventing use of interventions that would result in unwarranted toxicity in patients unlikely to benefit from therapy, whilst justifying more radical treatment approaches in those who would have a survival benefit (25). Patient survival depends on both tumour and patient related factors. The recursive partitioning analysis (RPA) highlights 3 main factors contributing to survival of patients with BM (Table 1.1). These include performance status, control of extracranial disease and patient's age (15). In the Radiotherapy Oncology Group (RTOG) trials 3, prognostic groups were identified (19). Class 1 patients were characterized by having a KPS ≥70, age < 65, and controlled primary lesion with no extracranial metastases. This group of patients had the best median survival estimated at 7.1 months. Class 3 patients (KPS <70) had the worst median survival of 2.3 months whilst class 2 patients had an intermediate median survival of 4.2 months (26). The benefit of WBRT in the RPA class 3 group was also explored in "The Quartz trial" which compared WBRT versus best supportive care in non-small cell lung cancer patients who had a KPS <70. End points such as quality of life and overall survival in "The Quartz trial" suggest that WBRT was of little benefit in this group of patients (27)

The graded prognostic assessment (GPA) is another prognostic index which is used to account for the effect of the number of brain metastases, as patients with fewer BM (1– 3) were thought to survive longer than patients with multiple BM (Table 1.2). Factors required to calculate the GPA include the age, KPS, presence or absence of extracranial metastases and number of brain metastases (1, 2-3 and >3). Each factor is assigned to a score that predicts the expected median survival (28). A more recent diagnosis-specific GPA (DS-GPA) is another index used to further prognosticate patients with brain metastases according to histology (1,29). Using overall survival as the primary end point can be limiting in patients with BM as the presence of uncontrolled extracranial disease, has an effect on survival regardless of the intracranial disease control. Thus, improved intracranial control may not

necessarily always translate into improved overall survival (17).

Table 1.1: Recursive Partitioning Analysis (26)

Class	**Patient Characteristics**	**Median Survival (months)**
I	KPS ≥70, age <65, no extracranial metastases, controlled primary	7.1
II	All others, KPS ≥70 and at least one of the following: age ≥65 or extracranial metastases or uncontrolled primary	4.2
III	KPS <70	2.3

Table 1.2: Graded Prognostic Assessment (28)

	Score		
	0	0.5	1.0
Age (years)	> 60	50-59	< 50
KPS	< 70	70-80	90-100
Number of CNS metastases	> 3	2-3	1
Extracranial Metastases	Present	----	None

GPA score (Sum of the 4 scores above)	**Median survival (months)**
0-1	2.6
1.5-2.5	3.8
3	6.9
3.5-4	11

Despite the evolving management guidelines for patients with multiple brain metastases, survival remains low. WBRT has been shown to improve neurological symptoms experienced by this patient group, albeit at the cost of neurological toxicity which may not necessarily translate to improved quality of life. The relatively short survival of majority of these patients often negates the need to consider optimizing WBRT to circumvent late toxicities. Despite this, new advances in radio therapeutic management of patients with BM continue to develop. Patient selection with the aid of prognostic indices may be useful to determine which patients to consider palliating with WBRT and which to refer for best supportive palliative care.

We thus conducted a study to look at the treatment patterns and outcomes of patients who received WBRT at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

1.8 Study objectives

- To determine the overall survival of patients treated with WBRT
- To determine the response to treatment with WBRT in relation to symptoms

1.9 Methods

a. Study Design: This is a retrospective study.
b. Setting: Tertiary care radiation oncology clinic at the Department of Radiation Oncology, Charlotte Maxeke Johannesburg Academic Hospital.

1.10 Study Sample

At CMJAH, we treat approximately 100 patients with WBRT annually. A consecutive sampling method was used where-in patients were selected sequentially. Records of all the patients that had WBRT on the Cobalt 2 radiotherapy machine during the period 1 July 2016 - 30 June 2017 were included in the study.

Inclusion Criteria:

a. All adult patients who had a diagnosis of any primary cancer, or carcinoma of unknown primary with brain metastases and received WBRT.
b. Patients must have had imaging of the brain – at least a CT Brain or MRI of the brain to establish brain metastases.

Exclusion Criteria:

a. Patients with primary brain tumours.
b. Inadequate patient information and follow-up data.

1.11 Data Collection

Data was recorded from patient files onto a data collection sheet which included demographic variables. Other recorded variables include: primary cancer diagnosis, presenting symptoms, performance status of patient, examination findings, imaging modality for diagnosis of brain metastases, number of metastases, location of metastases in the central nervous system, recursive partition index and survival period (in months) following treatment. All collected data was entered into an excel database.

