A TALE OF TWO SITES: AN AUDIT OF CENTRAL NERVOUS SYSTEM METASTASES IN TWO JOHANNESBURG TERTIARY CENTRES

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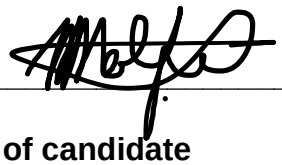
A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the Degree of Master of Medicine in the branch of Neurosurgery

Johannesburg, March 2023

DECLARATION

I Masechaba Molefe declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine in the branch of Neurosurgery at the University of the Witwatersrand (Wits), Johannesburg. This research report has not been submitted prior for any degree or examination at this or any other University.



Signature of candidate

13th_____ day of March _____2023

I dedicate this work to God my redeemer and my rock, apart from Whom I can do nothing. To my beloved mother Mildred Molefe who has lavished me with her unwavering love, patience and support throughout all the years and to my dear grandmothers Manstho Evelyn Molefe and Nomthandazo Ncala and my whole family for their prayers and support.

PRESENTATIONS RESULTING FROM THE RESEARCH PROJECT

This research project was presented at the 30th Society of Neurosurgeons of South Africa Congress held between the 29th of September to the 1st of October 2022 at the Radisson Hotel and Convention Centre, Johannesburg, O.R. Tambo.

ABSTRACT

Background: Literature reports the most common neoplasms of the CNS as metastases. Most studies are from the US and Europe with a paucity of data in the African setting.

Objective: To provide information among patients with histologically confirmed CNS metastases treated at the neurosurgical units of the University of the Witwatersrand, namely at CHBAH and CMJAH.

Methods: A retrospective record review of patients with histologically confirmed CNS metastases, presenting between 01 January 2015 and 31 December 2019 was conducted. The following data were collected and analysed: demographic, clinical, radiological and histopathological data.

Results: 88 patients were included in the study. The frequencies of brain and spine metastases were 13% and 48% respectively compared to all other operated primary tumours. More females were prevalent at 51.7% in the brain metastases cohort, while males were more prevalent in the spine metastases cohort at 57.1%. In brain metastases patients the median age at presentation was 49 and for those with spine metastases the mean age was 47.1. The distribution for brain metastases was: 65% supratentorially; 20% infratentorially; 15% mixed. The distribution for spine metastases was: thoracic 32.1%; lumbosacral 28.5%; cervical 14.3%, mixed 25%. The most prevalent histopathologies for brain metastases were: lung 21.7%; breast 11.7%; melanoma 11.7%. The most prevalent histopathologies for spine metastases were lymphoma and plasma cell neoplasms each comprising 21.4%.

Conclusion: More females presented with brain metastases and predominantly more males had spine metastases. There was a younger age of presentation compared to most studies conducted in Africa and globally.

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ABBREVIATIONS AND SYMBOLS

ASIA	American Spinal InjuryAssociation
cc	Cubic centimetre
CD	Cluster of differentiation
CHBAH	Chris Hani Baragwanath Academic Hospital
CK	Cytokeratin
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CNS	Central nervous system
CT	Computed tomography
DS-GPA	Diagnosis-specific graded prognostic assessment
GATA 3	GATA binding protein 3
GCS	Glasgow Coma Scale
GPA	Graded prognostic assessment
HREC	Human Research Ethics Committee
ICP	Intracranial pressure
IQR	Interquartile range
LCA	Leukocyte common antigen
mm	Millimetre
MRI	Magnetic resonance imaging
MUM1	Multiple myeloma 1
MyoD1	Myogenic differentiation antigen 1
NHLS	National Health Laboratory Service
NHRD	National Health Research Database
PACS	Picture Archiving and Communication System
SD	Standard deviation
T1WI	T1 weighted image
T2WI	T2 weighted image
TTF1	Thyroid transcription factor 1
US	United States
Wits	University of the Witwatersrand
~	Approximately
%	Percent
<	Less than
≤	Less than or equal to

≥	Greater than or equal to
±	Plus or minus

CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1.1 INTRODUCTION AND REASON FOR REVIEW

Tumours within the central nervous system (CNS), which encompasses the brain and spinal cord, are common and include primary and secondary (metastatic) tumours. They are a significant cause of morbidity and mortality. The most common CNS neoplasms in the West are metastatic, constituting in the brain, slightly more than half of all intracranial neoplasms.[1,2] These metastatic tumours can spread to the brain and spine by either local extension from surrounding structures, or from distant regions haematogenously.[1] The brain and spine are unique because they possess a blood brain barrier which provides them some protection, however, brain and spine metastases take advantage of this specialised microenvironment to infiltrate and gain a foothold. This blood brain barrier has proven to be a challenge for chemotherapeutic agents to penetrate, thus rendering the CNS a sanctuary site for cancerous cells to proliferate.[2,3]

In recent decades a greater proportion of cancer patients have presented with cerebral and spinal metastatic disease.[1] This is thought to be attributable to the improved life expectancy seen in cancer patients due to improvements in oncologic treatments, advancements in diagnostic tools i.e. the post computed tomography (CT) scan era, consequent to an ageing population, and a greater awareness of the disease.[1]

However, in preceding decades despite the large proportion of patients being affected by CNS metastases they were excluded from clinical trials and were subject to inattention due to perceived poor prognosis.[3] Although the reported global incidence of CNS metastases is high, it is difficult to corroborate this adequately in the South African setting because there is a paucity of data from African countries regarding the topic of CNS metastases.[4] Figure 1 below illustrates this point. Hence the reason for review of this topic, data of which would be vital in the South African context.

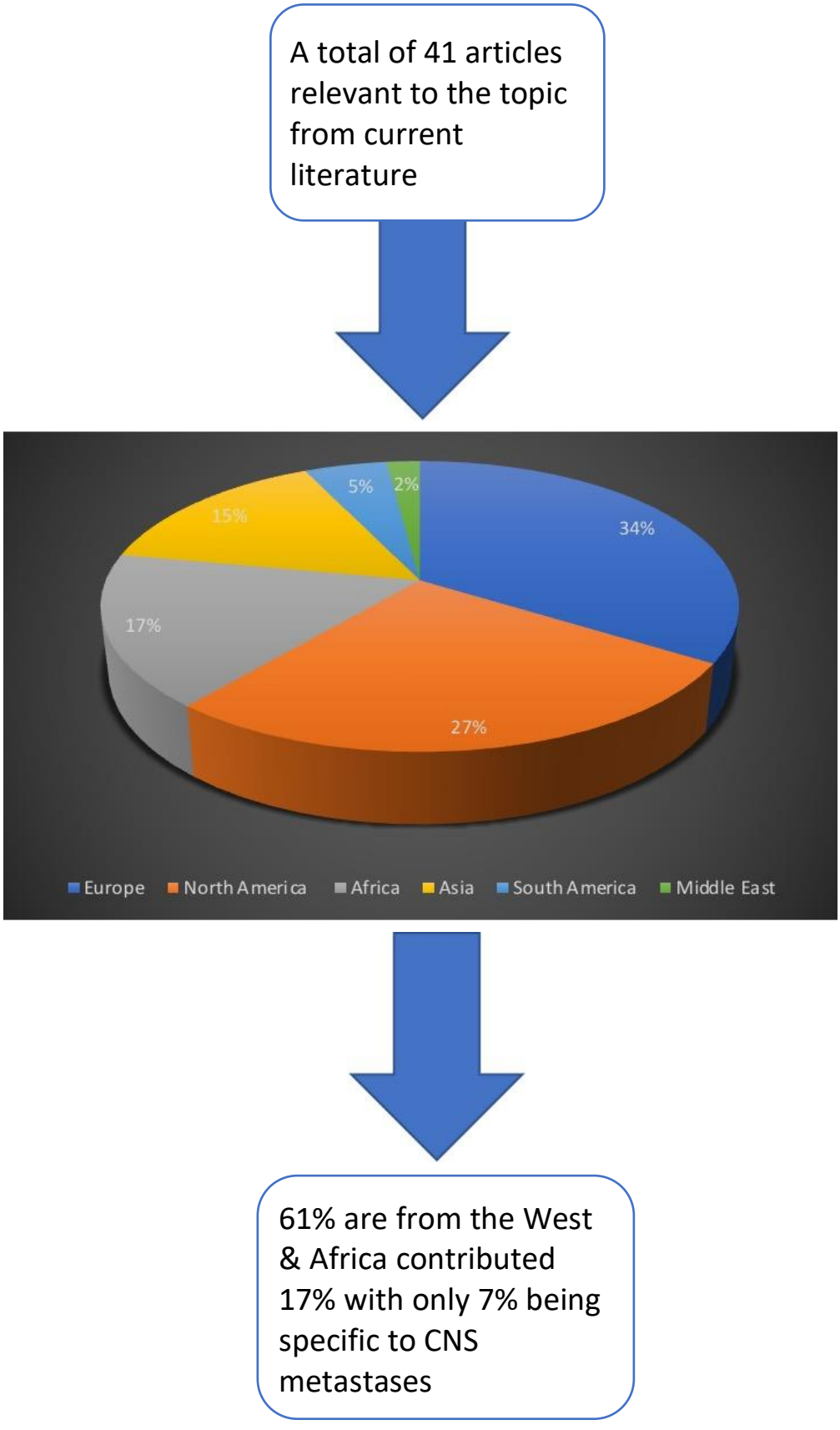

Figure 1: Overview of conducted literature review of central nervous system metastases in relation to continent of origin and its contribution

1.2 GLOBAL BURDEN OF DISEASE

1.2.1 Brain metastases

Secondary brain tumours occur ten times more frequently than primary malignant tumours.[3] Furthermore, one third of adult cancer patients are affected by brain metastases with approximately 170 000 to 200 000 patients being diagnosed yearly in the United States (US).[3,4] The global prevalence of patients with cerebral metastatic disease has currently been reported as ranging from 8.5% to 9.6%.[5,6] This is thought to be an underestimate, and the trend has been hypothesised to have increased over approximately the past three decades.[5] The annual age-adjusted incidence rate in a Swedish study had doubled from 7 to 14 per 100 000 between 1987 and 2006.[5] The estimated incidence rate of primary brain tumours in developed countries ranges from 5.1 per 100 000 to 6.6 per 100 000, but is lower at 3 per 100 000 in developing countries.[4,6] Conversely, the incidence rate of metastatic brain tumours in developed countries is higher and varied from 8.3 per 100 000 to 11 per 100 000.[6] This is not the case in paediatrics with brain metastases being rare, constituting only 6% of tumours.[1]

In contrast, the overall incidence rate of brain metastases is not known in Africa. However, a Cameroonian study estimated their annual incidence of brain tumours between, 2006 to 2010, to be 8 per 100 000 with the most prevalent histological subtypes being astrocytomas, meningiomas, pituitary adenomas and a lower rate of metastases.[4] Although global reports indicate brain metastases to be more prevalent than primary brain tumours a majority of the studies conducted in Africa do not reflect this. Only one study from Nigeria found brain metastases to be predominant comprising 23% of tumours, followed by glial tumours at a frequency of 20%.[7] This differed from other studies conducted in Nigeria,Tunisia, South Africa and Cameroon which showed low prevalences of 0.0%, 1.9%, 6.0% and 8.0% respectively.[4,8-10] Similarly two studies from Asia had low prevalences of 4.87% and 6.5% respectively, with the one conducted in China comprising a large cohort of 35 496 patients.[11,12]

1.2.2 Spine metastases

In comparison, spinal metastatic data sources are not as plentiful as for brain metastases, but spine metastases also bear a high burden of disease with reportedly 10% of cancer patients developing spinal metastases.[1] Another source estimated that 40% of patients with cancer will develop spinal metastases during the course of their disease.[13] With yet another reporting metastases to the bony spine to occur in as much

as 70% of patients with primary cancers.[14] Globally, as with intracranial tumours, spinal metastases are more prevalent than primary spinal tumours.[1,15] Data on spinal metastases is again sparse in the African setting. Similarly as with brain metastases a study conducted in Kenya showed a low frequency of spinal metastases compared to Western countries. In this study spinal metastases constituted 7% of spinal tumours in a cohort of 139 patients.[16] This is in contrast to a study from Nigeria with a smaller cohort of 59 patients, and yet with the highest prevalence of tumours being metastatic in 23% of patients.[17] However, in Pakistan, another developing country, it was found that spinal metastases were not the most prevalent neoplasms of the spine, and only found metastatic adenocarcinoma in 3 out of the 110 cases studied.[13]

1.3 DEMOGRAPHICS

1.3.1 Brain metastases

A study from Tunisia found the distribution of brain metastases to be more frequent in males than females.[9] Additionally in Cameroon there was an equal distribution of males and females.[4] In the Middle East females were predominant.[18] While in Asia half of the studies showed a female and the other half a male preponderance.[11,19-22] This was not the case in Europe and North America where males were predominant in approximately 75% of studies.[3,5,6,24-34]

Regarding age, in Africa, the mean age of patients diagnosed with brain metastases was mostly in the sixth decade while those diagnosed with breast metastases being younger, presenting in their fourth and fifth decades which is in keeping with global trends.[4.9] This was comparable with other developing countries in Asia.[19-22] This differed in the West with most patients presenting in the seventh decade, and slightly less in the sixth decade.[3,5,6,23-33]

1.3.2 Spine metastases

In Kenya there were more males with spinal metastases.[16] This differed to a study conducted in Pakistan in which females were predominant.[13] Whilst Europe showed a preponderance of males, and North America an equal distribution in the predominance of males and females in the studies conducted.[14,15,34-37]

Concerning age, the Kenyan study had more patients in their sixth decade.[16] This differed significantly from Pakistan which had younger patients in their fourth and fifth decades.[13] In comparison Western countries, similar to that seen with brain metastases, displayed an older population group with patients in their sixth and seventh decades.[14,15,34-37]

1.4 UNDERLYING RISK FACTORS

There's a dearth of research specifically identifying general risk factors for CNS metastases. There's controversy concerning gender predilection with some studies reporting being female as a risk factor while others showed no difference between the genders.[5] A study from India showed being female as a risk factor for developing brain metastases in their population due to a higher frequency of smoking and being subjected to the smoke resulting from cooking.[20] Conversely a large population based study consisting of 16 210 patients from the US showed the incidence proportions of brain metastases in males to be higher than for females, except for patients with primary lung cancer.[6] This study also associated various age ranges per primary tumour to have higher incidence proportions of brain metastases. That is those diagnosed at age 40 to 49 years with primary lung cancer; age 50 to 59 years with primary melanoma, renal, or colorectal cancers; and age 20 to 39 for those with primary breast cancer.[6] It also found African Americans to have the highest incidence proportions of brain metastases compared to white patients for lung, melanoma and breast cancers except for renal cancer which were lower.[6]

1.5 CLINICAL PRESENTATION

1.5.1 Brain metastases

It is impossible to differentiate primary from secondary CNS lesions on clinical grounds with most symptoms being chronic.[1] One study was found in Africa that reviewed the clinical profile of patients with brain metastases specifically. This study, conducted in Tunisia, reported the most common symptoms to be focal neurological deficits in 30% of patients, followed by headaches and seizures with a prevalence of 29% and 16% respectively.[9] In contrast several Asian studies all showed headaches to be the most common symptom followed by, with slight variations in predominant frequency, mental

state changes, neurological deficits, other signs of raised intracranial pressure such as vomiting, and seizures.[19-22] This was comparable to Western countries.[1]

1.5.2 Spine metastases

The most frequent presentation among patients with spine metastases was with motor deficits in 98% of Nigerian patients with only one patient having pain.[17] This was comparable to a study from the US.[14] This differed in Europe, with nocturnal pain being the chief symptom followed by motor deficits and sphincter dysfunction.[35]

1.6 PROGNOSTIC SCORES

1.6.1 Brain metastases

Metastases to the brain are a poor prognostic marker and represent the terminal stages of metastatic cancer.[19] Additionally a large prospective study, from Japan of 1194 patients, showed that in 92% of patients mortality was secondary to systemic disease progression rather than from brain metastases.[3] The overall survival of patients diagnosed with brain metastases has been reported to be one to two months if left untreated.[27] This overall survival can be improved to four to six months with systemic therapies, surgery or radiation with an even better survival, in selected cases, with a combination of these.[3,27] This has subsequently led to improved prognostication tools to identify patients that would benefit from these management strategies.[27] There are several of these prognostic scores described with the current most widely used being the graded prognostic assessment (GPA) score and the newer diagnosis-specific graded prognostic assessment (DS-GPA) score.[38] The correlation between scores and median survival times being directly proportional. These scores have been validated.[39]

1.6.2 Spine metastases

As with brain metastases survival of patients with spine metastases is attributed to the primary tumour's histopathology, systemic disease status, and underlying patient factors.[37] The most widely used are the modified Tokuhashi and Tomita scores which have also been validated.[37] They were both found to accurately predict patients with poor prognoses and would therefore benefit from palliative treatment. For patients with moderate and good prognoses, the modified Tokuhashi score was found to be more precise in predicting actual survival.[37] The correlation between the average survival

times of the modified Tokuhashi and Tomita scores being directly and inversely proportional respectively.

1.7 RADIOLOGICAL CHARACTERISTICS

1.7.1 Brain metastases

1.7.1.1 Number of lesions

The trend over the past few decades has shown a decline in patients with single brain metastases from 63% to 29% and consequently an increase in the number of patients with multiple brain metastases (three or more), from 17% to 36%.[5] Conversely in Tunisia there was a preponderance of patients with single brain lesions.[9] This was in contrast to Asia and the Middle East which had a preponderance of patients with multiple brain metastases.[18-21] In Europe there were slightly more studies that had patients harbouring single brain metastases.[23-27] Whilst in the US there was an equal distribution, with one study that showed more patients with single and in another, more patients had multiple brain lesions.[30,33]

1.7.1.2 Location of lesions

Globally most lesions were distributed in the cerebral hemispheres (supratentorially) in 74% to 97% of cases and in the cerebellum (infratentorially) in 15% to 26% of cases.[18-21,23,25,26] No study reviewing the locations of lesions was found in Africa. Literature reports the most common location to be frontoparietal with most showing a frontal distribution to be predominant, however, two studies from Asia showed a predominantly parietal distribution.[19-21,27]

1.7.2 Spine metastases

In comparison detailed data on the radiological features of spinal metastases is limited. Metastases to the spine can involve the bony elements, that is the vertebral column without extension into the spinal canal, or may encroach upon the spinal canal to compress the spinal cord extradurally. They may also solely involve the spinal cord or involve both the vertebral column and spinal cord unrelatedly. Within the spinal canal metastases can either be extradural as stated, causing impingement external to the spinal cord's dural layer, or intradural which is further subdivided into extramedullary or intramedullary; where in the latter, the parenchyma of the spinal cord is infiltrated. In an update from 2015, spinal metastatic neoplasms were predominantly extradural in 95%

of cases affecting the vertebral bodies and pedicles, 5% were extramedullary, and less than 1% were intramedullary.[12] In this update, in relation to the regions involved along the longitudinal spinal axis, the most common locations were thoracic, followed by the cervical and lumbar regions.[12] In contrast another report found 70% to be localised to the thoracic spine, 20% in the lumbosacral, and 10% in the cervical region.[35]

1.8 HISTOPATHOLOGICAL PROFILE

1.8.1 Brain metastases

Although radiological features are useful in diagnosing brain metastases, this is confounded with similarities of these lesions to infectious processes and some primary tumours.[19] Therefore histopathological investigation, including immunohistochemical staining, is a vital diagnostic tool to direct to a potential primary source.[19] In Africa the most prevalent histopathologies were lung and breast cancers, followed by colorectal cancer and lymphoma in each of the respective studies from Tunisia and Cameroon.[4,9] However, in Nigeria the most prevalent histopathologies were choriocarcinoma and Burkitt's lymphoma.[7] Globally, almost unanimously, the predominant histopathologies were comparable to the two studies mentioned initially, namely being lung and breast cancers; with a heterogeneity of the third most common lesion.[20-22,27,32,33] Two studies from the US and Europe differed from this with the most prevalent histopathologies being lung, melanoma and renal carcinomas in each.[5,6] In contrast, the histopathologies causing brain metastases in the paediatric population were leukaemia, lymphoma, sarcoma and rhabdomyosarcoma.[21]

1.8.2 Spine metastases

In Africa the most prevalent histopathology of spinal metastatic lesions was found to be prostate cancer.[17] This was comparable to a large prospective study of 1143 patients from Denmark in which prostate followed by lung cancer was most common.[34] In comparison to the rest of Europe and also in North America breast cancer was the most frequent followed by lung, prostate or renal cancers in varying prevalences.[14,15,35,36,40] Furthermore in a multi-continental study the Asian cohort showed lung, liver and gastrointestinal cancers to be most prevalent, with less cases of breast cancer metastasising to the spine in Asia.[15]

CNS metastases are a significant cause of morbidity and mortality. There's a paucity of research conducted in Africa and in South Africa in particular, with most of the data being from Europe and the US. Of those conducted in Africa there has not been a focus on CNS metastatic tumours, but rather a profile of CNS tumours in general. In the literature review presented and as depicted in tables 1.1 and 1.2 below, there's heterogeneity of results intercontinentally and within countries of the same continent. Therefore, having more data on this topic in the South African setting is vital.

