ADULT INTRACRANIAL NEOPLASMS: RADIOLOGIC AND HISTOPATHOLOGICAL CORRELATION

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In the fulfilment of the requirements for the degree of Master of Medicine in the Clinical Disciplines.

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I, Besley Mojapelo, declare that this research report is my own work. It is being submitted for the degree of MMed (RadD) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

I have acknowledged all sources and cited these in the reference section.
There are no conflicts of interest in creating the research paper.

This paper was prepared in a "submissible" format in line with the guidelines of the South African Journal of Radiology.

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The following individuals contributed as supervisors to the work undertaken by the candidate, Besley Mojapelo, student number 0501125T, as part of their research paper entitled "Adult intracranial neoplasms: Radiologic and histopathological correlation" in the fulfilment of the requirements for the degree of FC Rad Diag (SA) MMed.

Details of Candidate and Supervisors(including percentage contributions):

- Candidate: Besley Mojapelo (60%)
- Supervisor 1: Thandi Buthelezi (20%)
- Supervisor 2: Sugeshnee Pather (20%)

Contribution of work by supervisors and candidate for the above-mentioned research paper:

- The research paper is the original work of the candidate, Besley Mojapelo, who drafted the protocol and final research paper for this study.
- Supervisors reviewed draft manuscripts of the protocol and the final research paper and provided guidance regarding research methodology, improvements to content, general conduct, and conceptual ideas.
- This proposal and the research paper were submitted to Turnitin concerning plagiarism.

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Acknowledgements

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List of Abbreviations and Terminology

ADC	Apparent Diffusion Coefficient
BG	Basal ganglia
Cere	Cerebellum
DWI	Diffusion Weighted Imaging
CHBAH	Chris Hani Baragwanath Academic Hospital
CPA	Cerebello-pontine angle
CNS	Central Nervous System
CT	Computed Tomography
FR	Frontal
FrP	Fronto- parietal
FrT	Fronto-temporal
FrPT	Fronto-parietal and temporal
IDH	Isocitrate Dehydrogenase
PACS	Picture Archiving and Communication system
PO	Parieto-occipital
FrS	Fronto-suprasellar
POT	Parieto-occipital and temporal
HIV	Human Immunodeficiency Virus
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NHLS	National Health Laboratory Services
NAA	N-acetyleaspartate
PWI	Perfusion Weighted Imaging
rCBV	Residual cerebral blood volume
rCBF	Residual cerebral blood flow
SUP	Sellar/Suprasellar
SWI	Susceptibility Weighted Imaging
WHO	World Health Organisation

1. Abstract

Keywords: Adult, Intracranial, neoplasm, MRI, histopathology, correlation, diagnostic accuracy and agreement

Background: Imaging plays an important part in the management and prognosis of an intracranial neoplasm. MRI and its advancement with the addition of DWI/ ADC, PWI and MRS have greatly enhanced the diagnostic accuracy of MRI in that there is better characterisation and differentiation of intracranial neoplasms.

Aim: To document and evaluate the histopathological diagnoses and the MRI imaging findings of intracranial neoplasms in adult patients at CHBAH.

Method: A retrospective study was conducted using MRI and histopathology reports from January 2017 to September 2019. Statistical significance was met when p-value <0.05.

Results: The study included 53 (N=53) adult patients with confirmed intracranial neoplasms. There were 26 (49%) males and 27 (51%) females with an age range of 18 to 71 years. The most frequent anatomical sites were the sellar/suprasellar region 22 (42%) and the frontal lobe 8 (15%). Pituitary adenoma 18 (34%) was the most common neoplasm followed by meningioma 14 (26%) and glioblastoma 7 (13%). Low-grade (WHO I/II) neoplasms were more frequent 37 (70%) than the high-grade neoplasms (WHO III/IV) [16 (30 %)]. The overall concordance between the MRI and the histopathology diagnoses and grading demonstrated a good agreement with Kappa values of 0.63 and 0.71, respectively.

Conclusion:

Conventional MRI constitutes the most utilised MRI technique in the characterisation of intracranial neoplasms. Due to limitations thereof, advanced MRI techniques may improve the diagnostic accuracy. Conventional MRI, advanced MR techniques and histopathology are complementary diagnostic modalities for the classification of intracranial neoplasms.

2. Introduction

Primary intracranial neoplasms are a heterogeneous group of neoplasms comprising both benign and malignant tumours that arise from any of the various intracranial structures (1). These intracranial neoplasms result in diverse complications, significant morbidity and mortality due to the neoplasm itself or its mass effect on adjacent structures (1, 2).

The epidemiology of the intracranial neoplasms is only partially established. There is limited data available regarding their incidence and prevalence worldwide, in Africa and in South Africa with variations among different regions documented (1, 2). This variation may be linked to genetic factors, environment, variation in cancer registration systems, health infrastructure and access to health care (1, 2). The latter three reasons may contribute to falsely low incidence ratios (1, 3, 4). A systematic review and meta-analysis by de Robles *et al* concluded that the overall global incidence of brain neoplasms is 10.82 per 100 000 person-years (1), while the Global Burden of Disease Study 2016 and Bell *et al* reported global incidences of 4.63 and 4.25 per 100 000 person-years, respectively (4).

Miller *et al* contributed that malignant neoplasms accounted for less than 30% and were less common than non-malignant neoplasms (70%) (5). Several studies have documented that gliomas, meningioma and pituitary neoplasms are the most frequent intracranial neoplasms, while glioblastoma is the most common malignant intracranial neoplasm (5-7). In contrast, Bhavesh *et al* reported that metastases were the most common intracranial neoplasm and gliomas were the most common primary intracranial neoplasm (8).

South Africa has the largest human immunodeficiency virus (HIV) epidemic in the world (9). Intracranial lesions, in those living with HIV, pose a diagnostic challenge due to the higher risk for opportunistic infections and primary central nervous system (CNS) lymphoma. Notably, a significant improvement in the role out and access to antiretroviral treatment has reduced the incidence of primary CNS lymphoma (10).

Histopathological diagnosis of intracranial neoplasms, in tandem with the radiological imaging findings, is considered the ‘gold standard’ for the final diagnosis and the management of patients harbouring intracranial neoplasms (11). However, an invasive procedure is often required to obtain diagnostic tissue, and this is accompanied by a risk of

complications. The process of its acquirement may also lead to a delay in patient management.

At times, intracranial neoplasms are diagnosed non-invasively with the use of imaging modalities because some neoplasms are positioned in areas that are not accessible to biopsy or surgical resection, while others need to be treated primarily with radiation therapy (11). Notably, non-neoplastic lesions such as fungal infection, bacterial abscess, granulomatous inflammation, demyelination, infarction, radiation necrosis, gliosis, chronic haematoma and vascular lesions may also mimic neoplasms (2). Therefore, the pre-operative radiological evaluation of intracranial lesions and histopathological diagnosis is of primary importance, with a direct impact on clinical management.

Computed Tomography (CT) scan and Magnetic Resonance Imaging (MRI) are the initial diagnostic imaging modalities that are used to differentiate between neoplastic and non-neoplastic intracranial processes as well as between benign and non-benign neoplastic processes(2, 12). These investigations are furthermore used for the anatomical localisation and characterisation of the intracranial neoplasms(2, 12).

Although CT is more accessible than MRI, MRI is superior to CT in that there is no exposure to radiation and there is better detail in the image. MRI has improved diagnostic accuracy with enhanced anatomical localisation, characterisation of intracranial neoplasms and improved ability to differentiate benign from malignant neoplasms (13). Advances in MRI with the addition of diffusion- and perfusion-weighted imaging (DWI and PWI), apparent diffusion coefficient (ADC) and magnetic resonance spectroscopy (MRS), have greatly enhanced the diagnostic accuracy of MRI in that there is better characterisation and differentiation of neoplasms (13). However, these modalities are complementary and do not replace conventional MRI (14).

In combination, conventional MRI and advanced modalities may be helpful in cases where a difficult biopsy procedure is anticipated (12). This may also aid the aversion of an unnecessary biopsy of non-neoplastic intracranial lesions (12, 13). Avoidance of a delay in the initiation of treatment may also occur (13). Improvement of patient morbidity and mortality may ensue due to an early accurate diagnosis of an intracranial neoplasm through non-invasive imaging and the initiation of appropriate treatment.

In this study, the histopathological diagnosis of intracranial neoplasms in adult patients at the Chris Hani Baragwanath Academic Hospital (CHBAH), was utilised to determine the diagnostic accuracy of the MRI findings. The aim of this research was to document the histopathological diagnosis and compare or correlate it with the MRI diagnosis.

3. Research Methods and Design

Study design

A retrospective, cross-sectional study, was conducted.

Study setting

The study was conducted in the Department of Diagnostic Radiology and the Division of Anatomical Pathology, National Health Laboratory Service (NHLS) at CHBAH.

Study population

The study population derived from records of patients, above the age of 18 years, who had an MRI scan and underwent a biopsy for histopathological analysis from 01 January 2017 to 30 September 2019. The following inclusion and exclusion criteria considered:

Inclusion criteria

- Intracranial neoplasms
- Histopathological diagnosis
- MRI imaging (using intravenous contrast) of intracranial neoplasm with a diagnosis and/ or differential diagnosis
- In cases where a differential diagnosis was provided, the first diagnosis was considered as a final diagnosis

Exclusion criteria:

- Inconclusive histopathology diagnosis
- Inconclusive radiological diagnosis
- No radiological or pathological diagnosis or differential diagnosis

- Differential diagnosis incomplete for MRI studies
- Complete basic MRI protocol not followed

A total of 164 patients records with MRI imaging were found. However, only 53 satisfied the above-mentioned inclusion and exclusion criteria. Spectroscopy was only performed upon the radiologists request.

