EVALUATING CEREBRAL RADIATION NECROSIS IN PATIENTS WHO RECEIVED PARTIAL BRAIN RADIATION THERAPY AT CMJAH AND WDGMC BETWEEN 2014-2017

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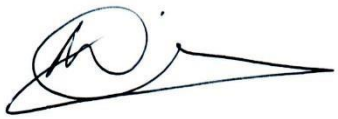
A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine in Radiation Oncology

Johannesburg, 2020

Declaration

I Mia Erasmus, 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 Radiation Oncology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



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Dedication

With deepest thanks to Pierre and Joshua.

Abstract

Cerebral radiation necrosis (RN) is a known late side effect of radiation to the brain. This retrospective study reviewed RN in patients who received partial brain radiation from 20142017 at CMJAH and WDGMC in Johannesburg. Results: 80 patients had follow up MRIs and were included in the sample. 5 patients developed RN in the time period, with an incidence of 6.25 % (5/80). Looking at biologically effective dose (BED) groups there was a much higher incidence of RN for $BED_3 \geq 100Gy_3$ (3/13; 23%) than for $BED_3 < 100Gy_3$ (2/54; 3.7%). Due to the small number of RN cases no statistically significant correlations were found with patient, clinical or treatment factors. However, total dose, BED and dose per fraction consistently showed a trend that higher dose was associated with radiation necrosis. Conclusion: The incidence for RN at CMJAH and WDGMC is similar to that found in other centres internationally. The total radiation dose (adjusted for BED) is the most important factor that affects the incidence of RN.

Acknowledgements

I wish to thank the following departments/people for assisting with this research and in particular wish to thank the participating radiation oncologists and radiation units for allowing access to their patient files.

- The department of radiation oncology, CMJAH
- Dr Jeffrey Kotzen
- Dr Owen Terreblanche
- Dr Edna Retter
- Dr Mariza Tunmer
- Wits Donald Gordon Radiation Unit
- Wits Research Centre Statisticians

I also wish to sincerely thank my supervisors Dr Jeffrey Kotzen and Dr Owen Terreblanche for their support and input into this research report.

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Nomenclature

ALK	Anaplastic Lymphoma Kinase
AVM	Arteriovenous Malformation
BED	Biologically effective dose
Cho	Choline
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CNS	Central Nervous System
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
Gy	Gray
FDG	18F fluorodeoxyglucose
KPS	Karnofsky performance scale
IMRT	Intensity Modulated Radiation Therapy
IT	Immunotherapy
IQR	Interquartile range
NCCTG	North Central Cancer Treatment Group
MRI	Magnetic Resonance Imaging
NAA	N-Acetyl-L-aspartate
NSCLC	Non-Small Cell Lung Cancer
PET	Positron Emission Tomography
PSR	Percentage of signal recovery
PTV	Planning Target Volume
QUANTEC	Quantitative Analysis of Normal Tissue Effects in the Clinic
RN	Radiation Necrosis
RTOG	Radiation Therapy Oncology Group
SD	Standard Deviation
SPECT	Single Photon Emission Computed Tomography
SRS	Stereotactic radiosurgery

SRT	Stereotactic radiation therapy
VEGF	Vascular endothelial growth factor
VMAT	Volume Modulated Arc Therapy
WBRT	Whole brain radiation therapy
WDGMC	Wits Donald Gordon Medical Centre
3DCRT	3D conformal radiation therapy

CHAPTER 1

Introduction and literature review

Background

Radiotherapy is an important aspect of cancer management and is utilised in more than half of all cancer patients (1). In the past few decades, we have seen increasing advances in surgical techniques, chemotherapy, and radiotherapy treatment of cancer patients, with patients surviving longer and presenting with late side effects of treatment. Monitoring late side effects of radiation therapy is an important aspect of good clinical practice and guides both local practice as well as contributes to the body of knowledge around caring for cancer patients.

Epidemiologists anticipate a significant increase in cancer rates in developing countries, with a projected 78% increase of cancer in South Africa by 2030 (2). In terms of Brain and CNS tumours the South African National Cancer Registry 2014 noted 176 new cases of brain and central nervous system (CNS) tumours, with an age standardised incidence rate of 0.68 per 100 000 (World standard population) (3). With an increase in cancer anticipated in South Africa it is imperative to monitor the effects of radiation treatment to provide safe and effective treatment.

It is important to accurately assess and record the morbidity of radiation treatment as this is a critical component of the assessment of treatment regimens (4). Perez and Brady noted in terms of brain radiation that the "end points for assessing long term radiation induced complications are typically radiation necrosis or asymptomatic radiologic changes as seen on serial magnetic resonance imaging (MRI)scans" (4).

Cerebral radiation necrosis (RN) is a known late side effect of radiation to the brain. This retrospective study reviews radiation necrosis in patients who received partial brain radiation over a three-year period, namely from 2014-2017 at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Wits Donald Gordon Medical Centre (WDGMC). This study reviews the late side effect of cerebral RN at these institutions and aims to inform local practice.

Literature review

Cerebral radiation necrosis as a late complication of treatment is a more severe and permanent form of white matter change (5). The cause of RN has several theories which include radiation induced glial or neuronal injury, vascular damage and an inflammatory response (6).

Demyelination and vascular abnormalities are the primary histological changes seen in radiation-induced CNS injury (7). Murovic et al noted that "compared with tumour cells, cerebral RN contains cells with fewer mitotic figures and a lower nucleus-to-cytoplasmic ratio" (6). Chao et al explained that vascular damage starts the process of RN (8). Rahmathulla et al suggested that there are two dominant theories as to the cause of RN, namely the vascular injury theory and the glial injury theory and note that RN is probably caused by both (9).

Clinically, RN in the brain can present with seizures, signs and symptoms of raised intracranial pressure, cognitive dysfunction or focal neurological deficits (6). Feng et al discussed that the most commonly seen symptoms with radiation necrosis in their review was "weakness (44%), headache (30%), and language problems (30%), with an average Karnofsky performance scale (KPS) score of 84.1" (5). Similarly, Rahmathulla et al also found the most frequent clinical presentations of RN to be headaches, seizures, confusion or lethargy (9).

Accurately determining the incidence of RN is problematic, given the difficulty in precisely diagnosing it (8). Murovic & Chang (6) noted an incidence of 1-24% for cerebral radiation necrosis following radiation but comment that it can be increased 3 times with concurrent chemotherapy (6). Feng et al noted an incidence of 2-24% for RN following radiation for glioblastomas and 25% after radiation for metastases (5). Ruben et al investigated the incidence of RN in their centre looking at a total of 439 patients with glioma and found an incidence of 4.9% (10). When their analysis was limited to patients who received a BED (biologically effective dose) of more than $85.5Gy_2$ (45Gy in 25 fractions), the prevalence of radiation necrosis increased to 6% (10). Ruben et al further noted that studies they looked at reported a 5% risk within 5 years after a total dose of 50 Gy using standard fractionation whereas treatment with total doses below 50 Gy had a very low incidence of radiation necrosis (10). Feng et al found that at total doses > 62 Gy the risk for RN doubles and at

doses > 78Gy the risk quadruples (5). Hong et al noted a 5% risk for RN after cranial radiation with standard fractionation at 55-60Gy (BED 91.7-100Gy_3) (11).

The incidence of RN is a function of dose. Chao et al reviewed a study that found that with " low dose radiation versus high dose radiation in the treatment of low grade gliomas the incidence of grade 3-5 toxicity, including radiation necrosis, was 2.5% for 5040 cGy and 5% for 6480 cGy" (8). Chao et al noted that white matter necrosis is a function of cumulative dose and duration of exposure (8). The North Central Cancer Treatment Group (NCCTG)/Radiation Therapy Oncology Group (RTOG) /Eastern Cooperative Oncology Group (ECOG) intergroup prospective trial of high- vs. low-dose radiotherapy for low-grade glioma reported on grade 3-5 RN and found an incidence of 6% in the 64.8Gy and 1% in the 50.4Gy arms (10).

Lawrence et al reviewed diverse fractionation schemes by using the biologically effective dose (BED) to compare them (12). It showed an incidence of RN of 5% at a BED of 120 Gy_3 (range 100 - 140 Gy_3), corresponding to 72 Gy in 2Gy per fraction; and an incidence of 10% at a BED of 150 Gy_3 (range 140- 170 Gy_3), corresponding to 90 Gy, in 2 Gy per fraction. They also noted that the brain is sensitive for fractionation sizes greater than 2Gy as well as very sensitive to twice daily radiation. They concluded that the dose for a 5% risk of RN at 5 years of the partial brain for normally fractionated RT is 72 Gy (range, 60– 84) (12). Kondziolka et al noted that the alpha-beta ration of the normal brain has been estimated at ~2 (13). Fowler noted that the α/β ratio for late normal tissue reactions in the CNS is 1.8-2.2 (14). In this study an α/β ratio for 2 was used for the brain to calculate the BED of radiation necrosis as a late tissue reaction.

Different beam qualities may influence the incidence of cerebral RN. Both proton and neutron beams may also result in radiation necrosis. Hong et al noted that cerebral RN can develop as a result of neutron beam radiation for salivary gland tumours and described a case where RN developed at 30 months post neutron radiotherapy for recurrent parotid adenocarcinoma and suggests continued monitoring for RN until at least this time frame post neutron beam radiation (11). Vernimmen et al showed that hypofractionated proton beam therapy has an advantage over photon radiosurgery for large arteriovenous malformations (AVMs) due to its favourable dose distribution in the brain (15). This study only evaluated the incidence of RN following photon beam radiation therapy.

Whole brain radiation therapy (WBRT) is typically given as a palliative treatment for patients with brain metastases, and the doses used for palliative regimens do not usually exceed 50 Gy in 2 Gy fractions (BED_3 of 83.3Gy), which has been identified as the threshold below which radiation necrosis is very rare (10). RN is uncommon in WBRT due to the lower total dose given (16). Typical radiation prescriptions for WBRT are 30 Gy in 10 fractions, or 20Gy in 5 fractions, with a BED_3 of 60Gy and 46.7Gy respectively for an alpha-beta ratio of 3. For the purposes of this study patients who received WBRT only were excluded.