1.12 Statistical Analysis

All collected data was entered into an Excel database. Descriptive analysis of both numerical and categorical data was done using STATA 13, statistics software package (StataCorp, Collage Station, TX). Both the Fisher's exact test and in some cases the Chi square test was used to detect statistically significant associations in our sample. Survival analysis was done using Kaplan Meier method. The log rank test was used to test for equality of survivor functions. All tests were considered statistically significant for $p<0.05$.

1.13 Limitations

Limitations of the study include its retrospective design. This study required information from patients' records whilst on radiotherapy treatment and on subsequent follow-up visits, as well as during admission as in-patients. Record keeping is a known problem in many institutions. All the data to be collected depended on others for accurate record keeping. Incomplete records or missing data, as well as loss of patients to follow-up affected the sample size. The resultant limited sample size affected the statistical power of subgroup analyses. In terms of primary end point of overall survival, there were limitations in firmly establishing neurologic versus other causes of death. Furthermore, symptom resolution and quality of life data confirming the clinical benefit of WBRT and its potential neurocognitive impact were subjectively evaluated.

1.14 Ethics

Ethical approval to conduct the study was obtained from the Human Medical Research Ethics Committee, of the University of the Witwatersrand, assigned number: M180756. All other appropriate permissions were sought and granted.

1.15 Schedule

Actions	MAY-JUN '18	JUL '18	JUL - OCT'18	OCT 18 - NOV'19		DEC '19	JAN '20	FEB '20	MAR '20	APR '20	MAY '20
Literature Study											
Protocol Submission											
Protocol assessment, Ethics Committee and DOH approval											
Data Collection											
Data analysis											
Write up results of the study											
Evaluation and Corrections by supervisor											
Submit for examination											

1.16 Funding

No funding was required.

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Chapter 2

Draft article

Brain Metastases: treatment patterns and outcomes at Charlotte Maxeke Johannesburg Academic Hospital Radiation Oncology Department

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Conflict of Interest: None

Keywords: Brain Metastases, Intracranial Metastatic Disease, Overall Survival, Whole Brain Radiation Therapy (WBRT), Best Supportive Care

Abstract

Aim: We reviewed treatment patterns and outcomes of patients with brain metastases following whole brain radiation therapy (WBRT)

Setting: Charlotte Maxeke Johannesburg Academic Hospital Department of Radiation Oncology, during the period 1 July 2016 - 30 June 2017

Methods: A retrospective record review of patients who received WBRT. Demographic and clinical data were collated in a data sheet and descriptive analysis performed using STATA Software 13 version. Survival analysis was done using Kaplan Meier method. All tests were considered statistically significant for $p<0.05$.

Results: A total of 89 patient records were reviewed of which 64 met inclusion criteria. The population mean age was 50.7 years, with a range of 24 to 76 years. Patients were predominantly female (n=51, 79.7%). The most common primary malignancies were breast (n=36, 56.3%) and lung (n=9, 14.1%). Only 2 (3.1%) cases were biopsy proven, with the majority of cases diagnosed radiographically by CT scan (n=60, 93.8%). Over half of the cohort, 33 (51.6%) patients presented with headache, followed by 31 (48.4%) patients with motor weakness/gait disturbances. All patients received steroids at some point in their treatment. The most frequent radiation prescription dose given was 20Gy in 5 fractions in 60 (93.8%) patients. Forty five patients (70.3%) completed their radiation therapy. At 3 and 6 months follow up, 14 (77.8%) and 9 (81.8%) patients respectively reported improvement in symptoms following treatment. The mortality rate at 1 year was 70.3% (n=45), with 41 (64%) patients having succumbed within the first month. The median survival of patients was 3.4 months. Patients in RPA class 3 predictably had the worst overall survival (p=0.0088). Breast cancer patients had a worse overall survival than lung cancer patients. There was no significant difference in survival for gender and age in subgroup analyses.

Conclusion: WBRT may improve symptoms in patients treated with brain

metastases, however the survival of majority of these patients remains poor in our clinical setting.

Introduction

Brain metastases are the most common intracranial tumours in adults. Globally approximately 20-40% of patients with systemic malignancies will develop brain metastases (1), with the most common primaries being lung, breast, melanoma, and renal cell carcinoma (2).

The increase in patients with brain metastases can be attributed to improved surveillance with more modern diagnostic imaging techniques such as computed tomography (CT) scan and magnetic resonance imaging (MRI) (3). Better therapies have also played a role in controlling systemic disease, but the challenge remains that many drugs do not cross the blood brain barrier well enough to prevent the brain becoming a sanctuary site for metastases (2).

Despite increasing local and systemic treatment options, in most cases the outcome of patients with brain metastases (BM) is symptom palliation as overall survival remains poor. The recursive partitioning analysis (RPA) is used for estimation of patient survival, in order to better select optimal treatment options (4). Patient factors (such as performance status and comorbidities), as well as tumor factors (local and distant control of the primary malignancy), must be considered when deciding on management. Whole brain radiation (WBRT) in combination with corticosteroids can be considered for patients presenting with an uncontrolled primary tumour or multiple extra cerebral metastases (1).