Data collection

MRI reports were retrieved from the hospital picture archiving and communication system (PACS – AGFA IMPAX 6.5.1.501). Histopathology reports were retrieved using the NHLS Corporate Data Warehouse (CDW) that employs the use of a Systemised Nomenclature of Medicine (SNOMED) search using the following codes: T-A0094 (brain), T-A600A (cerebellum), T-B2000 (pineal structure), T-B1000 (pituitary), M-80000 (neoplasm benign), M-80001 (neoplasm uncertain whether benign or malignant), M-80003 (malignant neoplasm primary), M-80006 (neoplasm, metastatic). Histopathological classification of the tumours occurred in accordance with the WHO 2016 diagnostic guidelines for tumours of the central nervous system.

MRI data were acquired using a Siemens Avanto 1.5 Tesla machine with a slice thickness of 5 mm. The following are the routine MRI sequences commonly acquired: T1WI 3D, axial T2WI and T2 FLAIR, coronal T2WI, axial DWI/ADC, axial SWI, axial and sagittal T1WI post-contrast (gadolinium). MRS was performed at the radiologist's request. For MRS only four metabolites i.e. Choline. Creatine, NAA and lipids, were assessed. No PWI was performed.

Data were collected using a data collection sheet and results were analysed and loaded in a spreadsheet using Microsoft Excel according to a predefined range of MRI characteristics of the intracranial neoplasm as described below:

- Age group
- Gender
- Anatomical location (cerebral lobe, cerebellum, brainstem)
- Composition(cystic/solid/ mixed)
- DWI restriction or not

- If spectroscopy – then note increase or decrease in metabolites (choline, creatine, NAA or lipids)
- Low-grade or High-grade neoplasm
- MRI diagnosis
- Histopathology diagnosis

The above information was derived from the MRI reports found on the PACS system. The HIV status was not considered in the study.

In this study, low-grade neoplasms were those of WHO grade I and II and the high-grade neoplasms were those belonging to WHO grade III and IV categories. The information about the neoplasm grade was deduced using each MRI and histopathological diagnosis provided on the reports and assigning the neoplasm grade according to the WHO classification of CNS tumours.

Data analysis

Figure 1 is a summary of the data analysis. Significance was met when statistical analysis attained probabilities below significance level alpha 0.05 (p-value < 0.05) at a 95% confidence interval. Kappa/ Gwet's coefficient values were applied as follows: <0.20 = Poor, 0.20 - 0.40 = Fair, 0.41 – 0.60 = Moderate, 0.61 – 0.80 = Good and >0.80 = Very good.

Cohen's kappa shows statistical independence and defines chance agreement as the sum of the products of the marginal classification probabilities of both raters.

4. Ethical Consideration

Ethical clearance was obtained from the Human Research Ethics Committee (Medical) at the University of the Witwatersrand. The ethics certificate number is M200254.

5. Results

Fifty-three patients (N=53) were included in the study, 26 (49%) were males and 27 (51%) were females. The male-to-female ratio was 0.96:1. The 50-59-year age group was the most common at 19 (36%).

Anatomical Location

The majority of the neoplasms, 46 (87%), were in the supratentorial region (***Figure 2***). Most of the neoplasms, 22 (42%), were located in the sellar/suprasellar region. An extra-axial location accounted for 34 (68%) of the neoplasms compared to 19 (36 %) in the intra-axial location (***Table 1***).

Composition

Solid composition, 30 (57%), of the neoplasm was more common than the mixed composition. Solid composition accounted for 26 (70%) of the low-grade and 4 (25%) of the high-grade neoplasms. Mixed composition, 23 (43%), was evident in 12 (75%) of the high-grade and 11 (30%) of the low-grade neoplasms.

Restricted Diffusion

Restricted diffusion (***Table 1***) was experienced in 21 (40%) tumours which comprised 10 (48%) high-grade and 11 (52%) low-grade neoplasms. No restricted diffusion occurred in 24 (45 %) of the patients of which 6 (25%) were high-grade and 18 (75%) low-grade neoplasms. DWI was also performed in 8 (15 %) of patients where there was no comment on the type of diffusion in the MRI report.

MRS

MRS was utilised in less than 5% (3 of 53) of the study population and demonstrated the following: High Lactate and Choline peaks with low NAA peaks in the cases of histopathologically proven glioblastoma, meningioma and high-grade astrocytoma. High lipid peaks were also found in the cases of meningioma and high-grade astrocytoma. A high

myoinositol peak in the case of high-grade astrocytoma and a low myoinositol peak in the case of glioblastoma.

Neoplasm grade and location

Low-grade neoplasms were documented in 38 (72%) of the MRI scans and 37 (69%) of the histopathology reports, comprising the majority, and these neoplasms were commonly found in the 50 – 59 age group (***Figure 3***(a)).
Sixty-eight percent of the high-grade neoplasms were in the intra-axial location while 91% of the low-grade neoplasms were extra-axial (p-value< 0.001).

Histopathologically confirmed high-grade neoplasms were located predominantly in the parietal lobe (22%) while low-grade neoplasms were located predominantly in the sellar/suprasellar region (44%) [p-value = 0.002], as depicted in ***Figure 2.***

Neoplasm spectrum

Table 2 shows MRI and Histopathology diagnoses and grades of the intracranial neoplasms.

Pituitary adenoma (PA) was the most common extra-axial and intracranial neoplasm comprising 18 (34%) cases, followed by meningioma which comprised 14 (26 %) of the cases (***Table 3***). Glioblastoma was documented in 7 (13%) patients and constituted the most frequent intra-axial high-grade neoplasm (***Table 3)***. Glioblastoma was documented predominantly in the 6th decade of life, but also occurred in 2 patients in the third and fourth decades.
There was no non-neoplastic lesion that was misdiagnosed as a neoplasm on MRI in our study.

In the context of meningioma, there is a female gender predilection with a male-to-female ratio of 1:2.5. No gender predilection was evident in patients who had PA or glioblastoma.

Neoplasm grade, composition and agreement

Within the histopathology reports, 95% of the MRI low-grade and 81% of the MRI high-grade neoplasms were confirmed (p-value < 0.001), as shown in ***Figure 3(***b).

Table 4 shows that solid composition occurred significantly in low-grade neoplasms, as confirmed by MRI and histopathology.
In histopathology, the mixed composition neoplasm were 7 times more likely (p-value 0.002), and 3.9 times more likely (p-value 0.037) in MRI to be definitively classified compared to the solid composition in both modalities (***Table 5***). For the axial location, intra-axial neoplasm on histopathology was 22 times more likely (p-value <0.001) and 17.7 times more likely (p-value <0.001) on MRI to be definitively classified compared to the extra-axial location on both modalities (***Table 5***).

The agreement between histopathology and MRI are summarised in ***Table 6***. There were 2 ratings for grading and 14 ratings for diagnosis. The percent agreement contains the observed proportion of agreement for Histopathology-MRI grading was 91% and the diagnosis was 69.8%. Cohen's kappa coefficient reported in the data correctly observed agreement for chance and was estimated as 0.77 and 0.626 respectively for Histopathology-MRI. Gwet's AC for the observations was 0.84 and 0.678 respectively. The benchmark scale for agreement in Kappa and Gwet's AC coefficients for Histopathology-MRI diagnosis was good.

6. Discussion

Our study found that majority of the neoplasms were in the supratentorial region. This was comparable with previous studies (8, 11). The age distribution of patients was also similar to those in previous studies (11, 15, 16). The correlation of age with neoplasm subtypes in our study was in accordance with previous studies such as in the case of glioblastoma and metastasis which were found in the 5th and 6th decade groups (8, 20).

Zahir *et al* found that composition was statistically insignificant in predicting malignant neoplasms(17). This is in agreement with our study. However, our study demonstrated that the solid composition occurred significantly in low-grade neoplasms.

Neoplasm Grade

The World Health Organisation classifies intracranial neoplasms based on histopathology characteristics into four grades as follows (18):
Grade I neoplasms are benign and slow-growing such a typical meningioma.
Grade II neoplasms can be benign or malignant. However, they are relatively slow-growing and occasionally recur as higher grade neoplasms.
Grade III neoplasms are malignant and often recur as higher grade neoplasms.
Grade IV neoplasms proliferate rapidly and are very aggressive malignant neoplasm such as glioblastioma.

An accurate pre-operative diagnosis of the type of neoplasm and its differentiation from a non-neoplastic process is important in deciding the optimal clinical management and prognosis.

Various processes or stimuli that alter a cell's environment and functioning can cause irreversible injury to the brain cells resulting in cell death and eventually necrosis. Some of the causes are infections, ischaemia/ hypoxia, drugs, radiation and chemotherapy which result in changes in the blood-brain barrier or release substances that initiate cell death. Coagulative, liquefactive and caseous necrosis are some of the types of necrosis that can occur in the brain. In gliomas, the presence of necrosis is an important diagnostic feature and prognostic indicator as it is a hallmark for glioblastoma (***Figure 4***(a)). It indicates high-grade or advanced disease and poorer prognosis (19).

Appropriate grading of a neoplasm is important as the management of an aggressively behaving WHO grade III/IV neoplasm is more intensive than that of a lower grade neoplasm (14). This was emphasised in the study by Lasocki *et al* that found that in patients with a grade II and III neoplasm based on histopathology, poor survival was evident in those documented to have necrosis on MRI compared to those without (14). Their survival was equivalent to those with grade IV histopathology (14). Mutation of isocitrate dehydrogenase (IDH) genes 1 and 2 was also found to be negative in patients with necrosis on MRI suggesting that these were primary glioblastoma (14). Lasocki *et al* also found that some of the patients (5 in total) with histopathology grade IV had no necrosis within the neoplasm on MRI and one patient had no enhancement of the neoplasm on MRI, showed improved survival compared to the rest of the patients with histopathology grade IV. The prognosis may also be affected by access to or availability of treatment, post-surgery complications and the presence or lack of neoplasm IDH mutation (14).

Two cases of high-grade neoplasms in our study that were diagnosed on MRI as metastasis were downgraded to low-grade meningiomas, meningothelial and fibroblastic types, based on the histopathology findings. Both these neoplasms were of solid composition on MRI, one neoplasm was intra-axial and the other extra-axial. MRS was not performed in these cases. Three cases of low-grade neoplasms diagnosed on MRI (***Figure 4)*** were upgraded to high-grade neoplasms on histopathology. These were meningioma to hemangiopericytoma, Grade II astrocytoma to anaplastic astrocytoma and an oligodendroglioma to glioblastoma. In the oligodendroglioma case, the error could be due to the radiologist's experience as the neoplasm was of mixed composition with a suggestion of necrosis on MRI and therefore alluding towards a Grade IV glioma. MRS was not utilised in all 3 cases. In the case of astrocytoma, the experience of the radiologist, suboptimal use of ADC maps and lack of utilisation of MRS could have contributed to the discrepancy between histopathology and MRI diagnoses.