Looking at RN in stereotactic radiation therapy (SRT) Chao et al noted that the consistent factor was the volume of 10 millilitre or more receiving 10-12 Gy in terms of RN in radiosurgery, and Lawrence et al also noted that the volume of brain receiving 12 Gy correlates with both the incidence of RN as well as asymptomatic radiologic changes (8, 12). Hong et al reported an incidence of cerebral RN after SRT higher than for conventional cranial irradiation with 2-year post-SRT RN rates between 11% and 50% (11). Burger et al noted that SRT and hypofractionated radiotherapy have a higher risk of late normal tissue complications and precaution must be taken to safeguard normal tissues (17). They also noted that the risk of RN in patients with brain metastases treated with SRT can be estimated on the volume of normal brain receiving 12 Gy (V12) and note the "reference RN risks at 1 year for V12 <3.3 cm3 and 3.3-5.9 cm3 as 0% and 16% respectively" (17). Vellayappan et al noted that for patients receiving SRT the risk of RN is increased when V10 > 10.5 cm3 or V12 > 7.9 cm3, with all patients having had prior radiation (18). They proposed that fractionated SRT may mitigate the risk of RN, but robust data is still needed (18). Kondziolka et al noted that salvage SRT can be used after WBRT or previous SRT but cautioned that the use of rescue SRT should be weighed against the possible adverse effects of retreatment, including RN (13). Lawrence et al noted that for radiosurgery the dose, volume and region irradiated affects the incidence of radiation necrosis (12). The RTOG conducted a dose-escalation study that sought to define the maximal dose for targets of different sizes in terms of radiosurgery; these patients had all previously undergone whole brain irradiation (12). The RTOG found that the "maximal tolerated dose for targets 31–40 mm in diameter was 15 Gy, and for targets 21–30 mm in diameter, it was 18 Gy. For targets <20 mm, the maximal tolerated dose was 24 Gy" (12, 18). The Planning Target Volume (PTV) margin also affects the incidence of RN after SRT. Vellayappan et al noted that a randomised trial compared the

PTV margins on the GTV and found that while local control was comparable in the 1mm and 3mm groups, the 3mm group had a higher incidence of biopsy-proven RN (12.5 vs. 2.5%, p = 0.1)" (18).

The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) review published in 2010 provides a summary of available data to provide normal tissue outcome estimates in a clinically useful manner (19). The QUANTEC data for radiation necrosis is summarised as follow in Table 1 below:

Table 1: QUANTEC data for symptomatic radiation necrosis of the brain

Organ	*Volume segmented*	*Irradiation type (partial organ unless otherwise stated)*	*Endpoint*	*Dose (Gy) or dose/volume parameters*	*Rate (%)*	*Notes on dose/volume parameters*
Brain	Whole organ	3D-CRT	Symptomatic necrosis	Dmax <60	<3	Data at 72 and 90 Gy, extrapolated from BED models
Brain	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 72	5	
Brain	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 90	10	
Brain	Whole organ	SRS (single fraction)	Symptomatic necrosis	V12 <5–10 cc	<20	Rapid rise when V12 > 5–10 cc

RN in the brain may be difficult to differentiate from tumour recurrence on imaging. Magnetic resonance imaging (MRI) changes that appear as an enlarging enhancing lesion can look very similar to tumour progression, making an exact diagnosis in the absence of a definitive biopsy difficult (5). To complicate diagnosis further, RN can occur concomitantly with tumour recurrence (5). There is currently no gold standard to diagnose RN on MRI or

other imaging modalities (16). There are however typical features of RN on MRI that are commonly used by radiologists to diagnose RN and to differentiate it from tumour recurrence: RN occurs most frequently at the site of maximum radiation dose, in and around the tumour bed (20). Cerebral blood volume is considered to be higher in tumour recurrence and lower in radiation necrosis (8). Murovic & Chang noted that hyperperfusion is seen with cases of tumour recurrence, but RN shows reduced relative cerebral blood flow due to occlusive vasculopathy which causes ischemia-related changes (6). Vidiri et al similarly found that perfusion parameters may help in distinguishing tumour recurrence from RN, since tumours generally show an increased cerebral blood volume (CBV) while this parameter is relatively low in RN (21).

Na et al noted that RN shows "variable, markedly hypointense foci with low relative cerebral blood volume and high apparent diffusion coefficient map on diffusion-weighted and perfusion MRI" (16). RN can present as necrotic lesions with poorly defined blurred margins, peri-lesional oedema and dispersed calcifications (22). Other imaging features of radiation necrosis on MRI is to look for a "swiss cheese" or "soap bubble" appearance (23). According to Fatterpekar et al this appearance "results from diffuse necrosis affecting the white matter and adjacent cortex and is seen as a diffusely enhancing lesion with intermixed foci of necrosis" (20). On MRI RN can appear as areas of cystic lesions with higher signal intensity in white matter on T2-weighted images, which often extend beyond the radiation portals; minimal local mass effect for the size of the lesion is also characteristic (24). Shah et al found that it is useful to use the lesion quotient and the percentage of signal recovery (PSR) in discerning between RN and tumour recurrence (25).

Feng et al discussed using different imaging modalities including MR spectroscopy and positron emission tomography (PET) in terms of differentiating between RN and tumour relapse and found value in combining modalities (5). Chen et al noted that functional FDG PET may be useful by measuring the uptake of 18F- fluorodeoxyglucose (FDG) (26). Tumours are considered to be usually hypermetabolic and therefore have a higher uptake of FDG, while RN is hypometabolic (26). PET and SPECT (Single Photon Emission Computed Tomography) were both found to be of some use to distinguish radiation necrosis and tumour progression/recurrence, but studies showed mixed results of either's value (8).

Some studies have researched the diagnostic value of diffusion MRI with quantitative apparent diffusion coefficient (ADC) measurements in distinguishing glioma recurrence from RN, but the findings have been incongruent and found it has moderate diagnostic performance in discerning glioma relapse from RN (23).

MR spectroscopy, while not widely available, can also improve diagnostic capabilities in brain tumour evaluation (27). During MR spectroscopy, higher choline indicates increased cellularity, as seen in tumours, and lower choline indicates RN (27). Similarly, Jansen van Rensburg found that the MRI follow up of glioblastoma multiforme can be enhanced by "MR spectroscopy where there is typically a reduction in NAA (N-acetylaspartate) corresponding to a decreased density of neuronal cells and increased choline as a result of higher cell membrane turnover" (28).

The only locally published study found about RN looked at 2 patients treated at CMJAH and evaluated the appearance of RN on computed tomography (CT) in 1978. It found that the appearance of RN in the 2 patients was indistinguishable on CT from that of tumour (residual in one and recurrent in another) and they concluded that CT scanning will not help in distinguishing RN from tumour (29).

There is currently no definitive standard to noninvasively diagnose RN (8). The gold standard to diagnose RN is histopathology (30). Lawrence et al found though that a biopsy was rarely performed to accurately diagnose RN (12). The working definition used by most studies they looked at for the incidence of radiation necrosis, defined RN as new symptoms with suggestive radiologic findings. For the purpose of this study, the radiologist opinion on MRI, considering typical features of RN on MRI as identified in the literature, was used to identify RN.

Feng et al showed that the average time to onset of RN is 1 year in patients who received a total radiation dose of greater than 50 Gray (Gy), and 80% of cases occur within 3 years (5). They further noted that the time to onset can differ from a few weeks to a decade after radiation. Murovic and Chang noted that cases of RN occur 3-12 months after chemoradiation, though can be up to 2 years (6). Similarly, Ruben et al found that the shortest latent period from radiation to the diagnosis of cerebral RN was 2.1 months and the mean latent time was 11.6 months (10). Shah et al also noted that the probability that RN is the

reason for the imaging abnormality also depends on the time since radiation (25). They found that RN is usually seen from 2-32 months after RT, with 85% of cases occurring within 2 years and that a new or worsening aberration starting 3 years after RT is very unlikely to be pure RN (25). Hong et al noted that though RN was reported as late as 47 years after RT for a pilocytic astrocytoma, most of the cases of cerebral RN after radiation of an intracranial lesion occur between 6 and 12 months (11).

Risk factors for RN include dose, fraction size, treatment duration, volume treated, chemotherapy, previous radiotherapy and male sex (8). Lawrence et al also noted that radiation dose, fraction size and volume are the major risk factors for radiation necrosis, and comments that additional risk factors could be chemotherapy, lower conformality index, shorter treatment time, older age and diabetes mellitus (12). Rahmathulla et al noted that though radiation induced injury can ensue with doses as low as 50Gy the radiation dose is directly proportionate to the risk of brain injury (9). The NCCTG/RTOG/ECOG intergroup prospective trial of high- vs. low-dose radiotherapy for low-grade glioma found that accelerated radiotherapy carries a high risk for cerebral radionecrosis (10). Risk factors for RN in SRT are volume treated, prior radiation exposure, use of chemotherapy, location of lesion, histology, planning target volume margin and intrinsic radiosensitivity (18). Vellayappan et al noted that the risk of RN with SRT in patients who had previous SRT to the same lesions was 20% at 1 year, 4% with previous WBRT, 8% when concurrent WBRT is used and 3% when no previous radiation received (18). Jimenez et al reviewed 156 patients who received SRT and found that all five patients who developed RN had previous radiation: either WBRT, SRT or both (31).

Certain histologies may increase the risk for RN for example in a NSCLC cohort, lung adenocarcinoma histology had an increased risk for RN versus other histologies (32). Renal carcinoma, lung adenocarcinoma, HER2-amplied breast cancer, and BRAF V600 wild-type melanoma seem to have an increased risk for RN (18). Furthermore, Loganadane et al noted that in NSCLC patients, both epidermal growth factor receptor (EGFR) mutated or anaplastic lymphoma kinase (ALK) positive patients on tyrosine kinase inhibitors had higher incidence rates of RN (32).

Chemotherapy resulted in a 4 times higher risk for cerebral RN even after adjusting for BED or survival in the NCCTG/RTOG/ECOG intergroup prospective trial (10). Chemotherapy

given in addition to radiation as a risk factor to exacerbate the risk of brain injury was first reported in children who received irradiation for leukaemia (9). Vellayappan et al noted that the use of capecitabine within 1 month of SRT seemed to increase the risk of RN (18). Similarly, pemetrexed given before or after SRT for brain metastases in non-small cell lung carcinoma (NSCLC) patients increased the risk for radiographic RN but not for symptomatic RN, with a higher trend for RN in those who received pemetrexed before SRT (33). Targeted therapy such as alectinib in NSCLC patients may also increase the risk for cerebral RN (32, 34). Immunotherapy (IT) appears to increase the possibility of RN as well. In a series by Skrepnik et al he noted that more patients who received IT developed RN (12/63, 19%) than in the control group (4/49, 8%) but it was not statistically significant (35). Vellayappan et al found that location also influenced RN and suggested that the frontal lobe seems to have the highest risk for RN, with the brainstem less so (18).

Ruben et al found that giving corticosteroids during radiation had no effect on the development of cerebral RN on their patients (10). Although they expected diabetes and hypertension to enhance the vasculopathy and therefore increase radiation necrosis they found neither were related to RN in their study (10). Shah et al also did not find that the presence of hypertension or diabetes affected the likelihood of RN (25).