Table 1.1: Table depicting selected studies across the globe of brain metastatic disease and the heterogeneity of some findings

Country	Year of study	Author	Study Type	Sample size	Predominant gender (%)	Mean/ median age (years)	Histopathology (listed in descending order of prevalence)
Cameroon	2021	Motah et al	Retrospective	200 overall with 12 having metastases	Male=Female (50.0)	66.7% ≥ 55	Lung, breast, lymphoma
Tunisia	2018	Benna et al	Retrospective	139	Male (55.4)	54.0	Lung, breast, colorectal
India	2019	Sangati et al	Retrospective	36	Male (58.3)	50.0	Lung, breast, GIT*
India	2015	Ghosh et al	Retrospective	130	Female (64.6)	59.1	Lung, breast, melanoma
Iran	2019	Haghighatkhah et al	Retrospective	80	Female (62.5)	Not given	Breast, lung
Germany	2020	Schroeder et al	Retrospective	369	Female (50.1)	62	Lung, breast, skin
Germany	2013	Schackert et al	Retrospective	127	Male (62.2)	67	Lung, melanoma, GIT*
US	2004	Barnholtz et al	Retrospective	16 210	Male (51.0)	50-59 and 60-69 age ranges prevalent	Lung, melanoma, renal

***GIT: gastrointestinal**

Table 1.2: Table depicting selected studies across the globe of spinal metastatic disease and the heterogeneity of some findings

Country	Year of study	Author	Study Type	Sample size	Predominant gender (%)	Mean/ median age (years)	Histopathology (listed in descending order of prevalence)
Asian cohort in global study	2018	Wright et al	Prospective, multi-regional	235	Male (60.4)	60.0	Lung, liver, GIT
Denmark	2018	Morgen et al	Prospective	1143	Male (58.0)	66.0	Prostate, lung
Netherlands	2000	Kienstra et al	Prospective, multi-institutional	170	Female (57.0)	66.0	Breast, lung, prostate
North American cohort in global study	2018	Wright et al	Prospective, multi-regional	226	Male (59.7)	58.1	Lung, breast, renal
US	2012	Hoover et al	Retrospective	15	Male (60.0)	55.0	Breast, lung, melanoma

1.9 RESEARCH QUESTION

Are the demographics, clinical features, radiological characteristics and histopathological entities of central nervous system metastases in two Johannesburg tertiary centres in keeping with global trends?

1.10 AIM OF STUDY

I aim to evaluate the characteristics of patients with histologically confirmed CNS metastases treated at two neurosurgical units of the University of the Witwatersrand, namely at the Chris Hani Baragwanath Academic and Charlotte Maxeke Johannesburg Academic Hospitals, South Africa.

1.11 OBJECTIVES

I. To describe the demographics and clinical features of CNS metastases.
II. To evaluate the radiological features of CNS metastases.
III. To evaluate the histopathologies of CNS metastases.

1.12 METHODOLOGY

Study design

A descriptive, retrospective, record review of patients with CNS metastases with an analytical element.

Study population

All consecutive patients of all ages with histologically confirmed CNS metastases presenting to two, tertiary neurosurgical units, namely at the Chris Hani Baragwanath Academic Hospital (CHBAH) and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between 01 January 2015 to 31 December 2019 (5 year period).

Sampling strategy

Convenience sampling was employed of all patients who had undergone surgical resection of CNS tumours with subsequent histopathological confirmation of metastatic lesions. These were patients referred to the two tertiary centres from

surrounding, secondary and primary centres in Johannesburg in which neurosurgical services were unavailable. Referrals were also received from the North West province in earlier years.

Sample size

An initial sample size of 139 patients was expected. However, due to missing and incomplete records final samples of 60 and 28 for brain and spine metastases respectively were obtained, resulting in a final sample size of 88 patients.

Inclusion criteria

All consecutive patients of all ages with histologically confirmed CNS metastases presenting to CHBAH and CMJAH between 01 January 2015 to 31 December 2019.

Exclusion criteria

- Patients who had spinal metastases from primary cerebral tumours or vice versa
- Patients presenting twice or more with cerebral and spinal metastases from either the same or different primary site(s) so as to avoid duplication, that is, patients were considered on initial presentation.

Data sources

Three data sources were used namely patients' files, data from Histopathology and Radiology departments. Data was retrieved from patients' files for all those patients who have undergone surgery for brain and spinal tumours and found to have metastases. This record of patients was initially determined after searching histopathological data of all patients with malignant CNS neoplasms from the National Health Laboratory Service's (NHLS') electronic database. Radiological information was subsequently obtained from the Radiology Department, via their Picture Archiving and Communication System (PACS).

Data collection

Once all mandatory approval from the respective departments and ethics committee was obtained data was collected on specifically designed data sheets for brain and

spinal metastases respectively. Examples of these are shown in (Appendices B and C). Multiple variables were then captured, details of which can be seen in aforementioned appendices, comprising:

- **Demographic data**: age, gender, race, social background, in patients with known primary cancers the time interval from primary cancer diagnosis to that of CNS metastasis.
- **Clinical features**: symptoms, clinical signs, American Spinal Injury Association (ASIA) Impairment Scale grades (spine metastases) and prognostic scores namely: GPA score (brain metastases), Tomita and modified Tokuhashi prognostic scores for spinal metastases (please see Appendix D for scores).
- **Radiological characteristics for brain metastases**: modality [CT or magnetic resonance imaging (MRI) scans with typical features], location, number and size of lesions, extra-cranial metastases, midline shift, hydrocephalus.
- **Radiological characteristics for spinal metastases**: modality and typical features, location, component of vertebra involved, number of lesions; and if there are multiple lesions, whether contiguous or non-contiguous, involvement of the spinal cord, extra-spinal metastases.
- **Histopathological diagnoses**

Data management

Raw data once collected, was transferred to Google forms for spine and brain metastases respectively. With subsequent transfer of data to excel spreadsheets where further data cleaning was done prior to data analysis. A summary of a interim contingency table formulated in process is found below:

OBJECTIVE	VARIABLE	TYPE	*STATISTICAL ANALYSIS
Ia. Demographics- i) age ii) race, gender and social background	Exposure	Continuous (i) Categorical (ii)	(i) Means/medians (ii) Frequency (proportions)
Ib. Clinical features (including grading scores)	Outcome	Categorical	Frequency (proportions)
II. Radiological features	Outcome	(i) Continuous for midline shift (brain metastases); Categorical (ii) for most	(i) Means/medians (ii) Frequency (proportions)
III. Histopathology	Outcome	Categorical	Frequency (proportions)

*** See data analysis below for further details**

1.13 DATA ANALYSIS

The data was then transferred to Stata version 15 (STATA corp Ltd, Texas, USA) and analysed as follows:

Continuous variables, namely age and mid-line shift:

- analysed by computing their means with standard deviations if normally distributed or medians and interquartile ranges if not normally distributed
- ages were thereafter grouped i.e. 0-18, 19-30 etc. and their associations with the histopathologies was determined via Fisher's exact test
- The non-parametric Kruskal-Wallis H test was also performed for associations between ungrouped ages and midline shift respectively per histopathology categories
- p-values were determined with a value of ≤ 0.05 (two tailed) considered statistically significant (this p-value was used throughout for all the analyses).

Discrete variables:

- Frequencies and proportions were determined
- The Fisher's exact test or chi-squared test as appropriate was performed to determine associations for the following categorical variables (bivariate analyses) in the brain metastases cohort only (due to a larger sample size):
  a) total numbers per racial groups per histopathological data
  b) gender and histopathological data
  c) social demographic and histopathological data
  d) GPA scores and histopathological data
  e) radiological features and histopathological data

- The frequency of brain and spine metastases per yearly interval was noted and linear regression analyses were performed respectively to assess for trends. P-values were determined to assess the significance of the associations. The correlation coefficients were also determined to measure the strength of these associations.
- Selected demographic and clinical data were depicted in pie charts and bar graphs respectively

1.14 ETHICAL CONSIDERATIONS

Approval to conduct research was received from CHBAH and CMJAH hospital management teams, from the Radiology and NHLS Anatomical Pathology heads of department. Approval was received from the University of the Witwatersrand (Wits) Postgraduate Committee. Subsequent ethics approval was obtained from the Human Research Ethics Committee (HREC) with ethics clearance certificate number **M201113** (see Appendix A). An application was also made to the National Health Research Database (NHRD) [reference number: GP_202112_007]. Thereafter applications were made to the CHBAH and CMJAH clinical records departments to gain access to patient files. Patients were de-identified with specific reference numbers assigned per patient to ensure confidentiality. Original data was only available to the primary researcher. Please see (Appendices E to I) for hospital management and other approvals.

1.15 TIMING

TIMELINE								
	Aug-Dec 2019	**Dec- Mar 2019-2020**	**Mar 2020**	**Apr-Sep 2020**	**Oct-Mar 2020-2021**	**Oct-Feb 2021-2022**	**Mar-May 2022**	**Jun-Nov 2022**
Literature review	X							
Preparing protocol		X						
Protocol submission			X					
Protocol assessment				X				
Ethics Application					X			
Data Collection						X		
Data Analysis							X	
Writing up report								X

1.16 FUNDING AND BUDGET

All costs incurred were funded by the principal investigator and included printing and photocopying, stationery, transport and internet usage:

ITEMS	AMOUNT
Printing and photocopying	R500.00
Stationery	R200.00
Transport	R1000.00
Internet usage	R1500.00
TOTAL	R3200.00

1.17 STUDY LIMITATIONS

- This is a retrospective study so information collected was dependent on the doctors who attended to the patients and may not have been accurate and/or complete
- Missing patient records
- The study will have limited applicability outside of the setting in which the research was conducted.
- Relatively small sample size

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CHAPTER 2: SUBMISSIBLE ARTICLE

TITLE: A TALE OF TWO SITES: AN AUDIT OF CENTRAL NERVOUS SYSTEM METASTASES IN TWO JOHANNESBURG TERTIARY CENTRES

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Conflict of interest: Nil

Keywords: Brain metastases, spine metastases, demographics, radiological features, CNS

Word count (including references): 5000

Abstract word count: 250

ABSTRACT

Background: Literature reports the most common neoplasms of the CNS as metastases. Most studies are from the US and Europe with a paucity of data in the African setting.

Objective: To provide information among patients with histologically confirmed CNS metastases treated at the neurosurgical units of the University of the Witwatersrand, namely at CHBAH and CMJAH.

Methods: A retrospective record review of patients with histologically confirmed CNS metastases, presenting between 01 January 2015 and 31 December 2019 was conducted. The following data were collected and analysed: demographic, clinical, radiological and histopathological data.

Results: 88 patients were included in the study. The frequencies of brain and spine metastases were 13% and 48% respectively compared to all other operated primary tumours. More females were prevalent at 51.7% in the brain metastases cohort, while males were more prevalent in the spine metastases cohort at 57.1%. In brain metastases patients the median age at presentation was 49 and for those with spine metastases the mean age was 47.1. The distribution for brain metastases was: 65% supratentorially; 20% infratentorially; 15% mixed. The distribution for spine metastases was: thoracic 32.1%; lumbosacral 28.5%; cervical 14.3%, mixed 25%. The most prevalent histopathologies for brain metastases were: lung 21.7%; breast 11.7%; melanoma 11.7%. The most prevalent histopathologies for spine metastases were lymphoma and plasma cell neoplasms each comprising 21.4%.

Conclusion: More females presented with brain metastases and predominantly more males had spine metastases. There was a younger age of presentation compared to most studies conducted in Africa and globally.

Introduction

Tumours within the central nervous system (CNS), which encompasses the brain and spinal cord, are common and include primary and secondary (metastatic) tumours.The most common CNS neoplasms in the West are metastatic, constituting in the brain, slightly more than half of all intracranial neoplasms.[1] The brain and spine are unique because they possess a blood brain barrier which provides them some protection, but this has paradoxically proven to be a challenge for chemotherapeutic agents to penetrate, conversely rendering the CNS a sanctuary site for cancerous cells to proliferate.[2]

In recent decades a greater proportion of cancer patients have presented with CNS metastases.[1] This is thought to be attributable to the improved life expectancy seen in cancer patients due to improvements in oncologic treatments, advancements in diagnostic tools, consequent to an ageing population, and a greater awareness of the disease.[1] Although the reported global incidence of CNS metastases is high, it is difficult to corroborate this in the South African setting, because there is a paucity of data regarding this topic within Africa.[3]

Secondary brain tumours are ten times more common than primary malignant tumours.[4] Furthermore, one third of adult cancer patients are affected by brain metastases with approximately 170 000 to 200 000 patients being diagnosed per year in the United States (US).[3,4]

Although global reports indicate CNS metastases to be more common than primary CNS tumours a majority of the studies conducted in Africa do not reflect this with only one study from Nigeria correlating with this. This study found brain metastases to be predominant in 23% of participants.[5] This contrasted with the remaining studies conducted in Africa which featured lower prevalences of brain metastases of 0.0%, 1.9%, 6.0% and 8.0% respectively.[3,6-8]

Similarly spine metastases also bear a high burden of disease with reportedly 10% of cancer patients developing spinal metastases.[1] Another source estimated that 40% of patients with cancer will develop spinal metastases during the course of their

disease.[9] With yet another reporting metastases to the bony spine to occur in as much as 70% of patients with primary cancers.[10] However, A study from Kenya showed a low frequency of spinal metastases where they constituted 7% of spinal tumours in a cohort of 139 patients.[11] This was in contrast to a study from Nigeria with metastatic spine tumours being most prevalent in 23% of patients.[12]

Regarding gender predilection for patients with brain metastases, males were more prevalent than females in a study from Tunisia.[13] This was not the case in Europe and North America where males were predominant in approximately 75% of studies.[4,14-25] In Africa, the mean age of patients diagnosed with brain metastases was mostly in the sixth decade.[3,7,12] This differed in the West with most patients presenting in the seventh decade, and slightly less in the sixth decade.[4,14-25]

Concerning spinal metastases, males were predominant in Kenya.[11] This differed to a study conducted in Pakistan in which females were predominant.[9] Whilst Europe showed a preponderance of males, and North America an equal distribution in the predominance of males and females with some studies having more males and others more female participants.[10,26-29] Concerning age, the Kenyan cohort had more patients in their sixth decade.[11] In comparison Western countries, similar to that seen with brain metastases, displayed an older population group with patients in their sixth and seventh decades.[10,26-29]

In Africa the most prevalent histopathologies were lung and breast cancers, followed by colorectal cancer and lymphoma in each of the respective studies from Tunisia and Cameroon.[3,7] However, in Nigeria the most prevalent histopathologies were choriocarcinoma and Burkitt's lymphoma.[5] Globally, almost unanimously, the predominant histopathologies were lung and breast cancers with a heterogeneity of the third most common lesion.[18, 23,24,30,31]

In Africa the most prevalent histopathology of spinal metastatic lesions was found to be prostate cancer.[12] This was comparable to a large prospective study of 1143 patients from Denmark in which prostate followed by lung cancer was most common.[25] In comparison to the rest of Europe and North America breast cancer

was the most frequent followed by lung, prostate or renal cancers in varying prevalences.[10,24,26-28]

CNS metastases are a significant cause of morbidity and mortality. Furthermore, there's a paucity of research conducted in Africa and in South Africa in particular, with most of the data being from Europe and the US. Of those conducted in Africa there has not been a focus on CNS metastatic tumours, but rather a profile of CNS neoplasms in general. Additionally, there's heterogeneity of results intercontinentally and within countries of the same continent, therefore this data cannot be reliably extrapolated to our population. With an absence of studies, as known to the authors, in South Africa evaluating patients with histologically confirmed CNS metastases we aimed to profile these patients and to assess whether findings are in keeping with global trends.

Methods

Study design

A descriptive, retrospective, record review of patients with CNS metastases.

Study population

All consecutive patients of all ages with histologically confirmed CNS metastases presenting to two, tertiary neurosurgical units of the Chris Hani Baragwanath Academic Hospital (CHBAH) and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between 01January 2015 to 31 December 2019.

Data collection

Data was collected once all mandatory approval was obtained including ethics approval from the local Human Research Ethics Committee (HREC). Convenience sampling was employed of all patients who had undergone surgical resection of CNS tumours with subsequent histopathological confirmation of metastatic lesions. Patients who had spinal metastases from primary brain tumours or vice versa and those presenting twice or more with CNS metastases were excluded. Demographic and clinical data were retrieved from patients' files. Histopathological and radiological

data were retrieved from the National Health Laboratory Service's (NHLS') electronic database and the Radiology Department's Picture Archiving and Communication System (PACS) respectively.