Although histopathology diagnosis is considered the gold standard, this procedure provides limited information about a region of a neoplasm. It also does not provide any information about the rest of the heterogeneous differentiated neoplasm that is not included within the biopsy specimen, which is important in the grading of gliomas. When tissue is obtained from a less aggressive area within the neoplasm, it might be erroneously classified as a low-grade neoplasm. Therefore, close correlation with the radiological characteristics is of paramount importance for histopathological diagnostic accuracy (13, 20). Intra- and interobserver variability amongst

radiologists and interobserver correlation in histopathology amongst pathologists may also impact the grading of gliomas (14). Multimodal MRI provides more comprehensive information about the entire neoplasm (14). Therefore, MRI and histopathology are complementary diagnostic modalities. The attainment of an accurate MRI diagnosis of an intracranial neoplasm does not negate the need for biopsy by neurosurgeon.

Concordance/ Agreement

The concordance between conventional MRI diagnosis and the histopathology diagnosis was shown to be fair (kappa value 0.38) by Abdul-Kasim *et al*, while in our study a good concordance was demonstrated (kappa value 0.63). This is likely attributed to the utilisation of the DW/ADC in our study. Similar and better accuracy trends were seen, with 93% of the multimodal MRI diagnosis compatible with histopathology obtained by Abdul-Kasim *et al* (added DWI/PWI and MRS), 88 % by Alam *et al* (added DWI/ MRS only), 68% in our study. Conventional MRI had an accuracy of 39 % in the study by Abdul-Kasim *et al* (12, 13). This likely attributed to the suboptimal utilisation of DWI/ADC, MRS and lack of PWI in our study.

Advances in MRI with the addition of DWI, PWI and MRS have greatly enhanced the diagnostic accuracy of MRI in that there is better characterisation and differentiation of neoplasms (13). However, PWI and MRS are not routinely used for imaging of all intracranial neoplasms.

The study by Alam *et al.*, which evaluated the diagnostic accuracy of MRS in addition to conventional MRI, recorded a good kappa value of 0.63 hereby supportive that the use of advanced MRI technique improves diagnostic confidence (12).
Another study by Mansour (2) who evaluated MRS in addition to conventional MRI found a kappa value of 0.63 and accuracy of 88.6 % which is comparable to the study by Alam *et al* (12). Ahmed & Mokhtar found that MRS was a non-invasive and accurate diagnostic tool that was superior to DWI with ADC value measurements in the differentiation and therapeutic planning of multicentric cerebral focal lesions (21). MRS achieved a statistically high accuracy of 96% and was unchanged when DWI was utilised. An insignificant lower accuracy of 78 % from conventional MRI and 87 % from DWI/ADC alone were achieved in the aforementioned study (21).

The extra-axial, anatomical location of pituitary adenomas and meningiomas as well as visualisation of the dura-tail or broad-dural base associated with meningioma are likely to be attributed to correct diagnoses of these neoplasms. This is compatible with the study by Yan *et al*

which looked at 762 cases and found that the diagnostic ability of conventional MRI varies amongst neoplasm types. Moreover, meningioma, pituitary adenomas, schwannomas and cholesteatomas were more likely to be diagnosed correctly (22).

Abdul-Kasim *et al* further demonstrated a substantial concordance between multimodal MRI diagnosis and histopathological diagnosis with a kappa value of 0.92, which confirmed a high diagnostic accuracy for multimodal imaging in differentiating various intracranial neoplasms compared to conventional MRI (13). Our study demonstrated that 95% of neoplasms graded as low-grade on MRI were confirmed by histopathology to be low-grade while histopathology confirmed that 81% of the high-grade MRI neoplasms to be high-grade (p-value < 0.005). The kappa agreement (kappa 0.77, p-value < 0.00001) on neoplasm grading between MRI and histopathology confirms a good concordance. For the purposes of this study, WHO Grade I and II neoplasms were grouped as low-grade while Grade III and IV as high-grade neoplasms, which may pose bias.

PWI

Hakyemez *et al* found that contrast enhancement may sometimes be misleading in the grading of gliomas as 2 (of 11) low-grade gliomas in their study showed marked enhancement while 3 (of 22) high-grade gliomas showed minimal to no enhancement post-contrast (23). Similar findings were also reported by Kono *et al* (16). Hakyemez *et al* further demonstrated that PWI was more useful in grading gliomas and showed significant differences in the relative cerebral blood volume (rCBV) and relative cerebral blood flow (rCBF) values which were higher in high-grade than low-grade gliomas (23). This was in agreement with Calli *et al* and other previous studies that showed that rCBV maps and measurements of PWI correlated with the neoplasm vascularity (24). These studies were able to differentiate between GBM and anaplastic astrocytoma on PWI. No statistical difference in the rCBV was found within the neoplasm but in the peritumoral region in the case of glioblastoma and metastasis (16, 23, 24). No PWI was performed in our study.

MRS

MRS analysis of various metabolites peaks within the neoplasm in comparison to the adjacent normal brain tissue helps in differentiating neoplastic lesions from non-neoplastic lesions. It can also help in differentiating between various neoplastic lesions such as meningioma and metastasis. Kaddah & Khalil highlighted the contribution of MRS in neoplasm grading as demonstrated by an increasing ratio of the Choline-Creatine and Choline-NAA from low- to high-grade gliomas and

metastasis (25). Our study showed that there was very poor utilisation of MRS in our institution (only 3 of 53 patients), even though it was available. It was only utilised upon the radiologist's request as it is utilised for specific cases and not routinely for all brain imaging. Lack of training in advanced MRI neuroradiology imaging techniques and an absence of stringent protocols are likely to be the contributing factors.

Kaddah & Khalil contributed that gliomas usually show spectroscopic abnormalities with a high Choline-NAA ratio extending beyond the enhancing margin of neoplasm which is helpful in distinguishing it from a metastasis (25). This was in agreement with the study by Abdul-Kasim *et al* and could have been useful in our study whereby a glioblastoma was diagnosed on MRI while the histopathology diagnosis was metastasis (13). Tsougos *et al* demonstrated the ability of MRS in the peritumoral region to differentiate between glioblastoma and metastasis and cited pathophysiology and/or particular tumour molecular mechanisms as reasons (15).

Kumar *et al* reported an increase in specificity from 75% to 87% in the diagnosis of malignant neoplasms when adding MRS to conventional MRI (26). The study by Abdul-Kasim *et al* also found that the outcomes of the PWI and MRS modalities were often supportive of each other and therefore performing one or the other may be sufficient to reach a conclusive diagnosis (13). This is important in our facility where there are limited resources.

DWI/ADC

DWI allows for the evaluation of the neoplasm's cellularity and necrotic components by evaluating the Brownian motion of water molecules within tissue while the ADC is a parameter calculated from the DWI (27). Highly cellular neoplasms demonstrate restricted diffusion which is high-intensity signal on DWI and low-intensity signal on ADC. Raisi-Nafchi *et al* studied DWI and ADC maps of various astrocytic neoplasms and recorded their minimum, maximum and mean DWI and ADC values by selecting cut-off values yielding the highest sensitivity, specificity, positive and negative predictive values to differentiate between low- and high-grade gliomas (27). The study found that there was a statistically significant inverse relationship between the ADC values and the neoplasm grade in line with previous studies (27). The study also found that there was a direct correlation between the maximum ADC values and maximum DWI signal intensities with the neoplasm grade. However, there was a some overlap between the values of the lw and high grade astrocytomas (27). The cut-off values of 0.843×10^{-3} mm^2/s, 2.117×10^{-3} mm^2/s and 165.2 were selected, in order to achieve the minimum ADC, maximum ADC and maximum DWI with the best combination of sensitivity and specificity for

differentiating high-grade and low-grade astrocytomas (27). Due to some overlap in ADC values of the low (WHO grade I and II) and high (WHO grade III and IV) grade neoplasms, other studies proposed slightly varying cut-off ADC values for a GBM ranging from 0.82 – 0.96 x 10-3 mm^2/s (16, 24, 28, 29). Zulfiqar *et al* found that low ADC values were a prognostic factor for poor survival and were independent of the WHO neoplasm grade. He also added that ADC values negatively correlated with the Ki-67 labelling index (29). Calli *et al* reported statistically significant lower ADC and rCBV values in lymphoma compared to glioblastoma which may aid in their differentiation. Meningioma demonstrated a wide range of ADC values and therefore types of meningiomas cannot be differentiated based on the ADC values (16).

In our study, only a note was made about the type of diffusion of the neoplasm. No DWI or ADC values were evaluated or recorded. This shows suboptimal use and analysis of the DWI and ADC in our institution. The suboptimal use of DWI/ADC and MRS may have contributed to the relatively poor concordance obtained in our study.

Strengths and limitations

The study was a retrospective single-centre study which might have limitations on the target population for analysis. The small study sample affected the confidence interval for the results. However, the understanding of the rareness of the disease hindered getting a good large sample size to minimize marginal errors. Furthermore, some patients with typical meningiomas on CT would not have been imaged by means of MRI because of the limited resources at CHBAH. And not all patients who were imaged by means of MRI and were found to have a brain tumour would have been biopsied.

Experience of the radiology consultants (ranging from junior to senior) varied while non-stringent protocols in the usage of available advanced MRI may have been the cause of the few histopathology-radiology discordances.

A super-specialised neuropathology diagnostic service is not available at CHBAH.

Interobserver agreement between radiologists was not evaluated, it could have assisted in assessing the reporting structure adherence.

The strength of the study showed how important a non-invasive procedure like MRI could benefit the patient if more information is obtained.

Implications or recommendations

Conventional MRI is utilised more for characterisation and anatomical location of the neoplasm and its effect on adjacent structures. However, we still rely on histopathology for the final diagnosis. The disadvantages of multimodal MRI include the increased cost of the MRI examination and increased examination time especially in a resource-poor or limited setting. There is a need to enhance the training of radiographers and radiologists for the optimal acquisition and analysis of the DWI/ADC maps and MRS data.
In our data, the good comparison of MRI and histopathology provides motivation for MRI as an invaluable radiological modality. With good protocols in place and advanced MRI imaging modalities, patients can be monitored non-invasively. The human error will be reduced as advanced technology in MRI and AI increase thereby increasing patient care and management in a non-invasive manner.
Future studies will be needed to investigate the benefit of optimal utilisation of the available DWI/ADC and MRS in our institution including other modalities, like PWI, if available.

7. Conclusion

Conventional MRI constitutes the most utilised MRI technique in the characterisation of intracranial neoplasms. However, this radiological investigation can be unreliable as various neoplasms can have similar features on conventional MRI. Higher accuracy is necessary for grading and diagnosis of the intracranial neoplasm to optimise patient management and prognosis. Advanced MRI techniques, optimally utilised, improve the diagnostic accuracy of MRI by providing additional information related to the histopathological features of the neoplasm such as vascularity, necrosis and cellularity metabolites. Hence, it should be used where available. In concert, conventional MRI, advanced MR techniques and histopathology are modalities that are complementary.

Competing interests

The authors declare that they have no conflict of interest in the article.

Author(s) contributions

TB devised the original idea. TB and SP both supervised the project. BM developed the study design, data collection and analysis. BM took the lead in writing the manuscript with TB and SP supervising and contributing to the final version submitted.

Funding information

The authors received no financial support for the research, authorship and/or publication of this article.

Data availability statement

The data supporting the findings of this study are available from the corresponding author, BM, upon reasonable request.

Disclaimer

Views expressed in this submitted article are the authors own and not an official position of the institute.

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Appendix A: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

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

TO: Dr B Mojapelo
School of Clinical Medicine
Department of Radiation Sciences
Division of Diagnostic Radiology
Medical School
University

E-mail: besley.mojapelo@gmail.com

CC: Supervisor: Drs S Pather and T Buthelezi <Sugeshnee.Pather@nhls.ac.za>
and <HREC-Medical.ResearchOffice@wits.ac.za>

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

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

DATE: 2020/07/03

REF: *R14/49*

PROTOCOL NO: **M200254** *(*This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study*)*

PROJECT TITLE: *Adult intracranial neoplasms: radiologic and histopathological correlation*

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

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr B Mojapelo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200254

NAME: (Principal Investigator)	Dr B Mojapelo
DEPARTMENT:	School of Clinical Medicine Department of Radiation Sciences Division of Diagnostic Radiology Medical School University
PROJECT TITLE:	Adult intracranial neoplasms: radiologic and histopathological correlation
DATE CONSIDERED:	2020/02/28
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Drs S Pather and T Buthelezi
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/07/03

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 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 **February** and will therefore reports and re-certification will be due early in the month of **February** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

03/08/2020
Date

Appendix B: Figures

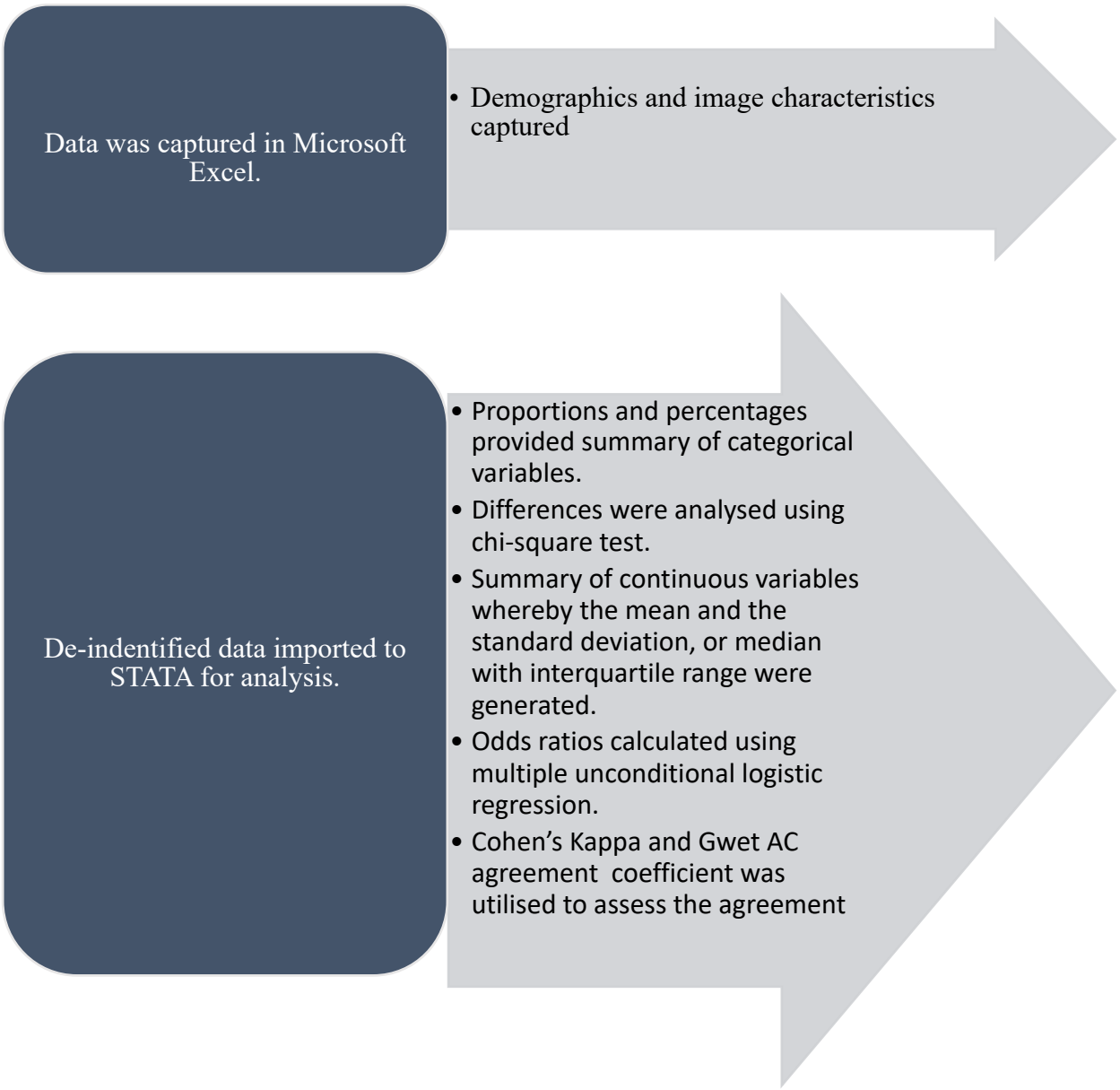


Figure 1: Data Analysis plan

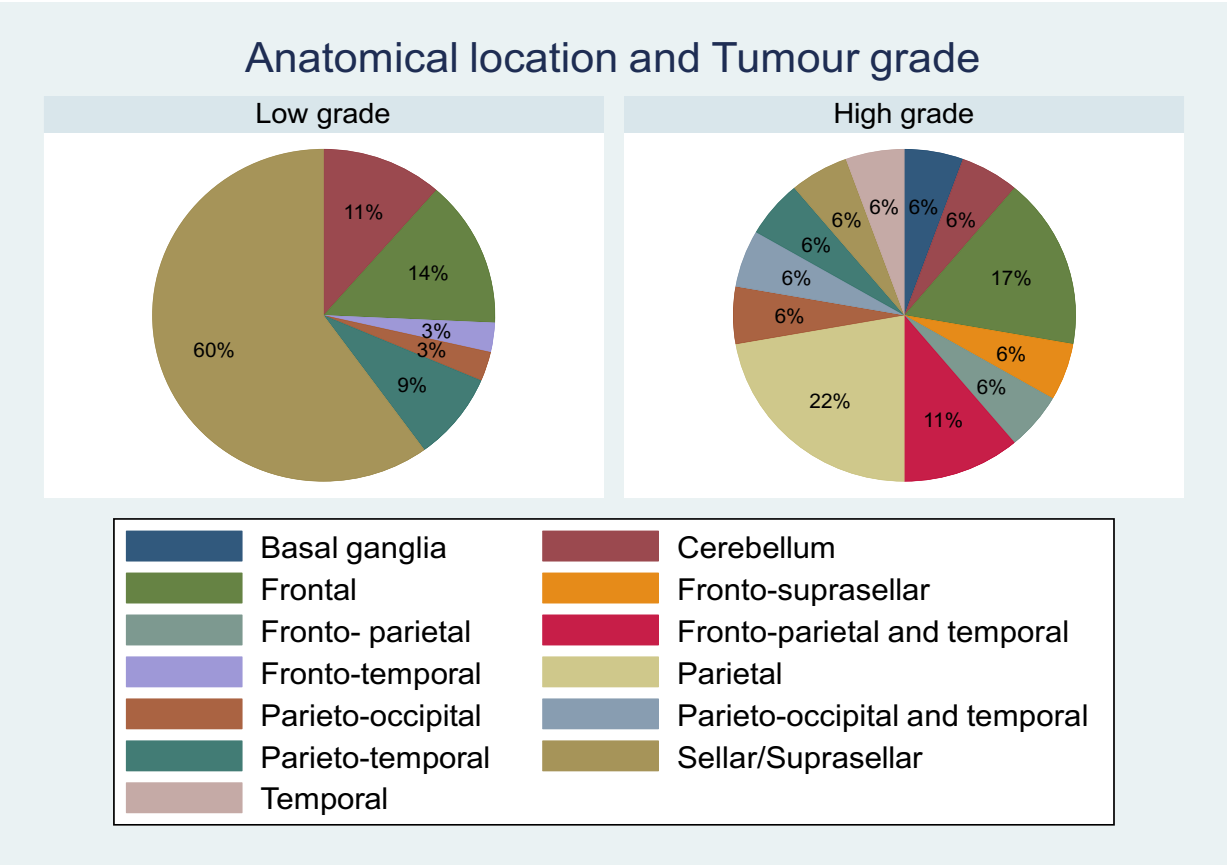
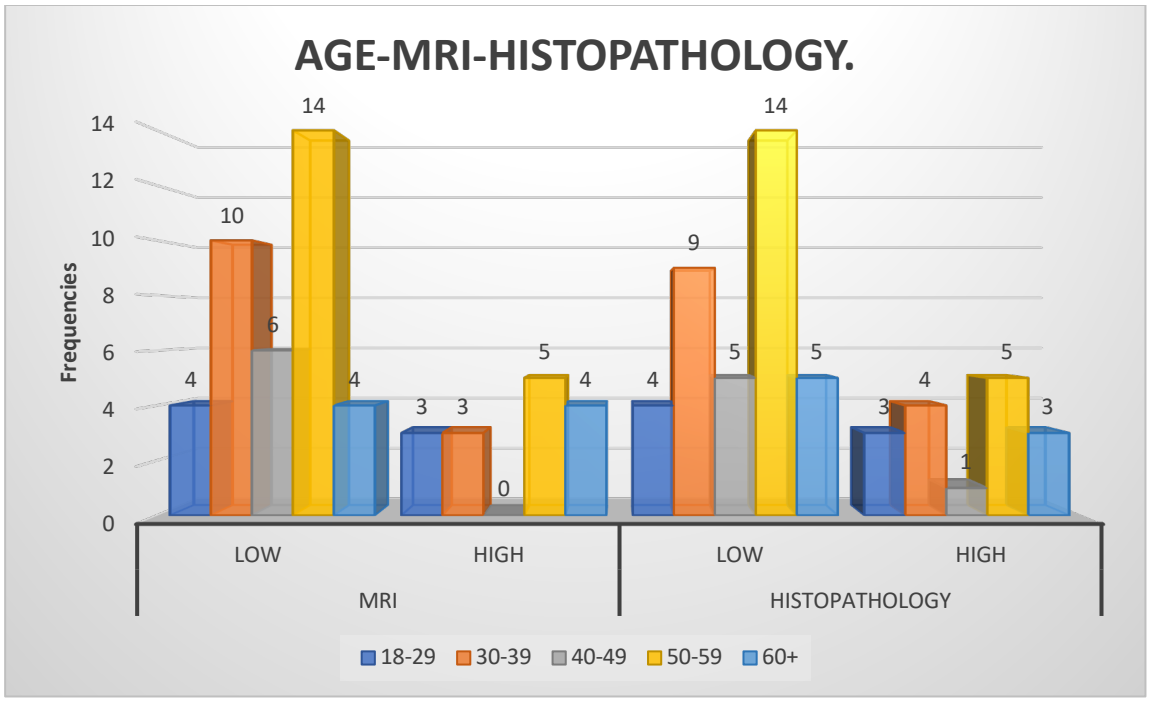
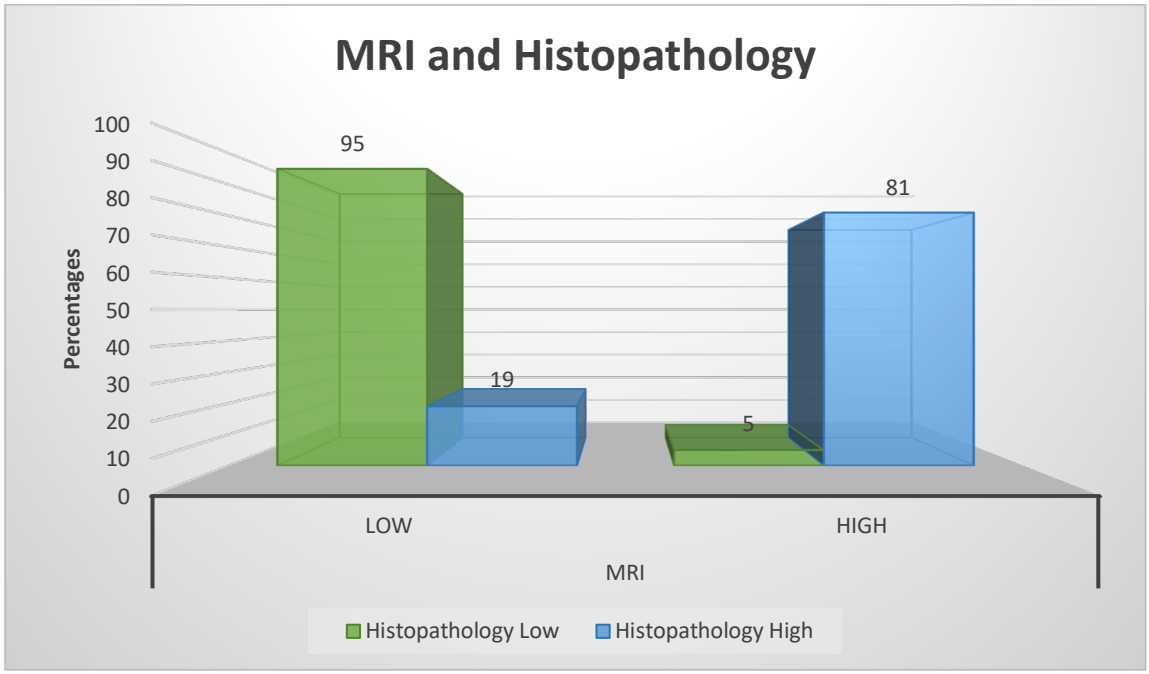


Figure 2: Shows low-grade and high-grade neoplasms based on histopathology and their anatomical distribution.

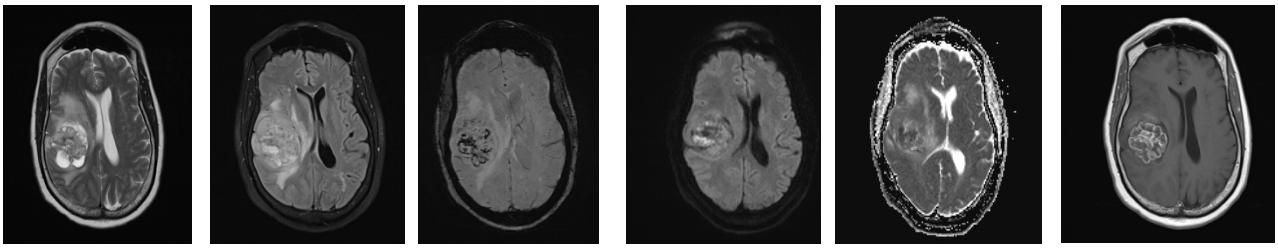


(a)

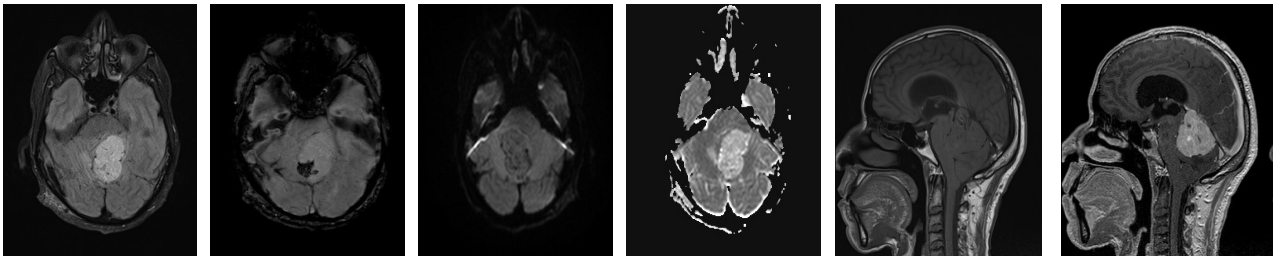


(b)

Figure 3: ***(a)***Age distribution and neoplasm frequency according to grade on MRI and histopathology. ***(b)*** Comparison of MRI and histopathology grading - shows the percentage of histopathology neoplasm grade compatible with each MRI grading for low- and high-grade neoplasm group (p-value < 0.001).



(a)



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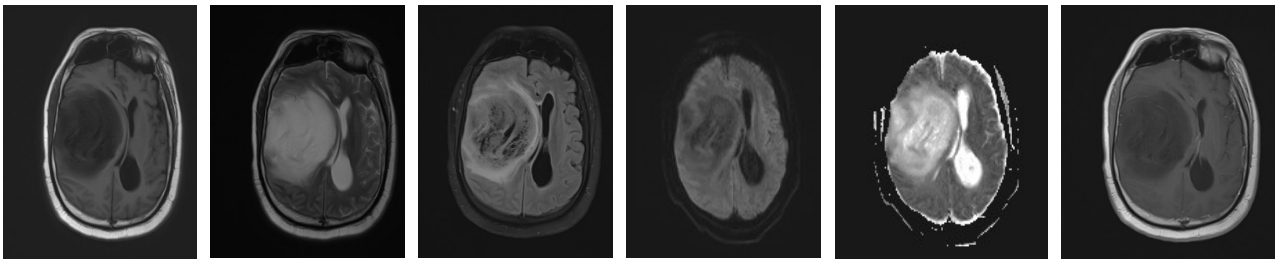

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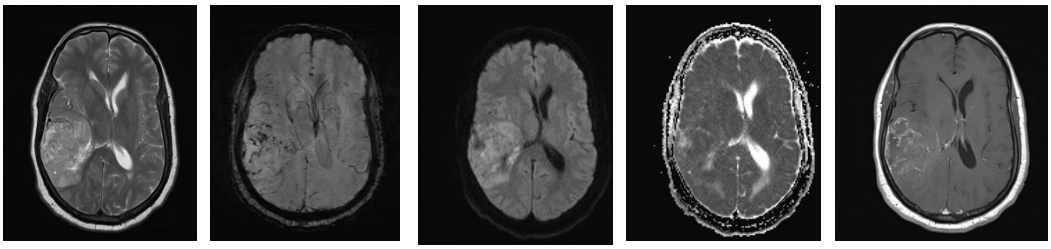


(d)

Figure 4: MRI imaging of the histopathologically proven intracranial neoplasms (a) Glioblastoma- and (b) Haemangiopericytoma - FLAIR, SWI, DWI, ADC, T1WI and T1WI post-contrast.(c) Anaplastic Astrocytoma - T1WI, T2WI, FLAIR, DWI, ADC and T1WI post-contrast. (d) Glioblastoma – T2WI, SWI, DWI, ADC and T1WI post-contrast.