It is important to diagnose RN as treatment may improve symptoms related to radiation necrosis. Radiation necrosis is associated with a higher expression of vascular endothelial growth factor (VEGF) (36). Bevacizumab (Avastin) is an anti-VEGF antibody that is given to treat cerebral RN (6, 37). The mechanism of improvement of RN is likely the "result of a relative normalization of the blood– brain barrier attained by decreasing the levels of VEGF through the use of bevacizumab" (38). Boothe et al found improvement in all but one patient with RN who were treated with bevacizumab (39). In another study all the patients receiving bevacizumab upfront for radiation necrosis and all the patients who were changed to bevacizumab improved both on MRI and in terms of neurological symptoms (40). Anti-VEGF treatment is not effective though as prevention of RN (37). Other treatments that can be considered to treat cerebral RN are cryoablation, high frequency ultrasound, radiofrequency ablation, and laser interstitial thermal therapy (LITT) (6). It is worth noting that RN is not always a progressive process and some patients who are asymptomatic can be observed if the lesion is small (8). Other treatment options noted by Chao et al include

steroids if there is significant swelling, resection especially if diagnosis is unclear, anticoagulants such as heparin and warfarin; pentoxyifylline and Vitamin E, and hyperbaric oxygen (8). Hyperbaric oxygen (HBO) has stronger evidence to be used as a prophylaxis to prevent rather than to treat RN (41). Over the past few years there are however more treatment options for RN, particularly with bevacizumab having become available. Identifying patients with RN accurately and treating these patients early may improve the morbidity of radiation necrosis (8).

Reviewing the alpha beta ratio for an isoeffect is helpful to define the dose for tumour control while minimizing normal tissue toxicity. Kondziolka et al noted that "the alpha beta ratio (a/b ratio) is based on preclinical and clinical data and is 2 for tissue in the CNS, 3 for late responding tissues, and 10 for early responding tissues" (13). Reciprocal dose plots can be prepared for isoeffective radiation treatments and Kocher et al noted that it is based on the finding that the linear-quadratic law "allows for calculation of α/β if the effect (E) is constant (isoeffective schemes) (42). The reciprocal dose plot results in a linear function with y-axis intercept at α/E and slope β/E, from which the alpha beta can be calculated" (42). Late developing radiation injury like brain necrosis tend to have values of the alpha beta ratio in the range of 1–7 Gy (43).

The aim of this study is to evaluate the incidence of RN in patients who received partial brain radiation therapy between 2014-2017, noting the time to onset of radiation necrosis and factors such as total dose, fractionation, volume treated, chemotherapy and sex of patient.

A search was conducted of different databases looking for South African studies that evaluated the incidence of cerebral radiation necrosis following brain radiation. A search of the databases of the University of the Witwatersrand, ClinicalKey and PubMed yielded no results. Searching Science Direct, one relevant article was found detailing proton beam stereotactic radiation of AVMs in South Africa that noted late effects on the brain following proton SRT (15). A Google search that found 3 South African articles that noted radiation necrosis in the text were: one of the same institution as the author dating from 1978 that looked at 2 cases of RN and the ability of computed tomography to identify RN, a second article that looked at different imaging of glioblastoma multiforme including RN (28), as well as a third that reviewed hypofractionated radiation therapy for acoustic neuromas (17).

No articles could be found that reviewed the incidence of radiation necrosis following brain radiation in any South African institutions.

This study therefore fulfils a need both institutionally and nationally to review the incidence of radiation necrosis following brain radiation.

Study Aim and Objectives

Study aim:

Evaluating cerebral radiation necrosis in patients who received partial brain radiation therapy at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Wits Donald Gordon Medical Centre (WDGMC) between 2014-2017.

Study objectives:

The objectives of this study are:

1. To determine the incidence of radiation necrosis in patients who received partial brain radiation therapy at CMJAH and WDGMC between 2014 and 2017.

2. To evaluate patient and clinical factors that may be associated with developing cerebral radiation necrosis on MRI.

CHAPTER 2

Methodology

Research Question

1. What is the incidence of radiation necrosis in patients who received partial brain radiation therapy at CMJAH and WDGMC between 2014 and 2017?

2. What are the patient and clinical factors that may be associated with developing cerebral radiation necrosis on MRI?

Research Design

- Retrospective patient record review
- Patients were stratified by the type of external beam radiation therapy received namely 3DCRT, VMAT, SRT.
- The retrospective file review evaluated post radiation MRI results for radiation necrosis noted in the MRI radiologist report.

Materials and Methods

This retrospective file review was conducted using a data collection sheet to collect data from the files. The data collection sheet questions were derived from the literature review in order to answer the research questions. Each file was reviewed to collect the answers to the questions on the data collection sheet. In some of the WDGMC files the volume treated was not available in the patient files for those patients who had post RT MRI's, and this information was obtained from the computerised radiation planning system with the help of a WDGMC radiation therapist working with the system. All information required was available in the CMJAH files. See Appendix A for a copy of the data collection sheet.

Sample

- The study included all patients who received partial radiation to the brain at CMJAH in the period January 2014- July 2017 as well as patients who

received partial radiation to the brain at WDGMC in the period January 2014-July 2017 who were treated by specialists who agreed to participate in the study.

- Inclusion criteria:
  - Patients who received partial brain radiation during the period Jan 2014 - Jul 2017
  - Patients who had partial brain radiation using either 3D conformal radiation (3DCRT)/ Volume Modulated Arc Therapy (VMAT) / Stereotactic radiation therapy (SRT)
- Exclusion criteria:
  - Patients who received only whole brain radiation
  - Patients who received only cranio-spinal radiation with no brain boost
  - Patients who did not have follow up imaging in the form of post radiation MRI to diagnose radiation necrosis
- A cross sectional study using the dates of January 2014 to July 2017 as a convenience sampling method was used. January 2014 was used as the starting date of the cross-sectional study as the WDGMC radiation unit started in 2014. The end date of July 2017 was used for the study period as this would give a year of follow up until July 2018, 12 months being the average time to radiation necrosis (10).
- The estimated sample size was calculated for a 95% confidence level and 5% level of precision with an expected incidence in the population of 5% radiation necrosis (10, 11). To estimate the sample size the formula for a cross sectional study with a qualitative variable (RN yes or no) was used:

$$n = \frac{(Z\alpha_{/2})^2 \times P(1-P)}{d^2}$$

Where n is the sample size, Z is the statistic corresponding to level of confidence (at 5% type 1 error P<0.05 it is 1.96) (44), P is expected prevalence (that can be obtained from previous studies or a pilot study conducted by the researchers), and d is the precision (corresponding to effect size) (45). In this study an expected prevalence of 5% was used (12). Using this formula, the estimated sample size needed was 72 patients. The final number of patients included in the sample was 80 patients.

- Population size: The initial population size was estimated based on numbers obtained from the list of patients who were planned for partial brain radiation at CMJAH and WDGMC to a total of 193 patients. On reviewing the list, it was found that some patients did not start or complete treatment or were changed to palliative courses. This left a pool of 158 patients who completed partial brain radiation at CMJAH and WDGMC during the study period of January 2014- July 2017 out of which the sample could then be drawn of patients who had a post radiation follow up MRI.

The file of each of the 158 patients was reviewed to determine if patients had follow up MRIs done. The radiology units that patients attended were contacted to determine if a follow up MRI was done if a report was not found in the file.

Figure 1 below shows that the sample size of patients that fulfilled all the inclusion and exclusion criteria, from the patient pool of 158 patients was 80 patients.

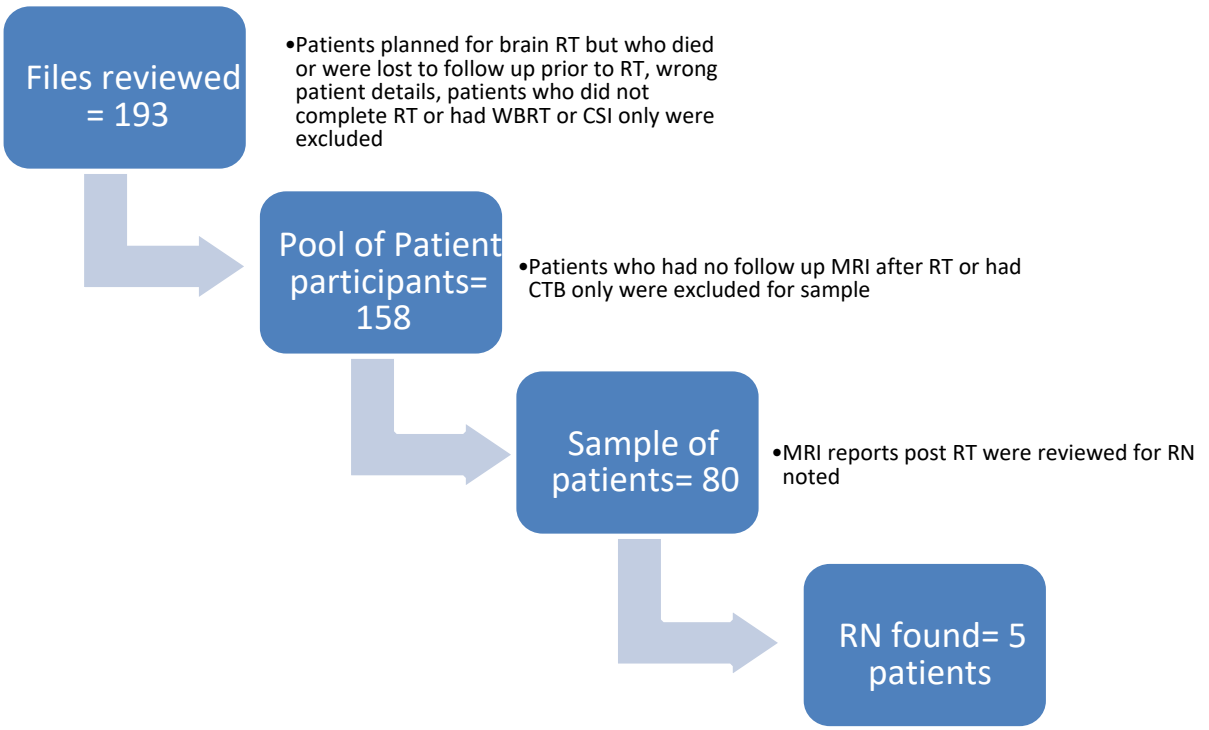

Figure 1: Sample selection process from files reviewed to final sample

Site of study

- Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)
- Wits Donald Gordon Medical Centre (WDGMC)

Data Collection

Retrospective data collection. Data was collected at each site in a retrospective file review and transcribed onto paper data collection sheets (see Appendix A) from each file by the author. The anonymised data was collated on an excel spread sheet.

Data Analysis

The excel spread sheet with the anonymised patient-data was imported into the statistical software program STATA software version 14 and analysis was done. Data cleaning processes included checking for duplicates, missing values, recoding and categorizing variables. This was a quality assurance process.