The following data were collected:

- **Demographics**: age, gender, race, social background, in patients with known primary cancers the time interval from primary cancer diagnosis to that of CNS metastasis diagnosis
- **Clinical presentation**: symptoms, clinical signs, American Spinal Injury Association (ASIA) Impairment Scale grades (spine metastases) and prognostic scores namely: GPA scores (brain metastases), Tomita and modified Tokuhashi prognostic scores for spinal metastases (see Appendix D)
- **Radiological characteristics for brain metastases**: modality [computed tomography (CT) and/or magnetic resonance imaging (MRI) scans] with typical features, location, number and size of lesions, extra-cranial metastases, midline shift, hydrocephalus
- **Radiological characteristics for spinal metastases**: modality and typical features, location, component column of vertebra involved, number of lesions; and if there are multiple lesions, whether contiguous or non-contiguous, involvement of the spinal cord, extra-spinal metastases
- **Histopathological diagnoses**

Data analysis

The captured data were transferred to excel spreadsheets and thereafter analysed using STATA version 15 (STATA corp Ltd, Texas, USA) as follows:

Continuous variables namely age:

- Analysed by computing their means with standard deviations if normally distributed or medians and interquartile ranges if not normally distributed
- The non-parametric Kruskal-Wallis H test was performed for associations between ungrouped ages per histopathology categories

Discrete variables:

- Frequencies and proportions were determined

- The Fisher's exact test or chi-squared test as appropriate was performed to determine associations for the following categorical variables (bivariate analyses):
  a) total numbers per racial groups and histopathological data
  b) gender and histopathological data
  c) socio-demographic and histopathological data
  d) GPA scores and histopathological data
  e) radiological features and histopathological data

- The frequencies of brain and spine metastases per yearly interval were noted and linear regression analyses were performed respectively to assess for trends, and correlation coefficients were also determined to measure the strength of these associations.
- Selected demographic and clinical data were presented pictorially using pie charts and bar graphs.
- P-values were determined with a value ≤ 0.05 (two-tailed) considered statistically significant.

Results

A total of 139 patients with potential CNS metastases were identified over a 60 month period from the two centres. After application of exclusion criteria 51 patients were excluded. This resulted in a final sample size of 88 patients, with the brain and spine metastases cohorts comprising 60 and 28 patients respectively (Figure 1).

Patient demographics

The frequency of brain metastases (n=60) compared to primary brain tumours (n=463) was 13% (Figure 2) and that for spine metastases (n=28) in relation to primary spine tumours (n=30) was comparably higher at 48% (Figure 3). The median age was 49 with a slight predominance of females with a ratio of 1.1:1. Paediatrics comprised 5% (n=3) of patients, all presenting with brain metastases. 32% of patients presented with a known cancer with a mean time interval from primary cancer to brain metastasis diagnosis of 27.3 ± 23.8 months. (Figure 4) can be viewed

for a repartition of patients with known primary cancers presenting with brain metastases. A similar distribution of demographics and risk factors were observed for those with spinal metastases with the following variations: males were predominant (1.3:1); a lower prevalence of patients with known primary cancers with a much shorter time interval to presentation with spine metastases by more than 50% (Table1).

Clinical presentation

Headaches and neurological deficits were the most prevalent symptoms amongst patients with brain metastases each at 64% (n= 38) followed by mental state changes in 33% (n=20). Almost 72% of patients had chronic symptoms for longer than a month. Among those with spinal metastases, limb dysfunction, with motor deficits being prevalent over sensory deficits, was the most common symptom in 96% followed by back pain in 68% (Table 2). A detailed description of neurological deficits and non-cerebral manifestations in patients with brain metastases are presented in Figures 5a and 5b and clinical presentations for those with spine metastases in Figures 6a and 6b.

Clinical signs

Brain metastases cohort

A majority of patients had good levels of consciousness reflected by mild Glasgow Coma Scale (GCS) scores in 90%. Those with neurological deficits had motor deficits as the most frequent manifestation in 37% of them [Table 3a(i)].

Spine metastases cohort

Slightly more than a third of patients had complete paraplegia being assigned as ASIA A (Table 3b). On this scale the predominant neurological level of injury was at the fourth thoracic dermomyotome (T4) [see Figures 7b and 7c]. For further details of brain and spinal metastatic clinical manifestations please refer to Figure 7a and Figures 7b and 7c respectively.

Prognostic scores

In patients with brain metastases the histopathological diagnosis of lymphoma seemed to have the worst prognosis as reflected by having the lowest mean GPA

score while the best prognosis was for those with metastatic breast cancer. However, the association between GPA or DS-GPA scores respectively, per histopathology type was not statistically significant. Overall the patients had a mean GPA score of 2.2 ± 1.0 [see Table 3a(ii)]. For patients with spinal metastases when grading via the modified Tokuhashi score slightly more than half of patients had poor prognostic scores. Conversely when the Tomita scores were determined three quarters of patients had good and moderate scores (Table 3b).

Radiological characteristics

Brain metastases cohort

A tenth of patients who had CT scans performed were found to have more metastases on subsequent MRI investigation with a median of 3.5 lesions. Most patients with brain metastases presented with solitary lesions in 87% with almost two thirds found supratentorially. The most frequent locations being in the frontal lobe followed by the parietal lobe with a right sided distribution being predominant in both supra- and infratentorial compartments. The tumour sizes were large with a median volume of 57.7 cc. There was evidence of substantial transhemispheric herniation in almost half of patients with a median distance of 8.6 mm. There were slightly more patients with extra-cranial metastases compared to those with metastases confined intracranially. Other details of tumour features and their characteristics per radiology modality can be reviewed in [Table 3a(i)].

Spine metastases cohort

The most frequent location along the longitudinal spinal axis was thoracic, followed by lumbosacral and cervical regions, whilst along the horizontal axis all three vertebral columns were involved in almost 70% of patients. In contrast to those with brain metastases, multiple bony spine involvement was predominant in nearly 80% with a median number of 3 vertebral lesions with a contiguous pattern of involvement in a quarter, and bony destruction in 21%.There was extradural spinal canal extension in three quarters of patients. With substantially more patients with distant metastases compared to those with brain metastases (61% vs 43%). Further details of radiological features of lesions can be viewed in (Table 3b).

Histopathological subtypes

The most prevalent histopathological diagnoses for brain metastases patients were lung in 22% (n=13), breast and melanoma at 12% (n=7) each. In paediatrics two harboured rhabdomyosarcoma with one being diagnosed with neuroblastoma. In the spinal metastases cohort the most prevalent histopathological diagnoses were lymphoma and plasma cell neoplasms constituting 21% in each, followed by breast, lung and thyroid at 7% each. The site of primary lesion could not be identified on histopathological investigation in 15% (n=9) and 14% (n=4) of brain and spine metastases patients respectively. See (Figures 8a- 8g) for histopathological images from selected patients' microscopic slides.

Associations of variables with histopathological subtypes (only for brain metastases)

Sociodemographic and histopathology

Patients with breast cancer presented with younger age groups in their fourth predominantly and fifth decades. Likewise those with melanoma, and even younger were those diagnosed with lymphoma. Conversely those with lung cancer were older presenting in their sixth and seventh decades. This was statistically significant (p-value= 0.040) as depicted in (Figure 9). Patients of black ethnicity had higher proportions of lung cancer and those of white ethnicity had higher proportions of melanoma. This reached statistical significance (p-value= 0.020). Likewise statistical significance was reached for the mean time interval (in months) between primary cancer and brain metastasis diagnosis with the shortest interval of presentation being amongst patients with lung cancer (0.4 ± 0.5), and the longest among those with melanoma (67.5 ± 10.6) and breast cancer (35 ± 21.2) with a p-value= 0.009 (Table 4).

Radiological characteristics and histopathology

Patients with lung cancer and melanoma had the largest median distances of midline shift compared to all other histopathologies while lymphoma caused the least amount of transhemispheric shifts, however, this was not statistically significant. The

tumour type with the highest predilection for distribution in the cerebral hemispheres was melanoma at 100% and those for the cerebellum were lung followed by breast cancer without reaching statistical significance. The largest tumour volume sizes were observed in patients with lymphoma with the smallest sizes found in those with melanoma, however, this was not statistically significant either. Breast cancer histopathology showed the most contrast enhancement when CT and MRI investigations were performed in conjunction, with lung cancer having the least amount of contrast enhancement and this was statistically significant (p-value 0.033). Please review (Figures 10a- 10e) for radiological images to depict this finding. All other parameters did not reach statistical significance. Further details can be observed in (Table 4).

Discussion

CNS metastases are a significant cause of morbidity and mortality being reportedly the most prevalent CNS neoplasms globally.[1-4] Despite this there's a paucity of research investigating CNS metastases in Africa, furthermore there's an absence of studies specifically investigating patients with histologically confirmed CNS metastases in South Africa. Therefore, the purpose of this study was to profile patients with histologically confirmed CNS metastases treated at the neurosurgical units of CHBAH and CMJAH, and to assess if findings are in keeping with global trends. Our results show that there are similarities with literature particularly as it relates to brain metastases; however, differences are also evident.

Our study found that both brain and spine metastases were not the most prevalent CNS neoplasms in contrast to global findings. However, this was in correlation with most studies conducted in Africa and other developing countries in Asia, contrasting with only one from Nigeria.[3,5,6] This may be a true reflection of lower incidences due to ethnic differences. However, it could also be due to less access to health care facilities in developing countries and therefore undiagnosed cases of CNS metastases.

Similarly some of the demographic findings of our patients varied to that of Western countries with a younger age of presentation in the fifth decade in both spine and brain metastases cohorts, while being in the seventh with slightly less in the sixth decades in developed countries.[4,10,14-25,29] Furthermore this age of presentation was also younger than that reported in other African countries with their patients predominantly presenting in their sixth decade.[3,7,11,12]

However, this relatively younger age of presentation of our patients was in keeping with that found in India for patients with brain metastases.[32] The reason for this could be due to the high absolute numbers of HIV infected adults in both countries and particularly within this age group and younger, and the associated increased risk of having both HIV and non-HIV associated malignancies.[33,34] Nevertheless, this would need further investigation as it relates to CNS metastases. Additionally, it was also found that the youngest patients were those with lymphoma, followed by breast and melanoma and the oldest being those with lung cancer. This result was statistically significant and is an area of potential future research.

Furthermore the time intervals for patients presenting with breast cancer were longer than those with lung cancer in keeping with several studies.[15,30] Additionally, those with melanoma had a far longer interval between primary cancer and brain metastasis diagnosis compared to that in the literature, being 2.4 times and 5.1 times longer than that reported in Germany and Netherlands respectively.[15,20] This finding was statistically significant in our study and requires further investigation regarding potential reasons for this.

Our results showed that patients with brain metastases mostly presented with headaches and focal neurological deficits followed by mental state changes. Similarly, these findings were in correlation with those found in several Asian countries in terms of headaches being the most prevalent symptom with a slight variation in frequencies of other symptoms.[30-32] In the spinal metastases cohort motor deficits were most frequent, followed by back pain and sphincter dysfunction. This was comparable to studies conducted in Nigeria and the US.[10,12]

With regards to prognostication of patients, those harbouring brain metastases with a diagnosis of lymphoma, had lower GPA scores while those with breast cancer had the highest DS-GPA scores reflecting poor and good prognoses respectively. Concerning breast cancer this is supported by literature in which good outcomes were seen, contrasted with worse outcomes for those with lung cancer, however lymphoma is rarely reported outside of Africa and warrants further investigation.[7] There seemed to be incongruity between the modified Tokuhashi and Tomita scores with more patients having poor prognoses when graded using the modified Tokuhashi and yet predominantly good and moderate scores using the Tomita scale. This could be explained by the modified Tokuhashi score being found to be more accurate than the Tomita particularly for determining the actual survival in patients with moderate and good prognoses.[29]

Additionally, more had lesions supratentorially which correlates with multiple studies from Asia, the Middle East, Europe and US.[15-17,21,30-32] Further findings revealed that melanoma had the greatest predilection for the supratentorial region with all cases being distributed there, while the most frequent histopathologies located in the infratentorial region were lung and breast cancers. This corresponded with that reported in a novel study from Germany, which found skin cancer to have a propensity to metastasise to the supratentorial region and breast, lung and gastrointestinal cancers to the infratentorial location.[18] They found this result to be statistically significant and could be potentially used in the future, particularly in resource limited regions, to facilitate investigation for a primary source.

Furthermore, literature reports the frontoparietal distribution to be the most prevalent which was in keeping with our findings.[19,30-32] Additionally our tumours sizes were relatively larger than that reported in the literature with our median volume being 57.7 cc being approximately tenfold that found in a study from Germany.[18] This could be due patients presenting later as a result of relatively limited access to health care facilities or ethnic differences. The largest tumour volumes were observed in those with lymphoma, and conversely having absent or the least amount of midline shift. With regards to midline shift it was paradoxically found to be a good prognostic factor in a large, randomised prospective study from the US. [21] With the observation that patients with lymphoma had the lowest GPA scores corresponding with poorer

prognoses and were found to have the least amount of midline shift, this could be a potential area of research.

Our study further found that patients with breast cancer metastatic brain lesions showed the most contrast enhancement when CT and MRI scans were performed in conjunction, and lung cancer the least, which was statistically significant. Studies were not found in the literature evaluating contrast enhancement patterns as they relate to various brain metastastic histopathologies, which could be another potential area of research.

Findings in those patients with spinal metastases showed that most had extramedullary lesions, in correspondence with the literature.[10,35] Furthermore in keeping with that reported, the distribution of lesions in our patients were predominantly thoracic followed by lumobosacral and cervical locations.[10,27]
The most prevalent histopathologies in the brain metastases cohort were found to be lung followed by breast and melanoma which was in keeping with that reported in studies from India and the US.[30,35] Although lymphoma (all being non-Hodgkins lymphomas) was only the fifth most frequent histopathology in our study, this is proportionally higher compared to that found in the literature not being reported outside of Africa.[14,15,30-32] This could be attributable to the higher HIV disease burden seen in South Africa.[34]

Likewise, we found an even higher proportion of metastases from lymphoma in the spine metastases cohort, being the most frequent along with plasma cell neoplasms at 21%, followed by breast, lung and thyroid cancers in equal proportions at 7.1%. This differed to that reported in Nigeria and Denmark where prostate was the most prevalent metastatic neoplasm.[12,25] Furthermore breast, lung and prostate were most frequent in other studies from Europe and North America.[10,24,26-28] Additionally lower prevalences of 1.7% to 3.2% and 3.2% to 6.8% for lymphoma and plasma cell neoplasms were observed in a large prospective, multi-continental study of 2143 patients, with all those enrolled being from developed countries.[26] Again these differences could be attributable to the high HIV disease burden in South Africa and the association of non-Hodgkin's lymphoma with HIV.[34,36]

Strengths of the study

This is the first study known to the authors conducted in South Africa profiling patients with histologically confirmed CNS metastases, and also evaluating the associations between demographic and radiological characteristics of brain metastases as they relate to various histopathological subtypes.

Limitations of the study

The retrospective nature of the study is the main limiting factor with consequent incomplete data and missing patients' records. We evaluated patients who had undergone surgical resection of their CNS lesions and this creates an inherent bias of patients with better prognoses being reviewed as they would have been better surgical candidates, and subsequently those with poor prognoses might have been missed. Some of these limitations could be overcome in the future, through a prospective study over a longer period of time being conducted.

Conclusion

This study highlighted that although there were many similarities in correspondence with global trends of patients with CNS metastases, significant differences were also observed and therefore having our own data is vital. Some similarities observed were the radiological distribution of CNS metastases. Differences were observed in the higher proportion of metastatic CNS lymphoma in our study, with those patients seemingly having poorer prognostic indicators. This could guide future research to better evaluate this finding. Another compelling finding is the pattern of contrast enhancement observed when CT and MRI investigations were performed in conjunction. This revealed a statistically significant increased uptake of contrast in those with brain metastases secondary to breast cancer compared to other tumour types, and with the least uptake found in lung cancer. This is another potential area of research and could prove to be useful in pointing to a potential primary cancer site where resources for extensive investigations are limited.

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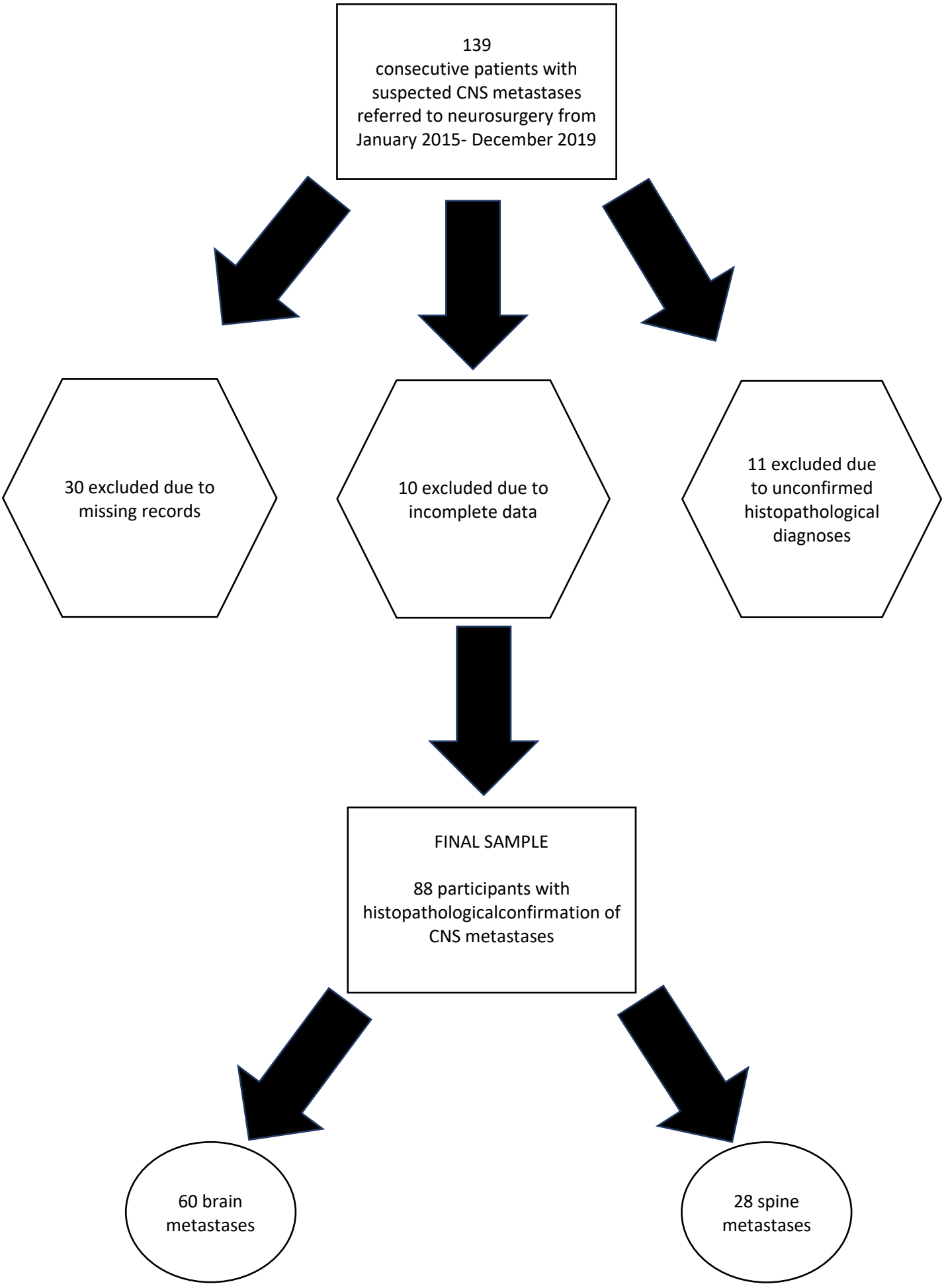