Descriptive studies can provide clinically meaningful insight into treatment patterns of practice and outcomes and help guide clinical decision making. We thus aimed to retrospectively look at the profile of patients treated with WBRT at our radiation oncology center, their primary diagnoses, symptoms at presentation, imaging modality used to diagnose, fractionation schedules of radiation given and ultimately their outcomes of treatment and patient survival at one year following WBRT.

Methods

This is a retrospective descriptive review of patients treated at Charlotte Maxeke Johannesburg Academic Hospital, Department of Radiation Oncology. Consecutive records of patients eligible for the study were identified on LANTIS, an oncologic electronic medical record system by Siemens.

Inclusion criteria:

- Histologically confirmed adult cancer patients who had a diagnosis of any primary cancer or carcinoma of unknown primary, with brain metastases
- Patients must have received whole brain radiation therapy (WBRT).
- Patients must have had imaging of the brain – at least a CT Brain or MRI of the brain to establish the diagnosis of brain metastases.

Exclusion criteria:

- Patients with primary brain tumours
- Patients with incomplete records

A total of 89 patients who had received WBRT during the period 1 July 2016 - 30 June 2017 on the Cobalt 60 therapy machines were identified. Of these, 64 patients met inclusion criteria. Twenty-five records were excluded: 11 of these, were patients who had primary brain tumour, 1 had a primary spinal cord tumour and in 13patients, the records were incomplete.

Data was collected from patient's radiotherapy and oncology treatment files (both in outpatient and inpatient departments). Information extracted included:

- Demographic variables such as age and gender,
- Site of primary cancer,
- Presenting symptoms and complaints,
- Extracranial metastatic disease sites,
- Imaging modalities used at diagnosis and their findings,

- Supportive therapies such as high dose steroid use,
- Performance status of patient
- Radiotherapy treatment dose and schedule.

Follow-up records at approximately 3 month intervals, as well as response to treatment up to 1 year following WBRT were also retrieved. This included a documented patient account of improvement in symptoms. The subjective evaluation of recorded presenting complaints and examination findings at presentation and at each follow-up, was used to determine the improvement in symptoms. When not recorded, a date of death was confirmed using patients identity numbers via the Verify ID website (5). Anonymized data was recorded into a single database on Microsoft Excel. Descriptive analysis of recorded data was done using STATA statistical software 13th version. Both the Fisher's exact test and Chi square test were used to determine statistically significant associations. Survival analysis was performed using the Kaplan Meier method. All tests were considered statistically significant for $p<0.05$.

Ethical considerations:
Ethical approval to conduct the study was obtained from the Human Medical Research Ethics Committee at the University of the Witwatersrand, assigned number: M180756. All other appropriate permissions were sought and granted.

Results

We identified 64 BM patients treated at the CMJAH radiotherapy center during the study period. Over half were referred from CMJAH (n=36, 56.5%), the remainder were mainly from the Chris Hani Baragwanath Academic Hospital (n=14, 21.8%) and Helen Joseph Academic Hospital (n=10, 15.6%), with the few remaining (n=4, 6.1%) from Bertha Gxowa, Bheki Mlangeni, Pholosong and Tambo Memorial Hospitals.

The mean age was 50 years, with a range of 24 to 76 years. Patients were predominantly female (n=51, 79.7%) and male (n=13, 20.3%) (Table 1).

The most common primary malignancies were breast (n=36, 56.3%) and lung (n=9, 14.1%). Others included lymphoma (n=6, 9.3%), carcinoma of unknown primary (CUP) (n=3, 4.7%), melanoma, choriocarcinoma, cervical cancer, head and neck cancer each with 2 (3.1%) patients respectively, and ovary and colon each with 1 (1.6%) patient.
Majority of the patients (n=42, 65.60%) had extracranial metastatic sites, of which 27 (42.19%) patients were bone and 23 (35.90%) were lung metastases.

Only 2 (3.1%) patients had biopsy proven BM, with the remainder i.e. 62 (96.9%) being diagnosed radiographically. Brain CT scan was the diagnostic modality most often used and done in 60 (93.8%) patients, with only 8 (12.5%) patients having had an MRI. Metastases were cerebral in 53 (82.8%) patients, with the remainder in the posterior fossa (Table 2).

In terms of symptomatology at presentation, over half of the patients (n=33, 51%) presented with headache, followed by motor weakness/gait disturbances (n=31, 48%), nausea or vomiting (n=25, 39%), and 18 (28%) patients displayed confusion with the same number also experienced symptoms of higher cortical dysfunction (such as changes in memory, mood and personality) (Table 1). A history of either generalized or focal seizures was also reported in 16 (25%) patients. All patients received steroids at some point in their treatment.

Patients' performance status was recorded based on their ECOG scores with only 3 (4.7%) patients having a very poor performance of 4. In terms of RPA class, the majority of patients fell into class 2, (n=30, 46.9%), followed by 21 (32.8%) patients being categorized as class 3 and only 13 (20.3%) patients were RPA class 1 (Table 1).

The most frequent radiation prescription dose given was 20Gy in 5 fractions (n=59, 92.1%). Of these, 45 (70.3%) patients completed their radiation

therapy (Table 2). Alternate fraction dose schedules included 2 patients with a primary diagnosis of choriocarcinoma who received 26Gy in 13 fractions, 2 patients who received 12Gy in 2 fractions on alternate days, and 1 patient who received 18Gy in 3 fractions on alternate days.

The number of patients seen at 3 months follow up was 18 (28.1%), of which 14 (77.8%) reported improvement in symptoms. Similarly at 6 months follow up, the majority of patients (n=9, 81.8%) reviewed still reported improvement in symptoms (Table 4).

At one year following whole brain radiation, 45 (70.3%) deaths were registered. The median survival of patients was 3.4 months (Figure 1.1). A total of 41 (64.1%) patients died within the first month of treatment; 25 (39.1%) within first week of treatment (Figure 1.2). Of the initial cohort, at 3 months follow up, RPA class 1 patients had a 0.59 survival with a 95% confidence interval (CI) (0.28-0.81) p=0.0088. Conversely RPA class 3 patients had 0.10% survival with a 95% CI (0.01-0.31) p=0.0088 (Table 3).

When comparing the two most common cancers; breast and lung, breast cancer patients at 12 months had 0.16% survival, CI (0.10-0.31), whilst lung cancer patients had 0.27% survival, CI (0.10-0.70). There was no statistically significant difference in survival between males and females, or between younger (< 50 years) patients and older (> 50 years) patients in this cohort.

Table 1: Participants' Baseline Characteristics (64 Patients)

Demographics	**Mean**	**Range**
Age (years)	50	24-70
Gender	**N**	**%**
Male	13	20.3
Female	51	79.7
Primary Diagnosis	**N**	**%**

Breast	36	56.3
Lung	9	14.1
Lymphoma	6	9.3
Carcinoma of Unknown Primary (CUP)	3	4.7
Melanoma	2	3.1
**OTHER	8	12.5
ECOG	**N**	**%**
1	20	31.2
2	24	37.5
3	17	26.6
4	3	4.7
RPA	**N**	**%**
1	13	20.3
2	30	46.9
3	21	32.8
Neurological Symptoms	**N**	**%**
Headache	33	51.5
Motor weakness/Gait	31	48.4
Nausea & Vomiting	25	39.1
Sensory Fall out	22	34.3
Confusion	18	28.1
Higher Cortical Dysfunction	18	28.1
Seizures	16	25.0
Dizziness	3	4.1

*ECOG-Eastern Co-operative Oncology Group Performance Status, RPA-recursive partition analysis

**OTHER-Chroriocarcinoma, Head & Neck, Cervix, Colon & Ovary

Table 2: Metastases Diagnosis, Location and Treatment Characteristics

Extracranial Metastases	**N**	**%**
Yes	42	65.6
No	22	34.4
Imaging Modality used in Diagnosis	**N**	**%**
CT	60	93.8
MRI	8	12.5
CT + MRI	4	6.6
***Location of Brain Metastases**	**N**	**%**
Cerebrum	53	82.8
Cerebellum	16	25.0
Brainstem	6	9.4
Radiation dose/fractionation schedules prescribed for WBRT	**N**	**%**
20Gy/5#	59	92.2
Radiation treatment completed	**N**	**%**
Yes	45	70.3
No	19	29.7

- *Some patients had more than 1 metastasis; and in more than 1 region of the brain

Table 3: Survival Outcomes

Time (months)	Alive (n)	Dead (n)	Survival	95% Confidence Interval
RPA class 1				
3	7	5	0.59	(0.28-0.81)
6	6	6	0.50	(0.20-0.74)
12	3	0	0.30	(0.10-0.60)
RPA class 2				
3	14	13	0.52	(0.32-0.70)
6	10	15	0.42	(0.23-0.61)
12	6	18	0.30	(0.12-0.48)
RPA class 3				
3	3	18	0.10	(0.01-0.38)

Table 4: Symptom Outcomes

Follow-up Period	Number of Patients	Symptoms Improved	
		Yes (%)	No (%)
3 Months	18	14 (77.8)	4 (22.2)
6 Months	11	9 (81.8)	2 (18.2)