For categorical data the chi square test was used to give proportion and percentages. Proportions and percentages gave a summary of categorical variables. The differences in categorical variables were analysed using the chi-squared test or fisher exact test where values were less than 10. The mean and SD (standard deviation) or median and IQR (interquartile range) were used for continuous variables. Comparison of the mean was done by the student t-test. Logistical regression was considered to evaluate if any patient and clinical factors were associated with developing RN on MRI but due to the low number of patients who developed RN it could not be done. All statistical test analyses were two-sided z-test and p values <0.05 were statistically significant.

A Kaplan Meier curve was used for survival estimates considering the time in months post radiation to the event of diagnosis of RN.

CHAPTER 3

Results

Incidence of RN

From the sample of the 80 patients that had follow up MRIs done there were 5 patients that developed RN in the study period, with an incidence of 6.25 % (5/80).

The BED_3 and the BED_2 was calculated for the total doses received by each patient using the linear quadratic formula. The literature review found evaluations of RN using BED_3 in some studies and BED_2 in others (10, 12). Looking at the sample of 80 patients who received a $BED_2 \geq 85.5Gy_2$ there were 77 patients. The 5 patients identified with RN were within this group of 77 patients with $BED_2 \geq 85.5Gy_2$, with an incidence of 6.49% (5/77). Looking at the sample of 80 patients, patients with a BED_3 83.3Gy (corresponding to 50Gy in 2Gy per fraction) – $99Gy_3$ there were 54 patients, out of which 2 developed RN, with an incidence of 3.7% (2/54). In the group with a BED_3 of $100\text{-}140Gy_3$ there were 13 patients, out of which 3 had developed RN, with an incidence of 23% (3/13). In the group $140\text{-}233\ Gy_3$ there were 6 patients who had all received SRT as the technique, none of whom developed RN.
The incidence of RN by institution was 9.38% (3/32) for CMJAH and 4.16% (2/48) for WDGMC. Looking at technique, 3DCRT and VMAT were grouped together and SRT was reviewed separately since the treatment dose, fractionation and radiobiology of SRT is different to that of the conventional fractionation of 1.8-2 Gy per fraction employed in 3DCRT and VMAT used in this review. By technique, the incidence of RN was 6.56% (4/61) for 3DCRT +VMAT, and 5.26% (1/19) for SRT.

The incidence rate for RN in this study was 5.11%. The incidence rate is the number of new cases of RN during the specified period (Jan 2014- Jul 2017) divided by the time each person was observed (until disease (RN), death, lost to follow up or end of time period under observation), totalled for all persons. In epidemiology, incidence rates are often presented per 1,000 person-years. For this study, the incidence rate of RN was 51.15 per 1000 person years. The incidence rate for female patients was 51.39 per 1000 person years, while the incidence rate for males was 50.99 per 1000 person years.

Comparing the incidence rates at various time points in 1-year intervals during the study period the following is shown in table 2:

Table 2: Incidence rates of RN at various time points

Cohort year	Person-time in years	Failures (RN)	Rate per 1000 person years	[95% Conf. Interval]
(0 - 1] |	56.33	4	71.01	26.65- 189.19
(1 - 2] |	28.00	1	35.71	5.03 253.54
(2 - 3] |	10.75	0	0.00	-
> 3 |	2.67	0	0.00	-

Kaplan-Meier survival estimates:

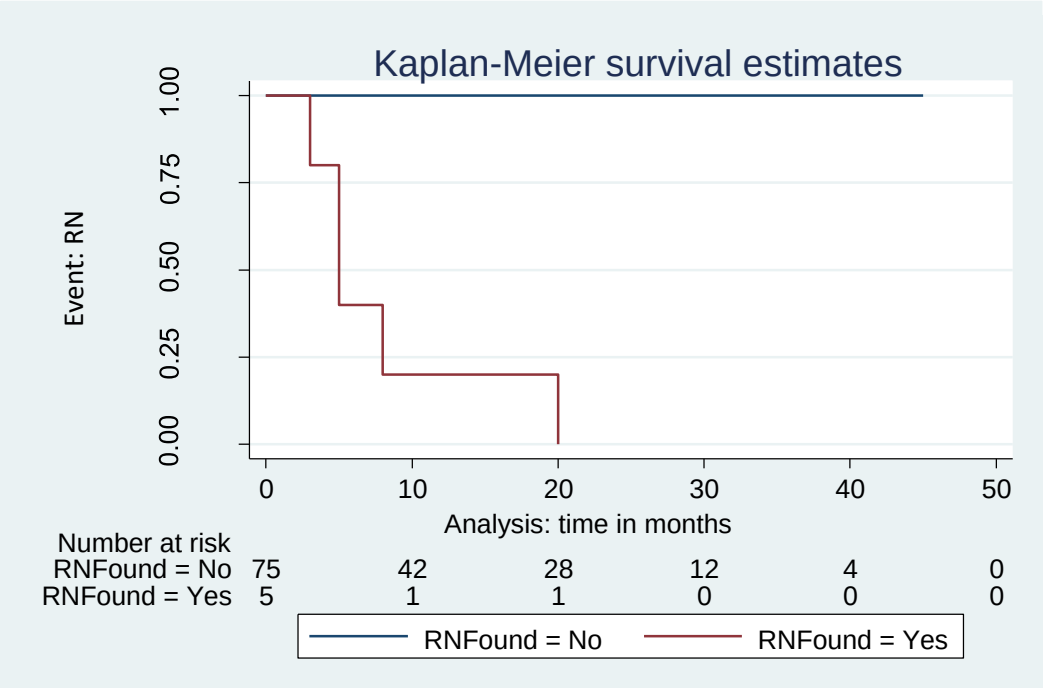

Figure 2: Kaplan Meier survival estimates for RN found

Total (80)	RN (No)	RN (Yes)
Median months 11.5	12	5
Min months 1	1	3
Max months 45	45	20

The Kaplan-Meier survival estimates looked at the time in months post radiation to the event of diagnosis of RN. Looking at the figure 2 one can see that all patients with RN were diagnosed by 20 months. The earliest that RN was found on post RT MRI was 3 months, and the median time was 5 months, with an average time of 8.2 months.

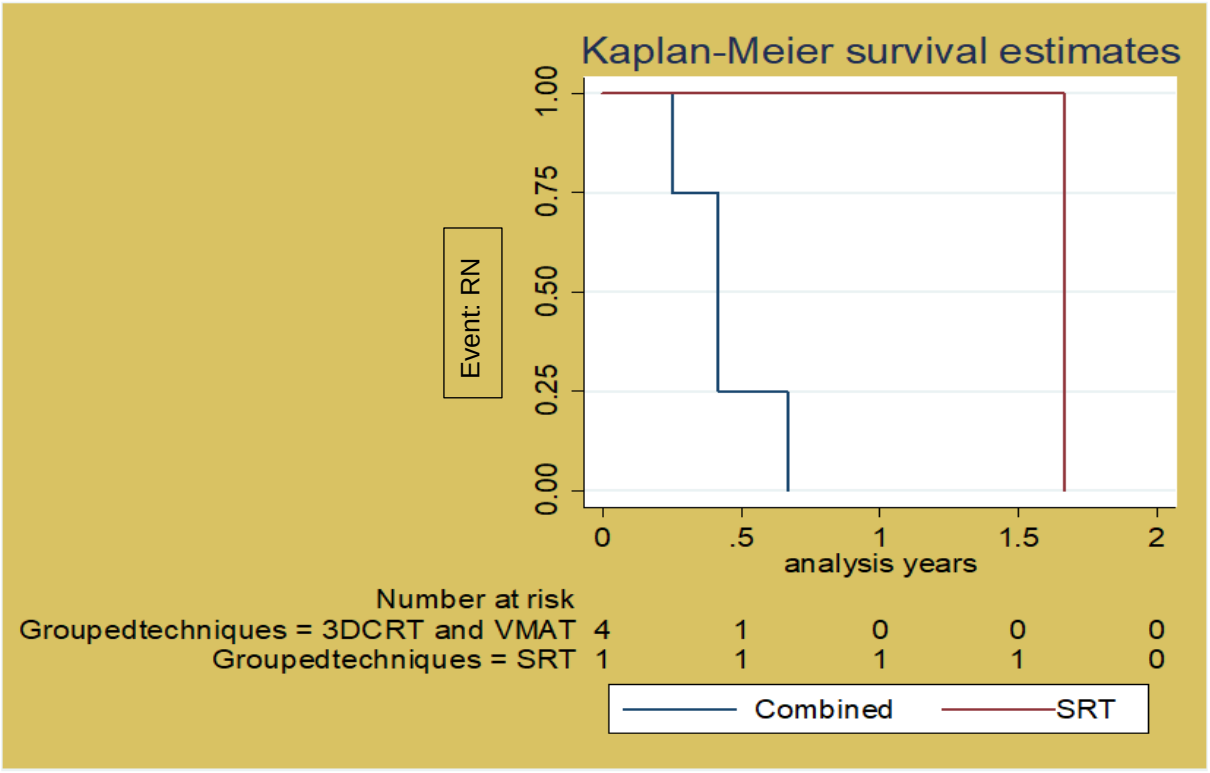

Figure 3: Kaplan Meier survival estimates for RN found per technique

Looking at the Kaplan Meier survival estimates for RT technique in Figure 3 all the RN cases that received 3DCRT and VMAT presented before one year, while the RN case that received SRT only presented at 20 months post RT. Since 3DCRT and VMAT are similar in dose fractionation, volumes treated and duration of treatment these techniques were grouped for this sub-analysis. SRT has different treatment parameters to 3DCRT and VMAT with generally small volumes, high doses and short fractionation schedules and was analysed separately. The incident rate for the combined group of 3DCRT and VMAT is 48 per 1000 person years, while the incident rate for SRT is 62 per 1000 person years, taking into account the number of new cases of RN (1) divided by the sum of the person-years under observation. The incidence for 3DCRT and VMAT (6.56%, 4/61) versus SRT (5.26%, 1/19) as a proportion differs from the incidence *rate* for 3DCRT and VMAT versus SRT due to the

denominator of totalled person-years under observation being dissimilar for the different techniques.

Characteristics of patients with post RT MRI by RN found

In terms of post RT follow up MRIs, only 51% of patients in the patient pool had one or more MRI's done as part of their follow up, while 17% only had a CT brain done (CTB) as follow up, which is not used to diagnose RN, while 32% had no post RT follow up imaging. In terms of the two institutions, there were 84 patient files reviewed at CMJAH, and 74 files at WDGMC to establish which patients could be included in the sample. Of these, 32/ 84 (38%) CMJAH patients and 48/74 (64%) of the WDGMC patients had follow up MRIs done that could be included in the sample. In the population pool there were 84 females and 74 males, but in the sample of patients who had post RT MRIs there were 47 males and 33 females.