Figure 1: Flowchart of patient recruitment and those excluded from the study

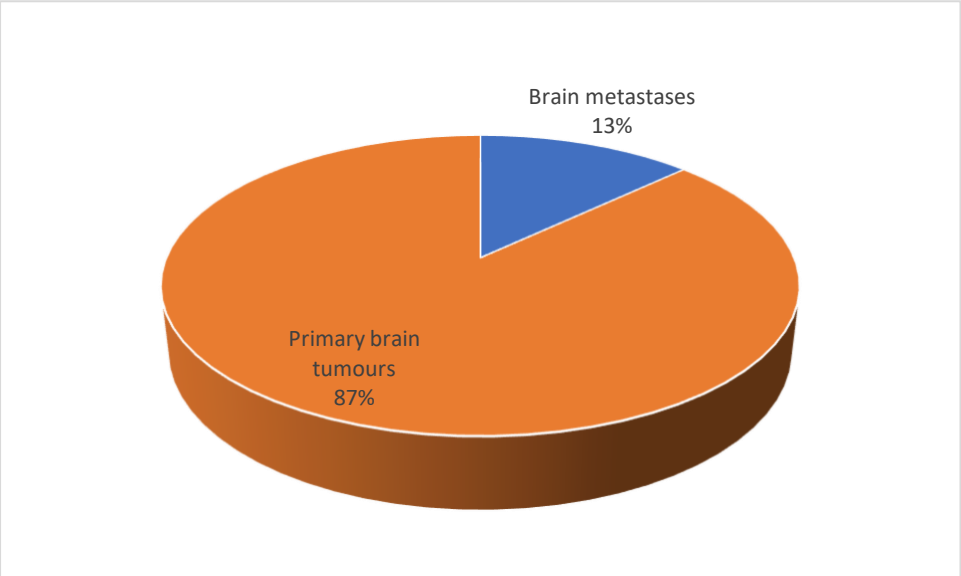


Figure 2: Repartition of patients with brain metastases vs all primary brain tumours in operated patients over the study period

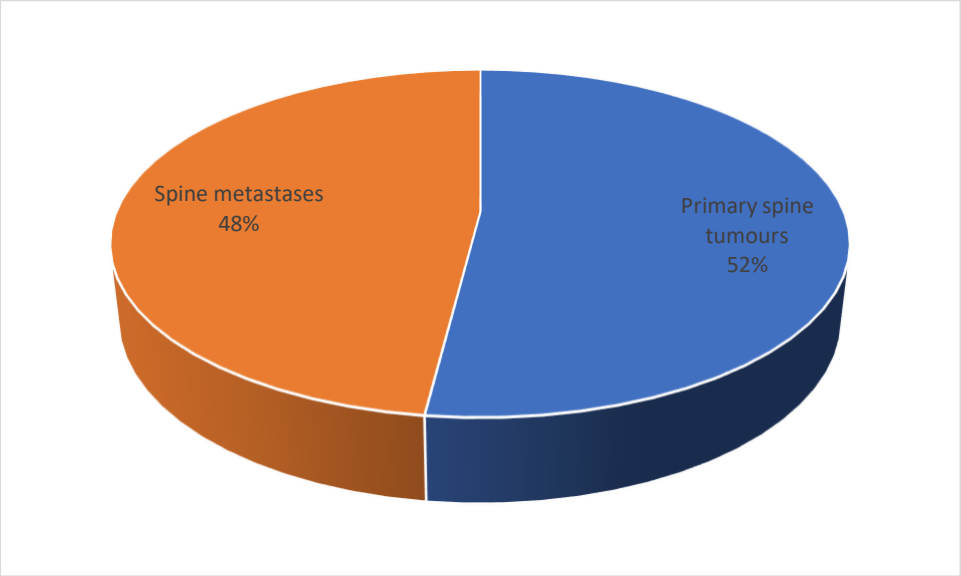


Figure 3: Repartition of patients with spine metastases vs all primary spine tumours in operated patients over the study period

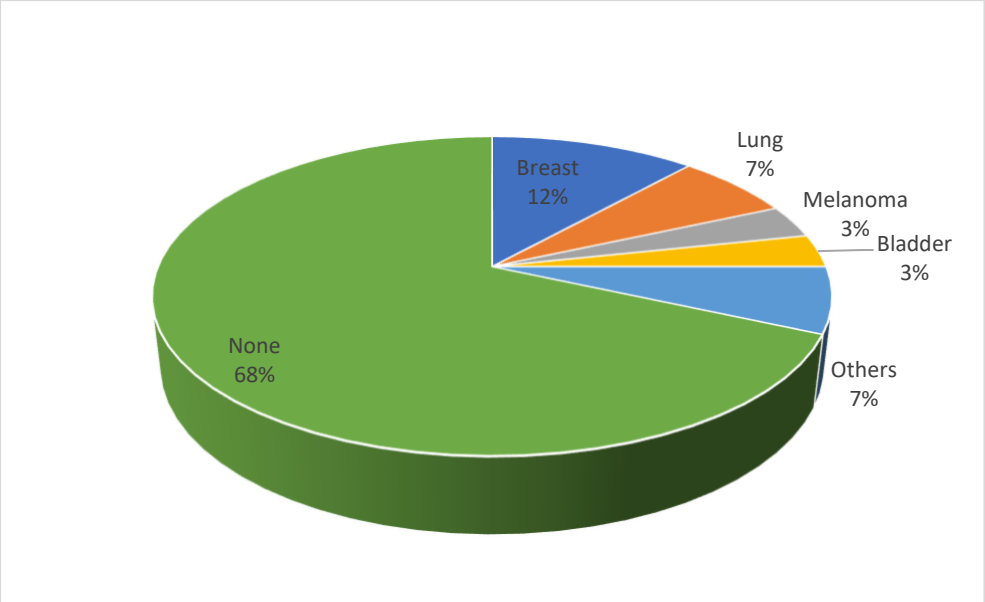


Figure 4: Repartition of patients with known primary tumours presenting with brain metastases compared to those without known primary tumours presenting with brain metastases

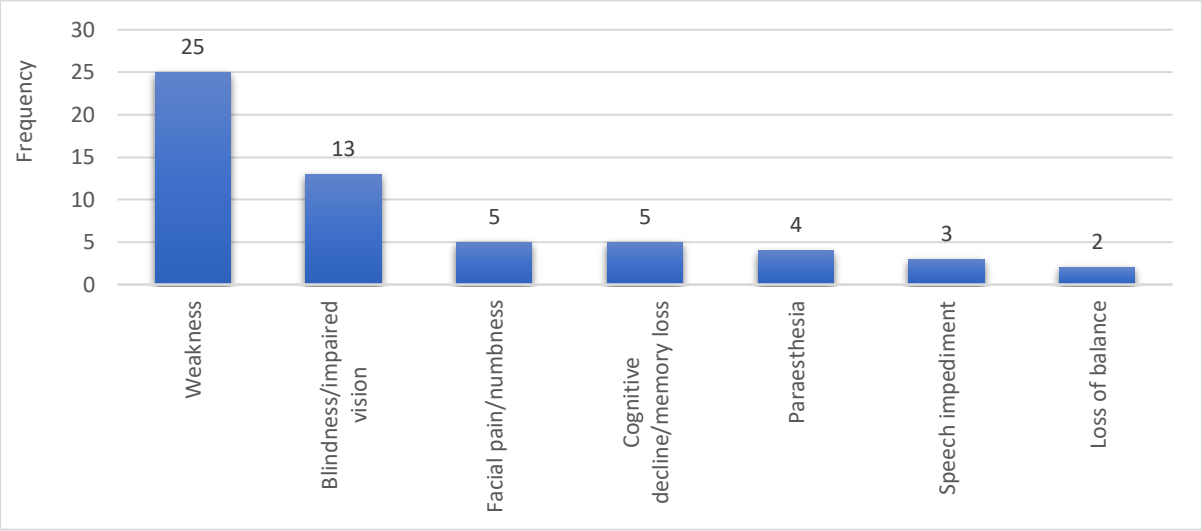


Figure 5a: Symptoms among patients with brain metastases who reported having neurological deficits (n=38)

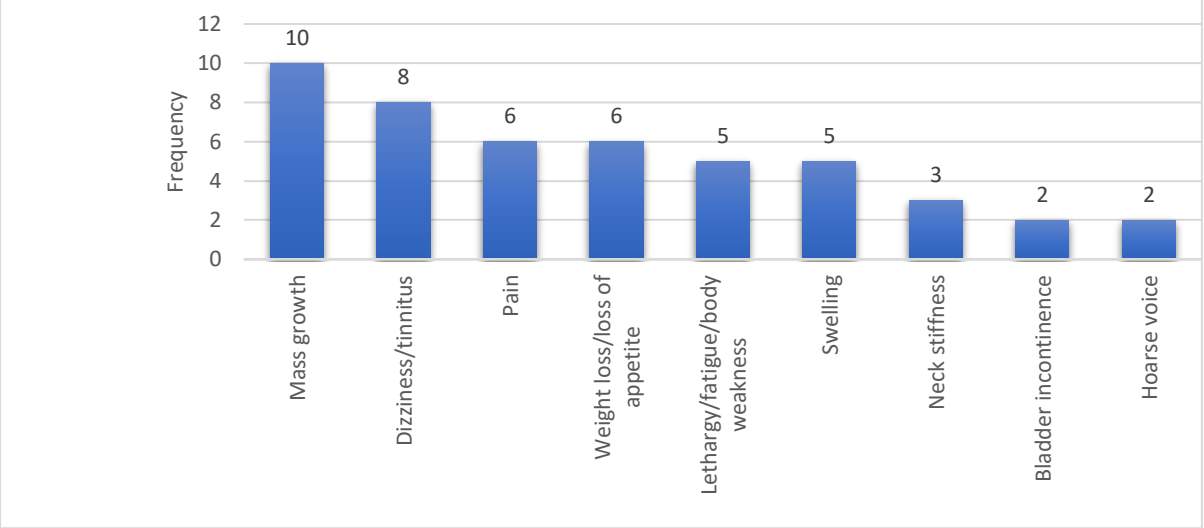


Figure 5b: Symptoms among patients with brain metastases who reported having non-cerebral manifestations (n=37)

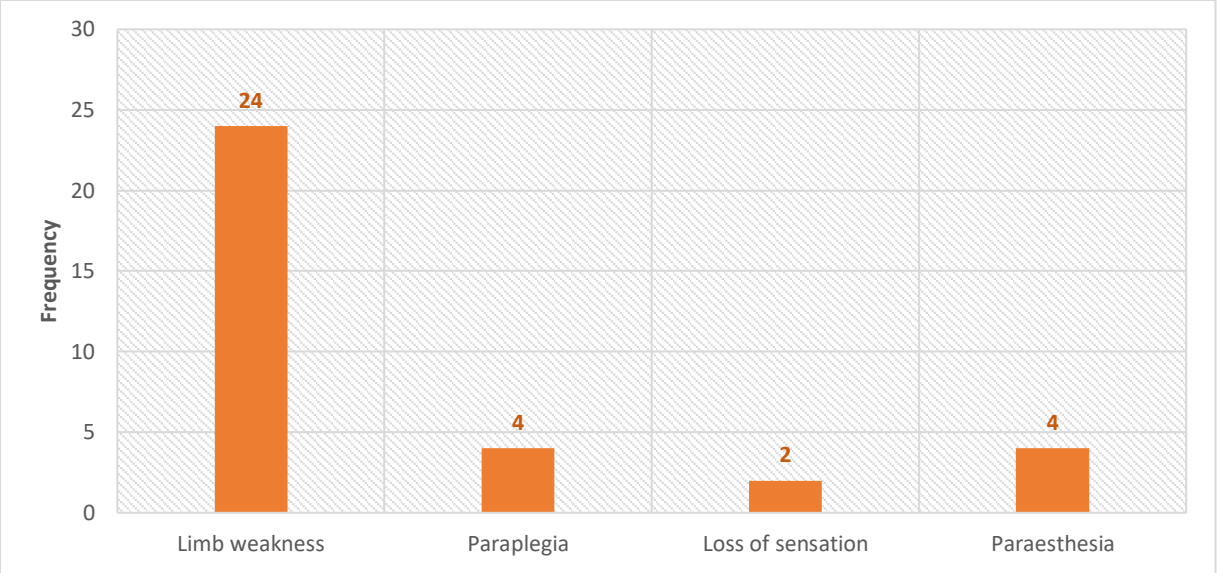


Figure 6a. Symptoms among patients with spine metastases who reported having limb dysfunction (n=27)

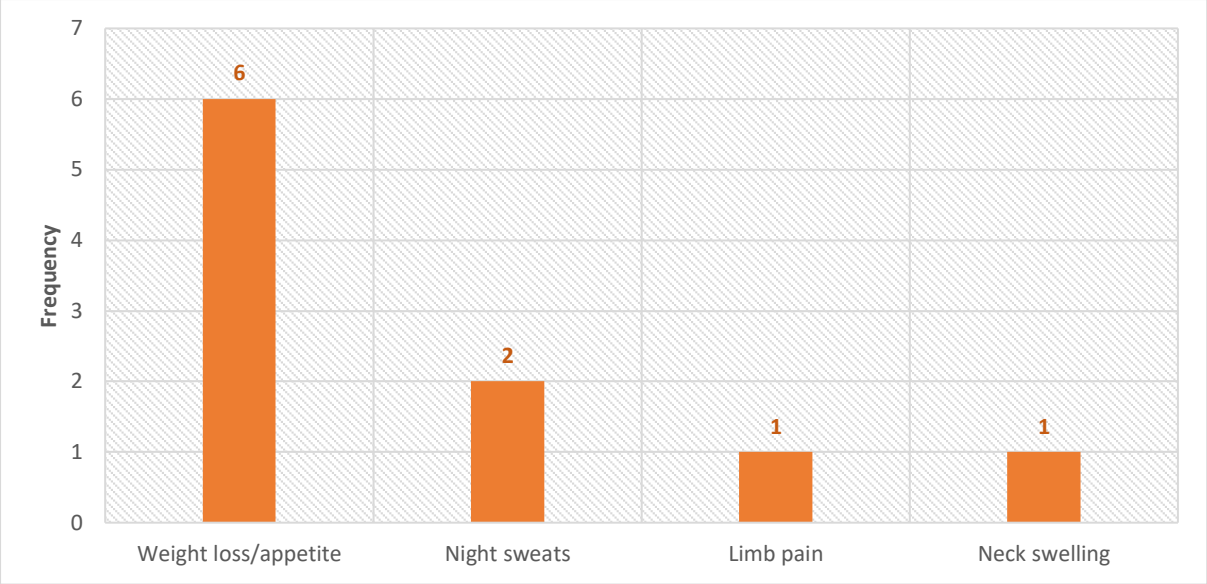


Figure 6b: Symptoms among patients with spine metastases who reported having non-spinal manifestations (n=9)