Appendix C: Tables

Table 1: Demographics, MRI characteristics of the neoplasm, frequency of the MRI, histopathological classification of the neoplasms and the grading of the intracranial neoplasms

Variable	Number of patients	Frequency %	Median (IQR)
Age	53	100	50 (34-57)
Age category			
18-29	7	13	
30-39	13	25	
40-49	6	11	
50-59	19	36	
60+	8	15	
Gender			
Male	26	49	
Female	27	51	
Anatomical location			
Frontal	8	15	
Parietal	4	8	
Temporal	1	2	
Sellar/Suprasellar	22	42	
Basal ganglia	1	2	
Infratentorial/ Cerebellopontine	2	4	
angle(CPA)	2	4	
Cerebellum	1	2	
Pineal	1	2	
Frontal/parietal	4	8	
Frontal/temporal	1	2	
Parietal/temporal	2	4	
Parietal/occipital/temporal	2	4	
Frontal/parietal/temporal	1	2	
Parietal/occipital	1	2	
Frontal/sellar			
Axial Location			

Intra **Extra**	19 34	36 64	
Composition **Solid** **Mixed**	 30 23	 57 43	
Restricted diffusion **No** **Yes** **N/A**	 24 21 8	 45 40 15	
Neoplasm MRI Grade **Low-grade** **High-grade**	 38 15	 72 28	
Neoplasm Histopathology Grade **Low-grade** **High-grade**	 37 16	 70 30	

Table 2: MRI and Histopathology neoplasm diagnosis and grading for the study of neoplasm.

Study No.	MRI Diagnosis	Grade	Histopathology Diagnosis	Grade
1	Craniopharyngioma	Low	Craniopharyngioma	Low
2	Glioblastoma	High	Glioblastoma	High
3	Glioblastoma	High	Glioblastoma	High
4	Pituitary Macroadenoma	Low	Pituitary adenoma	Low
5	Pituitary Macroadenoma	Low	Pituitary adenoma	Low
6	Pituitary Macroadenoma	Low	Pituitary adenoma	Low
7	Breast Carcinoma Metastasis	High	Breast Metastasis	High
8	Pituitary Macroadenoma	Low	Pituitary adenoma	Low
9	Anaplastic astrocytoma	High	Glioblastoma	High

10	Glioblastoma	High	Glioblastoma	High
11	Glioblastoma	High	Lung metastasis	High
12	Meningioma	Low	Atypical Meningioma	Low
13	Pituitary macroadenoma	Low	Pituitary adenoma	Low
14	Craniopharyngioma	Low	Craniopharyngioma adamatinomatous	Low
15	Metastasis	High	Meningoepithelial meningioma	Low
16	Pituitary macroadenoma	Low	Pituitary adenoma	Low
17	Pituitary macroadenoma	Low	Pituitary adenoma	Low
18	Pituitary macroadenoma	Low	Pituitary adenoma	Low
19	Cavernous meningioma	Low	Pituitary adenoma	Low
20	Pituitary macroadenoma	Low	Pituitary adenoma	Low
21	Pituitary macroadenoma	Low	Pituitary adenoma	Low
22	Glioblastoma	High	Anaplastic Oligodedroglioma	High
23	Pituitary macroadenoma	Low	Pituitary adenoma	Low
24	Pituitary macroadenoma	Low	Pituitary adenoma	Low
25	High grade astrocytoma	High	High grade astrocytoma	High
26	Metastasis	High	Fibrous meningioma	Low
27	Pituitary macroadenoma	Low	Pituitary adenoma	Low
28	Pleomorphic xanthoastrocytoma	Low	Meningioma	Low

29	Haemangiopericytoma	High	Anaplastic meningioma	High
30	Meningioma	Low	Haemangiopericytoma	High
31	Meningioma	Low	Atypical Meningioma	Low
32	Pituitary macroadenoma	Low	Pituitary adenoma	Low
33	Glioblastoma	High	Glioblastoma	High
34	Meningioma	Low	Meningothelial meningioma	Low
35	Meningioma	Low	Meningioma	Low
36	High grade Astrocytoma	High	Anaplastic ependymoma	High
37	Meningioma	Low	Meningothelial meningioma	Low
38	Ependymoma	Low	Diffuse astrocytoma	Low
39	Meningioma	Low	Atypical Meningioma	Low
40	Pituitary macroadenoma	Low	Pituitary adenoma	Low
41	Pituitary macroadenoma	Low	Pituitary adenoma	Low
42	Haemangioblastoma	Low	Haemangioblastoma	Low
43	Meningioma	Low	Atypical Meningioma	Low
44	Grade II Astrocytoma	Low	Anaplastic Astrocytoma	High
45	Craniopharyngioma	Low	Pilocytic astrocytoma	Low
46	Pituitary macroadenoma	Low	Meningothelial meningioma	Low
47	Haemangiopericytoma	High	Haemangiopericytoma	High
48	Meningioma	Low	Meningothelial meningioma	Low
49	Pituitary macroadenoma	Low	Pituitary adenoma	Low
50	Glioblastoma	High	Glioblastoma	High
51	Oligodendroglioma	Low	Glioblastoma	High

52	Pleomorphic xanthoastrocytoma	Low	Pleomorphic xanthoastrocytoma	Low
53	Germinoma	Low	Meningothelial meningioma	Low

Table 3 : Total number and frequency of the intracranial neoplasms according to MRI and Histopathology diagnoses.

	MRI diagnosis	**Frequency (%)**	**Histopathology diagnosis**	**Frequency (%)**
Glial neoplasms				
Glioblastoma	7	13	7	13
Anaplastic astrocytoma	3	6	2	4
Diffuse astrocytoma	1	2	1	2
Pleomorphic xanthostrocytoma	2	4	1	2
Pilocystic astrocytoma	0	0	1	2
Ependymoma	1	2	0	0
Anaplastic ependymoma	0	0	1	2
Oligodendroglioma	1	2	0	0
Anaplastic oligodendroglioma	0	0	1	2
Sellar/suprasellar neoplasms				
Pituitary adenoma	18	34	18	34
Craniopharyngioma	3	6	2	4
Pineal neoplasm				
Germinoma	1	2	0	0
Cerebellar neoplasms				
Heamangioblastoma	1	2	1	2
Extra-axial neoplasms				
Meningioma	10	19	14	26
Haemangiopericytoma	2	4	2	4
Metastasis	3	6	2	4

Table 4: Neoplasm composition compared to its *grading* on MRI *a*nd histopathology.

Variable	Total	Solid	Mixed	p-value
MRI Neoplasm				
Low	38(72)	25(83)	13(57)	0.032
High	15(28)	5(17)	10(43)	
Histopathology				
Low	37(70)	26(87)	11(48)	0.002
High	16(30)	4(13)	12(52)	

Table 5: Logistic regression composition and Axial location

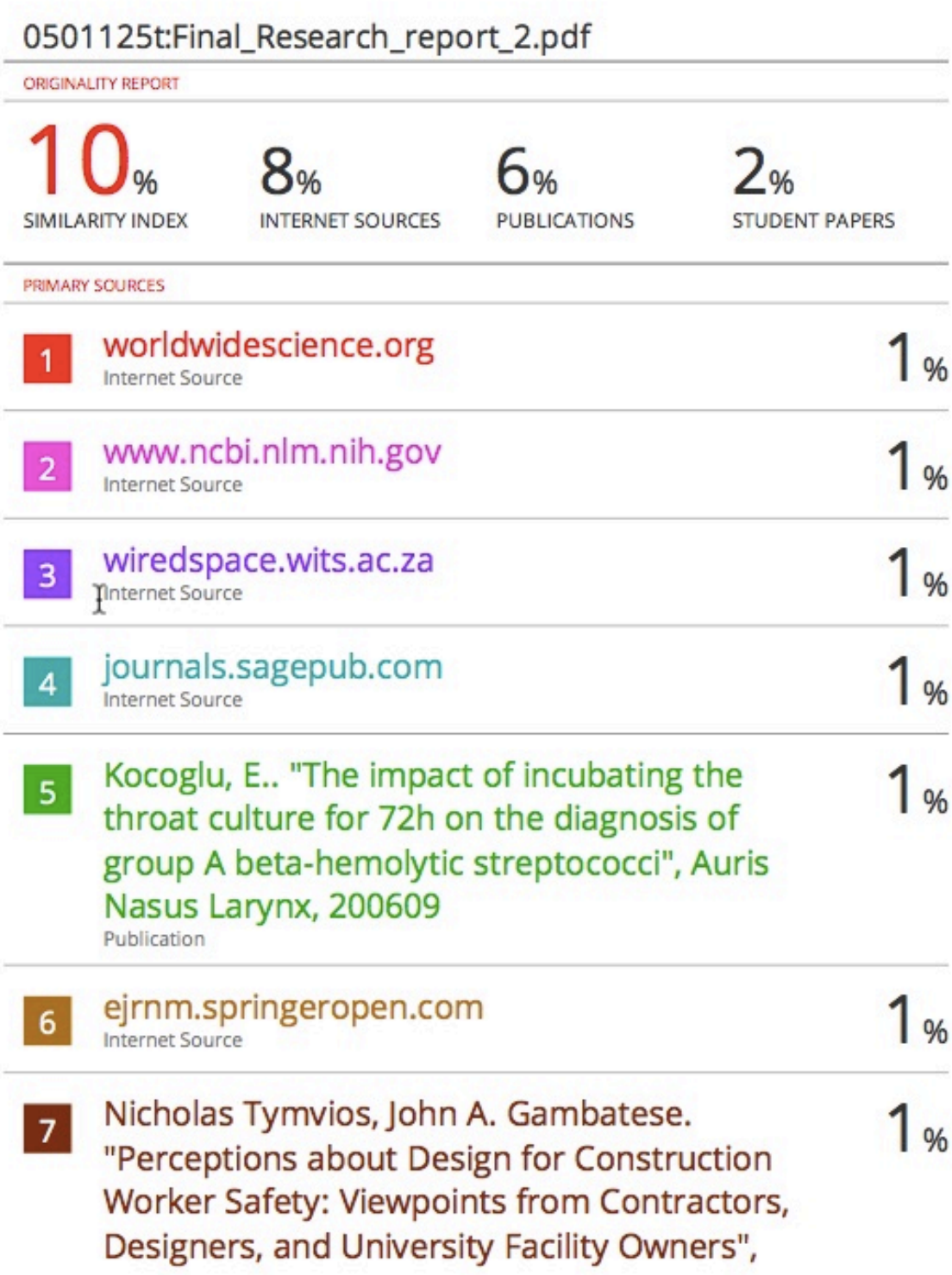
	Histopathology		MRI	
Variable	OR(CI)	p-value	OR(CI)	p-value
Composition				
Solid	1	0.002	1	0.037
Mixed	7.09(1.87-27.9)		3.85(1.08-13.6)	
Axial location				
Extra	1	<0.0001	1	<0.001
Intra	22.4(4.84-103.4)		17.7(3.92-80)	

Table 6: Agreement of Histopathology and MRI

Rater	**Percentage agreement**	**CI**	**Benchmark scale**	**Cohen kappa**	**CI**	**Gwet' s AC**	**CI**	**Number of rating category**	**p-value**
Histo-MRI Grading	91	0.82-0.99	**<0.20 Poor 0.20-0.40 Fair 0.41-0.60 Moderate 0.61-0.80 Good > 0.80 Very good**	0.77	0.58-0.97	0.84	0.69-0.98	2	<0.001
Histo-MRI Diagnosis	69.8	0.57-0.83		0.626	0.48-0.77	0.678	0.54-0.82	14	<0.001
Pineal	50	-		0	-	0.200	-	2	-
Axial	33	-		0.1429	-	0.1429	-	4	0.1932

Sellar	50	-		33	-	0.2727	-	3	0.0786
Glial	22	.-0		-0.09	.	0.06	.-0	5	0.6819

Appendix D: Turnitin Report



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Appendix E: |Original Protocol

ADULT INTRACRANIAL NEOPLASMS: RADIOLOGIC AND HISTOPATHOLOGICAL CORRELATION

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Table of contents

1. Rationale

The biopsy of an intracranial neoplasm is an invasive procedure associated with many complications and the process of its acquirement results in the delay of patient management. The goal of this study is to correlate the MRI imaging findings of intracranial neoplasms in adult patients with the histopathology findings to determine their accuracy with hope to improve patient management and morbidity.

2. Introduction

Intracranial neoplasms are a heterogenous group of neoplasms comprising both benign and malignant neoplasms that arise from any of the various intracranial structures[1]. These intracranial neoplasms result in numerous complications, significant morbidity and mortality due to the neoplasm itself or its mass effect on adjacent structures[1,2].

2.1. Epidemiology of Intracranial neoplasms

The epidemiology of the intracranial neoplasms is only partially established and there is limited data available regarding their incidence and prevalence world-wide, in Africa as well as in South Africa with variations among different regions[1,2]. This variation may be linked to genetic factors, environment, variation in cancer registration systems, health infrastructure and access to health care[1,2]. The latter three reasons may contribute to falsely low incidence ratios noted[2]. A recent systematic review and meta-analysis by de Robles et al. concluded that the overall global incidence of brain neoplasms is 10.82 per 100 000 person-years[1], whereas Leece et al. subsequently found that the overall global incidence, which included all age groups, was 5.57 per 100 000 persons-year[2].
The National cancer registry of South Africa from 2014 documented a total of 487 histologically diagnosed neoplasms and GLOBOCAN from 2018 reported a total of 900 neoplasms (0.84 % of all cancers) – comprising of neoplasms arising from both the brain and central nervous system[3,4]. However, Both the GLOBOCAN and South African National cancer registries do not include data on the incidence or prevalence of the intracranial neoplasms as a group distinct from the rest of the central nervous system[3,4].

Fox et al. reported that metastases are the most common intracranial neoplasm and that there may be an underestimation in their true incidence of up to 11 million per 100 000 population per

year. The underestimation thereof is suggested to be linked to poor diagnostic modalities or inaccurate reporting[5]. Moreover, post-mortem studies have demonstrated that 25% of intracranial metastases were found in those who were known to have a cancer diagnosis whilst living[5].

Glioblastoma multiforme is regarded as the most common malignant primary intracranial neoplasms contributing to about 12-15% of all intracranial neoplasms and accounting for about 60-75% of all astrocytic neoplasms with a peak incidence between the ages 45- 75 years[6].

As a result of the retroviral disease epidemic as a cause for immunosuppression, primary CNS lymphoma is increasing in incidence throughout the world and constituting up to 6.6% of the primary intracranial neoplasms[7].

Meningioma is the most common benign intracranial neoplasm affecting the middle age and elderly population with a slight female predominance[8]. Meningiomas contribute to about 33.8% of primary intracranial neoplasms in the United states of America as documented for 2002 to 2006[8], while atypical and malignant meningiomas contributed to about 5% of all meningiomas. It was further noted that a slight male predominance is evident for atypical and malignant meningiomas[8].

Only one study by Ibebuike et al was done at the University of Witwatersrand (WITS) in 2013 which looked at the frequency of intracranial neoplasms in the region of Johannesburg[9]. The study looked at histologically diagnosed intracranial neoplasm data from the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH) and found that meningiomas were the most common intracranial neoplasms and constituting 31.8 % of all intracranial neoplasms[9].

Schwannoma, is another benign intracranial neoplasm, contributing to 8 % of all intracranial neoplasms with about 85% of these neoplasms located in the cerebellopontine angle and a peak incidence occurring between the fourth and sixth decades of life[10].

The World Health Organisation classifies intracranial neoplasms based on histopathology characteristics into four grades (listed in appendix A) as follows:[11]

Grade I neoplasms are benign and slow-growing.

Grade II neoplasms can be benign or malignant. However, they are relatively slow-growing and occasionally recur as higher grade neoplasms.

Grade III neoplasms are malignant and often recur as higher grade neoplasms.

Grade IV neoplasms proliferate rapidly and are very aggressive malignant neoplasm.

2.2. Imaging modalities of intracranial neoplasms

Intracranial lesions such as infection, inflammation, trauma and vascular lesions may mimic neoplasms [10,19]. Pre-operative diagnosis of intracranial neoplasms is of primary importance in clinical management[18].

Computed Tomography (CT) scan and Magnetic Resonance Imaging (MRI) are the initial diagnostic imaging modalities which are used to determine whether intracranial lesions are benign, non-benign or non-neoplastic in nature. These investigations are furthermore used for the anatomical localization and characterization of the intracranial neoplasms. CT scan is more accessible than MRI. However, MRI is superior to CT in that there is no exposure to radiation, improved diagnostic accuracy with better anatomical localization, characterisation of intracranial neoplasms and improved ability to differentiate benign from malignant neoplasms[12,14,18].

Advances in MRI with the addition of diffusion- and perfusion-weighted imaging as well as spectroscopy have greatly enhanced the diagnostic accuracy of MRI in that there is better characterisation and differentiation of neoplasms[14,18]. However, these modalities are complementary and do not replace conventional MRI.[10,14]

2.3. Biopsy of intracranial neoplasms

World Health Organisation has recently revised and updated the classification of intracranial tumours according to their molecular (genotype) features and histopathology[11].

Histopathological diagnosis of intracranial neoplasms has always been considered the 'gold standard' for final diagnosis and management of the intracranial neoplasms[18]. However, an invasive procedure is often required to obtain diagnostic tissue and this is accompanied by risk of complications.

At times, intracranial neoplasms need to be diagnosed non-invasively with the use of imaging modalities because some neoplasms are positioned in areas that are not accessible to biopsy or surgical resection while others need to be treated primarily with radiation therapy.[14]

At times, a biopsy procedure may only render limited tissue for histopathological analysis. Hence, there might be unsampled areas of the neoplasm which directly impacts classification thereof [13,14]. This is important in grading of neoplasms such as gliomas and meningioma, among others. When tissue is obtained from a less aggressive area within the neoplasm, it might be erroneously classified as a low-grade neoplasm. Therefore, close correlation with the radiological characteristics is of paramount importance for diagnostic accuracy[13,14,20]

Diagnostic neuropathology is a very challenging field. A further confounding factor is that of interpretative diagnostic variability among histopathologists[14]. Furthermore, differentiating a

low-grade astrocytoma from gliosis can be vexing, during an intra-operative pathology consultation. Therefore, details regarding MRI and CT scan imaging are crucial for the pathological diagnosis of intracranial neoplasms[20].

2.4. Comparison to literature on the topic

Multiple studies have affirmed that conventional MRI with the addition of new modalities such as Spectroscopy has high diagnostic accuracy of intracranial neoplasms[10,12,19]. These studies demonstrated diagnostic accuracies of Multimodal MRI ranging from 78 - 98.57 %[5,6]. High sensitivities ranging from 93 – 94.5 % with relatively poor specificities ranging 70 - 75% were demonstrated for diagnosing neoplastic lesions on MRI[10,12,14,19].

Taghipour et al. reported a high sensitivity of 92 % with a very low specificity of 25% for MRI diagnosis of intracranial neoplasm in unison with histopathology[17]. In this study, it was not clearly stated whether only conventional or newer modalities were utilised in acquiring the MRI diagnosis.

Radiologically misdiagnosed intracranial lesions may include infections such as abscess, chronic reactive tissue, inflammatory lesions and vascular lesions[10,19]. One study found less specificity (50%) in diagnosis of infective lesions compared to 100% specificity of inflammatory lesions on MRI[21]. While all cases of vascular aetiology were correctly diagnosed on MRI[19].

These studies found that MRS was able to differentiate between neoplastic and non-neoplastic lesions in evaluation of intracranial neoplasm with inconclusive diagnosis on conventional MRI and that MRS should be should as an added tool in multimodal MRI and does not replace conventional MRI.[10,14]

The goal of the study is to compare and correlate the MRI diagnosis of intracranial neoplasms in adult patients with the histopathology diagnosis to determine its diagnostic accuracy of MRI. This may be helpful in cases where a difficult biopsy procedure is anticipated. This may also aid the aversion of an unnecessary biopsy of non-neoplastic intracranial lesions. Avoidance of a delay in the initiation of treatment may also occur[12,14]. Improvement of morbidity and mortality may ultimately benefit the patient who has an intracranial lesion.

3. Aim

In context of adult intracranial neoplasms in the South African setting, we aim to correlate and compare MRI imaging findings with the histopathological diagnosis.

4. Primary Objectives

- To document the histopathological diagnosis
- To compare MRI imaging findings with histopathological findings.

5. Methods

5.1. Study design

This is a retrospective cross-sectional study.

5.2. Sample

5.2.1. Inclusion Criteria

- Patients above age of 18 years.
- Patients who have reports of intracranial neoplasms and histopathological diagnosis
- Patients reports with MRI imaging intracranial neoplasm diagnosis and /or differential diagnosis
- Patients who received intravenous contrast.

5.2.2. Exclusion criteria

- Inconclusive histopathology diagnosis
- Inconclusive radiological diagnosis i.e. no diagnosis or differential diagnosis
- Patient MRI reports generated from incomplete MRI study or where full basic MRI protocol was not followed.

5.3. Materials and Methods

The study will be conducted in the Department of Diagnostic Radiology and the Division of Anatomical Pathology, National Health Laboratory Service (NHLS) at the Chris Hani Baragwanath Academic Hospital (CHBAH). MRI and histopathology reports will be retrieved from January 2017 to September 2019. The PACS system and NHLS Corporate Data Warehouse (CDW) will be used to retrieve the reports. The latter will employ the use of a Systemised Nomenclature of Medicine (SNOMED) search using the following codes: T-

A0094(brain), T-A600A(cerebellum), T-B2000(pineal structure), T-B1000(pituitary), M-80000(neoplasm benign), M-80001(neoplasm uncertain whether benign or malignant), M-80003(malignant neoplasm primary), M-80006(neoplasm, metastatic).
The data will be reviewed and analysed by the primary investigator.
MRI data was acquired using a Siemens Avanto 1.5 Tesla machine at the above-mentioned hospitals with a slice thickness of 5 mm. Acquired MRI sequences for imaging of intracranial neoplasms are not standard in our institution and may vary as per radiologist. However, the following are some of the routine MRI sequences commonly acquired: T1WI 3D, axial T2WI and T2 FLAIR, coronal T2WI, axial DWI, axial SWI, axial and sagittal T1WI post contrast (gadolinium). Spectroscopy may be performed on radiologist request.
All patients are preferred to have had a CT brain acquired prior to the MRI being done.

5.4. Data collection

Patients who have confirmed intracranial neoplasms diagnosed as per histopathology and had prior MRI diagnosis or intracranial neoplastic differential diagnosis will be included.
Data will be collected with assistance from the NHLS CDW and MRI reports on PACS system at CHBAH.
Data will be collected using a data collection sheet - Appendix B - and results will be analysed and loaded in a spreadsheet using Microsoft Excel according to a predefined range of MRI characteristics of the intracranial neoplasm as described below:

- Age group
- Gender
- Anatomical location (cerebral lobe, cerebellum, brainstem)
- Composition(cystic/solid/ mixed)
- DWI restriction or not
- If spectroscopy – then note increase or decrease in metabolites (choline, creatine, NAA or lipids)
- Low-grade or High-grade neoplasm
- MRI diagnosis
- Histopathology diagnosis

The above information will be derived from the MRI reports found on the PACS system. The most likely neoplastic diagnosis from the MRI report will be considered a final MRI diagnosis. In the case where a differential diagnosis is provided, the first neoplastic diagnosis will be considered most likely and the final one.

For Spectroscopy only four metabolites i.e. Choline. Creatine, NAA and lipids, will be assessed. Low-grade neoplasms will be those in WHO grade I and II and the High-grade neoplasm will be those belonging to WHO grade III and IV category.

Only histopathology reports with a conclusive diagnosis will be considered.

5.5. Reliability and validity

The final radiological diagnosis on reports based on MRI imaging findings will be compared to the histopathology diagnosis which is a gold standard.

5.6. Bias

Histopathology interpretation of results are based on the tissue specimens that are obtained from certain regions within a neoplasm. These specimens are usually representative of the general morphology of the neoplasm. However, it is possible that a specimen obtained may represent the regions within the neoplasm that are appear benign or well differentiated thus leading to a diagnosis of a low grade neoplasm[10,11]. The neurosurgical sampling technique has a direct impact on whether the specimen, that is submitted to histopathology, is truly representative of the neoplasm[11,17].
Radiological diagnosis based on MRI imaging findings can be based on the radiologist's experience and interests. The reports included will be those approved by radiology consultants.

6. Data analysis and statistics

Data will be collected and documented on Microsoft excel spreadsheet using tick boxes. Data will be assessed for sensitivity, specificity, positive/negative predictive values and diagnostic accuracy of MRI in comparison to histopathological diagnosis.
A software programme, Statistica, will used to perform data analysis.

The outcomes of the study will be considered to be statically significant provided that statistical analysis attains probabilities below significance level alpha 0.05 (p -value < 0.05) at a 95% confidence interval.

The Chi-square test of independence will be used to determine the relationship between the categorical data.

Cohen's Kappa coefficient will be utilised to assess the agreement between MRI reporting and histopathological diagnosis. Kappa values will be considered as follows: <0.20= Poor, 0.20 - 0.40 = Fair, 0.41 – 0.60 = Moderate, 0.61 – 0.80 = Good and >0.80 = Very good.

7. Ethics

An application for ethical clearance of this project will be submitted to the Human Research Ethics Committee (Medical) at the University of the Witwatersrand.

7.1. Consent forms

This is a retrospective study that will be using data collected prior to the commencement of the research. Permission to access the pathology data will be obtained from the Division of Anatomical Pathology at CHBAH/CMJAH.

7.2. Data safety

The raw data that contains the patient identification details will only be accessible to the primary investigator and supervisors. There will be no identifiable factors. The individual's name and hospital number will not appear in the data collection sheets or manuscript.
The patients will be anonymised by a specially allocated study reference number which will be used for data analysis when capturing information for this research. Hereby, patient confidentiality will be maintained.

8. Timing

Please refer to Appendix C.

9. Budget

This research will be funded fully by the primary investigator. No external funding will be required.

10. Anticipated problems

Data retrieval from the NHLS CDW may take up to 6 months.

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Appendix A: WHO Classification of intracranial Neoplasms

Neoplasm type	Grade I	Grade II	Grade III	Grade IV
Astrocytic neoplasms	Subependymal giant cell astrocytoma	Diffuse Astrocytoma	Anaplastic astrocytoma	Glioblastoma
	Pilocytic astrocytoma	Pleomorphic xanthoastrocytoma		Gliosarcoma
		Pilomyxoid astrocytoma		
Oligodendroglial neoplasms		Oligodendroglioma	Anaplastic Oligodendroglioma	
Oligoastrocytic neoplasms		Oligoastrocytoma	Anaplastic Oligoastrocytoma	
Ependymal neoplasms	Subependymoma			
	Myxopapillary ependymoma	Ependymoma	Anaplastic ependymoma	

Choroid plexus neoplasm	Choroid plexus papilloma	Atypical choroid plexus papilloma	Choroid plexus carcinoma
Other neuroepithelial neoplasms	Angiocentric glioma	Choroid glioma of the third ventricle	
Neuronal and mixed neuronal-glial neoplasms	Gangliocytoma	Central neurocytoma	
	Ganglioglioma	Extraventricular neurocytoma	Anaplastic ganglioglioma
	Dysembryoplastic neuroepithelial tumour / ganglioglioma		
	Papillary glioneural neoplasm	Cerebellar liponeurocytoma	
	Rosette-forming glioneural tumour of the fourth ventricle		

Pineal Neoplasms	Pineocytoma	Pineal parenchymal tumour with intermediate differentiation	
		Papillary tumor of the pineal gland	
Embryonal Neoplasms			Medulloblastoma
Neoplasm of cranial or spinal nerves	Schwannoma /neurofibroma/ Perineuroma	Malignant peripheral nerve sheath tumour	
Meningiomas	Meningioma	Atypical meningioma	Anaplastic meningioma
Mesenchymal non-epithelial neoplasm	Hemangiopericytoma		
	Hemangioblastoma		
Neoplasms of the sellar region	Craniopharyngioma		
	Pituicytoma		
	Granular cell tumour		
	Spindle cell oncocytoma		
Other neoplasms of unknown grade	Primary CNS lymphoma	Pituitary adenoma	

Appendix B: Data Collection Sheet

STUDY NO.	AGE	GENDER		ANATOMICAL LOCATION						COMPOSITION			RESTRICTED DIFFUSION		SPECTROSCOPY METABOLITES Increased: ↑ or Decreased: ↓				MRI DIAGNOSIS	NEOPLASM MRI GRADING	
		M	F	Fr	P	O	T	B	C	Solid	Cystic	mixed	Y	N	Choline	NAA	Creatine	Lipids		Low Grade	High Grade
001																					
002																					
003																					
004																					
005																					
006																					

M = male, F = female, Fr = frontal, P = parietal, O = occipital, T = temporal, B = brainstem, C = cerebellum, NAA = N-acetylaspartate, N/A = not available.

Appendix C: Timing

Month of the year	Aug	Sep	Oct	Nov	Dec-Jan	Feb – Mar	Apr - May	Jun	Jul
Literature research									
Reading literature									
Preparing Protocol									
Ethics application									
Collecting data									
Data analysis									
Writing up thesis									
Submit marking									
Writing up paper									