Looking at the 80 patients that had follow up post RT MRIs, the population tested for RN, the following patient, clinical and radiation characteristics were found:

Table 3: Patient characteristics and association with RN

Variable	Total	RN Absent	RN Present	P value
	(N=80)	(N=75)	(N=5)	
Sex -- no (%)				
Male	47 (58.8)	44 (58.7)	3 (60.0)	1.000
Female	33 (41.3)	31 (41.3)	2 (40.0)	
Age -- yr				
Mean (SD)	40.7(±23.0)	40.6(±23.5)	42.4(±14.6)	0.866
Median (Range)	44 (2-79)	45 (2-79)	36 (27-58)	
Age category -- no (%)				
≤17	19 (23.8)	19 (25.3)	-	0.097
18-30	8 (10.0)	7 (9.3)	1 (20.0)	
31-40	10 (12.5)	8 (10.7)	2 (40.0)	
>40	43 (53.8)	41 (54.7)	2 (40.0)	
Institution -- no (%)				
CMJAH	32 (40.0)	29 (38.7)	3 (60.0)	0.384
WDGMC	48 (60.0)	46 (61.3)	2 (40.0)	
MRI post RT -- no (%)				
Post	80 (100.0)	75 (100.0)	5 (100.0)	
CTB only	-	-	-	
No post	-	-	-	
Time of first MRI post RT -- median (range)	6 (1-23)	6 (1-23)	5 (2-8)	0.303
Time of last MRI post RT -- median (range)	12 (1-45)	12 (1-45)	13 (3-31)	0.987

Looking at table 3, there were 47 males and 33 females, of which 3 males developed RN (3/47; 6.4%) and 2 females (2/33; 6.1%). In table 3 the median age for all patients was 44 years of age, with patients with RN absent having a median age of 45 (2-79), and those with RN present had a median age of 9 years younger at 36 years (27-58). In table 3 the younger age groups had fewer cases of RN: none of the patients younger than 17 years had RN, the group aged 18-30 had 1 case of RN, while those patients aged 30-40 years and older than 40 years of age had 2 cases of RN per age group.

Of the 80 patients who had follow up MRIs post RT 32 (40%) came from CMJAH and the majority (48 (60%) came from WDGMC. 3 of the patients from CMJAH developed RN (3/32), and 2 from WDGMC (2/48) developed RN.

The median time to the first follow up post RT MRI was 6 months (1-23), and in this sample the median time to the last/latest MRI post RT was 12 months.

Table 4: Clinical characteristics and association with RN

Variable	Total	RN Absent	RN Present	P value
	(N=80)	(N=75)	(N=5)	
Chemotherapy* -- no (%)				
None	42 (52.5)	39 (52.0)	3 (60.0)	1.000
Temozolamide	16 (20.0)	15 (20.0)	1 (20.0)	
Metastatic	12 (15.0)	11 (14.7)	1 (20.0)	
Other	10 (12.5)	10 (13.3)	-	
Targeted therapy/Immunotherapy** no (%)				
None	77 (96.3)	73 (97.3)	4 (80.0)	0.178
Other	3 (3.8)	2 (2.7)	1 (20.0)	
Previous Brain RT -- no (%)				
None	72 (90.0)	67 (89.3)	5 (100.0)	1.000
RT > 50Gy	4 (5.0)	4 (5.3)	-	
WBRT30Gy	4 (5.0)	4 (5.3)	-	
Diagnosis -- no (%)				
Metastatic brain tumour	11 (13.8)	10 (13.3)	1 (20.0)	1.000
Glioblastoma	11 (13.8)	10 (13.3)	1 (20.0)	
Medulloblastoma	9 (11.3)	9 (12.0)	-	
Astrocytoma	13 (16.3)	12 (16.0)	1 (20.0)	
Meningioma	10 (12.5)	9 (12.0)	1 (20.0)	
Ependymoma	4 (5.0)	4 (5.3)	-	
Pituitary Adenoma	5 (6.3)	5 (6.7)	-	

Acoustic neuroma	2 (2.5)	2 (2.7)	-
Craniopharyngioma	3 (3.8)	3 (4.0)	-
PNET	3 (3.8)	3 (4.0)	-
Other gliomas	9 (11.3)	8 (10.7)	1 (20.0)

*In terms of chemotherapy, the groups were "none" – no chemo received, or no chemo recorded in file; "Temozolamide" - concurrent ± post RT temozolamide (of which only the patients at WDGMC received temozolamide as it is not available in CMJAH); "Other" which includes chemotherapy for primary CNS tumours like medulloblastoma but does not include temozolamide, and "Metastatic" which is a grouping for patients who received chemotherapy for cancer other than brain tumours and who developed brain metastases that was treated with partial brain RT.

** In terms of targeted therapy or immunotherapy the use of any targeted therapy such as tyrosine kinase inhibitors, targeted monoclonal antibodies e.g. bevacizumab or immunotherapy such as immune check point inhibitors were recorded

The majority of patients, 42 (52.5%) did not receive chemotherapy, with the other categories being almost evenly divided between temozolamide 16 (20%), other 10 (12.5%) and metastatic 12 (15%). Three patients that developed RN received no chemotherapy, 1 patient received chemotherapy for metastatic cancer and 1 patient received temozolamide. In terms of targeted therapy or immunotherapy there were only 3 out of the 80 patients with recorded treatment of this nature: namely pazopanib for metastatic renal cell cancer, bevacizumab for metastatic lung cancer, bevacizumab for metastatic cervical cancer. No patients in the sample received immunotherapy (e.g. immune check point inhibitors) according to the retrospective file review at the time of the study. Looking at the 5 patients that developed RN in table 4, 1 patient received targeted therapy (pazopanib); the other 4 received none.

Looking at previous brain radiation, in the sample of 80 patients there were 8 patients with prior brain radiation – 4 that had received RT > 50Gy and 4 that had received palliative WBRT 30Gy in 10 fractions previously. None of the patients that developed RN had previous brain radiation.

Considering the diagnosis of the 5 patients in whom RN was found there were one each of the diagnoses of glioblastoma, meningioma, astrocytoma, metastatic brain tumour and other gliomas ("Other gliomas and other primary brain tumours" included patients in whom only a radiological diagnosis was available e.g. brainstem gliomas, and other diagnoses not grouped. The patient in this group who developed RN had a diagnosis of left thalamic glioma.)

Table 5: Radiation characteristics and association with RN

Variable	Total	RN Absent	RN Present	P value
	(N=158)	(N=75)	(N=5)	
Technique -- no (%)				
3DCRT	84 (53.2)	29 (38.7)	3 (60.0)	0.841
VMAT	42 (26.6)	28 (37.3)	1 (20.0)	
SRT	32 (20.3)	18 (24.0)	1 (20.0)	
Total dose -- median (IQR)	54.0 (50.4-59.4)	54.0 (45.0-59.4)	59.4 (54.0-60.0)	0.612
Eqd2ab2gy -- median (IQR)	53.0 (51.3-58.1)	56.4 (51.3-60.0)	60.0 (56.4-60.0)	0.970
Eqd2ab3gy -- median (IQR)	53.6 (51.8-57.0)	53.9 (51.8-58.8)	60.0 (57.0-60.0)	0.970
Bed2gy -- median (IQR)	106.0 (102.6-116.3)	112.9 (102.6-120.0)	120.0 (112.9-120.0)	0.971
Bed3gy -- median (IQR)	89.3 (86.4-95.0)	89.8 (86.4-97.9)	100.0 (95.0-100.0)	0.970
Number of fractions -- median (IQR)	30.0 (28.0-33.0)	30.0 (5.0-33.0)	30.0 (30.0-30.0)	0.914
Dose per fraction -- median (IQR)	1.8 (1.8-2.0)	1.8 (1.8-3.6)	2.0 (1.8-2.0)	0.738
Duration of RT in days -- median (IQR)	45.0 (39.0-49.0)	44.0 (14.0-49.0)	48.0 (41.0-48.0)	0.813
Volume treated (cm3) post MRIs -- median (IQR)	106.5 (21.2-231.2)	106.5 (19.4-216.1)	61.3 (28.5-408.6)	0.287

Evaluating the continuous variables one can see in table 5 that the total dose for those with RN Absent was 54 Gy, while for those with RN Present it was 59.4 Gy (p=0.612). Since the literature refers to both BED_3 and BED_2 in terms of evaluating late CNS reactions, both were determined for the sample group. The BED_2 for those with RN Absent was 112Gy (50-337) while for those with RN Present 120Gy (102-148), (p=0.971). The median BED_3 for those with RN Absent was 89Gy (39-233) and for those with RN Present was 100Gy (86-108) (p=0.970).

Looking at the fractionation the median dose per fraction was lower for those with RN Absent (1.8Gy) than for RN Present (2Gy). The median duration of treatment was longer for RN Present (48 days) than for RN Absent (44 days).

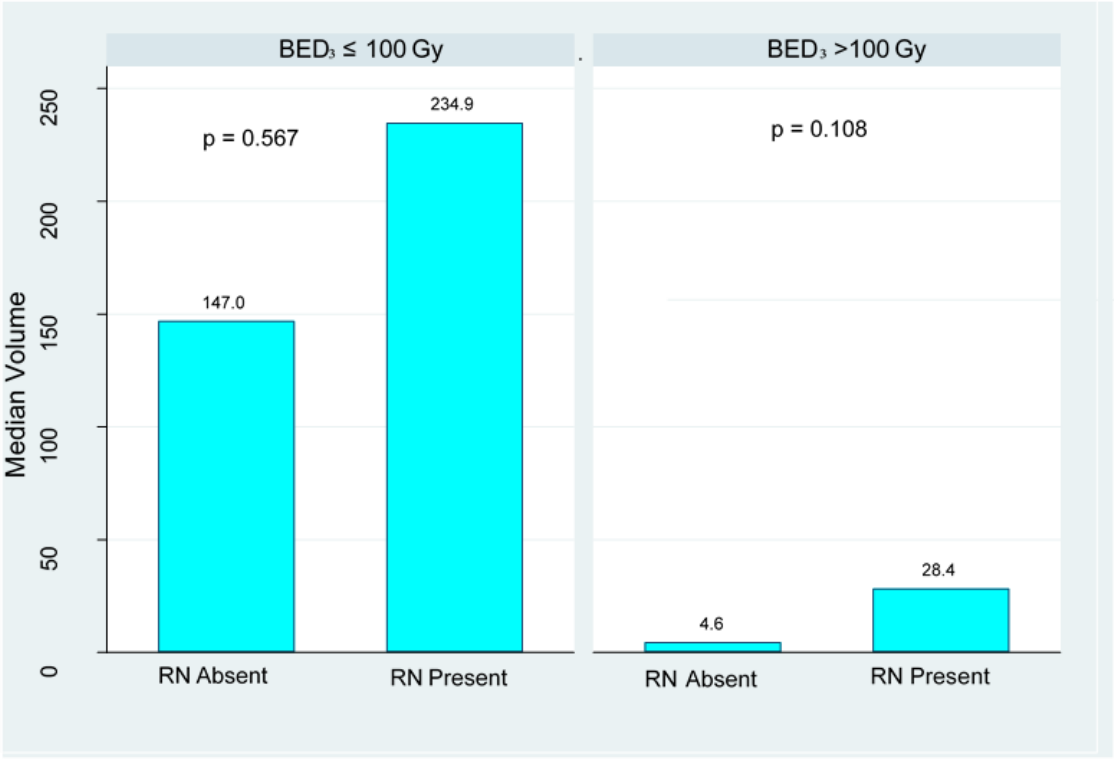

Figure 4: Volume treated by biologically effective dose by radiation necrosis

Looking at figure 4 the median volume treated by BED_3 ≤100Gy_3 or >100Gy_3 there is a trend to a higher median volume treated for both BED_3 ≤100Gy_3 and >100Gy_3 for RN present, though not statistically significant in either BED_3 group.