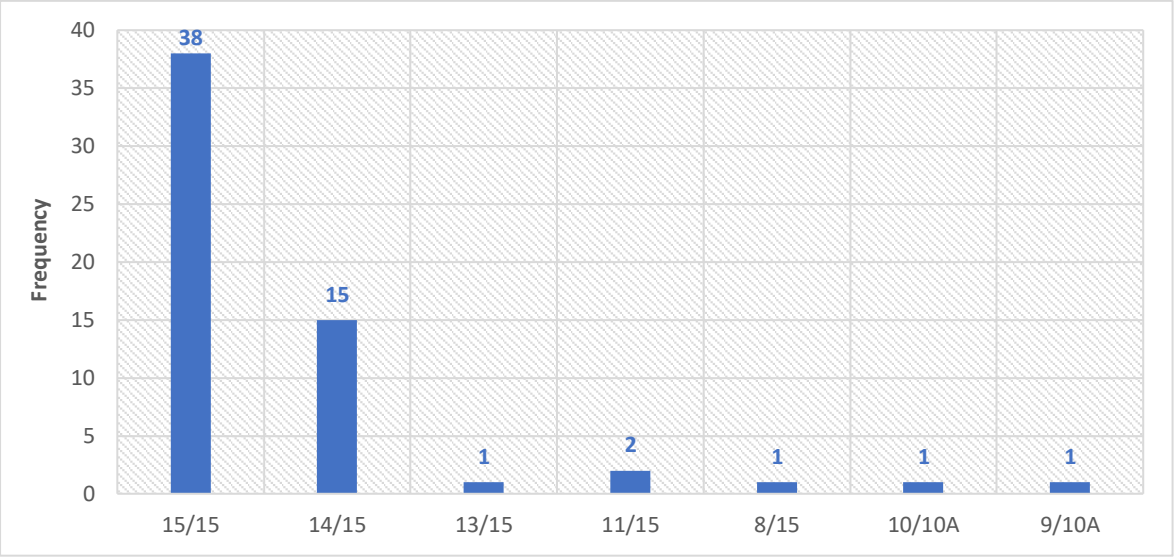


Figure 7a: GCS scores among patients with brain metastases

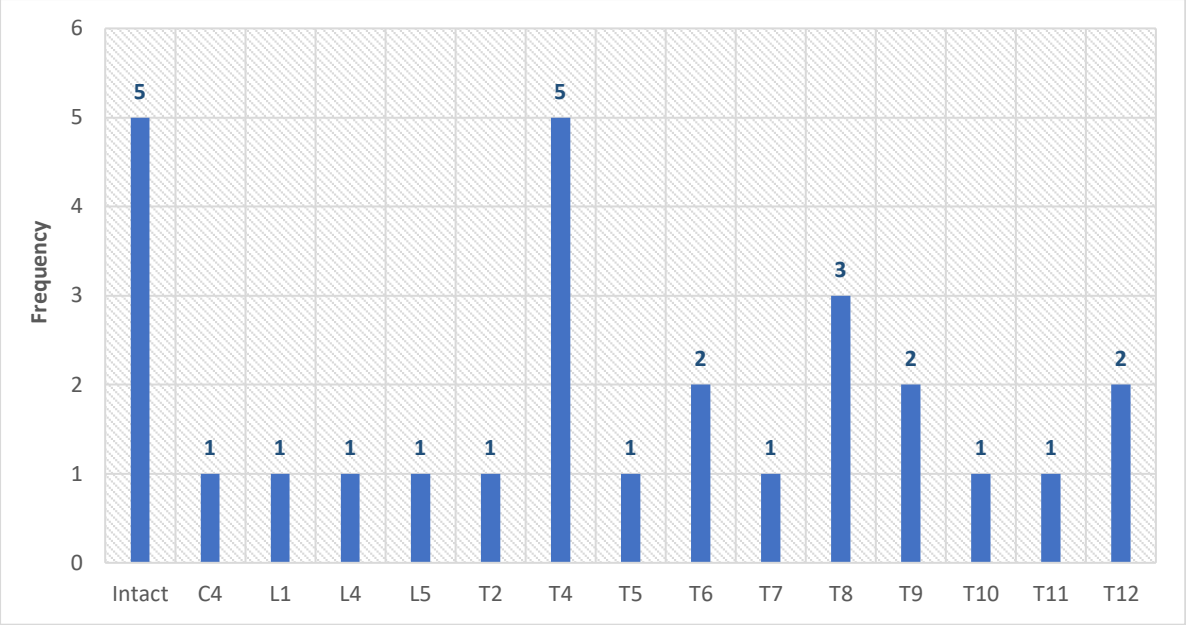


Figure 7b: Sensory levels among patients with spinal metastases

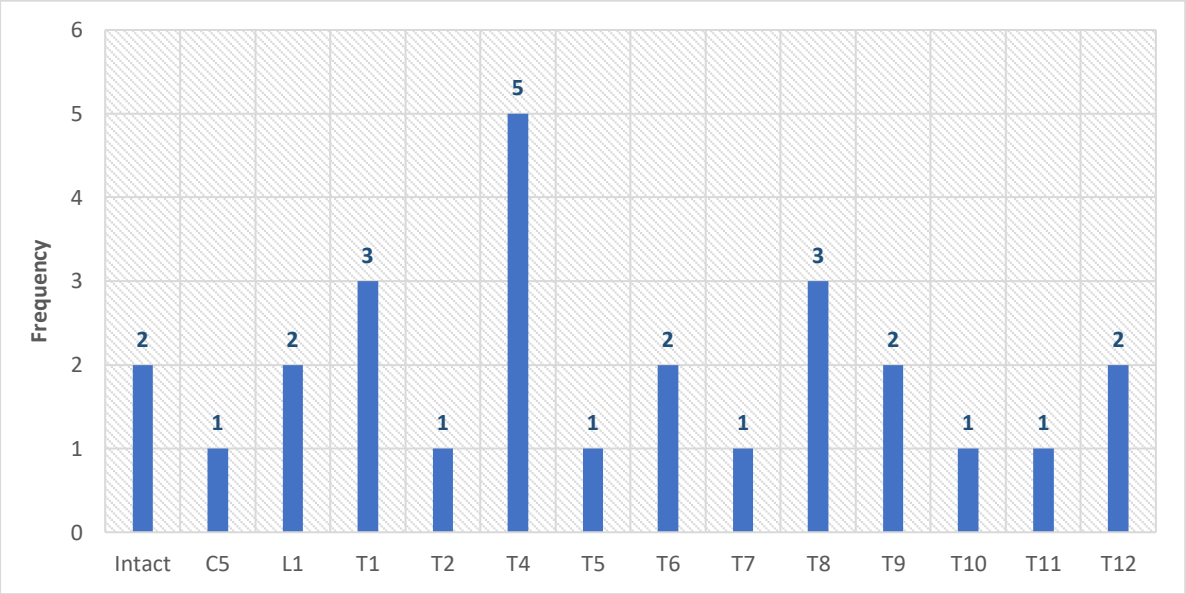


Figure 7c: Motor levels among patients with spinal metastases

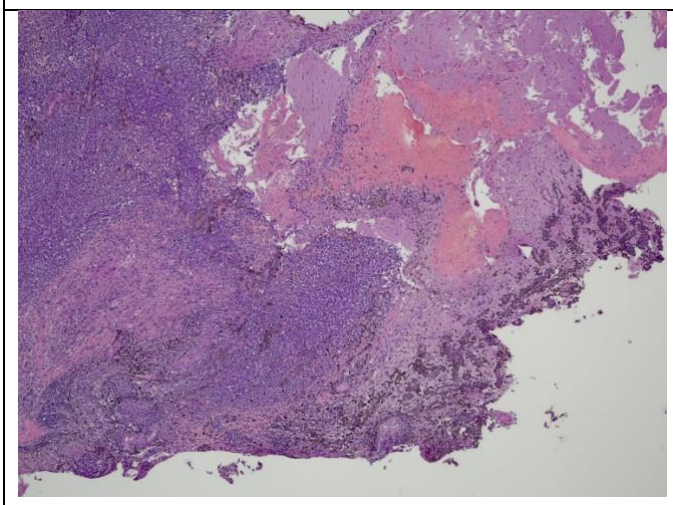
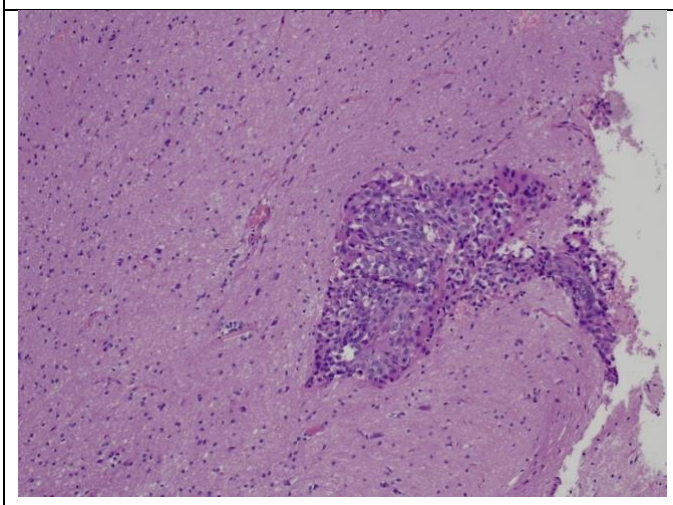
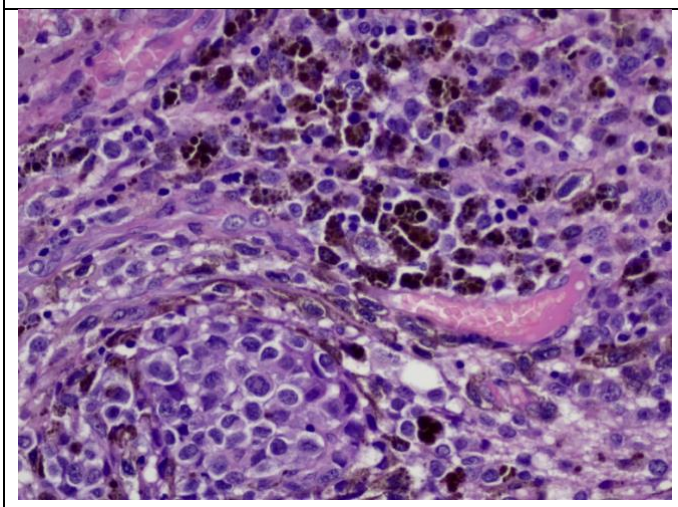
Melanoma	
	Low power image of metastatic melanoma. Melanin pigment is evident within the tumour as brown staining. (Haematoxylin and eosin stain, 4x magnification)
	Glial parenchyma with an invasive nest of malignant melanoma. (Haematoxylin and eosin stain, 10x magnification)
	High power image of metastatic melanoma demonstrating pleomorphic cells with coarse brown melanin pigment. (Haematoxylin and eosin stain, 40x magnification)

Figure 8a: Histopathology image depicting morphological pattern of melanoma microscopically

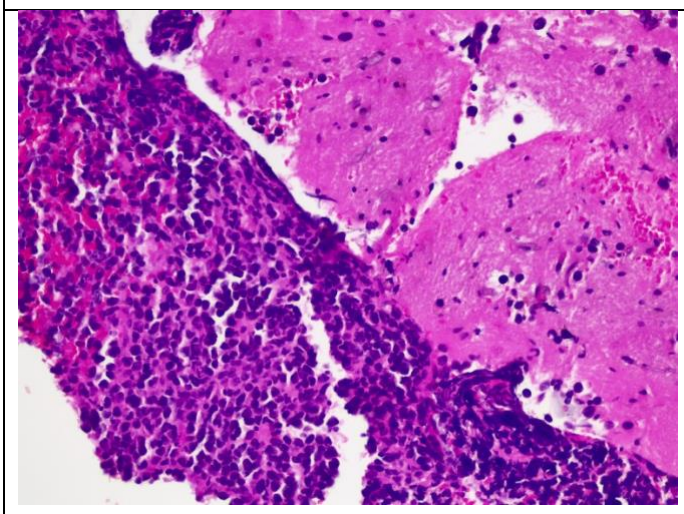
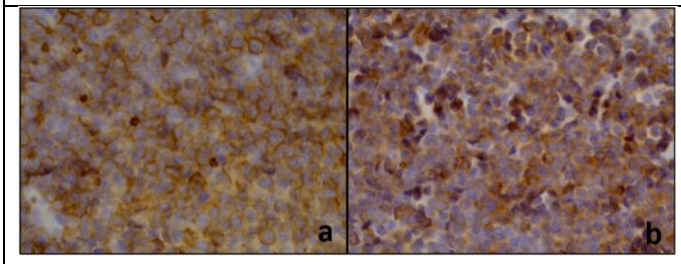
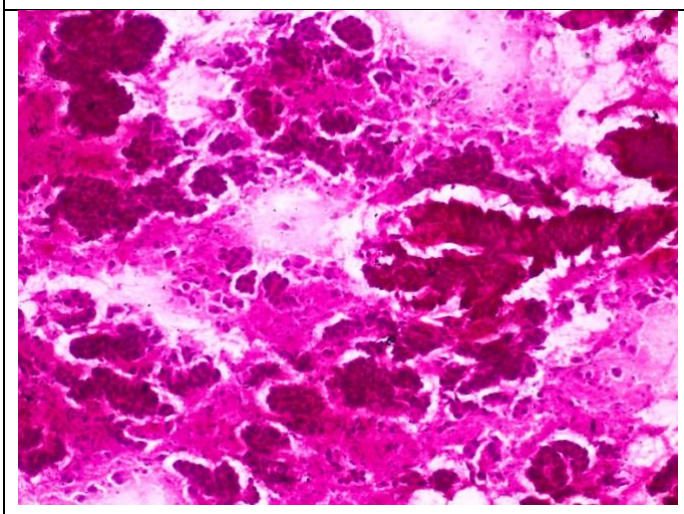
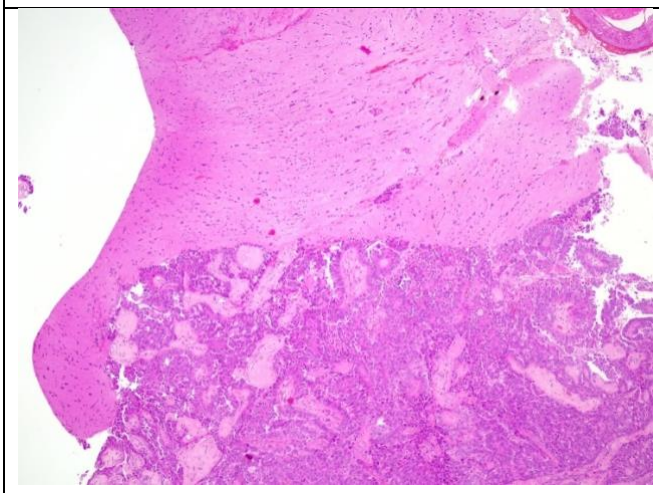
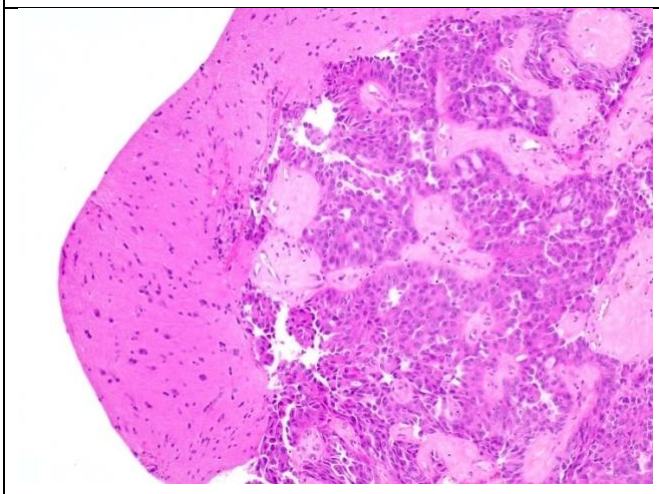
Lymphoma	
	Medium power image of a high-grade B-cell lymphoma that has metastasised to the brain. Glial parenchyma is present in the upper right of the image with a diffuse infiltrate of hyperchromatic cells with raised nuclear to cytoplasmic ratios at the lower left of the image. (Haematoxylin and eosin stain, 20x magnification)
	(a) Leukocyte common antigen (LCA) immunohistochemical stain confirming lymphoid origin of the neoplastic cells. (LCA stain, 40x magnification) (b) Cluster of differentiation (CD) 79a immunohistochemical stain confirming B-cell lineage of the neoplastic cells. (CD79a stain, 40x magnification)

Figure 8b: Histopathology image depicting morphological pattern of lymphoma microscopically

Metastatic lung adenocarcinoma	
	Brain smear demonstrating a metastatic adenocarcinoma with cells in cohesive groups forming papillary structures. There is extensive background necrosis. (Haematoxylin and eosin stain, 10x magnification)
	Metastatic lung adenocarcinoma to the brain with glial parenchyma at the upper aspect of the image with the tumour present at the bottom. (Haematoxylin and eosin stain, 4x magnification)
	Metastatic lung adenocarcinoma with the tumour cells forming papillae with central fibrovascular cores. Glial parenchyma is present at the left of the image. (Haematoxylin and eosin stain, 20x magnification)

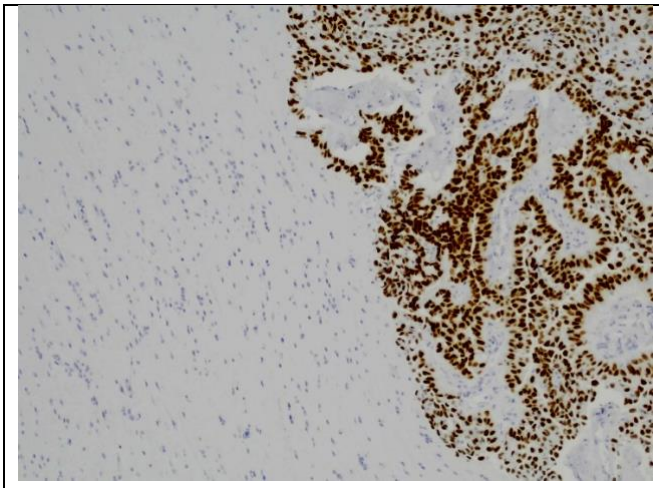
	Thyroid transcription factor 1 (TTF1) immunohistochemical stain demonstrating nuclear positivity in the tumour cells, confirming origin from the lung. The background glial parenchyma is negative. (TTF1 stain, 10x magnification)

Figure 8c: Histopathology image depicting morphological pattern of metastatic lung adenocarcinoma microscopically

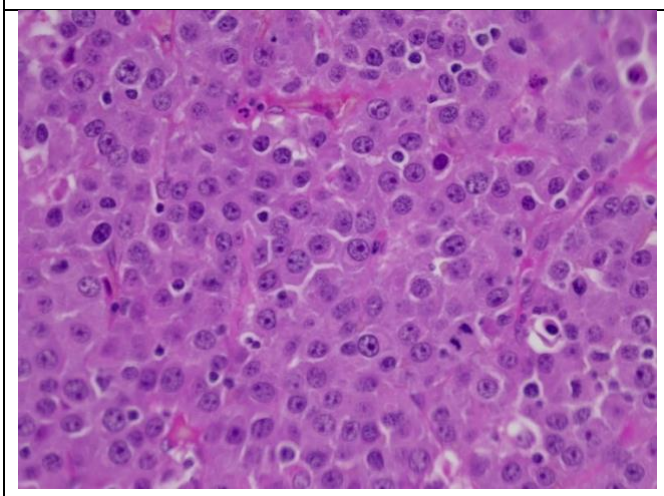
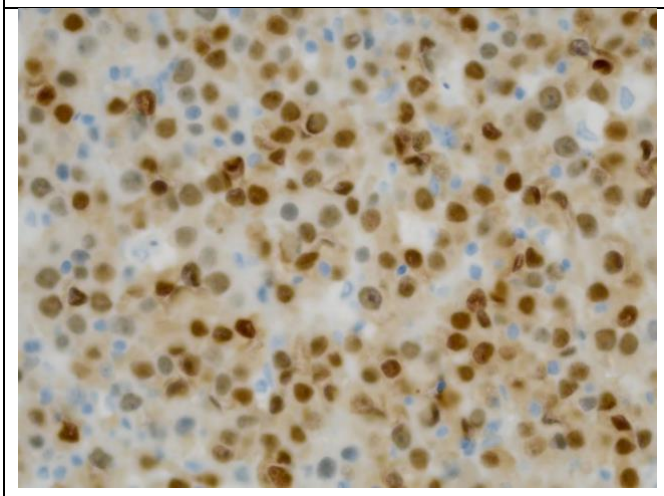
Plasmacytoma	
	Sheet like proliferation of neoplastic plasma cells. The cells have eccentric cytoplasm with a paranuclear hof present in many cells. The nuclei are round with prominent nucleoli. (Haematoxylin and eosin stain, 40x magnification)
	Multiple myeloma 1 (MUM1) immunohistochemical stain demonstrating nuclear positivity of the tumour cells confirming plasma cell origin. (MUM1 stain, 40x magnification)

Figure 8d: Histopathology image depicting morphological pattern of plasmacytoma microscopically

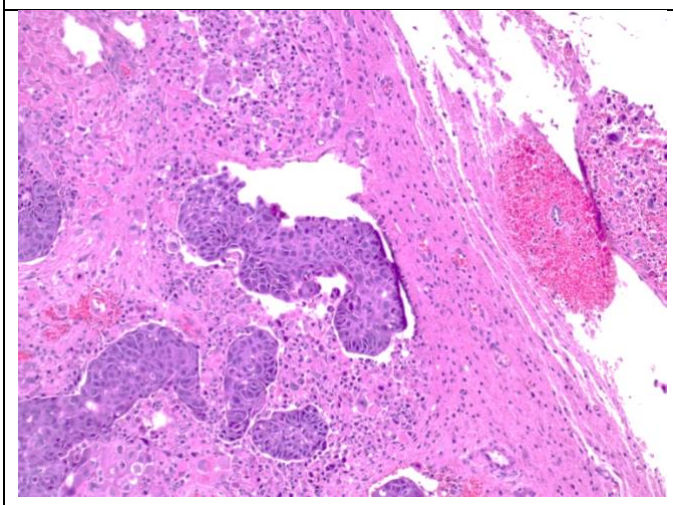
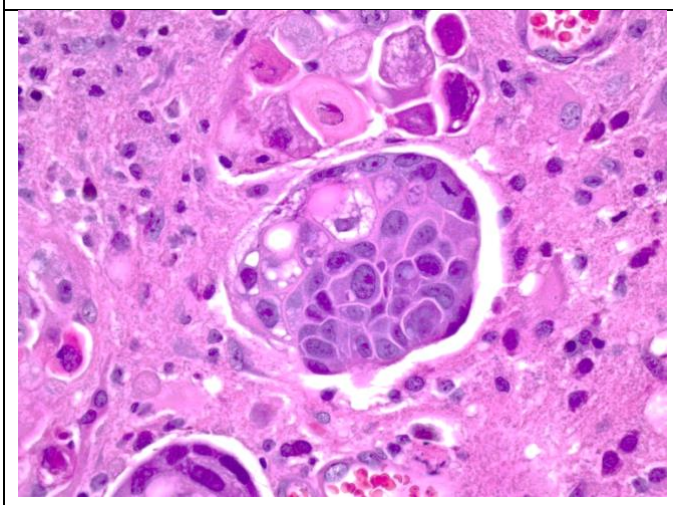
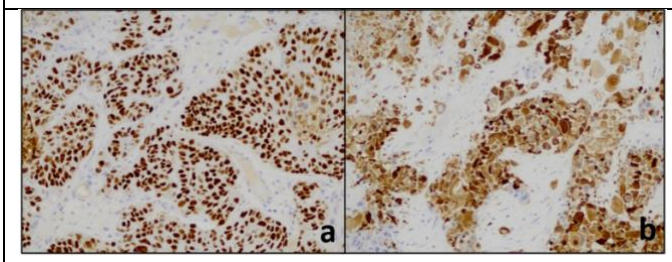
Metastatic squamous cell carcinoma	
	Metastatic squamous cell carcinoma seen as invasive nests of cohesive cells in background glial parenchyma. (Haematoxylin and eosin stain, 10x magnification)
	High power image of metastatic squamous cells. Intercellular bridges are seen between the pleomorphic cells. (Haematoxylin and eosin stain, 40x magnification)
	(a) P63 immunohistochemical stain demonstrating nuclear positivity of the tumour cells. (P63 stain, 20x magnification) (b) Cytokeratin (CK) 5/6 immunohistochemical stain demonstrating cytoplasmic staining of tumour cells. The CK5/6 with the P63 confirms squamous origin of the tumour cells. (CK5/6 stain, 20x magnification)

Figure 8e: Histopathology image depicting morphological pattern of metastatic squamous cell carcinoma microscopically

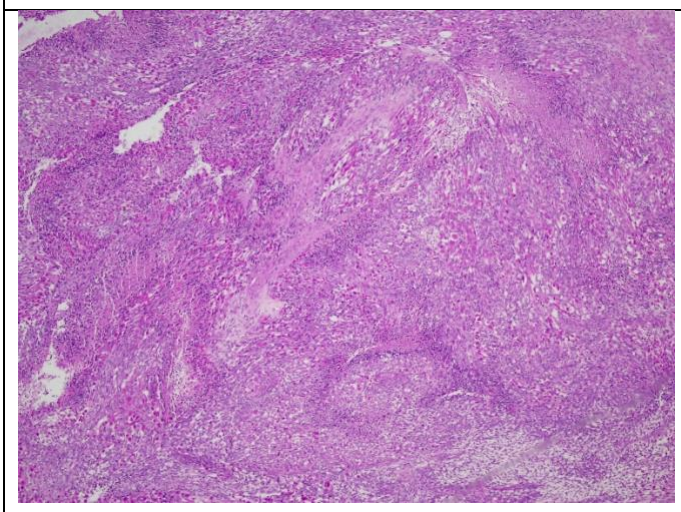
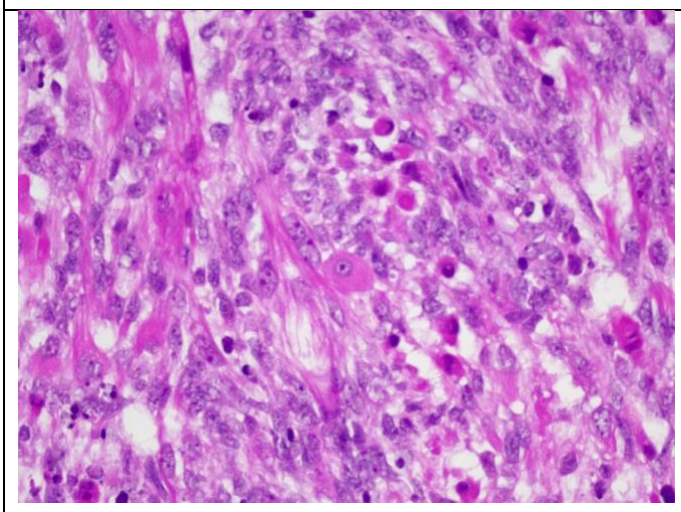
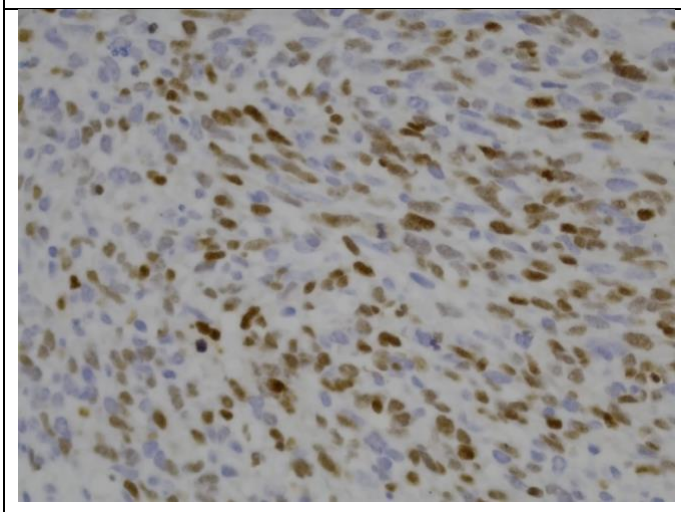
Rhabdomyosarcoma	
	Low power image of a metastatic spindle cell neoplasm. (Haematoxylin and eosin stain, 4x magnification)
	Metastatic rhabdomyosarcoma showing varying degrees of maturation into skeletal muscle with small primitive cells, round cells and elongated strap cells. (Haematoxylin and eosin stain, 40x magnification)
	Myogenic differentiation antigen 1 (MyoD1) immunohistochemical stain demonstrating nuclear positivity of tumour cells confirming rhabdomyosarcoma. (MyoD1 stain, 40x magnification)

Figure 8f: Histopathology image depicting morphological pattern of rhabdomyosarcoma microscopically

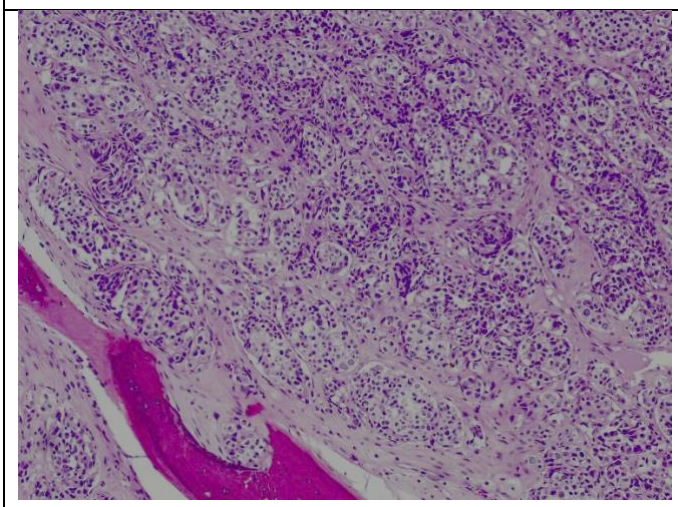
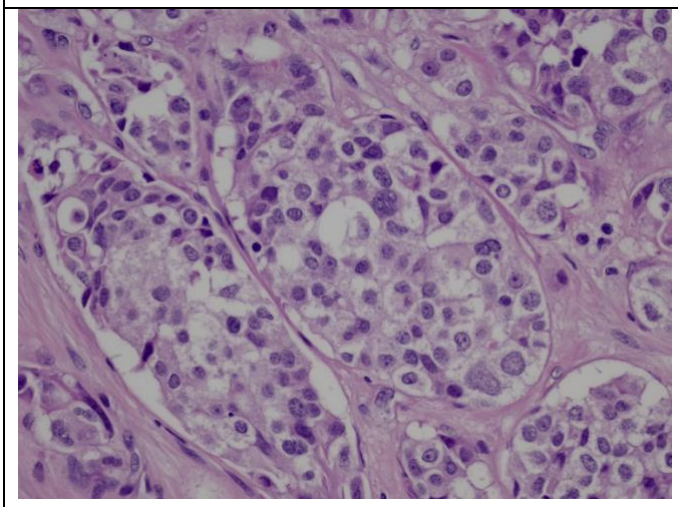
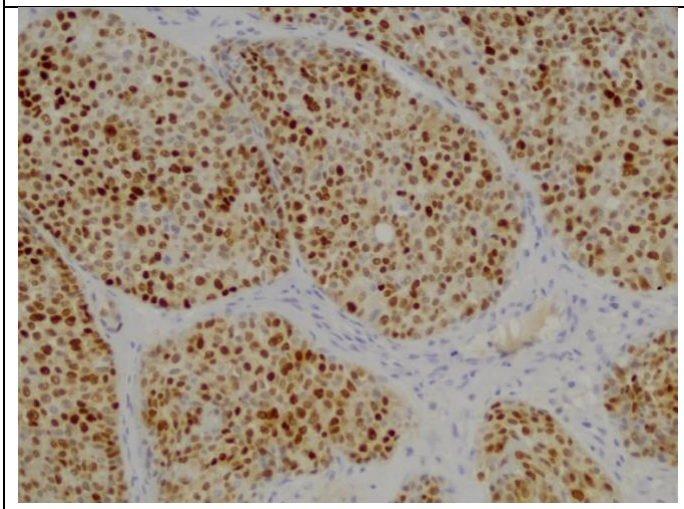
Metastatic breast carcinoma	
	Metastatic breast carcinoma seen as nests of tumour cells. Bone is present at the lower left aspect of the image. (Haematoxylin and eosin stain, 10x magnification)
	High power of the nests of tumour cells demonstrating markedly pleomorphic cells with an attempt at gland formation seen in the centre. (Haematoxylin and eosin stain, 40x magnification)
	GATA 3 immunohistochemical stain demonstrating nuclear positivity confirming origin from the breast. (GATA3 stain, 20x magnification)

Figure 8g: Histopathology image depicting morphological pattern of metastatic breast carcinoma microscopically

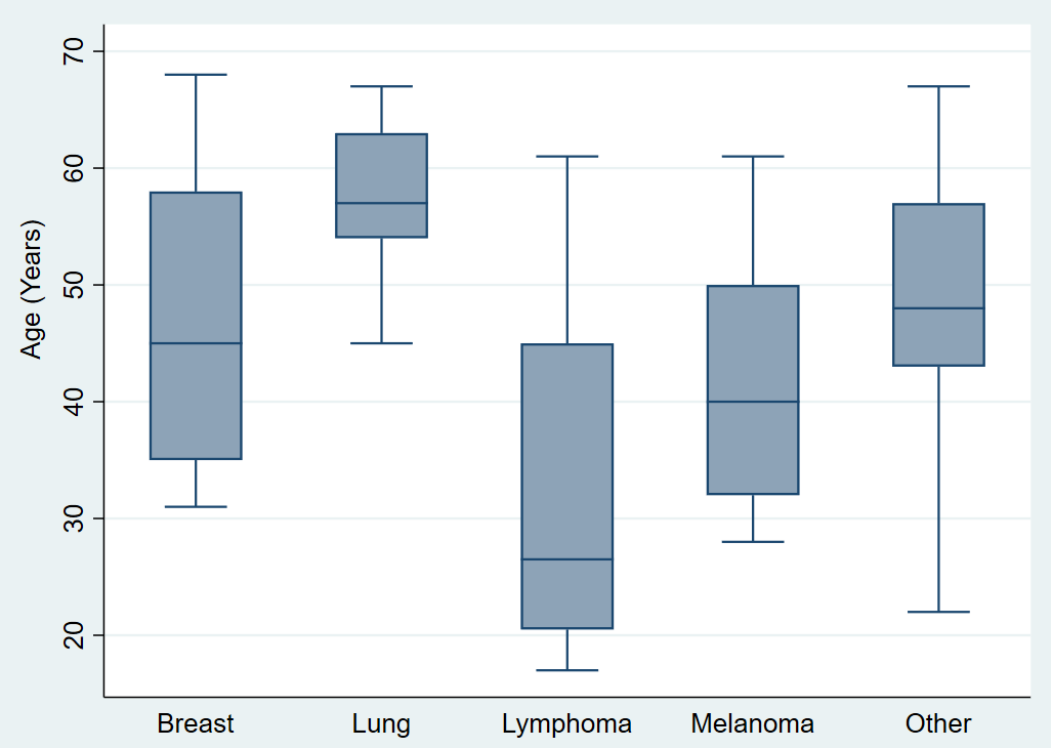


Figure 9: Comparison of median age by histopathology type in patients with brain metastases (Kruskal-Wallis H test p-value= 0.040).

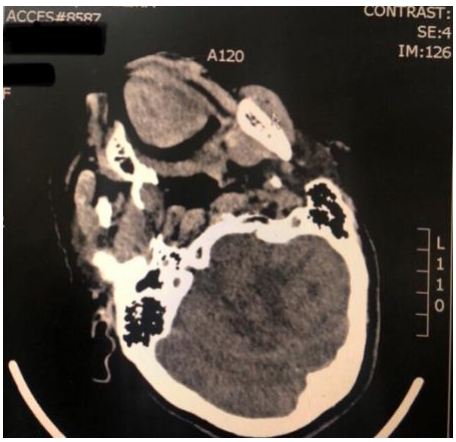


Figure 10a:Metastatic lung cancer CT brain image post contrast

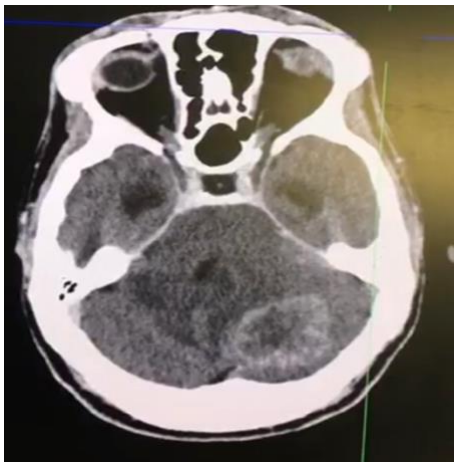


Figure 10b:Metastatic lung cancer CT brain image post contrast

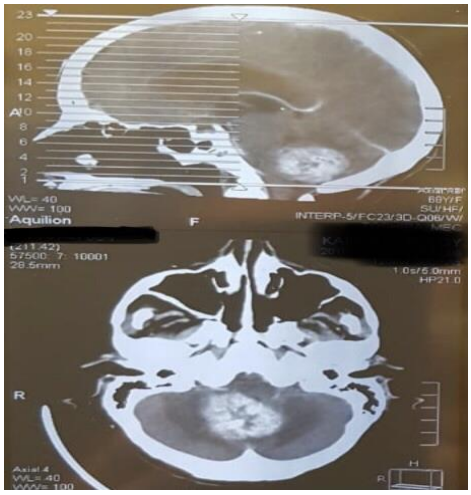


Figure 10c: Metastatic breast cancer CT brain images post contrast

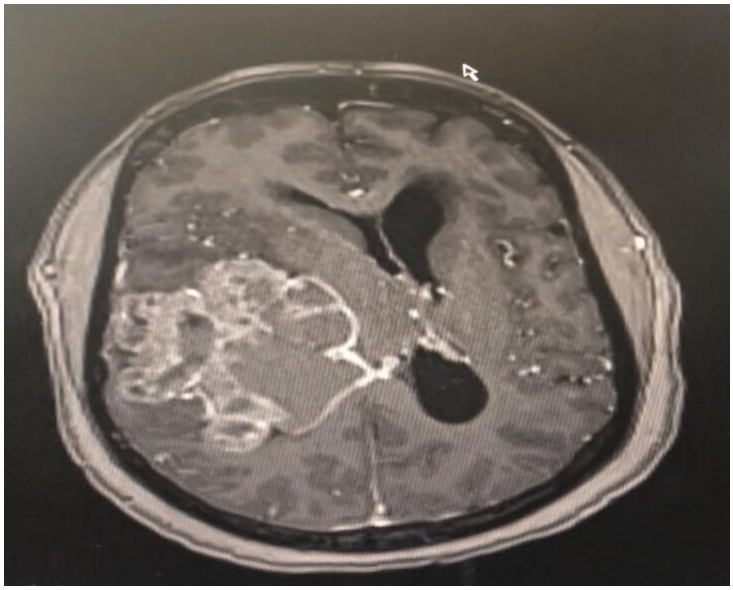


Figure 10d: Metastatic lung cancer,T1WI MRI brain scan post gadolinium contrast

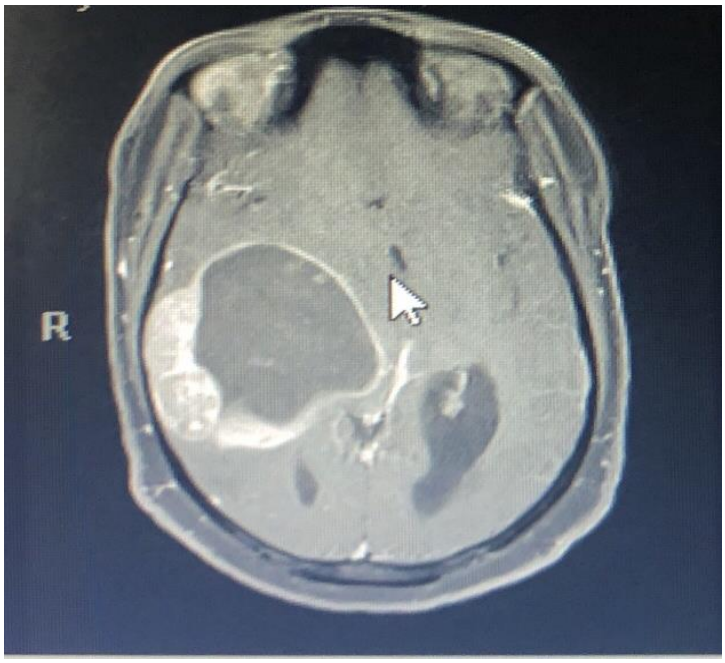


Figure 10e: Metastatic breast cancer, T1WI MRI brain scan post gadolinium contrast

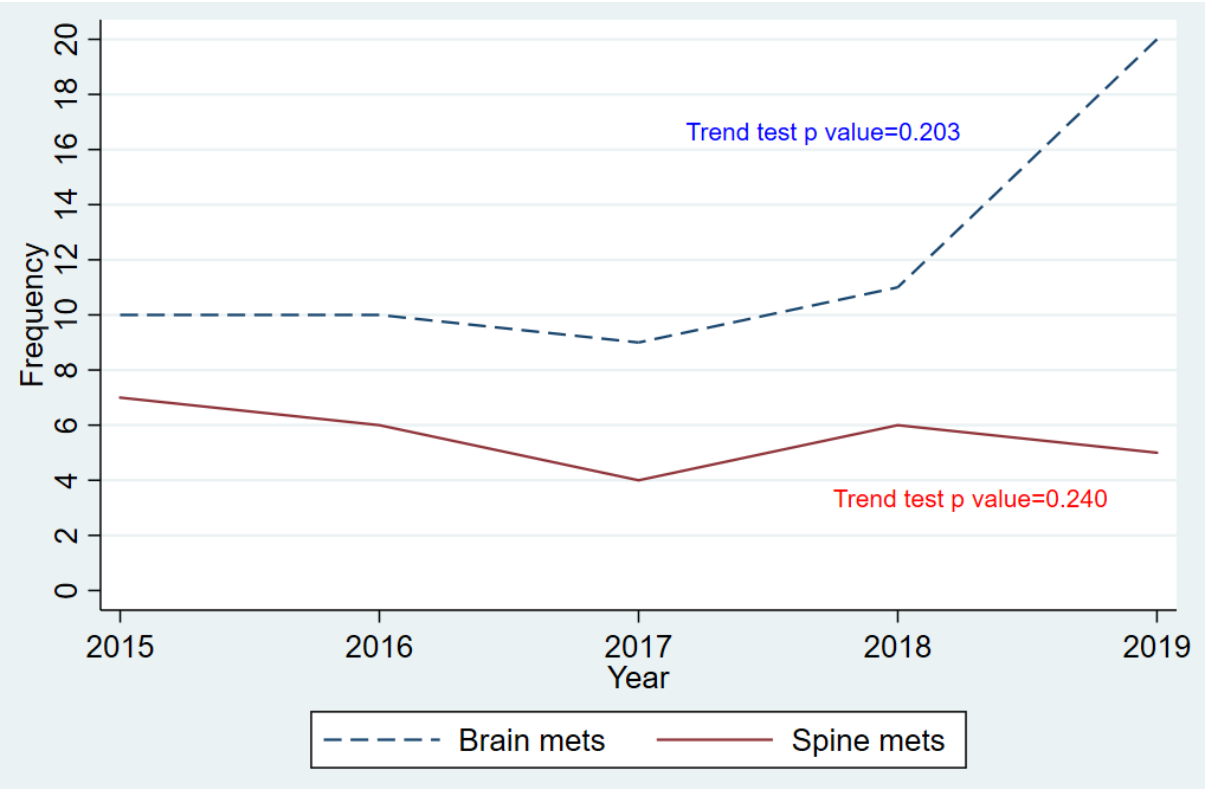


Figure 11: Trends in number of metastases per year. Correlation coefficients and trend tests for brain and spine metastases between 2015-2019.