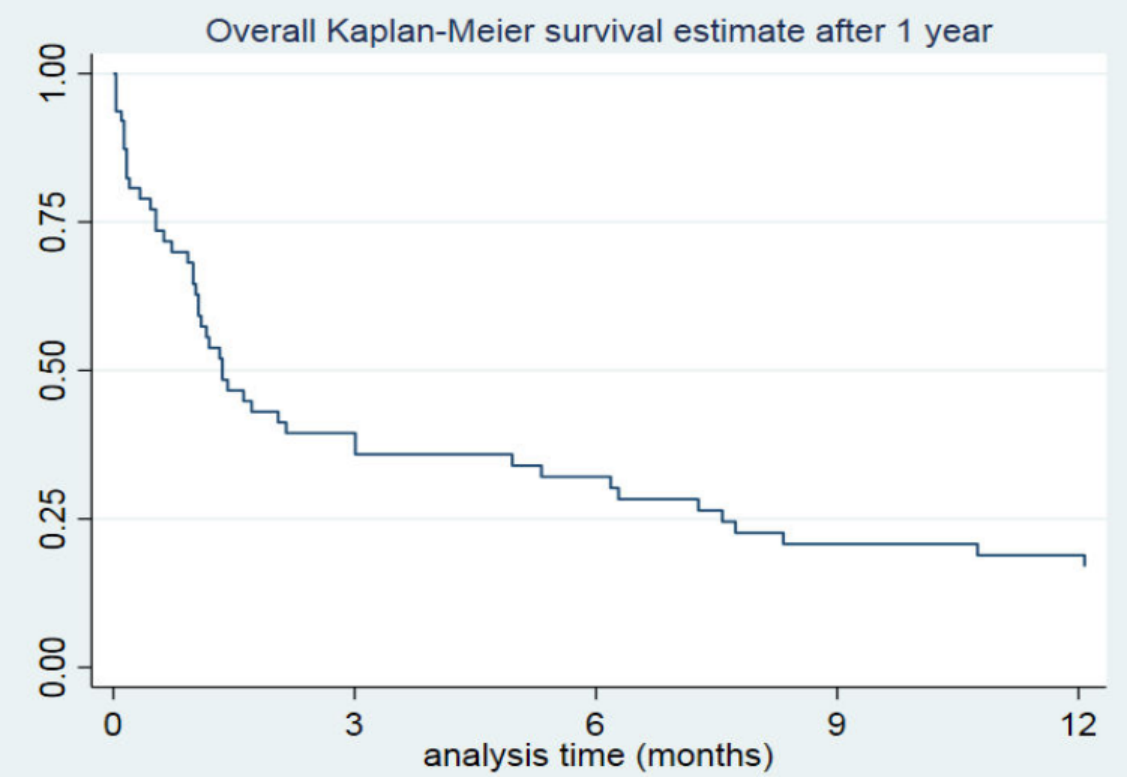

Figure 1.1: Participant overall survival in 1 year

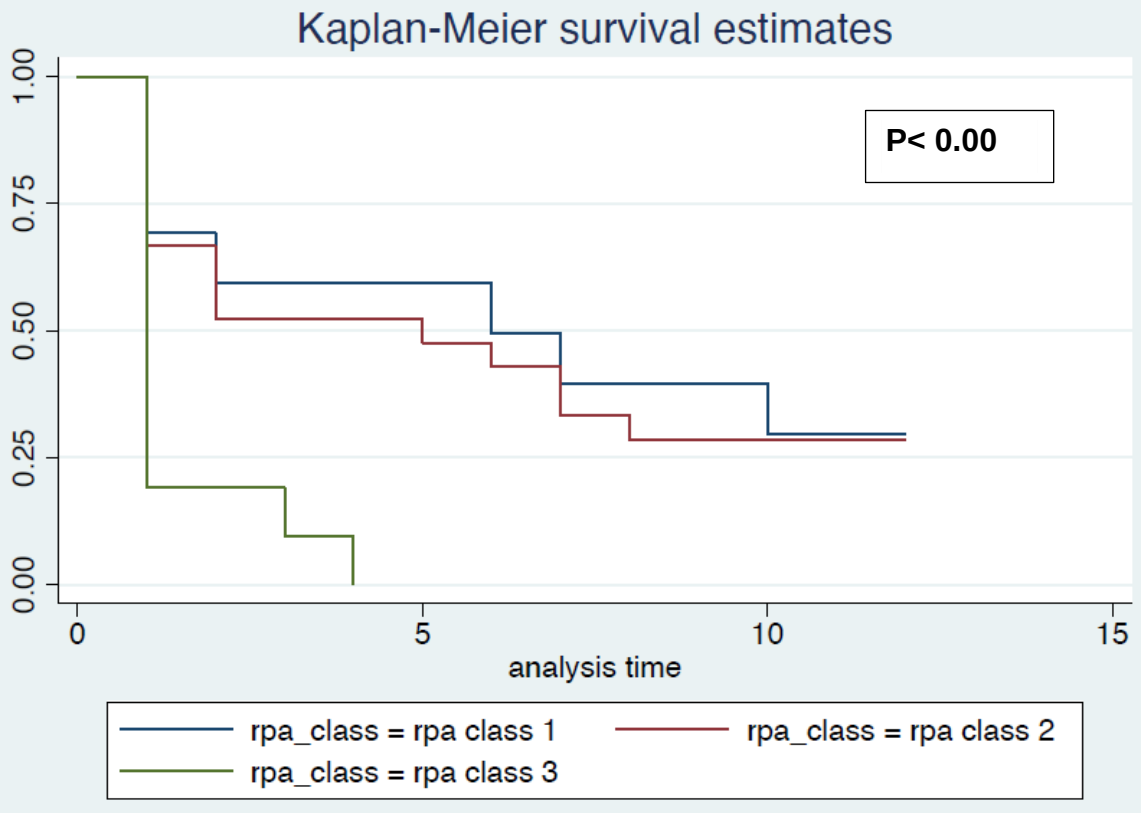

Figure 1.2: Participant overall survival according to RPA class

Discussion

This study provides insight into patient characteristics, patterns of practice and outcomes of patients treated with WBRT at our facility.

Brain metastases are the most common intracranial tumours in adults (5). The age group at greatest odds of presenting with brain metastases are those between 41–60 years (6). This was mirrored in our results by the mean age in our sample which was 50 years.

In the adult population, BM are most frequently secondary to primary tumours of the lung (50–60%), breast (15–20%), skin i.e. melanoma (5–10%) and the gastrointestinal tract (4–6%) (7). In our study, the most common primary sites identified were breast (56.3%) and lung (14.1%). This discrepancy in our primary source of BM is not unexpected. There are almost five times as many new patients diagnosed with breast cancer than lung cancer in South Africa (8). Whilst not as common as breast or lung cancer, renal cell carcinoma is reported to have the highest propensity for haematogenous spread to the brain parenchyma of all malignancies (6). No patients with renal cell carcinoma were identified in our population group, unsurprisingly as it accounts for <1% of malignancies in South Africa (9).

Lung cancer affects more males than females globally as well as in South Africa but breast cancer is the most common cancer in South African females (8,9). According to the 2016 South African cancer registry data, there were more females diagnosed with new malignancies than males. The commonest recorded malignancy in females was breast cancer and approximately 10–30% of patients with breast cancer are diagnosed with BM during the course of their disease (10). These findings may explain the female predominance in our study (79.7%).

The common symptoms documented in our patients were headache (51.5%), motor deficits (48.4%), nausea and/or vomiting (39.1%) (Table 1). These findings are largely consistent with those published by Tsao et al (1). In their

review almost half (49%) of their patients had headache and motor weakness and gait abnormalities were present in 51%. Unfortunately our records did not expand on the nature of headaches documented, but it is likely that it would be suggestive of the typical headache associated with raised intracranial pressure. Seizures occurred in one quarter (25%) of our patients which is marginally higher than their reported frequency of 18%. Nausea and vomiting were a common complaint in our cohort (39.1%) and likely represent advanced disease. The prevalence of these symptoms can be as high as 70% in patients with advanced cancer (11)

The diagnostic modality of choice in the diagnosis of brain metastases is MRI (12). The setting of the study was a tertiary level hospital in the public sector in Johannesburg, where there is only one MRI machine. The ability to obtain an MRI brain is often constrained (13). This is reflected in our diagnostic work-up as only 8 (12.5%) of our patients had MRI scans of the brain done. Contrast enhanced brain CT scan was the modality mostly used to diagnose BM. Contrast-enhanced MRI is more sensitive than either non-enhanced MRI or CT scanning in detecting, localizing and quantifying lesions in patients with suspected BM (14) This study entailed looking only at reports of imaging findings, and not the CT or MRI images. As such there was no accurate record regarding the number of brain metastases found or typical features that favored a radiological diagnosis of brain metastases. However the majority of the imaging reports reviewed, detailed that multiple metastases were present, with the most common location being the cerebral hemispheres (frontal/parietal/occipital lobes). This corroborates with findings where in the majority of BM are found in watershed areas and follow the distribution of blood flow in each area of the brain (15,16).

Adjuncts such as corticosteroids improve neurologic symptoms in up to 75% of patients with cerebral edema and should be used in any patient with BM with neurological symptoms, as well as preceding WBRT (17). Dexamethasone is the preferred agent of choice as it has a longer half -life and less toxicity. The guidelines suggest a dose of 4-8mg per day, twice daily. Majority of our patients were in-patients at the time of treatment, and all received steroids preceding their WBRT. The use of WBRT has been

documented to decrease steroid use in this population group, as steroids are known to have a wide toxicity profile (17). Unfortunately there was very little documentation on the continued use of steroids following WBRT to be able to evaluate this.

Management of patients with brain metastases is variable, dependent on patient and tumour factors. WBRT is indicated in the management of patients with poor ECOG or multiple brain metastases (1,3). Whilst some patient had very limited disease (less than 5 metastases reported on imaging findings), we do not offer stereotactic radiosurgery at our institution. As such, all patients received WBRT regardless of the number of brain metastases. The criticism on the above treatment in patients with limited disease and a better prognosis, is the toxicity associated with WBRT. Particularly with regards to neurocognitive decline (18). Our findings were lacking in quality of life data following WBRT. The physician's records during the follow up of patients following WBRT were not always adequate in exploring quality of life issues in terms of physical, social and emotional well-being. Whilst ECOG and KPS scores enable us to look at and assess how patients care for themselves and can carry out activities of daily living, these scales are often subjective and lack reproducibility (19). We thus used these subjective findings by reviewing the patients initial presenting complaints as well as clinical and symptomatic findings on follow up, in order to gauge improvement in symptoms following WBRT. Surprisingly, despite the known toxicities associated with WBRT, the majority of patients had subjective improvement in symptoms on follow up.

A Cochrane review suggests that there is no overall survival benefit or difference in various fractionation schedules for WBRT (1,20). During the study period the following fractionation schemes were used: conventional fractionation with daily fractions of 2 Gray (Gy), five days per week to a planned total dose of 26 Gy, hypofractionation with daily fractions of 4Gy, five days per week to a planned total dose of 20 Gy, as well as ultra hypofractionated doses of 18Gy in 3 fractions on alternate days, and 12Gy in 2 fractions on alternate days. No patients received 30Gy in 10 fractions which is a commonly described fractionation schedule. This may be due to our

resource limitations as 10 day treatment schedules would create more delays for access to patients who require radiation treatment. In our center, therapy time on the linear accelerators must be balanced in order to offer the majority of patients the benefit of treatment, both curative and palliative. Thus 20Gy in 5 fractions is the most commonly practiced regimen in our center.

Survival of patients depends on both tumour and patient related factors. The recursive partitioning analysis (RPA) highlights 3 main factors contributing to survival of patients with BM. These include performance status, control of extracranial disease and patient age (21). In the RTOG trials, 3 prognostic groups were identified . Class 1 patients are characterized by having a karnofsky performance score (KPS) ≥70, age <65, and controlled primary with no extracranial metastases. This group of patients have the best median survival estimated at 7.1 months. This was evident in our findings as proportionately the majority of patients alive at 1 year following WBRT were those in RPA class 1 as compared to class 2 and 3. Class 3 patients (KPS <70) had the worst median survival of 2.3 months whilst class 2 patients had an intermediate median survival of 4.2 months (17). These findings were clearly evident in our study, with patients in the RPA class 3 category having poor outcomes. More than a third of the patients demised within a week following WBRT. The benefit of WBRT in the poor prognostic RPA class 3 group was explored in “The Quartz trial” which compared WBRT versus best supportive care in non-small cell lung cancer patients who had a poor performance score (KPS <70). End points such as quality of life and overall survival in the Quartz trial suggest that WBRT was of little benefit in this group of patients (22). Whilst improvement in overall survival is considered the gold standard for oncology clinical trials, quality of life issues have become increasingly more valuable as an endpoint to evaluate in patients for whom overall survival still remains poor.

The increase in incidence of brain metastases has been attributed to improved systemic therapies, which do not cross the blood brain barrier, and as such render the brain a sanctuary site for metastases (23). The majority of our patients (65.6%) had poorly controlled disease as evidenced by the presence of extra-cranial metastatic disease sites. The presence of

uncontrolled extracranial disease, has an effect on survival regardless of the intracranial disease control (19).

This study was valuable in evaluating our practice as well as outcomes for patients with BM at CMJAH department of radiation oncology with many of the findings consistent with findings in the literature. Limitations of the present study include the limited number of patients, statistical power of subgroup analyses, and its retrospective design. In terms of primary end point of overall survival in many cases, we were unable to firmly establish neurologic versus other causes of death in our patients. Furthermore, symptom resolution and quality of life data confirming the clinical benefit of WBRT and its potential neurocognitive impact were very subjectively evaluated.

Conclusion

WBRT may improve the neurological symptoms experienced by patients with brain metastases. RPA class 1 patients benefit most in terms of survival benefit from WBRT. Majority of patients in our center at baseline have other extracranial metastatic sites, and are symptomatic with a decline in their performance status. Many patients fail to complete the scheduled course of WBRT and the overall survival of majority of these patients remains poor.

Competing interests

I declare that I have no financial or personal relationships that might have inappropriately influenced me in writing this article.

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Chapter 3 :…… Appendices

Appendix 1: Human Research Ethics Committee (Medical) approval

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Dr M Ndlovu
School of Clinical Medicine
Department of Radiation Sciences
Division of Radiation Oncology
Charlotte Maxeke Johannesburg Academic Hospital

E-mail: Masanandlove@gmail.com

CC: Supervisor: Prof V Sharma and Dr KR Hari <Vinay.Sharma@wits.ac.za> and <HREC-MedicalResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 02/10/2018

REF: *R14/49*

PROTOCOL NO: **M180756** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *Brain metastases treatment patterns and outcomes at Charlotte Maxeke Johannesburg Academic Hospital, Radiation Oncology Department*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

R14/49 Dr M Ndleve

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M180756

NAME: (Principal Investigator)	Dr M Ndleve
DEPARTMENT:	School of Clinical Medicine Department of Radiation Sciences Division of Radiation Oncology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Brain metastases treatment patterns and outcomes at Charlotte Maxeke Johannesburg Academic Hospital, Radiation Oncology Department
DATE CONSIDERED:	27/07/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof V Sharma and Dr KR Hari
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	02/10/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date of the meeting when the study was initially reviewed. In this case, the study was initially reviewed in July and will therefore reports and re-certification will be due early in the month of July each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 2: Approval from Department/Faculty

Department of Radiation Oncology

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

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Dated 12-9-2018

To

The Chairperson

Ethics Committee

University of Witwatersrand

re: Ethics Clearance of the proposal(M180756)

Dear Prof Clem Penny,

This is to inform you that Dr M.Ndleve (Student no. 1239311) is working as a registrar in the Department of Radiation oncology. She has already done the required changes as advised by ethics committee. I am satisfied with the changes and corrected version of the proposal should be accepted.

With best regards

Vinay Sharma

Prof Vinay Sharma

Head, Department of Radiation Oncology

Appendix 3: Approval letter from Chief Executive officer

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mzila
Office of the Clinical Director
Email:Nolwazi.Mzila@gauteng.gov.za
Tell: (011): 488-4812
6th July 2018

Dear Dr. M. Ndleve

STUDY TITTLE: Brain Metastases Treatment Patterns and Outcomes at Charlotte Maxeke Johannesburg Academic Hospital Radiation Oncology Department.

Permission to conduct the above mentioned study is provisional approved. Your study can only commence once Ethics approval is obtained. Please forward a copy of your Ethics Clearance Certificate as soon as the study is approved by the Ethics Committee for the CEO's office to give you the final approval to conduct the study.

Supported / ~~not supported~~

Dr. M.I. Mofokeng
Clinical Director
DATE: 6/07/2018

Approved / not approved

Ms. G. Bogoshi
Chief Executive Officer
DATE: 06-07-2018

Appendix 4: Approval letter from Gatekeeper

Department of Radiation Oncology

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Dated 12-9-2018

To

The Chairperson

Ethics Committee

University of Witwatersrand

re: Ethics Clearance of the proposal(M180756)

Dear Prof Clem Penny,

This is to inform you that Dr M. Ndleve (Student no. 1239311) is working as a registrar in the Department of Radiation oncology. I, as the gatekeeper of LANTIS system in the Department of radiation Oncology is granting permission to access the information from Lantis as and when needed.

With best regards

Vinay Sharma

Prof Vinay Sharma

Head, Department of Radiation Oncology

Appendix 5: Data collection sheet

Study Number			
Primary Malignancy			CUP ☐
Presenting Symptom			
Imaging Used to Diagnose	CT alone ☐	MRI alone ☐	Both CT & MRI ☐
Site	Cerebral ☐	Cerebellum ☐	Brainstem ☐
Number of Brain Mets	1-3	4-10	>10
Other Metastases Present	Yes ☐	No ☐	
Control of Metastases	controlled ☐	uncontrolled ☐	
Age			
Gender			
ECOG			
Clinical signs			
RPA class	class 1 ☐	class 2 ☐	class 3 ☐
Steroid Use	Yes ☐	No ☐	
Radiotherapy start date			
Radiotherapy completion date			
Total Dose Given (in Gray)			
Number of fractions			
Follow-up: up to maximum one year	3/12: Alive ☐	Deceased ☐	Lost to follow-up ☐
	6/12: Alive ☐	Deceased ☐	Lost to follow-up ☐
	1 year: ☐	Deceased ☐	Lost to follow-

	Alive	up
If Deceased – whilst inpatient or during radiation treatment : Date of Death		