Characteristics by technique:

From the 48 patients followed up at DGMC, 29 had VMAT and 19 had SRT, while at CMJAH all 32 patients followed up had 3DCRT. Looking at technique and its relation to RN, 3 patients out of 32 that had 3DCRT developed RN, 1 patient had VMAT (1/29) and 1 patient that received SRT (1/19) developed RN.

In terms of diagnosis the four most common diagnosis for 3DCRT/VMAT were Glioblastoma, Astrocytoma, Meningioma and Medulloblastoma. For SRT the five most common diagnosis were Metastatic brain tumour, Pituitary adenoma, Glioblastoma, Acoustic neuroma and Meningioma.

In terms of previous brain radiation, all 4 patients who had prior palliative WBRT in the sample received SRT, as well as 2 patients with previous brain RT to doses >50Gy. In the 3DCRT/VMAT group 2 patients had previous brain radiation to doses > 50Gy and there were no patients with prior WBRT.

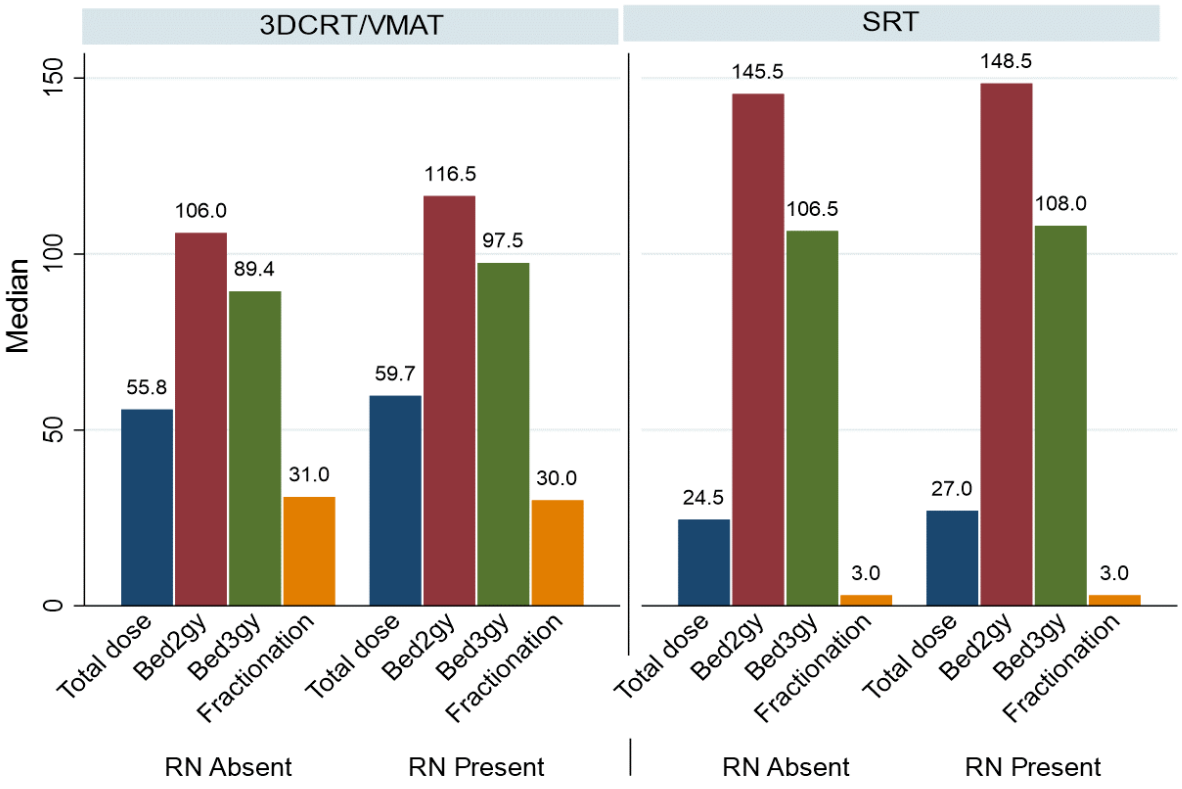

Figure 5: Radiation characteristics by RT technique for RN absent or RN present

As seen in figure 5, the median total dose for patients with RN absent was lower than for RN present for both 3DCRT/VMAT and SRT. The total doses of the four RN patients who received 3DCRT/VMAT were 60 Gy, 54Gy, 60 Gy and 59.4Gy, with a mean dose of 58.3 and a median dose of 59.7Gy, with the SRT RN case receiving a total dose of 27Gy. The BED_2 for 3DCRT/VMAT was 106 Gy for RN Absent and 116.5Gy for RN Present. The BED_3 for 3DCRT/VMAT was 89.5Gy for RN Absent and 97.5Gy for RN Present. Looking at SRT for RN Absent the BED_2 was 145.5Gy and the BED_3 was 106.5 Gy while for RN Present the BED_2 was 148.5Gy and the BED_3 was 108Gy.

The median number of fractions received for 3DCRT/VMAT was 31(30-32) and for SRT it was 3 (2-4). The median dose per fraction for 3DCRT /VMAT was 1.9 Gy (1.68-2.21) and for SRT the median dose was 10.8 Gy (7.58-14.1).

Looking at the 80 patients who had follow up MRI post RT the median volume treated for 3DCRT/VMAT was 205 cm^3 (160.6 - 250.5) while for SRT the median volume was 12 cm^3 (8.08-16.1). While it was not statistically significant the volume treated in the one SRT patient who developed RN was 28.4cm^3, which is significantly higher than the median of 12cm^3. The other 4 patients who received the same SRT regimen of 27 Gy in 9Gy per fraction for 3 fractions, had volumes of 4, 6.1 and 23.8cm^3 respectively.

CHAPTER 4

Discussion

Incidence of RN

The overall incidence of RN found in this study was 6.25 % (5/80) during the study period of 43 months from January 2014 to July 2017. Looking at the incidence rate for RN in this study, considering the time at risk and under observation, the incidence rate for RN was 5.11%, or in other words 51.15 per 1000 person years. The BED_3 and the BED_2 was calculated for the total doses received by each patient using the linear quadratic formula. The literature review found evaluations of RN using BED_3 in some studies and BED_2 in others (10, 12). Ruben et al looked at the BED_2 and found that patients who had BED_2 of $\geq 85.5Gy_2$ (equivalent to 45 Gy in 25 fractions using an alpha-beta of 2 for brain tissue) had an incidence of 6% of RN (10). Comparatively, in this study, patients with $BED_2 \geq 85.5Gy_2$ had an incidence of 6.49% (5/77). QUANTEC found that the dose for a 5% risk of RN at 5 years of the partial brain for normally fractionated RT is 72 Gy (range, 60–84Gy) (19). The incidence for patients with $BED_2 \geq 85.5Gy_2$ treated at CMJAH and WDGMC is therefore similar to that found in the literature.

Looking at the sample of 80 patients with a BED_3 83.3Gy (corresponding to 50Gy in 2Gy per fraction) – $99Gy_3$ (59.4Gy in 1.8 Gy per fraction has a BED_3 of 95.0 Gy_3) there were 54 patients, out of which 2 developed RN, with an incidence of 3.7% (2/54). This is slightly higher than the RN incidence rate of 2.5% reported by Chao et al for doses of 50.4Gy (BED_3 of 84Gy), but within the 5% incidence of RN within 5 years found by Ruben et al for total doses above 50Gy in standard fractionation (BED_3= 83.3Gy) (8, 10).

This confirms that brain radiation in CMJAH and WDGMC, in the range of BED_3 of 83.3 99Gy likely treats enough patients with curative intent within an appropriate safety margin.

In terms of the fractionation schemes commonly used by both centres that fall within this BED range they are: total dose of 54 Gy in 1.8 Gy per fraction (BED_3=86.4Gy_3), total dose 59.4Gy in 1.8 Gy per fraction (BED_3=95Gy_3), and a few other schedules in between. If the centre has too low a complication rate as compared to that found locally and internationally, then the question needs to be asked if patients are not treated to high enough doses as per standard of care recommendations and if the complication rate is too high then one needs to question the safety of the radiation.

In the group with BED_3 of 100-140Gy_3 (total dose 60Gy to 84 Gy in 2 Gy per fraction) there were 13 patients, out of which 3 had developed RN, with an incidence of 23% (3/13). This is higher than the 6.5% (10/155) RN incidence at 60Gy/30# Gy (BED 100 Gy_3) found by Ruben et al, as well as the 5% risk of RN found by Lawrence et al at a BED of 100-140Gy_3 (10, 12). The regimens in this BED_3 group for the 6 patients that received 3DCRT/VMAT for a BED_3 of 100Gy were a total dose of 60 Gy in 2 Gy per fraction (of whom 2 patients developed RN); and for the 7 patients that received SRT in this BED group the regimens were BED_3 = 108Gy in 9 Gy x 3 fractions, for 4 patients (including the one SRT patient who developed RN), and the other 3 were BED_3= 128Gy in 7.4Gy x 5 fractions; BED_3=105Gy in 7.5Gy x 4 fractions and BED_3=102Gy in 6.5Gy x 5 fractions.
The much higher incidence for RN in the BED_3 group of 100-140Gy (correlating to TD 60-84Gy in 2 Gy per fraction) as compared to the BED_3 group of 83.3 - 99Gy_3 (correlating to 50Gy in 2Gy per fraction to 59.4Gy in 1.8Gy per fraction) for CMJAH and WDGMC should give radiation oncologists pause to reconsider going to doses of BED_3 >100Gy, in particular with 3DCRT/VMAT as opposed to SRT. Closer follow up of patients who received these higher doses should be considered.