	Correlation coefficient with year	P value	Linear Trend test P value
Brain mets	0.77	0.159	0.203
Spine mets	-0.55	0.332	0.240

No statistically significant association between year and number of metastases for both brain and spinal metastases, and there was no linear trend either at the 5% level of significance.

Table 1: Demographics of brain and spinal metastases

Demographics	Brain Metastases N=60	Spinal metastases N=28
Age (Years)		
Median (IQR) or mean ± SD	49 (37-58.5)	47.1 ± 14.1
Age categories		
≤18	4 (6.7%)	1 (3.6%)
19-29	6 (10.0%)	1 (3.6%)
30-39	6 (10.0%)	7 (25.0%)
40-49	14 (23.3%)	8 (28.6%)
50-59	17 (28.3%)	4 (14.3%)
60+	13 (21.7%)	7 (25.0%)
Sex		
Female	31 (51.7%)	12 (42.9%)
Male	29 (48.3%)	16 (57.1%)
Race		
Black	39 (65.0%)	23 (82.1%)
White	16 (26.7%)	4 (14.3%)
Coloured	3 (5.0%)	1 (3.6%)
Indian	2 (3.3%)	0 (0.0%)
Occupation		
Professional/full time employee	6 (10.0%)	4 (14.3%)
Casual employee	4 (6.7%)	2 (7.1%)
Pensioner	10 (16.7%)	6 (21.4%)
Student	1 (1.7%)	1 (3.6%)
Minor	3 (5.0%)	0 (0.0%)
Unemployed	24 (40.0%)	13 (46.4%)
Unknown/missing	12 (20.0%)	2 (7.1%)
Risk factor history		
Smoking only	16 (26.7%)	3 (10.7%)
Ethanol only	0 (0.0%)	2 (7.1%)
Family cancer	1 (1.7%)	1 (3.6%)
Smoking + ethanol	6 (10.0%)	6 (21.4%)
Smoking + family cancer	2 (3.3%)	0 (0.0%)
Smoking + family cancer + ethanol	1 (1.7%)	1 (3.6%)
Not documented	34 (56.7%)	15 (53.6%)
Known primary cancer		
Breast	7 (11.7%)	2 (7.1%)
Lung	4 (6.7%)	0 (0.0%)
Melanoma	2 (3.3%)	0 (0.0%)
Bladder	2 (3.3%)	0 (0.0%)
Colorectal	1 (1.7%)	0 (0.0%)
Lymphoma	1 (1.7%)	0 (0.0%)
Thyroid	1 (1.7%)	1 (3.6%)
Ovarian	1 (1.7%)	0 (0.0%)
None	41 (68.3%)	25 (89.3%)
Time interval from primary cancer to metastasis diagnosis	(n=19)	(n=3)

Mean ± SD	27.3 ± 23.8	12.3 ± 11.5
<12 months	7 (36.8%)	1 (33.3%)
12-60 months	9 (47.4%)	2 (66.7%)
60+ months	3 (15.8%)	0 (0.0%)
Year of diagnosis		
2015	10 (16.7%)	7 (25.0%)
2016	10 (16.7%)	6 (21.4%)
2017	9 (15.0%)	4 (14.3%)
2018	11 (18.3%)	6 (21.4%)
2019	20 (33.3%)	5 (17.9%)

Table 2: Clinical presentations of brain and spine metastases

Symptoms (brain)	N (%)	Symptoms (spine)	N (%)
Headache	38 (63.3%)	Back pain	19 (67.9%)
Nausea and vomiting	16 (26.7%)	Bladder dysfunction	2 (7.1%)
Seizures	11 (18.3%)	Bowel dysfunction	2 (7.1%)
Mental state changes	20 (33.3%)	Bladder + bowel dysfunction	16 (57.1%)
Neurological deficits	38 (63.3%)	Limb dysfunction	27 (96.4%)
Non cerebral manifestations	37 (61.7%)	Non spinal manifestations	9 (32.1%)
Acute symptoms (<1 month)	22 (36.7%)	Acute symptoms (<1 month)	14 (50.0%)
Chronic symptoms ≥1 month)	43 (71.7%)	Chronic symptoms ≥1 month)	18 (64.3%)

Table 3a(i): Clinical signs among patients with brain metastases

CLINICAL SIGNS	N (%)
GCS scores	
Mild (13-15)	54 (90.0%)
Moderate (9-12)	3 (5.0%)
Severe (3-8)	2 (3.3%)
Unknown	1 (1.7%)
Neurological defects subgroups	
Motor	22 (36.7%)
Cranial nerve	17 (28.3%)
Cerebellar signs	10 (16.7%)
Seizures	1 (1.7%)
Absent	20 (33.3%)
Unknown	2 (3.3%)
Non cerebral manifestations	
Scalp/head/neck masses	11 (18.3%)
Emaciated	6 (10.0%)
Eye proptosis	5 (8.3%)
Other	8 (13.3%)
Absent	34 (56.7%)
Unknown	1 (1.7%)
RADIOLOGY	
CT: n (%) Median number of metastases (IQR)	30 (50.0%) 1 (1-2)
CT + MRI: n (%) Median number of metastases (IQR)	22 (36.7%) 1 (1-1)
CT + MRI + more metastases: n (%) Median number of metastases (IQR)	6 (10.0%) 3.5 (3-4)
MRI Median number of metastases (IQR)	2 (3.3%) 2.5 (2-3)
Location of tumour (s)	
Supratentorial (n=48)	
a) frontal	28 (58.3%)
b) Parietal	25 (52.0%)
c) Temporal	17 (35.4%)
d) Occipital	15 (31.3%)
e) Deep intracerebral	4 (8.3%)
f) Local extra-cranial spread/ other	30 (62.5%)
g) Left sided lesions	21 (43.8%)
h) Right sided lesions	33 (68.8%)
i) Left + right sides	8 (16.7%)
infratentorial (n=21)	
a) right and left cerebellar hemispheres	15 (71.4%)
b) Left cerebellum	7 (33.0%)
c) Right cerebellum	8 (38.0%)
d) Midline cerebellum	3 (14.3%)
e) Left + right cerebellar + midline	1 (4.8%)
f) Cerebellopontine angle (other)	2 (9.5%)
Supratentorial only	39 (65.0%)
Infratentorial only	12 (20.0%)

Supra-and infratentorial	9 (15.0%)
Location as it relates to the brain parenchyma	
a) Intra-axial	39 (65%)
b) Extra-axial	17 (28.3%)
c) Unknown	4 (6.7%)
Other associated features (n=28)	
a) Bone erosion	12 (20.0%)
b) Bony lytic lesions	3 (5.0%)
c) Leptomeningeal involvement	11 (18.3%)
d) Subdural fluid collection	2 (3.3%)
Tumour size (cm^3/cc)	
Median (IQR)	57.7 (33.9-193.3)
Presence of hydrocephalus	
No	43 (71.7%)
Yes	15 (25.0%)
Unknown	2 (3.3%)
Midline shift	
Yes	29 (48.3%)
Median distance (mm)	8.6 (4-11.2)
No	19 (31.7%)
Unknown	11 (18.3%)
Tumour features	
1) Consistency	
a) Homogenous	34 (56.7%)
Solid	29 (85.3%)
Cystic	5 (14.7%)
b) Heterogenous (mixed solid/cystic)	22 (36.7%)
c) Unknown	4 (6.7%)
2) Contrast uptake	
CT	27 (45.0%)
CT + MRI	26 (43.3%)
Unknown	5 (11.7%)
3) MRI Sequence	
T1 Post gadolinium contrast uptake	26 (43.3%)
4) CT Density (n=59)	
a) Hypodense	7 (11.9%)
b) Isodense	5 (8.5%)
c) Hyperdense	6 (10.2%)
d) Mixed density	36 (61.0%)
e) Unknown	5 (8.5%)
5) MRI T2 Intensity (n=29)	
a) Hypointense	1 (3.4%)
b) Isointense	2 (6.9%)
c) Hyperintense	14 (48.3%)
d) Mixed	12 (41.4%)
Extra-cranial metastases	
a) Present	26 (43.3%)
b) Absent	23 (38.3%)
c) Unknown	11 (18.3%)
HISTOPATHOLOGY	
Lung	13 (21.7%)

Breast	7 (11.7%)
Melanoma	7 (11.7%)
Squamous cell carcinoma	5 (8.3%)
Lymphoma (all non-Hodgkin)	4 (6.7%)
Other	24 (40.0%)
a) Metastatic adenocarcinoma (NOS)*	9 (15.0%)
b) Rhabdomyosarcoma	3 (5.0%)
c) Plasma cell neoplasm	3 (5.0%)
d) Urothelial	2 (3.3%)
e) Thyroid	2 (3.3%)
f) Gastrointestinal	1 (1.7%)
g) Ovarian	1 (1.7%)
h) Neuroblastoma	1 (1.7%)
i) Malignant skin adnexal carcinoma	1 (1.7%)
j) EBV associated smooth muscle	1 (1.7%)

Table 3a(ii): GPA scores stratified by histopathology among patients with brain metastases

Variable		Histopathology					P value
	Overall	Breast n=7	Lung n=13	Lymphoma n=4	Melanoma n=7	Other n=29	
Mean ± SD	2.2 ± 1.0	2.5 ± 1.1	2.1 ± 0.8	1.9 ± 1.0	2.1 ± 0.9	2.3 ± 1.1	0.862
0	2 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.9%)	
0.5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
1	9 (15.0%)	1 (14.3%)	2 (15.4%)	2 (50.0%)	2 (28.6%)	2 (6.9%)	
1.5	6 (10%)	1 (14.3%)	2 (15.4%)	0 (0.0%)	0 (0.0%)	3 (10.3%)	
2	9 (15.0%)	1 (14.3%)	2 (15.4%)	0 (0.0%)	2 (28.6%)	4 (13.8%)	
2.5	9 (15.0%)	1 (14.3%)	2 (15.4%)	1 (25.0%)	0 (0.0%)	5 (17.2%)	
3	10 (16.7%)	1 (14.3%)	2 (15.4%)	1 (25.0%)	3 (42.9%)	3 (10.3%)	
3.5	7 (11.7%)	1 (14.3%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	5 (17.2%)	
4	2 (3.3%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.5%)	
Unknown	6 (10%)	0 (0.0%)	2 (15.4%)	0 (0.0%)	0 (0.0%)	4 (13.8%)	

Table 3b. Clinical signs and classifications among patients with spinal metastases

CLINICAL SIGNS	N (%)
Tone	
Decreased	15 (53.6%)
Increased	7 (25.0%)
Normal	6 (21.4%)
Non spinal manifestations	
Emaciated	5 (17.9%)
Tenderness of vertebrae	6 (21.4%)
Other	4 (14.3%)
Absent	15 (53.6%)
ASIA scale	
A	10 (35.7%)
B	2 (7.1%)
C	9 (32.1%)
D	6 (21.4%)
E	1 (3.6%)
PROGNOSTIC SCORES	
Modified Tokuhashi	
>11	2 (7.1%)
9-11	7 (25.0%)
≤8	15 (53.6%)
Undetermined	4 (14.3%)
Tomita score	
2-4	12 (42.9%)
5-7	9 (32.1%)
8-10	5 (17.9%)
Undetermined	2 (7.1%)
RADIOLOGY	
Modality	
CT	2 (7.1%)
CT + MRI	15 (53.6%)
MRI	11 (39.3%)
Location	
Cervical	4 (14.3%)
Thoracic	9 (32.1%)
Lumbosacral	8 (28.5%)
Mixed (including all of cervical)	7 (25%)
Column involvement	
Anterior + Middle	3 (10.7%)
Anterior + Middle + Posterior	19 (67.9%)
Middle + Posterior	2 (7.1%)
Posterior	3 (10.7%)
Unknown	1 (3.6%)
Number of bones involved	
Single	6 (21.4%)
Multiple *Median number of metastases (IQR)*	22 (78.6%) *3 (3-6)*
Pattern of involvement	

Contiguous	7 (25.0%)
Non contiguous	3 (10.7%)
Both	11 (39.3%)
Unknown	7 (25.0%)
Bony features	
Osteoblastic/sclerotic	7 (25.0%)
Lytic	6 (21.4%)
Destructive (collapse/fracture)	11 (21.4%)
Spinal canal involvement (MRI)	
Extradural	21 (75.0%)
Intradural extramedullary	3 (10.7%)
Unknown	4 (14.3%)
Consistency of associated mass lesion(s)	
a) Homogenous (solid)	17 (60.7%)
b) Homogenous (cystic)	1 (3.6%)
c) Heterogenous	3 (10.7%)
d) Unknown	7 (25%)
Contrast uptake (CT/MRI)	21 (75%)
Extraspinal metastases	17 (60.7%)
HISTOPATHOLOGY	
Lymphoma (all non-Hodgkin)	6 (21.4%)
Plasma cell neoplasms	6 (21.4%)
Breast	2 (7.1%)
Lung	2 (7.1%)
Thyroid	2 (7.1%)
Other	10 (35.7%)
a) Metastatic adenocarcinoma NOS*	4 (14.3%)
b) Melanoma	1 (3.5%)
c) Prostate	1 (3.5%)
d) Hepatocellular	1 (3.6%)
e) Squamous cell carcinoma	1 (3.6%)
f) Neuroendocrine	1 (3.6%)
g) Malignant synovial sarcoma	1 (3.6%)

Table 4: Association of histopathological data with socio-demographics and radiological features (brain metastases)

Variable	Histopathology					P value
	Breast n=7	Lung n=13	Melanoma n=7	Lymphoma n=4	Other n=29	
Age groups/years						0.060
≤18	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	3 (10.3%)	
19-29	0 (0.0%)	0 (0.0%)	1 (14.3%)	2 (50.0%)	3 (10.3%)	
30-39	3 (42.9%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	1 (3.5%)	
40-49	2 (28.6%)	2 (15.4%)	2 (28.6%)	0 (0.0%)	8 (27.6%)	
50-59	1 (14.3%)	6 (46.2%)	1 (14.3%)	0 (0.0%)	9 (31.0%)	
60+	1 (14.3%)	5 (38.5%)	1 (14.3%)	1 (25.0%)	5 (17.2%)	
Sex						0.065
Female	7 (100.0%)	6 (46.2%)	3 (42.9%)	1 (25.0%)	14 (48.3%)	
Male	0 (0.0%)	7 (53.9%)	4 (57.1%)	3 (75.0%)	15 (51.7%)	
Race						**0.020**
Black	5 (71.4%)	10 (76.9%)	1 (14.3%)	3 (75.0%)	20 (69.0%)	
White	2 (28.6%)	3 (23.1%)	6 (85.7%)	0 (0.0%)	5 (17.2%)	
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	4 (13.8%)	
Occupation						0.877
Professional	2 (28.6%)	1 (7.7%)	1 (14.3%)	0 (0.0%)	2 (6.9%)	
Casual/general work	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	3 (10.3%)	
Pensioner	1 (14.3%)	4 (30.8%)	1 (14.3%)	1 (25.0%)	3 (10.3%)	
Scholar	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (13.8%)	
Unemployed/Unknown	4 (57.1%)	7 (53.9%)	5 (71.4%)	3 (75.0%)	17 (58.6%)	
Social risk factor history						0.806
Smoking only	1 (14.3%)	4 (30.8%)	2 (28.6%)	0 (0.0%)	9 (31.0%)	
Smoking + alcohol	0 (0.0%)	2 (15.4%)	1 (14.3%)	0 (0.0%)	3 (10.3%)	
Smoking + family cancer + alchohol	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	3 (10.3%)	
Unknown	6 (85.7%)	7 (53.9%)	3 (42.9%)	4 (100.0%)	14 (48.3%)	
Time interval from primary cancer to metastasis diagnosis (Months)/ mean ± SD	35 ± 21.2	0.4 ± 0.5	67.5 ± 10.6	5 ± 0.0	18.9 ± 14.8	**0.009**
Mid-line shift						
Number with mid-line shift	5 (71.4%)	7 (53.9%)	4 (57.1%)	1 (25.0%)	12 (41.4%)	0.533
Median distance (IQR)/mm	8.6 (3.8-9.0)	9.6 (5.8-13.3)	8.7 (5.2-12.7)	3.5 (3.5-3.5)	6.5 (3.9-11.6)	0.549
GPA score/ mean ± (SD)	2.5 ± 1.1	2.1 ± 0.9	2.1 ± 0.9	1.9 ± 1.0	2.3 ± 1.1	0.868
Radiology						
Supratentorial	5 (71.4%)	9 (69.2%)	7 (100.0%)	3 (75.0%)	24 (82.8%)	0.486
Infratentorial	3 (42.9%)	7 (53.9%)	0 (0.0%)	1 (25.0%)	9 (31.0%)	0.146
Median tumour size (IQR)/ (mm^3)	50.9 33.3-240.8	54.5 42.8-213	34.7 17.3-68.4	93.4 25.6-173	34.7 17.3-68.4	0.526
Homogenous (solid)	4 (28.6%)	5 (38.5%)	3 (42.9%)	2 (50.0%)	15 (51.7%)	0.908
Homogenous (cystic)	1 (14.3%)	2 (15.4%)	0 (0.0%)	2 (50.0%)	2 (6.9%)	0.662
Heterogenous	2 (28.6%)	6 (46.2%)	4 (57.1%)	0 (0.0%)	12 (41.4%)	0.818

Contrast uptake (CT Only)	1 (14.3%)	7 (53.9%)	1 (14.3%)	1 (25.0%)	17 (58.6%)	0.076
Contrast uptake (When both CT + MRI done)	6 (85.7%)	4 (30.8%)	5 (71.4%)	2 (50.0%)	9 (31.0%)	**0.033**

CHAPTER 3: APPENDICES

APPENDIX A: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr M Molefe

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M201113

NAME: (Principal Investigator)	Dr M Molefe
DEPARTMENT:	School of Clinical Medicine Department of Surgery Division of Neurosurgery Medical School University
PROJECT TITLE:	*A tale of two sites: an audit of central nervous system metastases in two Johannesburg tertiary centres*
DATE CONSIDERED:	2020/11/27
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor J Ouma
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/03/02

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

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

I/we fully understand the conditions under which I am/we are authorized 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 submit details 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 when the study was initially reviewed. In this case, the study was initially reviewed in **«Missing mail merge field»** and therefore reports and re-certification will be due in the month of **«Missing mail merge field»** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

01/04/2021
Date

APPENDIX B: Data collection sheet for brain metastases

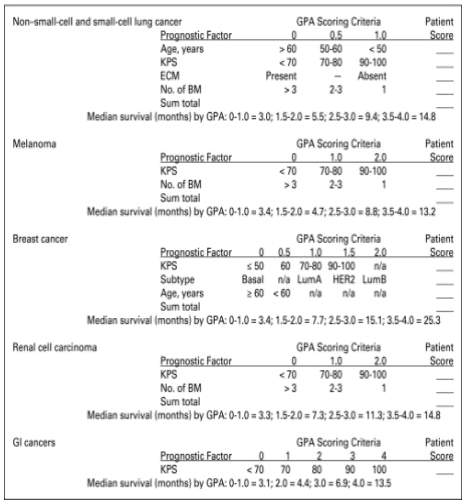
VARIABLES	CATEGORIES							
DEMOGRAPHIC								
1. Age								
2. Gender	Male				Female			
3. Race	Black		Indian		White		Other	
4. Social history	Occupation		Smoking	Ethanol	Cancer family history	Known primary cancer	Time interval from primary cancer diagnosis to met dx	
SYMPTOMS	Nil	Headache	Nausea &/Vomiting	Neurological deficit	Seizures	Mental state change	Onset: acute/chronic	Non-cerebral
SIGNS	GCS		Neurological deficit		Seizures	Non-cerebral manifestations		
GPA SCORE	0		1	2	3		4	
RADIOLOGY								
1. Modality	CT		MRI		More metastases detected on MRI? Number			
2. Location	Supratentorial				Infratentorial			
	Frontal	Parietal/ deep	Occipital	Temporal	Right cerebellum	Left cerebellum	Midline cerebellum	Brainstem
3. Number of metastases	1	2-3	4	>4	Extra-cranial spread & location (s) Yes		No	
4. Midline shift	Yes <5		>/=5		No			
5.Hydrocephalus	Yes				No			
6. Size(s) cc/cm³								
7. Features	Homogenous (solid/cystic)		Inhomogenous		Contrast uptake?	Density (CT)	Intensity (MRI) & sequence	
HISTOPATHOLOGY	Lung		Breast	Renal	Melanoma		Colorectal/GIT	Other

APPENDIX C: Data collection sheet for spinal metastases

VARIABLES	CATEGORIES									
DEMOGRAPHIC										
1. Age										
2. Gender	Male					Female				
3. Race	Black		Indian			White			Other	
4. Social history	Occupation		Smoking	Ethanol		Cancer family history	Known primary cancer		Time interval from primary cancer diagnosis to met dx	
SYMPTOMS	Nil	Back pain	Bladder and bowel dysfunction			Limb dysfunction			Onset: acute/chronic	Non-spinal
SIGNS	Tone		Sensory level	Motor level		maximum power below level			Non-spinal manifestations	
ASIA scale	A		B			C	D		E	
PROGNOSTIC SCORES	Tomita score					Modified Tokuhashi score				
RADIOLOGY										
1. Modality & features (i.e. homogeneity, solid/cystic, density, contrast uptake)	CT					MRI (spinal cord involvement)				
						Extradural			Intradural Extrame	Intramed
2. Location	Cervical			Thoracic			Lumbosacral			
3. Column involvement & greatest AP diameter	Anterior		Middle			Posterior			All	
4. Number of metastases (bony structures)	Single		Multiple						Extra-spinal spread (locations)	
			Contiguous			Non-contiguous			Yes	No
HISTOPATHOLOGY	Lung		Breast	Renal		Melanoma			Colorectal/GIT	Other

APPENDIX D:Definitions of prognostic/clinical scoring systems

Graded Prognostic Assessment score: a newer prognostic index for patients with brain metastases. This prognostic index was originally developed from a database of 1,960 patients accrued to four Radiation Therapy Oncology Group (RTOG) protocols for patients with brain metastases. The original GPA was validated and refined with diagnosis-specific prognostic indices based on a second study specific to each primary tumour studied.



Non-small-cell and small-cell lung cancer

Prognostic Factor	0	0.5	1.0	Patient Score
Age, years	> 60	50-60	< 50	___
KPS	< 70	70-80	90-100	___
ECM	Present	--	Absent	___
No. of BM	> 3	2-3	1	___
Sum total				___

Median survival (months) by GPA: 0-1.0 = 3.0; 1.5-2.0 = 5.5; 2.5-3.0 = 9.4; 3.5-4.0 = 14.8

Melanoma

Prognostic Factor	0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	___
No. of BM	> 3	2-3	1	___
Sum total				___

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 4.7; 2.5-3.0 = 8.8; 3.5-4.0 = 13.2

Breast cancer

Prognostic Factor	0	0.5	1.0	1.5	2.0	Patient Score
KPS	≤ 50	60	70-80	90-100	n/a	___
Subtype	Basal	n/a	LumA	HER2	LumB	___
Age, years	≥ 60	< 60	n/a	n/a	n/a	___
Sum total						___

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 7.7; 2.5-3.0 = 15.1; 3.5-4.0 = 25.3

Renal cell carcinoma

Prognostic Factor	0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	___
No. of BM	> 3	2-3	1	___
Sum total				___

Median survival (months) by GPA: 0-1.0 = 3.3; 1.5-2.0 = 7.3; 2.5-3.0 = 11.3; 3.5-4.0 = 14.8

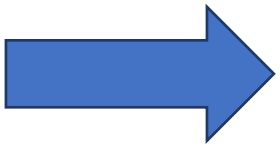
GI cancers

Prognostic Factor	0	1	2	3	4	Patient Score
KPS	< 70	70	80	90	100	___

Median survival (months) by GPA: 0-1.0 = 3.1; 2.0 = 4.4; 3.0 = 6.9; 4.0 = 13.5

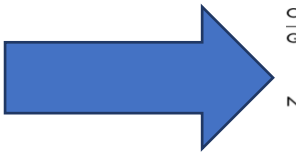
2) The two spinal metastases scores that will be used in this research were developed to determine the prognosis of patients with spinal metastases and therefore aid in their management, and will be defined below:

I. **Tomita score**- is composed of 3 parameters based on tumour growth, visceral metastases and number of bone metastasis lesions.



Prognosis parameter	score
Primary site	
Slow growth (breast, thyroid, etc.)	1
Moderate growth (kidneys, uterus, etc)	2
Rapid growth (lungs, stomach, etc.)	4
Visceral metastases	
None	0
Treatable	2
Not treatable	4
Bone metastases	
Solitary	1
Multiple	2

II. **Modified Tokuhashi score**- the original scoring system was based on 6 parameters, including patient condition, location of metastasis and the site of primary cancer with the modified Tokuhashi score including more primary site divisions as part of their prognosis parameters.



Characteristic	Score
General condition	
Poor (PS 10% to 40%)	0
Moderate (PS 50% to 70%)	1
Good (PS 80% to 100%)	2
Number of extraspinal metastatic foci	
≥3	0
1-2	1
0	2
Number of metastases in vertebral body	
≥3	0
2	1
1	2
Metastases to other internal organs	
Unresectable	0
Resectable	1
Absent	2
Primary site of malignancy	
Lung, osteosarcoma, stomach, bladder, esophagus, or pancreas	0
Liver, gallbladder, unidentified	1
Others	3
Kidney, uterus	4
Thyroid, breast, prostate, carcinoid	5
Palsy	
Complete (Frankel A, B)	0
Incomplete (Frankel C, D)	1
Non (Frankel E)	2
Total Score	**Months**
0-8	>6
9-11	≥6
12-15	≥12

9–11	Moderate	17	< 0.001
≤ 8	Poor	5	< 0.001
Tomita score			
2–4	Good	19	0.15
5–7	Moderate	16	0.15
8–10	Poor	3	< 0.001

3) **ASIA impairment scale**: The extent of spinal cord injury (SCI) is defined by the American Spinal Injury Association (ASIA) Impairment Scale (modified from the Frankel classification), using the following categories on the right side:

Grade	Description
A	Complete; no sensory or motor function preserved in the sacral segments S4–S5
B	Incomplete; sensory but not motor function preserved below the numerological level and extending through the sacral segment S4–S5
C	C Incomplete; motor function preserved below the neurological level; most (more than half) key muscles have a grade <3. Sensory function is present below the neurological level and includes sacral segments S4–S5
D	D Incomplete; motor function preserved below the neurological level; most (at least half) key muscles have a grade 3 or more. Sensory function is present below the neurological level and includes sacral segments S4–S5
E	Normal motor and sensory function

SOURCE: (McDonald JW & Sadowsky C., 2002)

APPENDIX E: Faculty protocol approval letter

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG | FACULTY OF HEALTH SCIENCES

2020/09/09
Person Number:
0701891N
PAG

Dr M Molefe

87 Ruby Street
Meredale
Johannesburg
2091

Dear Dr Masechaba Molefe

Master of Medicine – Neurosurgery: Approval of Proposal

We have pleasure in advising you that your proposal has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Title: *A tale of two sites: An audit of central nervous system metastases in two Johannesburg tertiary centres.*

Yours sincerely

Ms Kgomotso Tlala
On behalf of Mrs Sandra
Benn Faculty Registrar

Faculty: Postgraduate – Faculty of Health Sciences
Tel: +27 (0)11 717 2125; Email: Kgomotso.Tlala@wits.ac.za
Room 212, 2nd Floor, Phillip V Tobias Building, 29 Princess of Wales Terrace, Parktown, Johannesburg, 2193, SOUTH AFRICA

APPENDIX F: CMJAH management approval letter

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (CMJAH)
OFFICE OF THE SENIOR CLINICAL MANAGER

Enquiries: *Ms. TT Mahlangu*
Email: Thandi.Mahlangu4@gauteng.gov.za
Tel: *011 488 3365*
Ref: *1/7/2*
Date: 06 December 2021

GP_202112_007

Dear Dr. M Molefe

RE: FINAL APPROVAL OF STUDY

TITLE: A TALE OF TWO SITES: AN AUDIT OF CENTRAL NERVOUS SYSTEM METASTASES IN TWO JOHANNESBURG TERTIARY CENTERS

Permission is granted for you to conduct the above-mentioned study as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not in any way incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall always be observed.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or Sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported/~~Not Supported~~
Signed by:Jayshina Punwasi
Signed at:2021-12-07 07:00:05 +02:00
Reason:Witnessing Jayshina Punwasi

Dr J. Punwasi
Clinical Director

Approved/~~Not Approved~~
Signed by:Gladys Magugudi Bogoshi
Signed at:2021-12-07 20:08:04 +02:00
Reason:Witnessing Gladys Magugudi Bo

Ms. G Bogoshi
Chief Executive Officer: CMJAH

APPENDIX G: CHBAH management approval letter

GAUTENG PROVINCE

REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 7th September 2020

TITLE OF PROJECT:

A tale of two sites: An Audit of Central Nervous System Metastases in two Johannesburg Tertiary Centres.

UNIVERSITY: Witswatersrand

Principal Investigator: Dr M Molefe

Department: Neurosurgery

Supervisor : Prof JRB Ouma

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- **Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.**
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

.....
Recommended
(On behalf of the MAC)
Date: 7/9/2020

.....
Approved/~~Not Approved~~
Hospital Management
Date: 08/09/2020

APPENDIX H:Radiology Head of Department approval letter

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL (CHBAH) AND CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (CMJAH)

HEAD OF RADIOLOGY

PERMISSION TO CONDUCT RESEARCH

TITLE OF PROJECT: A tale of two sites: An Audit of Central Nervous System Metastases in two Johannesburg Tertiary Centres

UNIVERSITY: University of the Witwatersrand

PRINCIPAL INVESTIGATOR: Masechaba Molefe

SUPERVISOR: Prof J.R.B Ouma

PERMISSION FROM HEAD OF DEPARTMENT (where research is conducted): Yes

DATE OF START OF PROPOSED STUDY: August 2020

DATE OF COMPLETION OF DATA COLLECTION: October 2020

Approval to use Radiology's Picture Archiving and Communication System (PACS) is requested please, for the said MMED research.

The Medical Advisory Committee (MAC) recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO/management of the named institution is accordingly informed and the study is subject to:

- Permission having being granted by the Human Ethics Research Committee of the University of the Witwatersrand
- The hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee approval

.....

Approved/~~Not Approved~~

Head of Radiology

Date: 26/08/2020

APPENDIX I: Anatomical Pathology Head of Department approval letter

NATIONAL HEALTH LABORATORY SERVICE
UNIVERSITY OF THE WITWATERSRAND – JOHANNESBURG

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

SCHOOL OF PATHOLOGY
Division of Anatomical Pathology

NATIONAL HEALTH LABORATORY SERVICE

P.O. Box 1038, Johannesburg 2000
Tel : +27-11-489-8477
+27-11- 489-8479
Fax::+27-11-489-8512

Division of Anatomical Pathology
Faculty of Health Sciences
York Road
Parktown e-mail : Yvonne.perner@nhls.ac.za

Dr Y Perner MBBCh (Witwatersrand) FCPath (SA); MMed (Witwatersrand)

Human Research Ethics Committee (Medical)
University of the Witwatersrand
Johannesburg
20000

September 7, 2020

Re: Consent for access to NHLS database

This letter serves to confirm that the Department of Anatomical Pathology at the University of the Witwatersrand and NHLS is happy to assist Dr Masechaba Molefe with her study entitled "A tale of two sites: An Audit of Central Nervous System Metastases in two Johannesburg Tertiary Centres".

Publication of such work is encouraged and in the event that the information used comprises the diagnosis only then joint authorship from a member of staff in the Department of Anatomical Pathology would not be expected. However, should additional information be extracted from the report for purposes of further interpretation such as morphological details and immunohistochemical profiles, it would be expected that this would be done in conjunction with a member of staff in the Department of Anatomical Pathology and that joint authorship would follow in resulting publications. Dr Molefe will be in contact with the Department of Anatomical Pathology in respect of this. Dr Molefe must also contact the Anatomical Pathology department as it is required that an Anatomical Pathologist assist in the interpretation of histology results. Dr Dawn van der Byl has agreed to collaborate with Dr Molefe on this project.

Dr Molefe will ensure that she registers on the NHLS AARMS system.

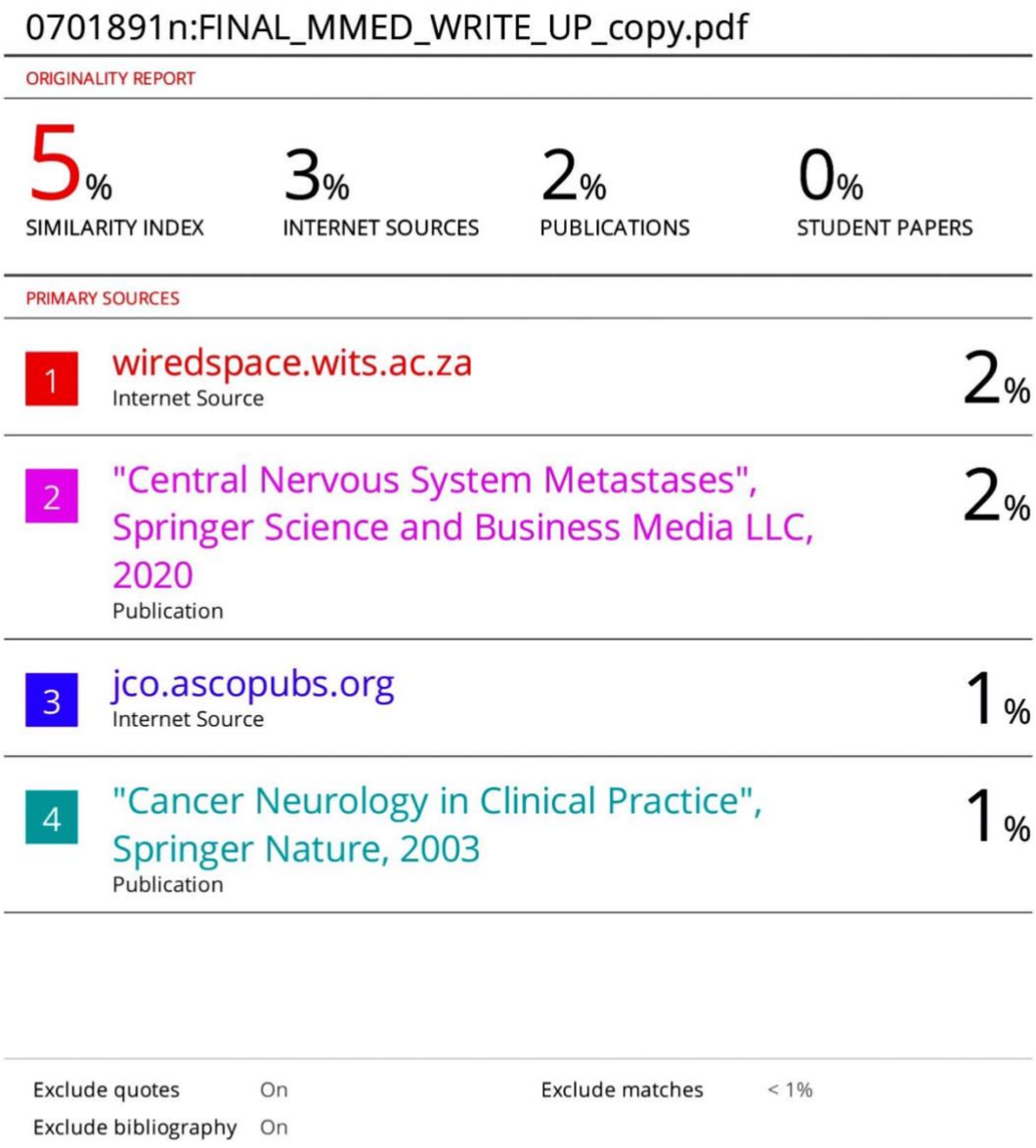
Assuring you of the Department of Anatomical Pathology's co-operation in this and future research projects.

With best wishes.

Yours sincerely,

Dr Yvonne Perner
Head: Department of Anatomical Pathology

APPENDIX J: Turn-it-in (plagiarism) report



0701891n:FINAL_MMED_WRITE_UP_copy.pdf

ORIGINALITY REPORT

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PRIMARY SOURCES

1	wiredspace.wits.ac.za Internet Source	2%
2	"Central Nervous System Metastases", Springer Science and Business Media LLC, 2020 Publication	2%
3	jco.ascopubs.org Internet Source	1%
4	"Cancer Neurology in Clinical Practice", Springer Nature, 2003 Publication	1%

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