In the group BED_3 140-233 Gy_3 there were 6 patients who had all received SRT as the technique, none of whom developed RN. The reason may be that small brain volumes were treated (mean volume 3.54cm^3 for the 5 patients who had single fractions of 20-25Gy to the brain; 1 patient had 50Gy/5# to a total volume of 15.7cm^3 for recurrent sinonasal adenocarcinoma of sphenoid and anterior frontal lobe)

The incidence of RN by institution was 9.38% (3/32) for CMJAH and 4.16% (2/48) for WDGMC. The difference in incidence by institution is confounded by the fact that there was a much smaller percentage of follow up MRIs done in the public sector (38%) as opposed to

the private sector (64%). However, the difference in RN incidence between the two institutions should give one pause to assure rigorous patient follow up with imaging post radiation.

Looking at the sex of the patients in the sample there were 47 males and 33 females, of which three males developed RN (3/47; 6.4%) and 2 females (2/33; 6.1%). Looking at the incidence rate for female patients it was 51.39 per 1000 person years, while the incidence rate for males was 50.99 per 1000 person years. The slightly higher incidence rate for female patients for RN is contrary to the findings in the literature that male sex is a risk factor for RN (8).

Kaplan Meier:

The Kaplan-Meier survival estimates looked at the time in months post radiation to the diagnosis of RN. Looking at figure 2 one can see that all patients with RN were diagnosed by 20 months. The earliest that RN was found on post RT MRI was 3 months. The literature review found that the mean time to RN is 12 months; in this study the median time was 5 months, and the mean time to RN 8.2 months (10). This is earlier than reported but still concurs with the findings that most RN will present within 1 year. Since the earliest presentation of RN was at 3 months in this study , and in the literature it also notes the time to RN 3-12 months, with 85% of cases presenting within 2 years, it can guide decisions on how to schedule post radiation follow up MRIs (6, 25).

Looking at the Kaplan Meier graph grouped by technique – SRT versus the combination of 3DCRT/VMAT, the incidence of RN for SRT over time was slightly higher than the combination of techniques, namely 62 per 1000 person years versus 48 per 1000 person years. This finding mirrors that in the literature with SRT having a higher risk for RN (11).

Patient characteristics:

The pool of patients that received partial brain radiation at both CMJAH and WDGMC (under the three participating radiation oncologists) totalled 158 patients out of which 80 (51%) patients had post radiation follow up MRI's done. The reason for this low post RT MRI imaging number could be explained by firstly the cost of MRI in public and private and the gate keeping applied by medical aids. In the government sector access to MRI is restricted by long waiting lists for the two available MRIs in the government sector in greater Johannesburg, namely CMJAH and Chris Hani Baragwanath Academic Hospital (CHBAH).

Secondly, the diagnoses of the patient pool are such that patients' clinical condition may deteriorate during the study period before they had follow up imaging. For example, glioblastoma in adults with IDH wild type glioblastoma has a median survival of 11-15 months with standard treatment which may explain some of the patients lost to follow up and some of the 32% of patients who had no follow up imaging done (46).

Of the 80 patients who had follow up MRIs post RT 32 (40%) came from CMJAH and 48 (60%) came from DGMC. This would seem to indicate that it is more likely for a patient to have a follow up MRI done in private, most likely due to financial constraints in the public sector.

The sample of patients had more males 47 (58.8%) than females 33 (41.3%), out of a patient population with more females than males. This raised a question about the follow up of male and female patients with a larger proportion of males 47/74 (64%) than females 33/84 (39%) included in the sample of patients who had post RT MRIs done out of the initial population pool. These numbers suggest that more effort should be made by radiation departments to encourage follow up by female patients and to ensure that follow up imaging is done equally for both female and male patients. Further investigation of the reasons for the lower follow up MRI imaging of female patients post brain RT is recommended.

The age group ranged from 2 to 79 years, showing the large variety of ages treated in both CMJAH and WDGMC. None of the patients younger than 17 years had RN, the group 18-30 had 1 case of RN, while those patients grouped 30-40 years and older than 40 years of age each had 2 cases of RN per age group. In some studies it was suggested that older age may be a risk factor to develop RN, while others did not support the idea of older age as a risk factor (8, 12). While not statistically significant this study suggests that older age may be associated with developing RN, more so than in younger patients.

Looking at the time after RT to the first follow up MRI, the shortest period was 1 month and the longest time was 23 months, the longest follow up to have an MRI post RT was 45 months for patients included in the study. This showed that there is no standardised approach regarding the timing of follow up MRIs in both the public and private sector.

Considering chemotherapy in this patient group one can see that the majority of patients, 42 (58 %), did not receive any chemotherapy and the other groups being nearly evenly divided between receiving temozolamide 16 (20 %), chemotherapy for metastatic cancer 12 (15 %) and other (chemotherapy for primary brain tumour other than temozolamide) 10 (12%). One of the reasons that the majority did not receive chemotherapy may be that temozolamide is not available in CMJAH and patients with metastatic brain tumours who would have received chemotherapy for metastatic cancer do not usually receive partial brain radiation in CMJAH but rather receive whole brain radiation and were thus excluded from the study.

In this sample the 16 patients who received temozolamide all received it at WDGMC. In both the public and the private sector one of the 6 most common diagnoses treated is glioblastoma, however temozolomide is only available in the private sector, despite temozolomide providing a 7.6 month overall survival benefit in glioblastoma (47). Since this study did not show an association between radiation necrosis and temozolomide, the addition of temozolomide to treatment protocols in CMJAH for certain glioblastoma patients is encouraged.

In patients treated at CMJAH they only received no chemotherapy, or other (chemotherapy for primary brain tumours other than temozolamide). Out of the group of 80 patients only 3 patients had received targeted therapy (in WDGMC) as recorded in their files.

Of the 5 patients with RN 3(60) had no chemotherapy, 1(20) had temozolamide, and 1(20) had chemotherapy for metastatic cancer. This latter patient is also the one patient of the RN Present group that had targeted therapy, in addition to chemotherapy.

While some studies showed an association between chemotherapy, targeted therapy or immunotherapy and RN, most patients did not receive chemotherapy, a very small minority received targeted therapy in this study, and none received immunotherapy, therefore it is not possible to draw accurate conclusions about associations with RN and chemotherapy or targeted/immunotherapy in this study (10, 32, 35).

None of the patients in this study identified with RN received any treatment for RN. From the clinical notes it was not clear if patients were symptomatic from the RN found on MRI, or if morbidity was assumed to be from the underlying tumour treated, but radiation oncologists in

both CMJAH and DGMC should evaluate the patient clinically and if RN found on MRI to consider giving treatment, particularly bevacizumab if available as it has been shown to improve neurological symptoms and radiographic findings on MRI (40).

Looking at previous brain radiation the overwhelming majority, 72 (90%), did not have a history of previous brain radiation. Four patients (5%) had previous whole brain radiation to a dose of 30Gy and four patients (5%) had previous brain radiation to doses >50Gy. Interestingly the 5 patients with RN had no history of any previous brain RT, despite previous brain RT being a risk factor for RN (8, 18). Both institutions had patients with previous brain RT to over 50 Gy (2 at CMJAH and 3 at WDGMC) but only WDGMC had patients who had previous whole brain radiation that received re-irradiation. This may be due to the different approaches to metastatic brain tumours, with stereotactic reirradiation for metastases employed at WDGMC but not at CMJAH.

The most common diagnoses that received brain radiation in this study was astrocytoma 13 (16.3%), glioblastoma 11 (13.8%), metastatic brain tumour 11 (13.8%), meningioma 10 (12.5%), medulloblastoma 9(11.3%) and other gliomas 9 (11.3%). This is mirrored in the five patients who developed RN with one each of the most common diagnoses namely astrocytoma, glioblastoma, metastatic cancer (in this case metastatic renal cancer), meningioma and other gliomas. There is therefore no association found between histology and developing RN in this file review. Renal carcinoma, lung adenocarcinoma, HER2-amplified breast cancer, and BRAF V600 wild-type melanoma seem to have an increased risk for RN, and the one metastatic cancer case that developed RN in this study was a patient with renal cell carcinoma which seems to correspond with the literature (18).

Patient Radiation Characteristics:

The median total dose for those with RN absent was 54Gy (45-59.4) and the median total dose for those with RN present was 59.4 Gy (54-60). While there was no statistically significant correlation between total dose and RN in this study, the 5 patients who developed RN had a higher median dose than those with no RN, which is in keeping with the literature that a higher total dose increases the risk for RN. QUANTEC notes that a dose of >60Gy carries a 3% rate and 72Gy carries a 5% rate of RN over 5 years (19). The median total dose of 59.4Gy (54-60) also confirms findings in the literature that indicate that RN is unlikely with a total dose below 50Gy in conventional fractionation (10, 11).

Looking at the median EQD2 values (for an α/β of 2Gy and 3Gy) as well as the median BED_2 and BED_3 values for those patients with RN absent and those with RN present there were, in all 4 analyses, higher values in those with RN present. While the number of patients found with RN was too small to give a statistically significant result the findings seem to concur with the literature that a higher dose, in particular a $BED_3 > 100$ Gy (equivalent to 60Gy in 2 Gy per fraction) is a risk factor for RN. These findings correlate with the literature in that radiation necrosis is a function of cumulative dose (8).

The median dose per fraction for RN absent was 1.8Gy and the median dose per fraction for RN present was 2 Gy. While it did not have a statistically significant correlation it also concurs with the findings in the literature that a higher dose per fraction is associated with RN.

Duration of radiation therapy for the group RN absent was 44 days (14-49 days) while it was longer for the group with RN present namely 48 days (41-48), although not a statistically significant correlation. The literature referenced hyperfractionation as a risk for RN, but there was no association found in the literature between longer total duration of RT and RN.

The volume treated (cm^3) for patients who had follow up MRIs varied from a minimum of $1.4cm^3$ to a maximum of $662.5cm^3$. Looking at the median volume treated by $BED_3 \leq 100Gy_3$ or $>100Gy_3$ there is a difference in volume in both groups for those patients with RN absent versus RN present, though not statistically significant in either BED_3 group. In both $BED_3 \leq 100Gy_3$ and $>100Gy_3$ the patients with RN present had a larger median volume treated than the patients with RN absent. This concurs with the findings in the literature that larger volumes treated are associated with a risk for RN (12, 18)

Characteristics of patients by RT technique

From the 48 patients followed up at WDGMC with MRI, 29 had VMAT and 19 had SRT, while at CMJAH all 32 patients followed up with MRI had 3DCRT, none had SRT. This may be due to a difference in equipment available in the private and public sector, with the radiation equipment available in CMJAH at the time not being able to plan and deliver SRT as safely and easily as the equipment in WDGMC.

The difference in the most common diagnoses for the two main technique groups is illustrated in that the four most common diagnoses for 3DCRT/VMAT were Glioblastoma ,

Astrocytoma, Meningioma and Medulloblastoma and for SRT the five most common diagnosis were Metastatic brain tumour, Pituitary adenoma, Glioblastoma, Acoustic neuroma and Meningioma.

Patients who received SRT were more likely to have had chemo for metastatic cancer than either no chemo, temozolamide or other chemo for primary CNS tumours. In addition, the only three patients whose files indicated that they had received targeted/immunotherapy all received SRT as a technique. This would resonate with the fact that most patients receiving SRT had metastatic brain lesions and were more likely to receive chemotherapy or targeted/immunotherapy for metastatic cancer.

In terms of previous brain radiation, all 4 patients who had prior palliative WBRT in the patient pool received SRT, as well as 2 patients with previous brain RT to doses >50Gy. In the 3DCRT/VMAT group 2 patients had previous brain radiation to doses > 50Gy and there were no patients with prior WBRT. In this study it showed that patients with previous brain RT are more likely to get SRT as follow up radiation therapy than to receive 3DCRT/VMAT again. As none of the patients who developed RN had previous brain radiation it may indicate that previous radiation is not as high a risk for RN as is the total dose of the current treatment regimen and would need further investigation. A gap in this study is that the time period between the previous radiation and re-irradiation was not captured.

The total doses of the four RN patients who received 3DCRT/VMAT were 60 Gy, 54Gy, 60 Gy and 59.4Gy, with a mean dose of 58.35 Gy (2.91) and a median dose of 59.7Gy, with the SRT RN present case receiving a total dose of 27Gy in 3 fractions. The higher total dose in the patients who developed RN in both the 3DCRT/VMAT and SRT groups, relates well with the findings in the literature that total dose is one of the most important risk factors in developing RN.

The median number of fractions received for 3DCRT/VMAT was 31(30-32) and for SRT it was 3(2-4). This indicates that most cases who received SRT did not receive a single dose but rather had SRT in a few fractions. Vellayappan et al proposed that fractionated SRT may mitigate the risk of RN (18). However, due to the small number of SRT cases in this study that correlation could not be tested sufficiently. In the BED_3 100-140Gy group there were 7

patients who received SRT, and the one SRT patient who developed RN received a regimen of 9Gy x 3 fractions.

Looking at the 80 patients who had follow up MRI post RT the median volume treated for 3DCRT/VMAT was 205 cm^3 (160.6-250.5) while for SRT the median volume was 12 cm^3 (8.08-16.1). Vellayappan et al noted that for patients receiving SRT the risk of RN is higher when V10 > 10.5 cm3 or V12 > 7.9 cm3 (18). Despite the median volume being 12cm^3 there was only one patient who developed RN in the SRT group (1 out of 19 patients). While it was not statistically significant the volume treated in the one SRT patient who developed RN was 28.4cm^3, which is significantly higher than 7.9cm^3. The other 3 patients who received the same SRT regimen of 27 Gy in 9Gy per fraction x 3 fractions had volumes of 4, 6.1 and 23.8cm^3 respectively. Since the patient with the largest volume treated with the 27Gy/3# regimen with a BED_3 of 108Gy was the SRT patient who developed RN it seems to confirm the literature findings that the larger the SRT volume the higher the risk for RN (18).

Limitations

One of the limitations of the study design is the convenience sampling over a period of 3.5 years. While this allowed time for follow up of patients to include the average time of 1 year in which RN develops, it limited the number of participants entered into the study, with a resulting smaller sample size. Of the 193 patients that were initially identified as patients who were planned for partial brain radiation there were 35 patients excluded from the pool because they did not have a full course of partial brain radiation / did not start/ had wrong details entered which reduced the population pool to 158. Only 50.6% of the population pool of 158 patients had post RT MRI's done and could be included in the sample to evaluate for RN. Ideally a larger percentage of the patients out of the population pool should have been included in the sample to make the results more precise but the study was limited by requiring a post RT MRI as the method to note RN diagnosed. There was a consideration to also include post RT CT scans since many patients in the government sector only had post RT CT scans for follow up due to resource constraints, as this would have increased the sample to 107, but the literature review did not support CT scans as being able to identify radiation necrosis.

The study was also limited by a retrospective review of MRI reports that diagnosed radiation necrosis. These MRI's were read by different radiologists, in particular in the government

sector, and radiation necrosis was reported by different radiologists. All the reports that noted radiation necrosis as well as those that noted changes that could potentially have been RN were reviewed by one radiologist, the participating supervisor. On his review one MRI report that queried RN and was included in the "yes" group was changed from "Yes RN found" to "No RN found" after he reviewed the scan. Those MRI reports that the author initially listed as "Maybe RN" because of changes noted suggestive of RN (although not diagnosed as RN) were reviewed by the radiologist and found not to be typical of RN and included in the "No RN found". Due to the retrospective review of MRI reports done at 7 different hospitals it was not practical to have one radiologist re-read all 80 scans to have complete consistency in reporting but having him review the MRI reports that noted RN or suspicious changes improved the validity of results. In terms of the MRI sequences and the diagnosis of RN, a limitation was that not all MRI scans had perfusion sequences done, which is currently the most reliable MRI indicator of RN versus progression.

A further limitation was that RN was only diagnosed on MRI reports and not coupled with confirmatory biopsies. While brain biopsies are the gold standard to definitively diagnose radiation necrosis, they are seldom done due to the invasive nature of it.

Another limitation of the study was that very few of the patients had additional special investigations done in concert with the MRIs. One patient had a PET CT done which confirmed radiation necrosis as opposed to tumour recurrence. It would have been informative if all the patients with RN found had other special investigations such as PET CT, SPECT or MR Spectroscopy done. The reality of the financial constraint for patients with cancer in both the public and private sector is that only 51% of patients in this study even had follow up MRI's done, and financial considerations may have precluded additional special investigations.

Summary of findings:

The overall incidence for RN in this study was 6.25% (5/80), which is similar to that found in the literature. The incidence between different BED_3 total dose groups varied considerably with a much higher incidence of RN with BED_3 schedules > 100 Gy in this study.

While this study did not find a statistically significant correlation between any of the patient, clinical or radiation factors examined due to the low number of cases found, there was a clear association between radiation necrosis and radiation doses – for total dose, dose per fraction,

and total dose adjusted for BED_2 and BED_3. While many patient and treatment characteristics are noted in the literature to impact radiation necrosis the only one found in this study that clearly impacted the outcome is the total dose of radiation received, adjusted for BED.

Since only one case of RN was found among patients who had SRT one cannot draw accurate conclusions about associations. It is noteworthy though that the 1 case of RN in the SRT group, was found in the BED_3 group 100-140Gy, the same BED level that 3 out of 4 RN cases in the 3DCRT/VMAT group had. The patient who developed RN in the SRT group also received dose to a higher volume than the other 3 patients who received the same SRT dose and fractionation schedule. The higher incidence rate for SRT than for the 3DCRT/VMAT concurs with the literature but needs to be considered with caution as only one case was found.

This study also gives insight into the patient follow up imaging practices for patients undergoing partial brain radiation in the South African public and private sector. Understanding the main patient characteristics of patients undergoing partial brain radiation can also influence local policy.

The study was limited mainly by the time period that restricted patient numbers as well as the low percentage (51) of patients that had follow up MRIs.

Recommendations

Based on the results from this study the following recommendations are made:

1. From the outcome of this study the recommendation is that radiation oncologists need to be particularly cognisant of the total dose, adjusted for BED_3 given to patients receiving partial brain radiation as radiation necrosis is most determined by the total dose to the brain. In particular, radiation oncologists need to be aware of the higher risk associated with going to a BED_3 of 100Gy when treating with 3DCRT/VMAT, as doses 83.3-99Gy_3 in this study had an incidence of RN of 3.7%, but doses of 100-140Gy_3 had a RN incidence of 23%.
2. Radiation oncologists in CMJAH and WDGMC need to plan post radiation follow up imaging as this study showed that follow up brain MRIs were not done for many patients, in particular for female patients, and timing of MRIs

varied a great deal. From this study the recommendation would be that where possible, MRIs need to be scheduled at 24-48 hours post-surgery, 3-, 6- and 12-months post radiation, and again at 2 years post radiation to screen for radiation necrosis. Since the median time to RN in this study was5 months, it is recommended that screening starts at 3 months.

CHAPTER 5

Conclusion

In conclusion this study added to the body of knowledge by showing the incidence of RN at a South African institution. It found that the incidence of RN in patients receiving partial brain radiation at CMJAH and WDGMC between 2014-2017 was 6.25%. The incidence of RN was similar to that found in the literature at other institutions. However, there was a big difference in the incidence of patients treated to a total dose with BED_3 lower than 100Gy (typically 59.4Gy in 1.8Gy per fraction), than those treated to a BED_3 of higher than 100Gy using 3DCRT/VMAT (corresponding to 60Gy in 2 Gy per fraction). The volume treated also needs to be carefully considered with larger volumes more likely to develop radiation necrosis.

The most important treatment factor that determines the development of RN in a patient receiving partial brain radiation is the total dose received.

Future research recommendations arising from this study are

- To evaluate patient, social, treatment and institutional factors that may inhibit the follow up imaging of patients with brain tumours, in particular female patients.
- To evaluate a larger number of patients for the incidence of RN with radiation doses of greater than BED_3 $100Gy_3$ ($\geq$ 60 Gy in 2 Gy per fraction), since the results indicate a much higher incidence of RN than for a BED_3 $<100Gy_3$, more so than previously found in the literature.
- To evaluate the incidence of RN with re-irradiation of the brain, including if there is an association between RN and different time periods between initial and reirradiation. While no RN was found in the re-irradiated patients, the number of patients (8) was too small to draw any conclusions, and the time period between radiation courses was not investigated in this study, leaving room for further exploration of this question.

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Appendices

Appendix A:

Cerebral Radiation Necrosis Study: Data Sheet **Study no: _____**

	Information obtained from retrospective file review	
1.	Total radiation dose received	
2.	Technique used to plan and deliver treatment: 3DCRT/IMRT/VMAT/SRT	
3.	Number of fractions received	
4.	Dose per fraction	
5.	Volume treated, in patients who have post RT MRI	
6.	Time of treatment duration	
7.	Age of patient	
8.	Sex of patient	
9.	Diagnosis/histology	
10	Dates of follow up MRI/s	
11	Radiation necrosis found on MRI	
12	Time from end of RT to RN on MRI	
13	Chemotherapy received before, concurrently or after RT:	
14	Immunotherapy and/or targeted therapy received before, concurrently, or after RT:	
15	History of previous radiation to the brain:	
16	Treatment given for diagnosed radiation necrosis:	

Appendix B: Ethical Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Mia Erasmus

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180708

NAME: (Principal Investigator)	Dr Mia Erasmus
DEPARTMENT:	Radiation Oncology
PROJECT TITLE:	Evaluating cerebral radiation necrosis in patients who received partial brain radiation therapy at CMJAH and WDGMC between 2014-2017
DATE CONSIDERED:	27/07/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Jeffrey Kotzen and Dr Owen Terreblanche
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	04/09/2018

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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 resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **July** and will therefore be due in the month of **July** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES