Optimising the treatment of central nervous system cancers with radiotherapy in adult and paediatric patients

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Declaration

This is to certify that the content of this thesis is my own work. This thesis has not been submitted for any other degree or purpose.

I certify that the intellectual content of this thesis is the product of my own work, and that all assistance received in preparing this thesis and all sources have been acknowledged.

Alison L. Salkeld

19th of December 2025

Abstract

Central nervous system tumours in adults and children carry some of the worst prognoses of all cancers. Radiotherapy remains integral to their treatment, particularly for primary high-grade tumours and brain metastasis. The planning and delivery of therapy is technically demanding, requiring precise treatment of tumours that can rapidly progress, often delivered to unwell patients and in situations where treatment must be urgently commenced in a short time from patient presentation. Maximising tumour control whilst minimising dose to critical organs at risk, thereby minimising permanent late toxicities, remains challenging in the brain.

This thesis presents investigations into strategies to optimise the planning and delivery of radiotherapy in both adult and paediatric patients. Four interrelated studies were conducted across all stages of radiotherapy simulation, planning, quality assurance and treatment delivery. The focus of the research was to examine clinically important issues that could be used to improve treatment quality and accuracy.

The first study quantified the impact of the change in brain metastasis during the radiosurgical planning process, demonstrating that clinically significant variations necessitating re-planning occur in a substantial portion of patients. The second study examined the use of knowledge-based planning with RapidPlan for children with diffuse midline glioma, demonstrating that high-quality plans could be produced rapidly, in a clinically urgent situation. The third paper evaluated the introduction of a multi-disciplinary quality assurance checkpoint to improve plan conformity and reduce organ at risk doses. The final study analysed real-world patient setup accuracy and dosimetric impact in cranial-spinal radiotherapy for paediatric, adolescent, and young adult patients.

Collectively, these studies highlight practical and clinically implementable methods to improve the quality of central nervous system radiotherapy. Through focusing on real-world data this work contributes to bridging the gap between technological advances in radiotherapy and clinical practice to improve outcomes for patients with central nervous system tumours.

Contribution of Collaborators

Chapter 3 of this thesis was published as:

Salkeld AL, Hau E, Nahar N, Sykes J, Wang W, Thwaites DI. Changes in Brain Metastasis During Radiosurgical Planning. Internation Journal of Radiation Oncology Biology Physics. Volume 102, Issue 4p727-733. doi: 10.1016/j.ijrobp.2018.06.021.

My contribution is lead author of manuscript. I designed the study, analysed the data, reviewed the literature and wrote the drafts of the manuscript.

Collaborators roles: Hau E (conceptualization and methodology), Nahar N (conceptualization and methodology), Sykes J (supervision, methodology, reviewing and editing), Wang W (patient cases included in research), Thwaites DI (supervision, methodology, reviewing and editing)

Chapter 4 of this thesis has been submitted as a manuscript to the Journal of Medical Imaging and Radiation Oncology:

Salkeld AL, Sykes J, Fernandez J, Inskip L, Thwaites DI. Using Knowledge-Based Planning to Shorten Planning Time for Diffuse Midline Glioma. Journal of Medical Imaging and Radiation Oncology. 2025 (under review Sept 2025)

My contribution is lead author of manuscript. I designed the study, analysed the data, reviewed the literature and wrote the drafts of the manuscript.

Collaborators roles: Sykes J (supervision, methodology, reviewing, editing), , Fernandez J (completing technical treatment planning), Inskip L (completing technical treatment planning), Thwaites DI (supervision, methodology, reviewing and editing)

Chapter 5 of this thesis was presented as an oral presentation at a conference:

Salkeld AL, Sykes J, Nahar N, Hau EKC, Moodie T, Wang W, Thwaites DI. Implementation of a Formal Planning Quality Assurance Checkpoint with Multi-Disciplinary Team Review for Stereotactic Radiosurgery. 8th Annual Crown Princess Mary Cancer Centre Symposium. Sydney. 2019

Part of this work was also presented as a poster at a conference:

Salkeld AL, Sykes J, Nahar N, Hau EKC, Moodie T, Wang W, Thwaites DI. EP-2175: Improvement in radiosurgical plan dosimetry with implementation of a quality assurance program. ESTRO 37. Barcelona. 2018. *Abstract available Radiotherapy and Oncology. Volume 127, Suppl 1, S1201-S1202*

My contribution is lead author of manuscript. I designed the study, analysed the data, reviewed the literature and wrote the drafts of the manuscript.

Collaborators roles: Sykes J (supervision, methodology, reviewing and editing), Nahar N (conceptualisation, methodology), Hau EKC (conceptualisation, methodology), Moodie T (methodology), Wang W (patient cases included in research), Thwaites DI (supervision, methodology, reviewing and editing)

Chapter 6 of this thesis has been published as:

Salkeld AL, Sykes J, Fernandez J, Murphy L, Chard J, Thwaites DI. Quality assurance and other challenges in paediatric radiotherapy: Accurate delivery of cranial-spinal radiotherapy. Journal of Medical Imaging and Radiation Oncology. 2025. 69(3):388-394. doi: 10.1111/1754-9485.13721

My contribution is lead author of manuscript. I designed the study, collected and curated the data, analysed the data, reviewed the literature and wrote the drafts of the manuscript.

Collaborators roles: Sykes J (supervision, reviewing and editing), Fernandez J (completing treatment position review), Inskip L (completing treatment position review), Chard J (patient data included in analysis), Thwaites DI (supervision, reviewing and editing)

Signature

Alison Salkeld

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct

Signature

David Thwaites

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AI Statement

During the preparation of this thesis ChatGPT5.0, Claude, Microsoft Copilot was used for the purposes of text enhancement – not the generation of ideas or content. The use of this generative AI tool included spelling corrections and minor sentence restructuring for clarity enhancement. I confirm that where spelling and grammar was modified by generative AI, the content was reviewed for possible errors, inaccuracies, and bias. I takes full responsibility for the submitted thesis, confirm the work is my own, and that I have used generative AI in accordance with university guidelines and policies.

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Microsoft Corporation. Microsoft Copilot (internet). Redmond (WA): Microsoft. Available from http://copilot.microsoft.com

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Preface

This thesis incorporates all changes requested by the examiners. Short post-scripts have been added at the relevant points within published chapters to address specific queries. These additions provide clarification without altering the structure, methodology or conclusions of the thesis.

Contents

List of Figures

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List of Abbreviations

AYA – adolescent and young adult

ATRT – Atypical Teratoid/Rhabdoid Tumour

CNS – central nervous system

CSI – cranial-spinal radiotherapy or cranio-spinal radiotherapy

CTV – clinical target volume

DMG – diffuse midline glioma

GBM – glioblastoma multiforme

GTV – gross tumour volume

ILS – incident learning system

IMRT – intensity-modulated radiotherapy

KBP – knowledge-based planning

MRI – magnetic resonance imaging

OAR(s) – organ(s) at risk

PDSA – Plan-Do-Study-Act (cycle)

PTV – planning target volume

QA – Quality assurance

QI – Quality improvement

QUANTEC – Quantitative Analyses of Normal Tissue Effects in the Clinic

RCT – randomised control trial

RP – RapidPlan®

RS – radiosurgery

RT – radiotherapy

WBRT – whole brain radiotherapy

Research publication and awards

Peer-Reviewed Publications

Salkeld AL, Hau E, Nahar N, Sykes J, Wang W, Thwaites DI. Changes in Brain Metastasis During Radiosurgical Planning. Internation Journal of Radiation Oncology Biology Physics. Volume 102, Issue 4p727-733. doi: 10.1016/j.ijrobp.2018.06.021.

Salkeld AL, Sykes J, Fernandez J, Inskip L, Thwaites DI. Using Knowledge-Based Planning to Shorten Planning Time for Diffuse Midline Glioma. Journal of Medical Imaging and Radiation Oncology. 2025 (submitted September, 2025, under review December 2025) under review Sept 2025))

Salkeld AL, Sykes J, Fernandez J, Murphy L, Chard J, Thwaites DI. Quality assurance and other challenges in paediatric radiotherapy: Accurate delivery of cranial-spinal radiotherapy. Journal of Medical Imaging and Radiation Oncology. 2025. 69(3):388-394. doi: 10.1111/1754-9485.13721

Poster Presentation

Salkeld AL, Sykes J, Nahar N, Hau EKC, Moodie T, Wang W, Thwaites DI. EP-2175: Improvement in radiosurgical plan dosimetry with implementation of a quality assurance program. ESTRO 37. Barcelona. 2018. *Abstract available Radiotherapy and Oncology. Volume 127, Suppl 1, S1201-S1202*

Oral Presentations Related to this work

Salkeld AL, Sykes J, Nahar N, Moodie T, Wang W, Thwaites DI. Improving radiotherapy quality with multidisciplinary team plan review. 8th Annual Crown Princess Mary Cancer Centre Symposium. Sydney. 2019

Awards

University of Sydney Clinical Educator of the Year (2018)– Nepean Clinical School

Westmead Hospital Medical Council Awards (2024) – radiotherapy education and quality improvement award

Appointments and Committees

Clinical Lead AYA Neuro-Oncology Westmead Hospital (2018 – present)

Clinical lead Paediatric Neuro-oncology radiotherapy – Westmead Children's Hospital (2018-present)

EVI-Q national consensus guideline committee member brain metastasis and radiosurgery (2018/2019)

RANZCR – Paediatric Radiotherapy Special Interest Group Committee Member (2018 – present)

RANZCR – Particle therapy Specialist interest group member (2018 – present)

Head of Education – Department of Radiation Oncology Network(2021-present)

Chapter 1 Overview

1.1 Background and Context

The research presented in this thesis examines methods for optimising the planning and delivery of radiotherapy for cancers within the central nervous system (CNS) in both adult and paediatric patients. It studies a clinically relevant question at each step of the radiotherapy workflow - simulation, planning, quality assurance and treatment delivery with the goal of improving accuracy and treatment outcomes. The focus of the PhD was to research clinically relevant solutions that could be rapidly implemented within a busy department to improve the overall accuracy and delivery of radiotherapy to tumours within the CNS. The thesis deliberately focuses on some of the most challenging situations in CNS radiotherapy, including radiosurgery (RS) and the treatment of adolescent and young adult (AYA) and paediatric patients with CNS tumours.

The research has evolved over a period of part-time candidature with the publication of papers throughout this period. During this time changes in clinical practice (such as the increased use of stereotactic radiosurgery for brain metastasis) as well as technological advances (such as knowledge-based planning) have been examined and incorporated as they emerged.

1.2 Knowledge Gaps and Research Rationale

Some of the most complex and challenging clinical situations for CNS cancers involve paediatric patients and the delivery of their treatment (1). Due to the rarity of paediatric cancers and the limited number of radiotherapy centres specialised in paediatric treatments, studies on radiotherapy planning technology and delivery techniques are limited when compared to adults. This work, therefore, considers challenges in both adults and paediatric populations to address gaps in knowledge in all age groups receiving radiotherapy for CNS tumours.

Patient, tumour and treatment factors interplay to create a dynamic situation for patients through planning and treatment. An example of this is a multi-isocentre VMAT (volumetric arc therapy) for cranial-spinal (CSI) treatment setup for unwell paediatric patients. There is limited real-world data showing the impact of setup errors on dosimetry, with most data derived from modelling involving narrow parameters.

Despite the widespread implementation of knowledge-based planning (KBP) in clinical practice, there has been limited research into its potential impact on paediatric planning(2). This is due to the difficulty of generating models in paediatric patients with rare cancers where departmental numbers are low, even in specialised centres. Additionally, it is also perceived that planning time is too long for patients with diffuse midline glioma (DMG) to use more advanced techniques such as VMAT. Historically, national consensus guidelines refer to field-based planning methods for the treatment of these children(2).

MRI technology has increasingly become available in diagnostic radiology departments and radiation oncology departments. This has led to increased integration of MRI imaging into radiotherapy planning. There can be significant delays between the MRI used for radiotherapy planning and the delivery of radiotherapy. The impact of the timing of planning on target delineation and treatment delivery with the potential for a geometric miss is examined.

This thesis addresses these challenges in planning and delivering radiotherapy to the CNS by developing strategies for rapid implementation in clinical practice for adult and paediatric patients with tumours of the CNS.

1.3 Research Aims

The overall goal of this thesis is to optimise the treatment of CNS tumours in adults and children through examining each step of the planning and delivery of radiotherapy. It evaluates the radiotherapy pathway for CNS tumours as an integrated clinical system. The wider research aims are to consider ways to:

i. Strengthen the integration of imaging into planning;
ii. Improve planning efficiency and consistency;
iii. Strengthen quality assurance processes within radiotherapy planning;
iv. Improve the accuracy and robustness of radiotherapy treatment delivery

Through these objectives, this work aims to strengthen the link between imaging, planning and outcome-focused clinical implementation in adult and paediatric patients. The specific aims of the individual, but linked, studies presented in the thesis are to:

1. Quantify changes in brain metastasis volumes between planning and delivery of RS
2. Develop KBP approaches for DMG
3. Evaluate the impact of a multidisciplinary review step of RS plans for brain metastasis to improve plan quality

4. Analyse the impact of setup variations in patients receiving CSI using real-world data

1.4 Thesis Structure

Figure 1-1 gives a schematic thesis map to show the flow of the thesis paralleling the steps of radiotherapy planning and delivery as well as the chapter relationships to one another. Chapter 2 provides a general literature review, while more detailed discussions are presented in chapters 3-6, each providing focussed reviews underpinning the rationale, gaps in knowledge and place of each study within current knowledge.

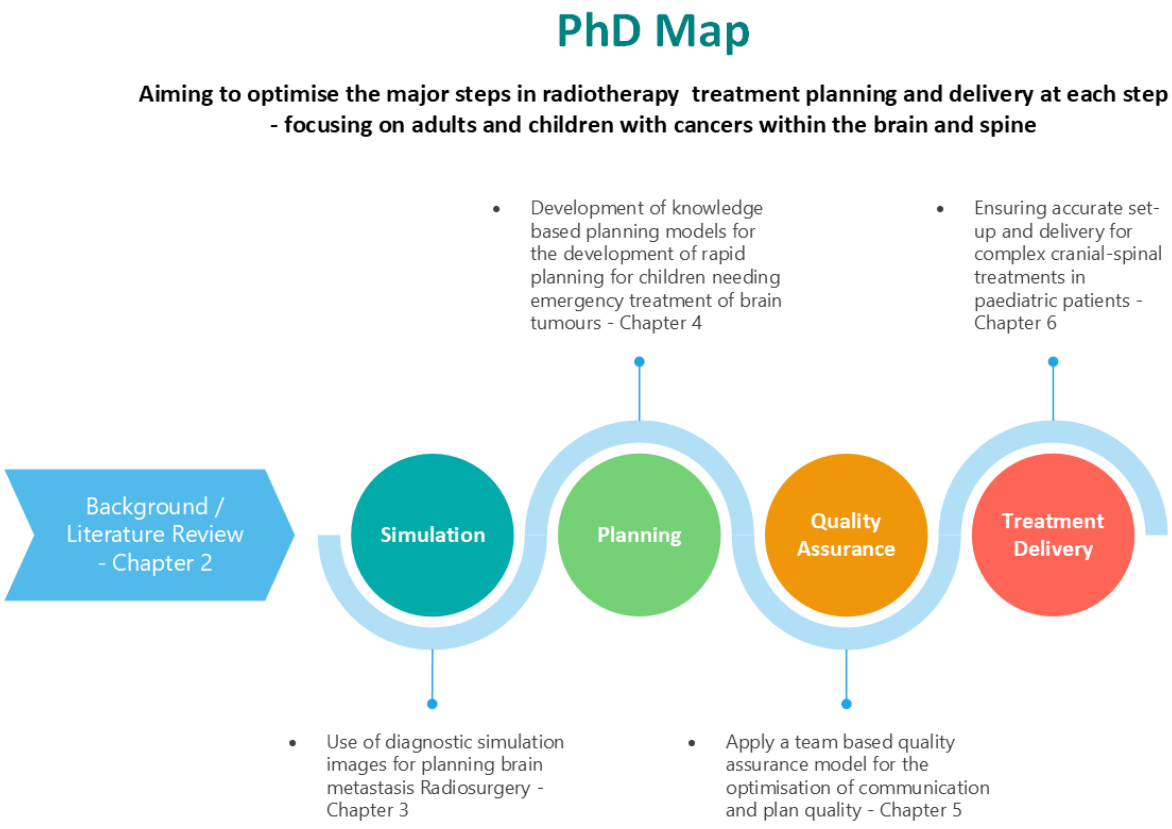

Figure 1-1: PhD map. The flow of the PhD follows the steps of a patient and their plan through the radiotherapy process.

Chapter 3 considers the impact of changes in brain metastasis during planning time. The aim was to determine if there were any changes in brain metastases or resection cavity volumes between planning magnetic resonance imaging (MRI-1) and RS treatment and if these led to a change in management or alteration in the RS plan. A second verification MRI (MRI-2) was performed before treatment to assess the changes. The conclusion was that measurable

changes occur in brain metastasis over a short period of time, with a change in management required in 41% of patients with 7 days between MRI-1 and MRI-2, increasing to 78% of patients when there is a delay longer than 7 days. This was the first published study examining the temporal change of brain metastasis. A google scholar search shows that it has been cited 63 times (google scholar December 9th 2025) in subsequent research, and when it was published, received a letter to the editor placing it in the broader context of RS controversies and establishing its importance in informing future studies.

Chapter 4 (submitted for publication in peer reviewed journal) addresses the planning challenge of providing high-quality radiotherapy plans quickly for patients needing urgent treatment for DMG. The aim of this study is to evaluate the application of KBP to expedite treatment planning while maintaining plan quality for paediatric patients with brainstem DMG. The results of this study show that knowledge-based planning using RapidPlan (RP) significantly reduces treatment planning time for paediatric DMG whilst maintaining plan quality and improving conformity. Importantly, this shows that model development can be accomplished in a rare cancer with limited patient numbers and that planning improvements occurred both for planners with paediatric planning expertise and those with limited experience (who may be rostered after hours or on weekends). The current Australian guidelines are for relatively simple radiotherapy planning and treatment approaches for these urgent cases. This work provides the basis for a more sophisticated and higher-quality approach.

Chapter 5 (oral conference presentation, 8th Annual Crown Princess Mary Cancer Symposium. Sydney. 2019 and part of this work presented as a Poster at ESTRO 37 Barcelona. 2018) examines the role of interdisciplinary communication in the quality assurance process by creating a formal QA checkpoint with a group review of plans. This study came at a time when QA assessment tools built into RS planning systems (such as scorecards) were limited. The aim of this study was to determine if the implementation of a formal dosimetric QA checkpoint in RS for brain metastasis led to an improvement in RS plan quality. Consecutive brain metastases RS cases were planned using a formal dosimetric QA checkpoint (scorecard) and compared to historic RS plans. The results of this study demonstrate that there was a significant improvement in dose conformity and organ at-risk doses with the introduction of the QA checkpoint.

Chapter 6 (published in a peer-reviewed journal) analyses the impact of setup errors during CSI in AYA and paediatric patients. The dosimetric impact of these changes on target volume and organs at risk (OARs) was assessed. The results show that in the real-world, setup errors ranged from 0.5 to 6.2 mm in different directions and were more pronounced in the cranio-caudal direction. However, despite these variations, there was minimal impact observed on the coverage of clinical target volumes (CTV) and doses to OARs (<1% relative change) across

the whole treatment. The importance of monitoring for changes and checking if they are not systematic is underlined.

Chapter 7 presents the conclusions and synthesises the body of work as a whole and examines its impact, providing recommendations for future studies.

Appendices detail additional work undertaken during candidature, including conference presentations and associated publications.

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Chapter 2 Background

2.1 Cancer in Australia

By the end of 2024 is it is estimated that there will be around 158 000 cases of cancer diagnosed in Australia(1). This is an increased incidence of around 93% over 24 years with the majority of the increase (86%) due to increases in population size and increasing numbers of people reaching older ages(2). The remaining 14% increase is due to increasing cancer incidence. Health system expenditure on cancer in Australia is estimated to exceed 10 billion dollars a year and ranks third in terms of Australia's total health system expenditure with CNS estimated to cost around 180 million a year(3).

Treatment of cancer patients usually involves a combination of surgery, radiotherapy and systemic treatments such as chemotherapy, target agents, radionuclides and immunotherapy(4). Over the last two decades, advancements in diagnostics, therapeutics, and technology have led to incremental improvements in overall survival. In Australia, the five-year survival rates from all cancers combined have improved from 51% in 1988–1992 to 70% in 2013–2017(2). However, for patients in Australia with brain cancer, the five-year relative survival rate has remained at less than 25% over the last 30 years(2).

2.1.1 CNS Cancer

Primary tumours of the CNS include tumours arising in the brain, spinal cord and surrounding/supporting structures, with brain cancer being the most common(5). Examples include high- and low-grade glioma, craniopharyngioma, medulloblastoma, and meningioma. Whilst primary brain cancer represents only 1.2% of the new cancers diagnosed in 2023, it represents the ninth most common cause of cancer death in 2023(2).

CNS cancers are classified based on(5, 6):

Type of cell they arise from, e.g. glioma from a nerve cell in the brain or spinal cord. Histologic, cytogenetic and molecular subclassification are also frequently used e.g. H3K27M DMG

Grade: Low grade I/2 (more benign) e.g. craniopharyngioma through to high-grade 3/4 (more aggressive/malignant) e.g. medulloblastoma. CNS grading of tumours has been designed to reflect the general principle that complete surgical excision of grade 1 or 2 tumours is curative usually without further treatment. This contrasts with grade 4 tumours which are highly malignant, leading to death in a short period of time without treatment.

Location: Primary tumours arising in the CNS (e.g. glioma), whilst secondary CNS tumours are those that arise in other parts of the body and metastasise to the CNS e.g. a brain metastasis from a lung cancer or breast cancer.

Both high-grade primary and secondary cancers of the brain are significant problems for patients(7). They are life-threatening, can have widespread effects on neurologic function (e.g. thinking and memory) and affect basic and complex motor functions (e.g. walking, writing) with significant impacts on patients' quality of life(8, 9). CNS cancers occur in both adult and paediatric populations; there are similarities and differences between these groups.

2.1.1.2 Adult CNS Cancer

Primary CNS Tumours

Gliomas are tumours that arise from nerve/glial cells within the CNS(10). High-grade adult-type diffuse gliomas are the most treated in adult neuro-oncology practice, e.g. glioblastoma multiforme (GBM) (11). For high-grade tumours, treatment generally involves a combination of surgery followed by radiotherapy to the tumour bed and/or chemotherapy(12). High-grade tumours that are unable to be resected are treated with definitive radiotherapy(13) with or without the addition of systemic therapy (such as temozolomide).

Secondary CNS Tumours – Brain Metastasis

Brain metastases are the most common adult tumours of the CNS with more than one third of cancer patients developing them(14). This reflects not only the tumour's capability to spread and grow in the brain, but also the inability of many systemic treatments (such as chemotherapy) to penetrate the brain(15). The most common types of cancer that metastasise to the brain include lung cancer, breast cancer, melanoma and renal cell carcinoma(14). Brain metastasis may be solitary or multiple. The reported incidence is increasing, likely due to a combination of improved therapeutics resulting in increased survival after diagnosis, an aging population, and improved diagnostic and screening mechanisms leading to earlier identification and treatment(14).

2.1.1.3 Paediatric CNS cancer

For children aged 1-14 years, cancer is the second leading cause of death after injury deaths, with brain cancer being the leading cause of cancer death in this age group(2). Around 120 cases of brain cancer are diagnosed each year in Australia, with a 55% survival rate for children under 5 (2). Brain metastasis(16) and tumours of the spine(17) are rare in children. They are classified by their type, grade and location (as in the adult classification) (5, 10). Major prognostic factors include age at diagnosis, tumour grade and type and tumour site(18). Figure 2-1 shows the survival of paediatric brain tumour patients by prognostic factors with data over 40 years(18). In contrast to adults, studies have shown that children diagnosed at an older age typically have a better survival compared to their younger counterparts with one factor being the inability and/or significant

difficulty using radiotherapy in young children due to late permanent side effects(18). The most common types of tumours diagnosed in Australia are gliomas, embryonal tumours, ependymomas and choroid plexus tumours(19).

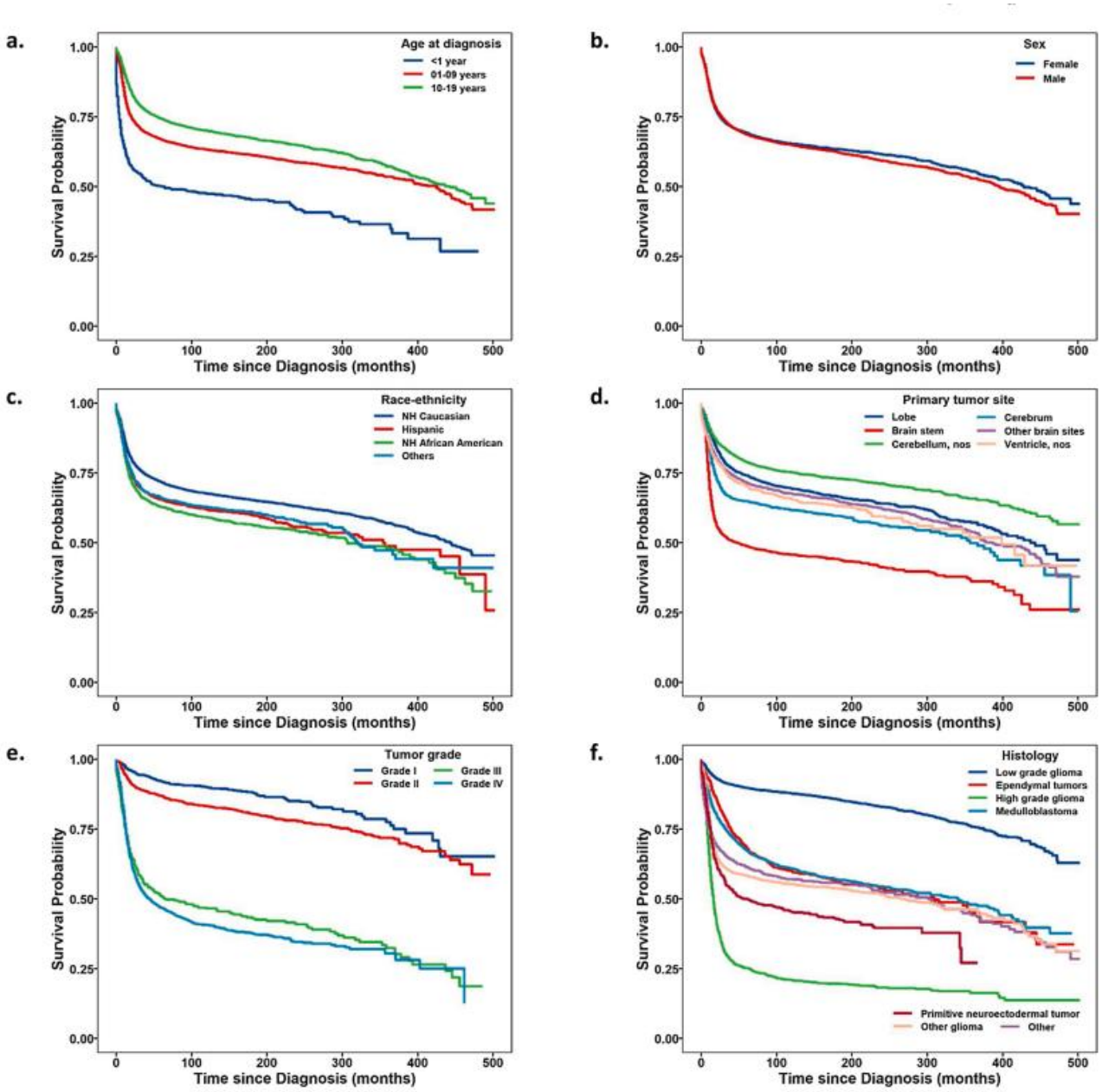

Figure 2-1: Survival of Paediatric Brain Tumour Patients by Prognostic Factors, SEER Data, 1975-2016. Prognostic factors included in the figures: age at diagnosis, sex, race-ethnicity, primary tumour site, tumour grade, histology. *Hossain MJ, Xiao W, Tayeb M, Khan S. Epidemiology and prognostic factors of paediatric brain tumour survival in the US: Evidence from four decades of population data. Cancer Epidemiol. 2021;72:101942(18)*.

2.2 Role of radiotherapy in Adult and Paediatric CNS Tumours

2.2.1 What is Radiotherapy

Radiotherapy is the use of high-energy radiation of various types and from various sources to kill cancer cells and shrink tumours (20). When this is generated from a machine outside the body (e.g. linear accelerator), it is referred to as external beam radiotherapy. This is the most common type of therapeutic radiotherapy, with MV x-rays being the most widely used modality. Radiotherapy can also come from radioactive material placed in the body near cancer cells (e.g. brachytherapy for cervical or prostate cancer). Radiotherapy causes ionisation of atoms that ultimately results in the breaking of chemical bonds leading to cell injury(21). The most significant effect in this context is cell killing, which directly or indirectly targets the cancer cells of tumours but, importantly, also damages the normal tissues surrounding the target/tumour, leading to permanent late side effects (see Figure 2-2). Figure 2-2a shows a tumour (in this case a medulloblastoma) lying near the brainstem, spinal cord and normal brain structures such as the cerebellum. Figure 2-2b represents radiotherapy targeting the tumour, with the highest radiotherapy dose shown in red. The normal structures around it receive 'collateral' lower doses, irradiating normal tissue and potentially leading to permanent late side-effects.

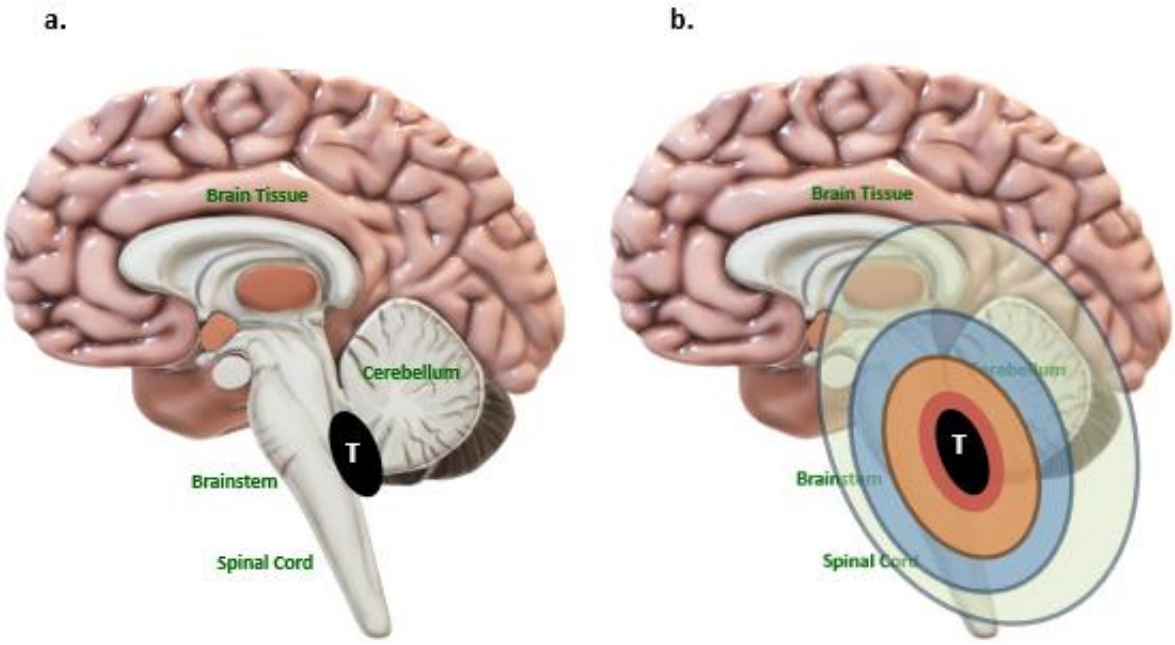

Figure 2-2: a. Labelled sagittal diagram of the brain with a tumour ('T' black) sitting between the brainstem and cerebellum i.e. typical location of a medulloblastoma. b. Shows radiotherapy targeting the tumour, with high dose (red), moderate dose (orange) and lower dose (blue and green) irradiating the tumour and the surrounding normal brain and spine tissue. Modified from 'Brain image' from Microsoft office stock images.

Optimising the treatment of tumours, at the same time considering the risk of harming surrounding tissues is termed the therapeutic ratio—in essence, a risk-versus-benefit approach to planning a radiotherapy treatment regimen(21, 22). A balance must be struck between what is considered an acceptable probability of a radiation-induced complication in a normal tissue and the probability of tumour control. For most normal tissues and organs, dose-volume constraints are documented in the literature to guide clinical practice e.g. the QUANTEC(23) (QUantitative Analysis of Normal Tissue Effects in the Clinic) data for adults and the more recent PENTEC(24) (PEdiatric Normal Tissue Effects in the Clinic) data in children. The challenge of brain tumours is their close location to critical structures which limits the dose of radiotherapy that can be given to the tumour.

2.2.2 Adult CNS Radiotherapy

Radiotherapy for primary CNS cancers

Primary CNS tumours are surgically excised where possible(25). High-grade inoperable tumours are treated with radiotherapy definitively, with or without chemotherapy(26). Radiotherapy may be given in the adjuvant setting, such as to high-grade tumours following excision(27). It may also be given to lower grade tumours which have recurred or are inoperable(28). Multimodality treatment with a combination of surgery, radiation and systemic agents are critical to optimise treatment outcomes for patients(29).

Treatment with radiotherapy typically involves highly conformal treatments with techniques such as VMAT, intensity modulated radiotherapy (IMRT), proton therapy or RS. Proton therapy is not available in Australia at present. Whole-brain radiotherapy is typically reserved for palliative settings(30).

VMAT and IMRT are used to treat the tumour/excision cavity with a margin of around 10-15mm for microscopic spread and a planning target margin of 3mm(27). This avoids treating as much normal brain structures as possible. Fractions are usually delivered in 1.8Gy or 2Gy per fraction, delivered daily for five consecutive days a week over a five to six-week period. RS for primary brain cancers (usually benign tumours such as meningioma or craniopharyngioma) treats a small margin of 0-2mm around a target to a high dose, avoiding normal brain(31). Treatment may be delivered in single or a small number of fractions (32).

Radiotherapy for brain metastasis

Traditionally, radiotherapy for brain metastasis involved treating the whole brain radiotherapy (WBRT) with treatment given daily over 1-2 weeks (5 to 10 fractions)(31). The rationale of this approach is to treat radiologically visible brain metastases present as well as microscopic tumour deposits throughout the brain to prevent the development of further macroscopic brain metastasis, as well as limit corticosteroid dependency(30). The landmark Patchell (32) study demonstrated

improvements in overall survival, local control and quality of life with the addition of WBRT to surgical resection for solitary brain metastasis.

For brain metastasis, RS uses ablative doses of radiotherapy, typically delivered in 1-5 fractions to the metastases, with small planning target margins (0-3mm) (33). It does not target microscopic disease which may be present in other areas of the brain. The dose of radiotherapy to the surrounding normal brain is minimised to minimise cognitive decline associated with whole-brain radiotherapy(34).

There have been three randomised controlled trials (RCT's) that compared WBRT + RS to RS radiotherapy alone, which included patients with 1-3 brain metastases(34-36) (one trial included up to four (37)) with good performance status. In addition, there are two trials that compared local therapy alone (surgery or RS) to local therapy + WBRT(38, 39). These trials demonstrated that whilst the addition of WBRT to RS improves intracranial control, it had no effect on overall survival. Two of the randomised controlled trials found that patients receiving WBRT in addition to RS had worse recall at 4 months. In addition, Study N0574 (35, 38) demonstrated worse neurocognitive deterioration and quality of life after RS + WBRT compared with RS alone. In patients receiving radiotherapy for brain metastasis, given that the addition of WBRT does not improve quality of life, neurocognition or overall survival, the use of RS for patients with 1-4 brain metastases has become standard of care, with treatment of >4 metastases in selected populations also within the standard of care(40, 41).

2.2.3 Paediatric CNS Radiotherapy

Radiotherapy remains an integral part of the treatment of CNS cancers in children with most of the treatment being for primary brain tumours (rather than brain metastasis)(42). As in adults, tumours are resected where possible(43). The radiotherapy target volume depends on the histology being treated. It is more common for children to get malignancies with a risk of spread throughout the CNS (brain and spine)(44). Therefore, CSI is commonly delivered in paediatric practices, e.g. for medulloblastoma, non-germ cell tumours, and embryonal tumours. The tumour bed is then boosted in a second phase. For other high-grade tumours, local radiotherapy to the tumour bed may be given following resection (e.g. diffuse high-grade glioma – paediatric type) or definitively for inoperable tumours e.g DMG(45).

Children are at risk of late permanent side effects from radiotherapy, which depend on the dose to normal brain structures, volume irradiated, use of systemic agents (e.g. methotrexate) and age of the child receiving irradiation(46). In addition, children have an increased risk of secondary malignancy(47). Children are at risk of late side effects including hormone dysfunction (pituitary irradiation), memory and cognition (temporal lobe/normal brain/ hippocampus), stroke/vascular events (Circle of Willis and brain radiotherapy), hearing loss (cochlear/inner ear), radionecrosis and other side effects(48). Highly conformal techniques are used to minimise dose to normal tissue. In

addition, children may be referred overseas for proton radiotherapy (not currently available in Australia)(49).

There are numerous challenges that can impact on the delivery of radiotherapy to the brain and spine which can influence the efficacy, accuracy and long-term outcomes of patients receiving radiotherapy. These can broadly be categorised into patient factors, tumour factors and treatment factors. These may have an impact on any of the steps used in the planning and delivery of treatment (see Figure 1-1, Chapter 1).

2.3 Patient Challenges in CNS Radiotherapy

Acute distress is common in both adults and paediatric patients receiving radiotherapy(50), despite radiotherapy being painless and non-invasive(51). For adults, lower education level, higher degree of loss of income, lower global quality of life and longer duration of treatment were all factors associated with higher distress(51). Children may fear unfamiliar environments with different people/staff and being separated from parents(52). Younger children are required to lie still for a prolonged period, which is not practical in the youngest age group (who require general anaesthesia(53)); for example CSI treatment and setup may take up to an hour depending on the number of isocentres and difficulty in setting up(53). Indicators that suggest the need for general anaesthesia include young age, anxiety or emotional immaturity for age, treatment complexity such as in a prone position, and history of not tolerating or cooperating with procedures (e.g. CT scans)(54, 55) .

All treatment techniques and supportive therapies (e.g. play therapy) must consider the patient's age, difference in cognitive ability, post-operative complications such as posterior fossa syndrome and ability to lie comfortably still, as well as the time pressure needed to treat patients who are often unwell. Whilst younger patients may require general anaesthesia, older patients are usually treated without it, using appropriate supportive measures such as play therapy, toys, movies or music.

Patients are often simulated in the first 2 weeks following surgery for high-grade brain tumours. A study by Armstrong et al(56) demonstrated that patients with brain tumours are highly symptomatic with more than half reporting 10 concurrent symptoms and 40% at least 3 moderate to severe symptoms including fatigue, pain, distress and sleep issues. These symptoms have an impact on the ability of a patient to be setup accurately and maintain the setup position through treatment. Patients may feel unwell, be irritable (e.g cerebellar syndrome) and unable to lie flat comfortably with an immobilisation face mask adding to setup uncertainty / changes.

The planning target volume (PTV) is a planning tool (rather than an anatomic volume) that compensates for internal movements e.g. breathing and setup uncertainties (e.g. patient positioning and equipment tolerances)(57). For the brain, whilst internal motion is minimal, setup uncertainties must be accounted for. The consequence of setup time and error may necessitate larger PTV margins (treating more normal brain tissue) or lead to re-planning if the treatment delivery position is significantly different to the treatment position e.g. head tilt. Inaccurate setup may not only increase the dose to normal tissues beyond what was planned but may also lead to geographic miss of the tumour (underdosing of the tumour) – particularly if the error is systematic(58).

Despite the critical importance of setup and its variability, there is a lack of real-world data within CNS tumours, particularly within the paediatric age group, and how setup changes throughout treatment directly impact the dosimetry of tumour target volumes and OAR's.

2.4 Tumour

High-grade tumours within the CNS behave aggressively, with rapid growth, within or close to sensitive areas of the brain, and require higher doses of radiotherapy to achieve local control. Balancing the treatment of the tumour with minimisation of dose to critical organs to limit permanent late-side effects presents a challenge.

2.4.1 Location

High-grade tumours of the CNS often have large volumes and lie within or adjacent to critical organs (for example a high-grade glioma close to the optic chiasm). To achieve adequate dose there may need to be modification of target volumes (decreased coverage) in order to meet critical organ dose constraints(13) – compromising local control or decrease in dose.

A study of the American National Cancer Database(16) examined patients 14 years and under presenting with diffuse astrocytic and oligodendroglial tumours and found that 63.6% of tumours involved midline structures. Many critical brain structures lie in the midline (e.g. brainstem, optic chiasm), presenting a challenge in paediatric radiotherapy.

Balancing CNS tumour location delineation relative to organ at risk positions requires knowledge and experience in centres and their staff. A systematic review by Weber et al (40) demonstrated the importance of institutional experience, workload, and infrastructure on quality of radiotherapy planning and delivery. Internationally, this has led to efforts such as the QUARTET(59) projects for paediatric and adolescent trials for the standardisation of treatment quality. Within the Australian paediatric radiotherapy community where the caseload of particular tumour types may be low, even in centralised centres, efforts such as national peer review are helpful in working towards treatment quality(60)

2.4.2 Grade

The most common grade of adult brain tumours is high-grade, with the most common pathology being GBM (61), grade III astrocytoma and grade I/II astrocytoma; with the most common location being the frontal lobe, temporal and parietal lobes. Unresected high-grade brain tumours in both adult and paediatric(45) patients require a higher dose of radiotherapy to achieve the best chance of cure/long-term survival(13, 26). As organ tolerances are related to the dose, this provides an additional challenge in treating tumours within the CNS.

As discussed earlier, primary CNS tumours have some of the worst survival outcomes of all cancers. Radiotherapy dose is limited by the tolerance of normal structures within the brain to maximise the chance of cure, whilst minimising the risks of late side effects such as radionecrosis. This is further complicated in paediatric patients where radiotherapy may be effective in achieving local control, but very young age may preclude the use of radiotherapy. For paediatric and adult patients, late side effects such as endocrine dysfunction(62), secondary cancers(63) and neurocognitive decline(46) can all have significant impacts on both quality of life (64) and survival.

Incorporating new processes and technology within the planning process is needed to improve plan consistency and quality. A focus both on achieving tumour control whilst minimising toxicity requires a focus on solutions that are ideally relatively inexpensive and accessible to departments.

2.5 Treatment Challenges

Radiotherapy simulation, planning and treatment to the CNS is complex. It requires the use of multiple imaging types that must be fused to image the target lesion and surrounding organs at risk and rapidly evolving radiotherapy technologies to deliver precise treatments. Since 1976, the International Commission on Radiation Units and Measurements (ICRU) has recommended that radiation dose be delivered to within 5% of the prescribed dose(65), requiring that the uncertainty in each step is minimised. This recommendation continued into the 1990s(66, 67). However, the widespread adoption of IMRT with more complex dose distributions gave rise to more nuanced accuracy recommendations. These are typically a requirement of 3-3.5% (one standard deviation) on main target volume doses and up to a few (2-4 mm) on geometric accuracy, but with additional requirements for dose and geometry accuracy in various specific scenarios. In addition, the required uncertainties in each step have tightened in many cases, as the processes have become more complex, to ensure the required overall accuracy can be achieved (68-70). Overall, uncertainty should be minimised such that the dose delivered is as close to the prescribed dose as possible.

For patients with tumours within the CNS the often-unwell patient needs to be accurately setup in the correct position for simulation and treatment and their planning completed in a timely and accurate manner on multiple sets of diagnostic and planning image data (MRI/CT). Treatment must then be delivered with minimal inter-fraction and intra-fraction variation to ensure treatment

optimally hits a target which may be quickly evolving or changing. Some of these challenges and advances are reviewed below.

2.5.1 Simulation

Unlike small errors in treatment delivery which may change daily and be random, uncertainties/errors introduced during the simulation and treatment planning process are much more likely to be systematic and constant over the entire course of treatment with potential to decrease tumour control and/or increase normal tissue complications(71) Accurate simulation imaging (e.g. CT) and fusion of diagnostic imaging (e.g. MRI) is key to delivering a high-quality reproducible plan where the prescribed radiotherapy treatment is delivered to a target avoiding adjacent critical organs. There can be significant delays and variability of practice between the time of the diagnostic imaging and planning or commencement of treatment.

Impact of temporal changes in the target

High-grade tumours (primary CNS tumours or metastasis) within the brain can have rapid changes in size and geometry. A study by Ellingson et al found that patients with GBM experienced a rapid growth rate with a median volume doubling time of 21 days(72). For tumours that have been resected, the remaining resection cavity can undergo rapid changes as the post-surgical changes resolve. It is therefore difficult to balance the planning process to maximise plan quality whilst minimising the risk of geographic miss from changes in the tumour or resection bed target or tumour progression. Barriers to obtaining additional MRIs close in time to the delivery of radiotherapy include cost, limited availability, patient preference (claustrophobia) and avoidance of delaying radiotherapy(73).

Changes in primary CNS high-grade tumours

A study by Stenjoen et al (74) of 106 patients awaiting surgery for GBM tracked the growth of tumours using diagnostic scans and immediately pre-operative planning scan with at least two weeks between scans. Their study demonstrated that almost 1/3 of patients experienced a doubled tumour volume, whilst a further 1/3 were stable or smaller. The small tumours grew quickest, and the non-enhancing (necrotic) components grew most. This study demonstrated the rapid changes that can occur over a relatively short period and is of concern for patients going through the planning process for unresectable high-grade tumours.

Primary CNS Tumour Resection Cavity

Several studies have compared the volumetric changes on diagnostic scans of the resection cavities of high-grade gliomas(73, 75-80). The overall trend is for a decrease in resection cavity and subsequent GTV, CTV and PTV volumes(73, 75, 78, 80). This is complicated by changing geometry, with displacement of the resection cavity(73) influenced by intrinsic cavity factors (e.g. cavity bleeding or tumour re-growth) and extrinsic factors such as resolution of oedema or subdural haematoma(73). The flair and oedema signal has also been shown to change on the scans(73). This is important, as the flair signal is included in CTV of high-grade gliomas such as GBM in the

European guidelines whereas oedema is not(13). All these factors can lead to geographical miss of the GTV(76), or increased volumes of radiotherapy and therefore increased dose to organs at risk.

Intact Brain Metastasis

Intact brain metastasis has been shown to increase in the time interval between diagnosis and planning / delivery of RS (81). At a mean time of 23 days between diagnosis and treatment MRI on the day of RS, there was a median 1.5-fold increase in the brain metastasis volume. In this cohort of patients with >14days between pretreatment and treatment MRI scans, this would have resulted in a 26% marginal miss rate using the standard 2mm margin on the planning MRI. Larger brain metastasis and melanoma histology were associated with an increased required margin. In another study, time greater than 2 weeks between RS planning MRI and RS delivery was associated with worse local control which could be accounted for by tumour growth and RS marginal miss(82).

Brain metastasis cavity

A study by Jarvis et al(83) examined the tumour bed dynamics after surgical resection of brain metastasis, finding that the immediate post-operative volume of the target was smaller than that seen in pre-operative imaging. However, they found that most cavities do not collapse further and that nearly 1/3 are larger at the time of RS. This was supported by a study by Scharl et al (84) that showed 17% of cavities had an increase in size. This supports the need to obtain CT and planning images as close as possible to treatment delivery to minimise geographic miss of the target. In addition, cases of radiographic tumour progression were also noted in the 4-week post-operative period. Whilst a strategy is to increase the CTV or PTV margin to account for potential uncertainties, target size has been shown in the landmark RTOG 90-05 trial(85) to be an important risk factor for the development of CNS toxicity.

Despite evidence that the size and geometry of brain metastasis and high-grade glioma (or the resection cavities) change rapidly with time, there are only a small number of studies, with limited information on the impact on dosimetry.

2.5.2 Planning

There is time pressure to produce accurate and high-quality plans in CNS radiotherapy, given the immediately life-threatening clinical problem of high-grade tumours or brain metastasis and their rapidly progressive nature(86). There needs to be timely and accurate delineation of the tumour and critical organs in an anatomically complex site(87) and production and checking of a high-quality plan, which requires the significant expertise of experienced planning and checking staff, who may not always be available, particularly in out-of-hours emergency situations(88).

Radiotherapy planning is a complex, comprehensive process that involves the use of sophisticated technology as well as clinical radiotherapy professions (radiation oncologist, medical physicist, radiation therapist) (89). Knowledge of clinical factors (e.g. prior surgery and pathology) and experience with planning technology (e.g. planning systems and quality assurance systems) are essential to the production of high-quality plans(90) and minimisation of error(91).

This raises several issues in paediatric radiotherapy (particularly emergency situations) where caseloads can be relatively low even in high volume centres within Australia, and experience may be limited to a small group of physicians, medical physicists and radiation therapists who may not always be available(60). Over the last decade, technology has increasingly been introduced into radiotherapy departments to address some of these challenges in planning and checking radiotherapy plans(91, 92). One such tool is knowledge-based planning (KBP), which has been integrated into standard planning systems.

Knowledge-Based Planning

KBP is a planning tool that has been shown to be able to efficiently produce high-quality, consistent, clinically acceptable plans, independent of planner skills and experience(93). It has been widely implemented in radiotherapy, utilizing anatomical measurements and geometric relationships to create predictive models(94, 95). These models learn the relationship between patient geometry (shape and location of target with respect to organs at risk) and achievable planned dose distribution from a cohort of patient treatment plans. The model can then be applied to predict dosimetric outcome, including dose-volume metrics and spatial radiation dose distributions. An example of a commercially available system is RapidPlan™ (RP) which is a KBP system designed to improve plan efficiency and quality.

KBP has been used more widely in adult radiotherapy, offering advantages of improved planning efficiency with reduction in planning time (96), enhanced plan quality and improved conformity of plans by standardising treatment plan quality(97, 98). While commercially available tools like Rapidplan exist, challenges persist in developing comprehensive models, particularly for paediatric cancers with limited patient populations. A large study by Chung et al (93) analysed auto planning models across 10 sites and found that on average, 88% of KBP-generated plans were clinically acceptable and 98% of plans were acceptable with minor edits. The plans produced were not edited by planners. In cases where the KBP-generated plans failed to meet OAR constraints, plans were in many cases still deemed clinically acceptable, considering the trade-off of tumour coverage and OAR deviations. It is of note that no CNS cases or paediatric cases were included in this large study.

KBP in Paediatric and CNS tumours

KBP has been shown to be an effective tool in supporting QA activities in the evaluation and production of consistent treatment plans in clinical practice and in clinical trials(94, 97, 99, 100). These are important aims in paediatric radiation oncology where the caseload of individual treatment centres may be low due to the rarity of tumours. In Australia, paediatric radiation oncology is concentrated in specialised radiation oncology centres in state capital cities – however each centre may still only have a small number of rarer tumours over several years.

There is a very limited number of publications using KBP in paediatric radiation oncology, reflecting the low numbers of cases in individual centres and the difficulties therefore in producing models. A high-quality study with a national collaboration of paediatric radiation oncology centres in Italy used

a total of 87 patient craniospinal plans which was validated on a set of 26 patients. The plans were from 2016 to 2022, showing that even with a national effort (Italy with a population of 59 million people) in a relatively common paediatric cancer the number of cases per year in any individual centre remains low. This highlights the difficulties in producing paediatric KBP models. Challenges that were identified in this study included – wide variation in the anatomical volume between the target and the OARs across the age spectrum and the inherent difficulties of multicentric studies with variations in clinical practices, treatment techniques and the long timeframe required to accrue patients with changes in techniques and technology occurring over this period.

These challenges have been addressed in a study evaluating three KBP training models: on the full data set, on a reduced data set and with a Rapidplan model (RP-model) trained on KBP-guided replanned cases. The RP-model, developed through replanning based on KBP-driven (101) optimization, significantly improved precision and overall quality. Despite the RP-model precision, there was reduced accuracy as shown by a reduced prediction success rate on the validation set, indicating the difficulty in applying RP-models to paediatric planning with clinical variability. In keeping with other adult studies, model accuracy can only be improved by carefully reducing the dosimetric variability of the sample(98, 99, 102, 103).

KBP in CNS tumours

Similar to paediatrics, there is only a small number of publications using KBP models for radiotherapy to brain tumours. Most of the published work is in WBRT with hippocampal sparing, given for brain metastasis(104-108). These studies demonstrated that KBP provided similar dose distributions to conventionally planned VMAT (volumetric arc therapy) and IMRT (intensity modulated radiotherapy therapy), but with improved plan consistency, improved efficiency and minimal manual intervention.

There are two studies using Rapidplan for high-grade glioma. The first is for photon radiotherapy and investigated the use of KBP in GBM patients(109). This is the most common brain tumour in adults, but presents planning challenges for the large size and the variability in relationship to small organs at risk (pituitary, cochlear, brainstem, optic chiasm, hippocampus). This study developed a model with 100 plans which were a mix of IMRT and VMAT techniques, with the final model validated on an independent set of 45 patients with GBM, anaplastic astrocytoma and meningioma. The KBP time was typically 7 minutes for IMRT and 13 minutes for VMAT compared with 4 hours for manual planning. This study demonstrated the improvement in planning efficiency and in superior PTV coverage with sparing of normal tissues, irrespective of tumour location within the brain.

The second paper, by a Danish group(110), focused on the prediction of dose-sparing by protons assessed by KBP in brain tumours. This then informed case selection and referral of patients for proton therapy nationally. For protons, this study showed a strong correlation between the predicted and actual/achieved DVH metrics for the normal brain. Interestingly, there was poor

correlation between predicted and conventionally planned dose for the cochlear and pituitary which was presumed to be due to the small volumes of these organs and the placement of tumours relative to these. The authors further also concluded that the inherent planning challenges in proton beam therapy, such as the uncertainty of the Bragg peak/range position and the increased linear energy transfer at the end of the range, necessitate increased manual intervention in planning for protons.

For patients with aggressive primary CNS tumours such as DMG and GBM, these models have the potential to reduce planning time and improve efficiency for patients where treatment is time critical.

2.5.3 Treatment

Accurate patient setup and immobilisation are crucial to minimise patient positioning uncertainties in radiotherapy treatments. Both inter- and intra-fraction motions are important in precise treatments of high-grade brain tumours. For patients receiving RS, high precision is necessary where only one or several fractions may be delivered to the target with minimal PTV added. Immobilisation devices need to accurately position the patient, limit movement, be comfortable for the patient and quick to construct and apply for radiation therapists(111, 112). The International Society for Radio Surgery (ISRS) consensus guidelines recommends that sub-millimetre geometry accuracy be achieved during treatment, requiring stringent patient positioning (with immobilisation devices) and target localisation (image-guidance) particularly for small targets(112).

Additional Challenges with Paediatric and AYA Radiotherapy

The patient challenges were reviewed previously noting that age and medical condition (from tumour complications and post-operative complications) are all complicating factors in the setup and delivery of radiotherapy in this age group. It is also common for paediatric cancers to require CSI, due to the propensity of diagnosis (such as medulloblastoma) to spread through the cerebrospinal fluid (CSF). The planning and delivery of CSI remains challenging for all treatment modalities (VMAT, IMRT, protons, 3D-conformal). For both adult and paediatric patient setup, immobilisation, simulation, and treatment are difficult due to the complex needs of patients with primary brain tumours.

Paediatric patients being treated with CSI have several challenges, with the planning target volume for CSI being the entire CSI axis. Traditionally this was treated using opposed bilateral cranial fields matched to a posterior field using one or two spinal isocentres(113). Modern techniques using VMAT, tomotherapy or protons have several advantages over traditional field-based techniques, including the more comfortable supine position, position reproducibility, ease of anaesthesia and decreased dose to organs at risk(114). However, the CTV to PTV margins are small (5-8mm), leaving minimal margin for error(115, 116).

Setup Accuracy in CSI

Novak et al evaluated CSI setup and reproducibility for 10 patients undergoing tomotherapy-based CSI(21). They demonstrated that the mean setup deviation in the AP plane was 2.5mm at the sella, 3.4mm at T1 and 3.8mm at L5. The mean lateral setup error was 2.9mm, 4.0mm and 5.5mm at the sella, T1 and L5 respectively. The effect on dose was not analysed. They recommended that a 10mm PTV margin be used in the spine. These patients were all adults, with only one patient having a primary CNS malignancy. In addition, the immobilisation techniques did not include standard cranial immobilisation techniques such as a thermoplastic mask. Immobilisation was with an Aquaplast mask over the arms. An older study by Al-Wassia et al(117) showed that the mean patient shifts in the medial-lateral, cranial-caudal and anterior-posterior direction were 0.5 ± 2.1 mm, 1.0 ± 2.7 mm, and 0.7 ± 1.1 mm, respectively. They recommend a PTV margin of 3mm. The effect on dose was not analysed. Gupta et al(11) evaluated the three-dimensional setup errors using image guided IMRT radiotherapy for CSI. They reported the mean displacements in the lateral, longitudinal, and vertical directions as -1.2, -1.4, and 1.4 mm; -1.3, -0.3, and 0.7 mm; and -1.5, -2.8, and 0.2 mm for the brain; upper spine; and lumbar spine respectively. The effect on dose was not analysed.

There is very limited data within the literature on positional variation of children and adolescent/young adult patients (AYA) during CSI and the impact of this on dose delivered to target volumes and organs at risk, particularly using a highly conformal VMAT technique(118).

2.6 Quality Improvement

Quality improvement (QI) has been defined as a set of techniques for the continuous study and enhancement of healthcare delivery to meet patients' needs and expectations(119). It involves systematic, data-guided activities designed to bring about direct improvements in healthcare delivery (120) with the aim of interventions to improve existing practices or to prevent potential adverse events (121).

Providing effective healthcare that achieves desired outcomes for individuals and populations requires the identification and tackling of issues. These may relate to any aspect of patient care such as access to diagnosis through to treatment, patient safety, medical advances and technology, care coordination and/or the provision of patient-centred care, and quality monitoring(122). The basic steps in improving quality of care are shown in Figure 2-3 and include measuring quality (quality assessment),identifying variation (quality assurance), and implementing the appropriate changes to address these variations (quality improvement)(123-125). These issues form the basis of study for this thesis.

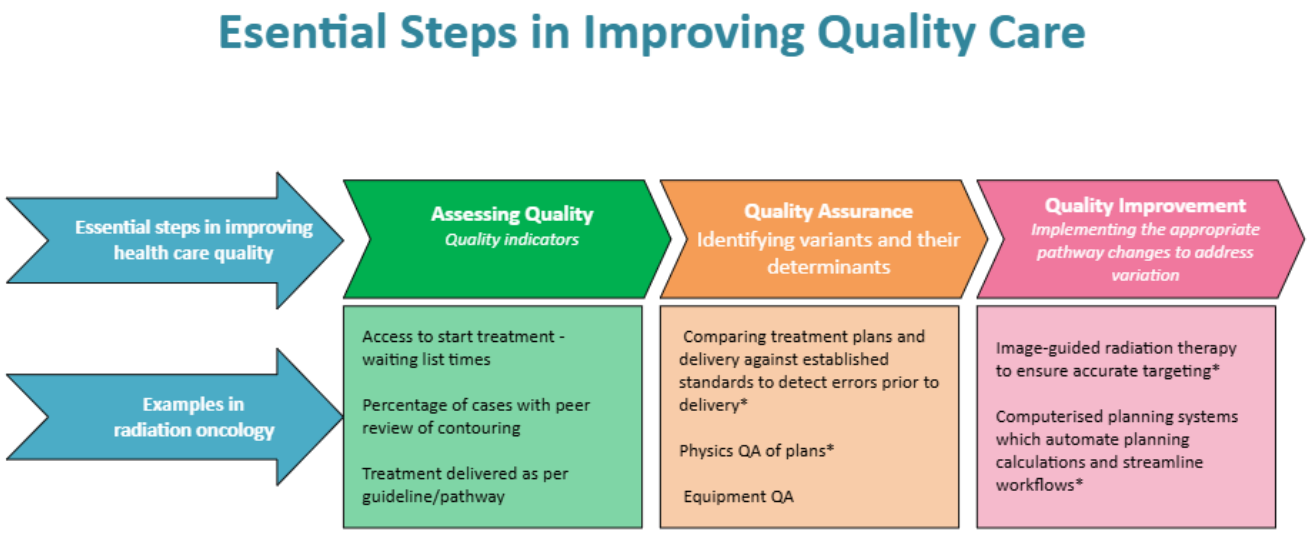

Figure 2-3: Essential steps in improving healthcare quality broadly and in radiation oncology. Areas focused on in this thesis have an asterisk

2.5.1 How to Approach Quality Improvement Within Radiotherapy

Quality improvement is a continuous activity such that the users of the quality system can learn from experience and feedback into the system (a learning healthcare system) to develop an even higher-quality system(126). Microsystems refers to small, organised groups of providers and staff caring for a defined population of patients(127). The clinical microsystem puts medical error and harm reduction into the broader context of safety and quality of care(128). It emphasises the small, replicable, functional service systems that enable efficient, excellent patient-centred clinical care to patients(129). In essence, a radiotherapy department may be viewed as a collection of interrelated 'microsystems'. Examples include:

i. CNS subspecialist microsystem comprised of CNS radiation oncologists, medical physicists, radiation therapists, nursing and clerical staff.
ii. Technique based e.g. radiosurgical or brachytherapy microsystem

The underlying principle of quality improvement is to be a continuous activity not a one-time event. A fundamental approach that serves as the basis for most health care improvement models is the PDSA cycle, which stands for Plan, Do, Study, Act (see Figure 2-4) which originated out of analysis of manufacturing quality improvements in Japan(130, 131). As illustrated in Figure 2-4, this cycle is a systematic series of steps for gaining valuable learning and knowledge for the continual improvement of a product or process.

Figure 2-4: Plan - Act – Study – Do 'PDSA' cycle. Adapted from New South Wales Government: Clinical Excellence Commission(132) and Langley et al(133).

Underlying the concept of PDSA is the idea that microsystems consist of interdependent and interacting elements that are unpredictable and nonlinear in operation(134). Therefore, small changes can have large effects on the system. Each study in this thesis was carried out with this methodology in mind with introductions to each chapter referring to this framework.

2.5.2 QI Interventions in Radiation Oncology

Analysis of national cancer registers/audits(123, 135, 136), as well as large cooperative group trial quality assurance programs(123, 137-139), has highlighted significant variations nationally and internationally in patient care and outcomes(123). Despite this, the interventions supporting quality improvement activities in individual departments remain poorly understood(123). A large

systematic review(123) of 7500 articles published on QI interventions in radiation oncology found that only 26 relevant studies were published between 2000 and 2024 and only 5 were conducted at regional(140-142) or national levels(143, 144) with the remaining being from individual centres. Only two studies examined QI in the Australian radiotherapy environment(140, 142). This highlights that there is a significant lack of published evidence on the impact of QI interventions in radiation oncology.

The main areas of focus have been in interventions to reduce waiting times(145-149) and increase radiotherapy usage (140, 141, 150) by targeting increasing referral rates. An Australian study by Job et al (145) examined the impact of direct referral to a palliative radiotherapy clinic. This study demonstrated a reduction in the mean waiting time of 3.5 days compared to 8.1 days for patients over the same period referred to standard clinics, which was statistically significant (P=< 0.001). Other areas studied include to decrease contour variability(143, 151, 152) and improve symptoms on or after treatment(153-155).

A prospective study by Gatfield(151) et al quantified the impact of a neuroradiologist during radiotherapy peer review of target volume and organs at risk volumes for head and neck cancer in a UK centre. When a neuroradiologist was present, 29/53 (55%) of plans had changes compared to 22/67 (33%) without. On multivariate analysis, the presence of a neuroradiologist significantly influenced the changes made during peer review meetings (OR 2.59; 95% CI 1.05-6.43; p = 0.039), improving consistency and enhancing quality assurance.

There was only one study identified that specifically looked at the impact of QI interventions in treatment of tumours within the CNS. This was a study by Kim(148) et al that examined operational improvement methods based on lean thinking to streamline radiotherapy treatment of patients with bone and brain metastasis. Lean thinking methodology centres around the concept of continuously improving performances by systematically eliminating waste in a process (156). In this study the number of steps to begin treatment was reduced from 27 to 16. This was achieved through a reduction in variability (e.g. education of clerical staff on medical terminology to improve appointment booking) and by standardising approaches (e.g. radiation oncology staff bring standardised simulation, billing and booking documents to clinical staff consulting with patients). The outcome was that the percentage of patient receiving consultation, simulation and treatment within the same day increased from 43% to 95%.

2.5.3 Safety Culture and Team Expertise

The ongoing and continuous nature of improvement in radiotherapy quality necessitates the development of a safety culture. The IAEA describes this within radiotherapy departments as the combination of attitudes, ideas, commitment and actions that determine how safety is managed and requires active participation from all workers, at all levels of an organisation(157). A widely cited definition is from the U.K. Health and Safety Commission(158). It notes that it is the product of individual and group values, attitudes, perceptions, competencies, and patterns of behaviour that

determine the commitment to, and the style and proficiency of, an organisation's health and safety management.

A study by Frank et al(159), demonstrated that a shift in departmental culture could be rapidly facilitated over a five-month period. The intervention used anonymous reporting with the use of an incident learning system (ILS), which was promoted and supported by practice leadership with a zero-blame approach. Report numbers increased from 45.4 reports/month to 138.4 reports/month (mean, 98.9; range, 3 – 162), demonstrating a rapid cultural shift. Recent similar studies have been undertaken in Australian centres evaluating the impact of anonymous reporting into ILSs with similar results(160-162).

2.5.4 QI summary

The studies summarised in section 2.5 demonstrate that QI intervention studies can improve efficiency and clinical care of patients receiving radiotherapy. They also show that studies can be performed at a local, national and international level, and that development of a safety culture can be rapidly instilled within radiotherapy departments. Overall, there is a lack of published data on the impact of QI interventions in radiation oncology, with very little published on the impact of QI studies in tumours of the CNS.

The radiation oncology community is well placed to study, implement and evaluate quality improvement initiatives through its departments, due to a combination of characteristics including its departmental micro-structures, measurement-based and evaluation-based approaches to process and practice, development of a culture of safety and a focus on quality assurance and radiation safety.

Whilst studies have focused on the identification of factors impacting radiation quality, there is a paucity of data examining how these affect clinical outcomes across different cancer types with the majority of data being derived in the palliative and head and neck settings. Furthermore, there is a lack of data examining how QI initiatives impact radiation quality and clinical outcomes such as overall survival and rates of late toxicity.

2.6 Conclusion

CNS cancers remain a significant clinical challenge with high-grade tumours carrying a very poor prognosis in both adults and children with limited effective treatment options. These tumours occur in or adjacent to vital areas of the brain critical to the brain's functioning. The proximity of the tumour target to critical organs at risk limits the safe radiotherapy dose. For paediatric patients, the risk of late permanent side-effects of radiotherapy at a young age also limits treatment choices.

The planning and delivery of CNS radiotherapy is a complex process that needs precision at all steps from simulation, immobilisation, image fusion and selection of planning margins. Both tumour

growth and changes in the resection cavity through planning and treatment add to the geometric uncertainties. Whilst highly conformal techniques such as VMAT, IMRT and RS have been developed to improve the therapeutic ratio, the accurate planning and delivery of treatment requires expert teams and strong quality assurance.

There are significant gaps in knowledge in the treatment of CNS tumours with radiotherapy, including limited real-world data on the impact of setup variation and anatomical changes on radiotherapy dosimetry and outcomes, particularly in the paediatric setting. Whilst there has been research into the impact of KBP models, there is minimal data on the use of KBP in rare CNS tumours and paediatric cancers. Further to this, there is a lack of CNS-specific quality improvement interventions linking directly to plan quality, tumour control, survival or late toxicity. Despite evidence that safety culture can improve rapidly, there is no consistent CNS-focused quality improvement framework, and a national systematic approach or data collection is lacking.

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Chapter 3 Changes in brain metastasis during radiosurgical planning

This chapter consists of the manuscript:

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The First page of the manuscript is included in Appendix A.

3.1 Abstract

Purpose: To determine whether there are any changes in brain metastases or resection cavity volumes between planning magnetic resonance imaging (MRI) and radiosurgery (RS) treatment and whether these led to a change in management or alteration in the RS plan.

Methods and Materials: Patients undergoing RS for brain metastasis or tumour resection cavities had a standardized planning MRI (MRI-1) performed and a repeat verification MRI (MRI-2) 24 hours before RS. Any change in management, including replanning based on MRI-2, was recorded.

Results: Thirty-four patients with a total of 59 lesions (44 metastases and 15 tumour resection cavities) were assessed with a median time between MRI-1 and MRI-2 of 7 days. Seventeen patients (50%) required a change in management based on the changes seen on MRI-2. For patients with 7 days or less between scans, 41% (9 of 22) required a change in management; among patients with 8 days or more between scans, 78% (7 of 9) required a change in management. Per lesion, 32 out of 59 lesions required replanning, including 7 of 15 (47%) cavities and 25 of 44 (57%) metastases, with the most common reason (23 lesions) being an increase in gross target volume (tumour) or clinical target volume (tumour cavity).

Conclusions: Measurable changes occur in brain metastasis over a short amount of time, with a change in management required in 41% of patients with 7 days between MRI-1 and MRI-2 and in 78% of patients when there is a delay longer than 7 days. We therefore recommend that the time between planning MRI and RS treatment be as short as possible.

3.2 Introduction

During the last decade there have been multiple studies published examining the treatment of patients with brain metastases. Overall, this has led to a shift away from whole-brain radiation therapy (WBRT) and toward local treatment modalities including radiosurgery (RS). Many patients with brain metastasis have poor survival; however, a subset of patients with a better prognosis may benefit from local treatment with radiation therapy and/or surgery (1-3). Importantly, more recent trials have also assessed the impact of WBRT on quality of life and cognition(4-7). For patients with limited unresected brain metastases, multiple randomized controlled trials and a meta-analysis have showed no survival benefit to the addition of WBRT to RS(5, 8-10). For those with limited resected brain metastases, a recent randomized controlled trial also showed equivalent survival and better cognitive preservation when comparing adjuvant RS to the surgical cavities with WBRT(11). Increasing evidence, coupled with improvements in technology, better systemic disease control with newer anticancer agents, and the widespread availability of RS and diagnostic magnetic resonance imaging (MRI) has seen a dramatic rise in the number of patients undergoing RS for the treatment of brain metastases(12, 13).

Practice varies among cancer centres with regard to timing of planning MRI and delivery of RS. It is widely acknowledged that a short time between planning MRI and RS is ideal; however, the logistics of RS planning and treatment, cost, availability of MRI, insurance processing, and patient factors means that a short period may not be possible.

At present, there is a paucity of prospective trials examining the impact that delays in imaging have on treatment planning and treatment delivery. Of concern is the potential for geographic miss when there are long delays between planning MRI and delivery of RS, considering the tight margins used.

To our knowledge, this is the first prospective clinical study to directly evaluate the impact of time between imaging and RS on treatment with RS for brain metastases. The aim of this prospective study was to determine whether there are any changes in brain metastases or resection cavity volumes between planning MRI and RS treatment and whether these led to a change in management or alteration in the RS plan.

3.3 Materials and Methods

Patient selection

Between February 2015 and January 2016, patients who were aged 18 years or older with 1 to 5 brain metastases and/or tumour resection cavities with histologically confirmed cancer were eligible for inclusion. Patients with hematologic malignancies or germinoma were excluded. Eligible patients had Radiation Therapy Oncology Group recursive partitioning analysis class I and II disease, with cases discussed by multidisciplinary teams involving radiation oncologists,

neurosurgeons, radiologists, pathologists, and medical oncologists. The protocol was approved by the local health district human research ethics committee.

MRI protocol

Standardized planning MRI (MRI-1) and repeat verification MRI (MRI-2) were performed on the same GE Signa HDxt 1.5T MR scanner (GE Healthcare, Waukesha, WI). Axial slices were obtained at a 1.25 mm slice thickness with non-contrast T1 and T2 sequences; afterward, contrast injection was used (gadobutrol, 0.1 mmol/kg body weight injected 10 minutes before image acquisition as per departmental protocol). This procedure was replicated for MRI-2 24 hours before RS.

Planning computed tomography protocol

Patients were simulated supine and immobilized with the BrainLAB cranial stereotactic radiotherapy mask system (BrainLAB AG, Feldkirchen, Germany) using a GE LightSpeed RT16 CT scanner (GE Healthcare). Non-contrast 1.25 mm sequences were obtained through the head and neck.

Planning procedure

Treatment planning was performed on a BrainLAB iPlan RT 4.1 treatment planning platform. The planning CT images were fused to MRI-1 using a standard departmental protocol, with the radiation therapist manually matching the scans and then using the iPlan 4.1 automated fusion algorithm. The radiation therapist then manually checked and altered the match based on the region of interest. An independent radiation therapist and clinician verified the fusion.

Gross tumour volume (GTV) on MRI-1 (GTV-1) (metastasis) and clinical target volume (CTV) on MRI-1 (CTV-1) (tumour resection cavity) were contoured, as were organs at risk including optic nerves, optic chiasm, ocular structure, and brain stem. Volumes were prospectively checked by a second radiation oncologist. The GTV-1/CTV-1 had a 2 mm circumferential expansion, creating a planning target volume (PTV)-1. Based on size and volume, 16 to 20 Gy in a single fraction was prescribed to the 80% isodose. For larger lesions, such as cavities, fractionated treatment using 21 to 30 Gy delivered in 3 to 6 fractions was prescribed to the 80% isodose line with a plan generated and physics check performed.

Twenty-four hours before RS, MRI-2 was performed and fused using the previously described methods. A new GTV-2/CTV-2 with 2 mm expansion to create PTV-2 was contoured by the treating clinician, and volumes were prospectively checked by a second radiation oncologist. The GTV/CTV and PTV volume changes between MRI-1 and MRI-2 were recorded, and the original plan was assessed visually by 2 radiation oncologists for coverage of the GTV-2/CTV-2 and PTV-2.

The GTV-2/CTV-2 coverage with the original PTV-1 was assessed by the treating radiation oncologist and a second radiation oncologist. [(Ps 3.1)] If any part of GTV-2 lay outside of the PTV-1 or if GTV-2 was contained within PTV-1 but touched the edge of PTV-1, a replan was required. This was recorded as a change in management (Fig. 3-1). An increased number of metastases on MRI-2 requiring either added target lesions or conversion to WBRT was also recorded as a change in management.

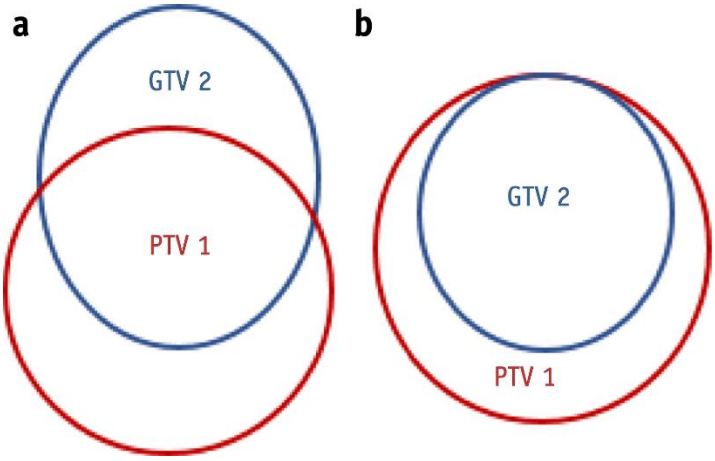

Figure 3-1: Scenarios requiring replanning. (a) The gross tumour volume on MRI-2 (GTV-2) outside of the original planning target volume (PTV-1). (b) Gross tumour volume on MRI-2 (GTV-2) immediately adjacent to PTV-1. Abbreviations: MRI = magnetic resonance imaging; MRI-1 = standardized planning MRI; MRI-2 = repeat verification MRI.

Statistics

Descriptive statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp, Armonk, NY).

Study design

The primary endpoint of the study was a change in management based on MRI-2. This included a change in treatment modality (from RS to WBRT, surgery, or best supportive care) or generation of a new RS plan.

3.4 Results

Between February 2015 and January 2016, 34 consecutive patients were planned for treatment with RS for brain metastases or resected tumour cavities. Table 3- 1 displays the patient characteristics. In total, there were 59 lesions, with 44 metastases and 15 resected tumour cavities.

Table 3-1: Characteristics of the 34 patients and lesions.

Characteristic	All Patients	Patients with a change in management based on MRI-2
Patient number	34	17 (50%)
Age in years (median, range)	57 (32-81)	62 (35-76)
Sex		
Female	16 (47%)	6 (35%)
Male	18 (53%)	11 (65%)
ECOG PS		
0	30 (88%)	16 (94%)
1	2 (6%)	1 (6%)
2	2 (6%)	0
[†]*RTOG RPA*		
Class I	13 (38%)	9 (53%)
Class II	21 (62%)	8 (47%)
[‡] *Lesions per patient*		
1	16 (47%)	6 (35%)
2	12 (35%)	6 (35%)
3	4 (12%)	2 (12%)
4	1 (3%)	0
5	1 (3%)	1 (6%)
Localisation of primary tumour		
Lung	13 (38%)	7 (41%)
Melanoma	12 (35%)	6 (35%)
Breast	4 (12%)	1 (6%)
Colo-rectal	2 (6%)	1 (6%)
Renal	2 (6%)	2 (12%)
Duodenal	1 (3%)	0
Systemic agent within 14 days prior to RS[§]	15 (44%)	9 (53%)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; RTOG RPA = Radiation Therapy Oncology Group Recursive Partitioning Analysis Class; RS = Radiosurgery.

* Brain metastases or resected tumour cavity.

The median time between MRI-1 and MRI-2 was 7 days; the time was 14 days or less in 31 patients (91%) and 7 days or less in 22 patients (65%). Of the 3 patients with an interval longer than 14 days between MRI-1 and MRI-2, 2 patients had a delay in treatment because they were unwell, and 1 patient had a delay in scheduling resulting from attending from a distant location. For patients with 8 days or longer between MRI-1 and MRI-2, a change in management or replanning was more

common (Table 3-2). For those with an interval of 7 days or less, 41% (9 of 22) required replanning because GTV-2 was touching or was outside of PTV-1. For all patients with more than 7 days between MRI-1 and MRI-2, 78% required replanning, with 8 of 12 (67%) being due to GTV-2 touching or outside of PTV-1.

Overall, 17 (50%) of patients required a change in management based on changes seen on MRI-2. Whilst the most common change was re-planning of RS, three patients showed rapid intra-cranial progression. Two patients developed lepto-meningeal disease (with a change in management to WBRT), the time between MRI-1 and MRI-2 was 10 and 20 days respectively. One patient with 14 days between MRI-1 and MRI-2 developed an additional nine metastases and had best supportive care (BSC) alone

Of lesions, 54% (32 of 59) required replanning of RS based on MRI-2, including 47% of cavities (7 of 15) and 57% of metastases (25 of 44). Reasons for replanning metastasis included an increase in GTV volume with part of the GTV-2 volume lying outside of PTV-1 (21 of 44 metastases) or GTV-2 touching the original PTV-1 (2 of 44 metastases) (Table 3-3). Two metastases decreased in size with geometric shift, with part of GTV-2 outside of PTV-1 or touching PTV-1. Both patients had received systemic treatment within 14 days of RS. Three patients had an increase in the number of metastases. Figure 3-2 demonstrates individual lesion volume change information. A summary of lesion percentage change for more than or less than 7 days between scans is summarized in Table 4. Figure 3 demonstrates the changes seen in one of the patients GTV (original GTV shown in green) with 7 days between MRIs.

Table 3-2: Number of patients and lesions requiring a change in management based on time.

Time between MRI-1 and MRI-2	Lesions requiring re-planning	Number of patients requiring a change in management
7 Days or less	16/35 (46%)	9/22 (41%)
8-14 Days	13/21 (62%)	7/9 (78%)

Amongst the cavity lesions, five lesions required re-planning, two lesions increased in size with the verification GTV lying outside of the original PTV, and three lesions verification GTV became smaller and touched or lay outside the original PTV (due to geometric shift).

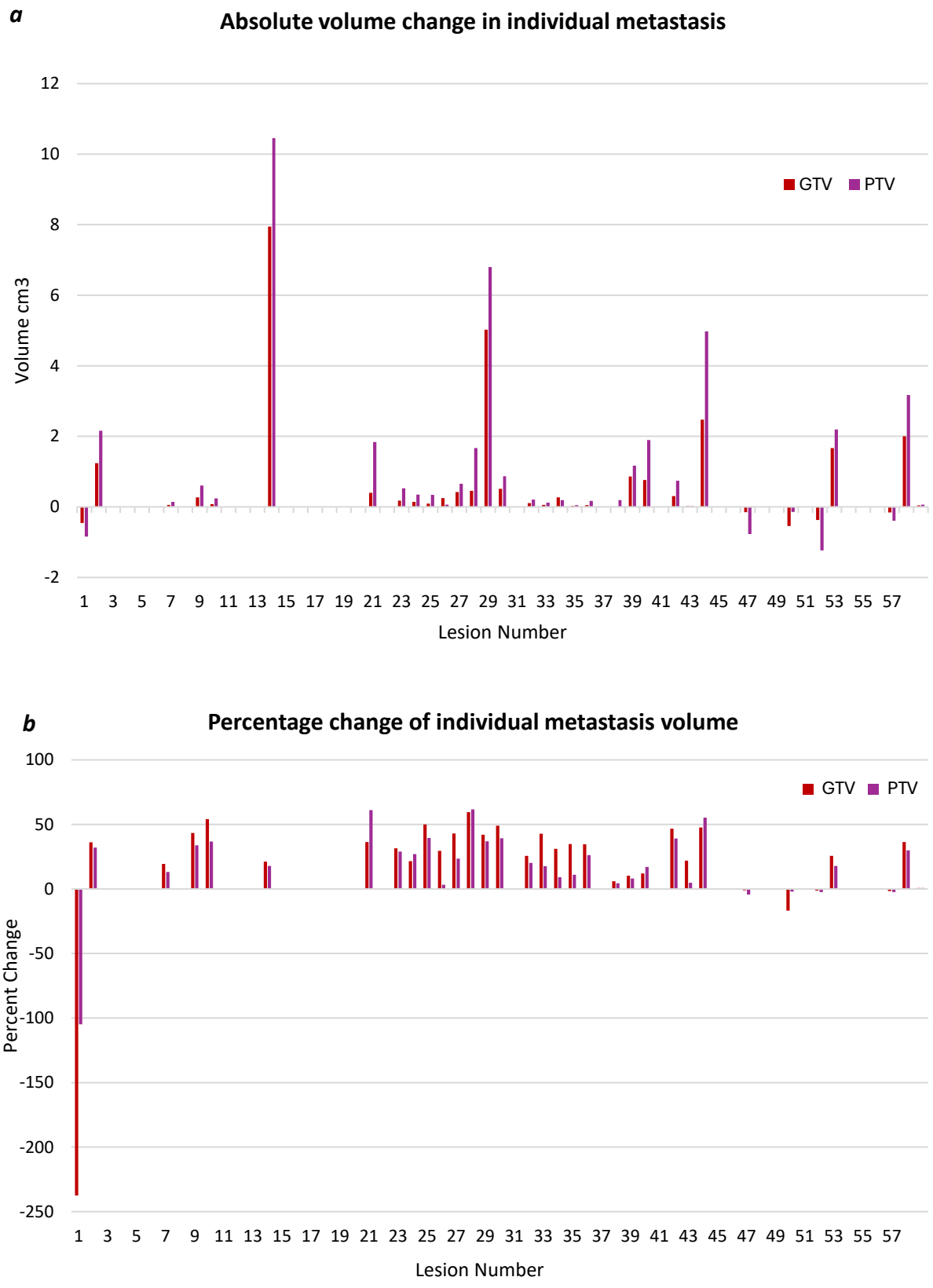

Figure 3-2: Absolute volume changes **(a)** and percentage volume change **(b)** in individual metastases and tumour resection cavity volumes between MRI-1 and MRI-2. Lesions 1-12 are resection cavities,

and lesions 13-56 are metastases. Abbreviations: MRI = magnetic resonance imaging; MRI-1 = standardized planning MRI; MRI-2 = repeat verification MRI.

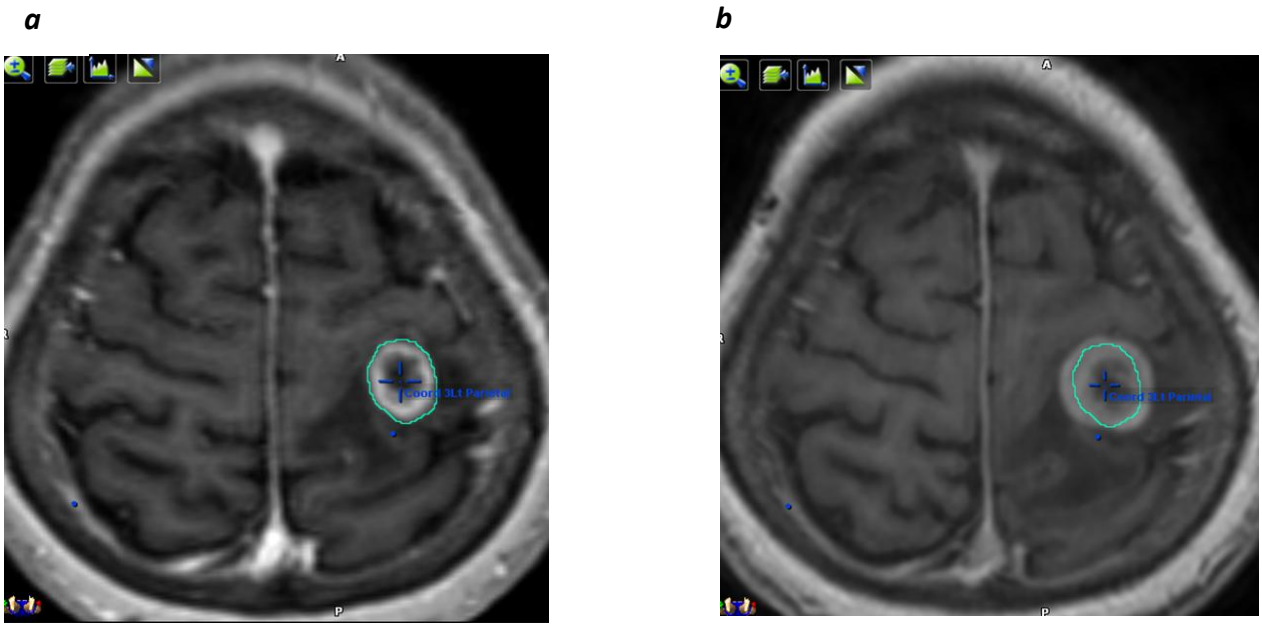

Figure 3-3:T1-gadolinium enhanced magnetic resonance imaging (MRI) of brain metastasis on planning MRI (a) and on verification MRI 7 days later (b). The original gross tumour volume is shown in green. (Ps3.2)

Table 3-3: Lesion GTV, PTV and CTV mean (range) volume on MRI-1 and MRI-2.

	MRI-1 (cm^3)	MRI-2 (cm^3)
Metastases GTV	2.13 (0.05-37.59)	2.28 (0.05-29.65)
Metastases PTV	4.14 (0.36-58.35)	4.47 (0.36-47.89)
Resection cavity CTV	14.83 (2.65-41.14)	14.87 (2.65-41.14)
Resection cavity PTV	22.83 (5.63-60.59)	22.80 (5.63-60.59)

Abbreviations: *GTV = Gross tumour volume; PTV = Planning target volume, CTV = Clinical target volume.*

3.5 Discussion

This is the first prospective study involving a standardized planning and MRI sequence specifically designed to evaluate the changes that occur during RS planning for brain metastases. We demonstrated that measurable changes occur in brain metastases over a short time, with a change in management required in 41% of patients with 7 days between MRI-1 and MRI-2, increasing to 78% of patients at intervals longer than 7 days. Changes led to alteration in management, including replanning of RS or changing the treatment modality to WBRT, surgery, or best supportive care. Changes more frequently occurred in patients undergoing definitive RS for

metastases in situ; however, changes also occurred in patients undergoing RS to surgical excision cavities.

There is limited information available to clinicians on how close to RS the planning MRI should be performed. RS is a complex treatment that requires coordination of multiple steps across many departments for accurate and safe delivery. Delays can occur because of institutional constraints, such as a limited number of MRI scanners or treatment appointments and availability of staff with expertise in RS simulation, planning, or delivery. The time taken for insurance approval for imaging or treatment also affects scheduling in some areas. Furthermore, patient factors such as distance to treatment facility or illness may delay any of the planning or treatment steps.

Seymour et al(14) completed a single-institution retrospective review evaluating workflow and patient outcomes for frameless stereotactic RS for brain metastasis. They demonstrated that local freedom from progression was lower in metastases with MRI performed ≥14 days before treatment (P = .0003, log rank), leading to their recommendation that the time from MRI to treatment should be <14 days.

Several retrospective studies have compared tumour cavity dynamics after surgery, with conflicting results regarding whether the cavity increased or decreased in size(15-17). The focus of these studies was to determine the optimum time for RS to minimize cavity volume treated. These studies compared the postoperative MRI volume to the RS planning MRI volume. It is not clear if the postoperative MRI used in these studies was fine-slice or if a standard contrast medium and administration technique was used to compare to the planning MRI; this makes volumetric comparison difficult. In addition, these studies did not specifically examine the effect of time on the geometry of the GTV/PTV. Given the tight margins used in RS, small changes in the volume or shape of the cavity can lead to geographic miss. The results of our study reflect the results of Shah et al, who indicated that tumour cavities are likely dynamic environments, with varying expansion and constriction over time(17). Uncertainty around this issue further supports the need for a short interval of time between the planning MRI and delivery of RS.

The precision of MRI in detecting the size and number of metastases changes with the thickness of MRI slices, field strength, choice and dose of contrast, and the timing and technique of image acquisition(18-20). A strength of this study is its prospective design, with standardized institutional protocols used to obtain both the planning and verification MRI.

The addition of the verification MRI is likely to have increased the diagnostic accuracy of very small metastases, with radiologists having 2 MRI scans to compare in a short amount of time. This was the case with the patient who received a diagnosis of very early leptomeningeal disease based on changes from MRI-1 to MRI-2.

One of the limitations of this study is the number of patients with a diagnosis of metastatic melanoma (because this is an Australian study). This patient population overall is known to have disease that can potentially progress rapidly. However, the most common diagnosis overall received by patients was lung cancer, followed by melanoma and then breast cancer. Table 1

shows the variety of other diagnoses within the patient population, reflective of the general burden of brain metastases in patients around the world. It should be noted that the presence of systemic therapy in the 2 weeks before treatment did not appear to stabilize the brain metastases requiring a change in treatment, and very few metastases or tumour resection cavities were seen to decrease in volume (Ps3.3).

Differences in image registration may also account for some of the changes seen. The original PTV should account for the uncertainties involved in image registration. For the cases that required replanning of RS, increases in tumour volume accompanied the verification GTV lying outside of the original PTV.

Before commencement of this study, our RS unit redesigned all planning and physics processes to be as streamlined as possible. Preliminary approved plans were produced for all patients using MRI-1, allowing all radiation therapy and physics staff to be aware of issues that may arise during quality assurance processes. This allowed for rapid replanning and maintenance of thorough quality assurance processes despite the short turnaround time between the verification MRI and RS. Currently, in our unit, patients undergo planning MRI 4 day before RS, which represents the shortest institutional time possible off study. We are actively working to decrease the time between planning MRI and RS to 24 hours as part of a larger departmental upgrade of equipment and our processes. (Ps 3.4)

This study is the first prospective study of the impact of MRI timing on the planning and delivery of RS for brain metastases. It has always been acknowledged that as short a time possible between MRI and treatment delivery is ideal, although this is not always feasible. Because of resource constraints, many departments will be unable to complete an additional MRI before treatment delivery. However, the results of this study provide the impetus for RS units to redesign and streamline all planning and physics processes and to shorten the interval from planning MRI to treatment delivery. We recommend that the interval between planning MRI and delivery of RS be kept as short as possible.

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Postscripts

Ps 3.1: If any part of GTV-2 lay outside PTV-1, or if GTV-2 was fully contained within PTV-2 but abutted its margin, a re-plan was mandated. This was to avoid geographic miss and to ensure there was an adequate margin for set-up uncertainty and intrafraction motion, given the steep dose gradients inherent to radiosurgery

Ps 3.2: Note: apparent differences in the image appearance reflect display and post-processing factors rather than resolution differences, therefore not affecting GTV delineation.

Ps 3.3: It should be noted that the presence of systemic therapy in the 2 weeks before treatment did not appear to stabilize the brain metastases, requiring a change in treatment, and very few metastases or tumour resection cavities were seen to decrease in volume (see Figure 3-2). The apparent decrease in a small number of metastases is likely due to the initiation of corticosteroids prior to therapy, leading to reduction in intra-tumoural oedema.

Ps 3.4: Strategies to decrease the time between planning MRI and treatment include: streamlining of referral and scheduling within hospital MRI radiology departments, engagement with private vendors' fast-track referrals, utilisation of 'in-house' radiation oncology planning MRI's as part of the planning process.

3.6 Strengths and Impacts

This study was one of the earliest quantitative analyses of changes in brain metastases during radiosurgical planning and demonstrated that significant volumetric and geometric variations occur within days, leading to the re-planning of cases. This work directly influenced clinical policy both nationally and internationally, as well as informing subsequent adaptive radiotherapy studies and clinical workflows—setting a benchmark for image-integrated quality assurance in radiosurgery.

Chapter 4 Using Knowledge-Based Planning to Shorten Planning Time for Diffuse Midline Glioma

This chapter consists of the manuscript:

Submitted as: Salkeld AL, Sykes J, Fernandez J, Inskip L, Thwaites DI. Using Knowledge-Based Planning to Shorten Planning Time for Diffuse Midline Glioma. Journal of Medical Imaging and Radiation Oncology. 2025 (under review)

Currently under review: September 2025

The First page of the manuscript is included in Appendix A.

4.1 Abstract

Purpose: Diffuse midline glioma (DMG) is an aggressive CNS malignancy typically affecting children that requires urgent radiotherapy treatment. This study evaluates the application of knowledge-based planning to expedite treatment planning while maintaining plan quality for paediatric patients with brainstem DMG.

Methods: Ten consecutive paediatric patients (ages 3-15) treated over a four-year period were retrospectively analysed. A RapidPlan (RP) model was built using 21 historical cases. Two radiation therapists—one paediatric specialist and one non-specialist—created both conventional VMAT and RP-generated plans for comparison. Planning time, target coverage, conformity index (CI95%), and doses to organs at risk were evaluated.

Results: The average planning time for RP was significantly shorter at 17 minutes (range 9-28) compared to 47 minutes (range 22-71) for conventional VMAT planning—a reduction of 64%. All plans achieved clinically acceptable coverage, with mean PTV coverage of 98.1% for VMAT versus 97.2% for RP. RP plans demonstrated superior conformity (mean CI95% 1.05 vs 1.24 for VMAT; p=0.00004). No significant differences were found in doses to organs at risk, though a trend toward lower pituitary doses was observed with RP plans (35.4Gy vs 39.4Gy).

Conclusion: Knowledge-based planning using RapidPlan significantly reduces treatment planning time for paediatric DMG while maintaining plan quality and improving conformity. This was for planners with paediatric planning expertise and those with limited experience. Implementation of knowledge-based planning can improve efficiency and reduce treatment delays for patients with DMG requiring urgent treatment.

4.2 Introduction

Diffuse midline glioma (DMG) is a rare but highly aggressive central nervous system (CNS) malignancy occurring primarily in children and young adults. The hallmark is a genetic alteration in the H3 gene, with the H3K27M altered tumour showing unrestrained growth and progression. The H3K27M altered tumour classification was added to the 2016 World Health Organization (WHO) classification of CNS tumour(1) with the 2021 WHO classification(2) further revised to include tumours with alternative mechanisms for the loss of H3K27M trimethylation (EZHIP overexpression DMG, EGFR mutant DMG).

DMGs are located in midline brain structures, most commonly in the brainstem (previously referred to as diffuse intrinsic pontine glioma; DIPG), but may also occur in other midline structures such as the thalamus and spine(3). Despite decades of trials, survival and prognosis have shown little improvement, with radiotherapy remaining the mainstay of treatment. The goal of radiotherapy is to slow tumour progression, relieve symptoms, and maximize tumour control, though cure remains rare.

A systematic review of the role of radiotherapy for DMG showed that the median overall survival and progression-free survival for patients with DMG treated with upfront radiotherapy (with or without systemic therapy) is 11.4 months and 7.7 months(4). Efforts by the radiotherapy community to examine the effects of hyperfractionated regimens, dose escalated regimens, or hypofractionated regimens have not led to improvements in outcomes(4).

The median age of DMG diagnosis is 6 -7 years(3) with patients typically presenting with varied symptoms depending on tumour location and brainstem involvement. These rapidly progressing neurological symptoms may include headache, coordination difficulties, weakness or paralysis, dysarthria, visual changes including diplopia, cranial nerve symptoms, seizures, and loss of consciousness. In addition, mood and behavioural changes may also be present. The tumour's location and rapid symptom progression frequently necessitate urgent radiotherapy.

The need for urgent radiotherapy planning and delivery has traditionally limited treatment to simple techniques such as parallel opposed beams or three-dimensional conformal radiotherapy (3D-CRT). While patients may initially receive parallel opposed beam treatment before transitioning to more conformal plans, field-based techniques using anatomic landmarks may inadequately cover the tumour or provide insufficient margins for clinical spread.

RapidPlan™ (RP) is a knowledge-based planning system designed to improve plan efficiency and quality (5). This study evaluates the application of knowledge-based planning using an RP model developed specifically for DIPG to expedite treatment planning while maintaining plan quality, including minimising dose to critical organs.

4.3 Methods

Patient Selection

This single-centre retrospective analysis included ten consecutive paediatric patients aged 3-15 years treated over a 4-year period (2020-2023) with a mix of VMAT, IMRT and 3D-CRT techniques. Patients with supratentorial tumours and tumours of the spine were excluded.

Simulation

All patients underwent CT simulation at diagnosis according to standard departmental protocol. Simulation was performed using a SOMATOM go.OPEN PRO CT scanner (Siemens, Munich, Germany) with 2.5-mm slice thickness. Patients were positioned supine with arms at their sides and immobilised using individualized thermoplastic head masks. Diagnostic magnetic resonance imaging (MRI) was acquired on a 1.5T scanner and fused with the planning CT. The MRI protocol included axial T1- and T2-weighted sequences, diffusion-weighted imaging, T2 FLAIR sequences, and gadolinium-enhanced images.

Initial Treatment Planning – Original Treatment Plans

Contours for target volumes and organs at risk were not changed from the original treatment plans which were completed as per departmental protocol under urgent treatment conditions. Urgent planning conditions were defined as a clinician recommendation for treatment to commence within 24-48 hours of the initial patient consultation and simulation, due to rapid clinical progression. The VMAT plans were then generated under urgent planning conditions. Gross tumour volume (GTV) was defined using the T1 and T2 MRI sequences with 10mm added to create a clinical target volume (CTV) which was cropped to anatomic structures (e.g. bone). The diffusion weighted images and contrast enhanced imaging were also available for contouring. GTV was expanded by 3mm to create a PTV. Organs at risk (OAR) volumes were contoured at the time of original treatment and were not changed. These included the spinal cord, cochlear, temporal lobes, optic chiasm, optic nerves and pituitary gland with 3mm added to create a planning organ at risk volumes (PRV). The original plans used a mix of palliative and radical doses; however, for the study plans all patients were planned with 54Gy in 30 fractions to PTV using a VMAT technique. This prescription was used for the re-planning study with new VMAT plans and RP plans generated.

Knowledge-based planning Model

A dataset of 21 plans for patients treated between 2013 and 2021 were imported to RP to build the model. Each patient dataset included planning CT and volumes. Seven of the later patients had been treated with VMAT and these plans were used to build the model. The remaining 14 plans required re-planning with a VMAT technique having previously been treated with 3D conformal or IMRT. The model was developed using the RP knowledge-based planning module within Eclipse version 16.1.2 (Varian Medical Systems, Palo Alta, CA) using the photon optimiser algorithm version 16.1.2. Given the limited number of cases available, model validation focused on internal comparison rather than independent cohort testing. Model performance was assessed by

comparing the dosimetry of the clinical VMAT plans with those generated by the RP model. Plan deliverability was assessed through standard QA evaluation.

Study Planning

Two radiation therapists participated in the planning comparison:

RT1: Senior radiation therapist (paediatric specialist)

RT2: Senior radiation therapist (non-paediatric specialist)

The planning assignment was structured as follows:

RT1: Cases 1-5 (VMAT), Cases 6-10 (RP)

RT2: Cases 1-5 (RP), Cases 6-10 (VMAT)

Neither planner had prior exposure to the cases before undertaking the planning process. Planning time was measured from opening the plan to final completion, using a standard paediatric VMAT brain protocol simulating urgent conditions. For the Rapidplan process, to simulate urgent clinical conditions typical for DMG cases, RP cases were limited to a maximum of two post RP optimization cycles to refine the initial plan produced by RP.

Dosimetry Review and Analysis

All plans were evaluated by a paediatric radiation oncologist for quality and clinical safety. The dose distribution was assessed visually for target dose coverage, conformity and hot spots both within and outside the target. Doses to OARs were also assessed visually. Both target and OAR standard dose-volume histograms (DVHs) were assessed and recorded, focusing on key metrics such as point minimums, maximums, means and the conformity index (CI95%). The CI95% is defined as the ratio of the volume of the planning target volume (PTV) receiving at least 95% of the prescribed dose to the total patient volume. Analysis focused on comparative dosimetric evaluation of target coverage conformity and OAR sparing between VMAT and RP plans. Key DVH parameters were compared with descriptive statistics; statistical significance between VMAT and Rapidplan plans was assessed using a paired sample t-test, with $p<0.05$ considered significant.

4.4 Results

Ten patients with DMG tumours located in the brainstem were identified. They were aged 3-15 years with a median age of 6 and comprised 6 female and 4 male patients. Planning time taken for generation of a VMAT plan and RP are shown in table 4-1 from opening the plan to closing.

The average for both planners for completion of VMAT planning was 47 minutes (range 22-71), and for RP planning was 17 minutes (range 9-28). Planner 1 (paediatric specialist radiation therapist) and Planner 2 (senior radiation therapist) both had similar times for completing VMAT and RP plans. For the VMAT plans this was a mean of 46 minutes (range 22-71) for the paediatric

radiation therapist vs 47 minutes (range 30-60mins) for the senior radiation therapist and for the RP plans 16minutes (range 9-21) vs 18 (range 10-28), respectively.

All plans achieved the planning objectives and were deemed clinically acceptable. Table 4-2 summarises the planning dosimetry results for the PTV and Table 4-3 the OAR dosimetry results. Overall, the PTV had similar coverage with mean 98.1% VMAT vs 97.2% RP. The average CI95% was more conformal (Figure 4-1) in the RP plans; i.e. CI95% closer to 1 for the RP plans, at 1.05 (RP) vs 1.24 (VMAT) which was significant (p=0.00004).

For the organs at risk there was no significant difference between the doses received between the VMAT and RP plans. There was a trend towards a lower RP pituitary mean dose with the mean VMAT dose 39.4Gy vs RP dose 35.4Gy but this was also not significant *(p = 0.12).*

Table 4-1: Comparison of time (in minutes) required for the generation of RapidPlan (RP) knowledge-based plans and manually optimised VMAT plans, measured from opening the plan to begin initial optimisation setup to final dose calculation.

Patient Number	**Planner 1**		**Planner 2**				
	RP (mins)	**VMAT (mins)**	**RP (mins)**	**VMAT (mins)**	**Difference (mins)**	**Median Difference Planner 1 (mins)**	**Median Difference Planner 2 (mins)**
1	16			60	44	35	23
2	9			40	31		
3	15			50	35		
4	18			55	37		
5	21			30	9		
6		51	28		23		
7		71	25		46		
8		22	14		8		
9		54	13		41		
10		33	10		23		
Mean	15.8	46.2	18	47			
Median	16	51	14	50			
Min	9	22	10	30			
Max	21	71	28	60			

Table 4-2: PTV volume receiving 95% of Dose. CI = conformity index.

Parameter	**VMAT**	**RP**	**t-test**	***P***

Mean	98.1%	97.2%		
SD	1.7	2.2		
Minimum	93.9%	94.0%		
Maximum	100%	100%		
PTV CI95% mean	1.24	1.05	-7.57	0.00004

Table 4-3: Organs at risk dosimetry. Gy = Gray.

Parameter	**VMAT mean (Gy)**	**RP mean (Gy)**
Cochlear Left Mean	29.3	30.1
Cochlear Right Mean	30.6	29.9
Optic Chiasm Maximum	48.6	48.4
Pituitary Mean	39.4	35.4
Spinal Cord Maximum	43.5	42.6

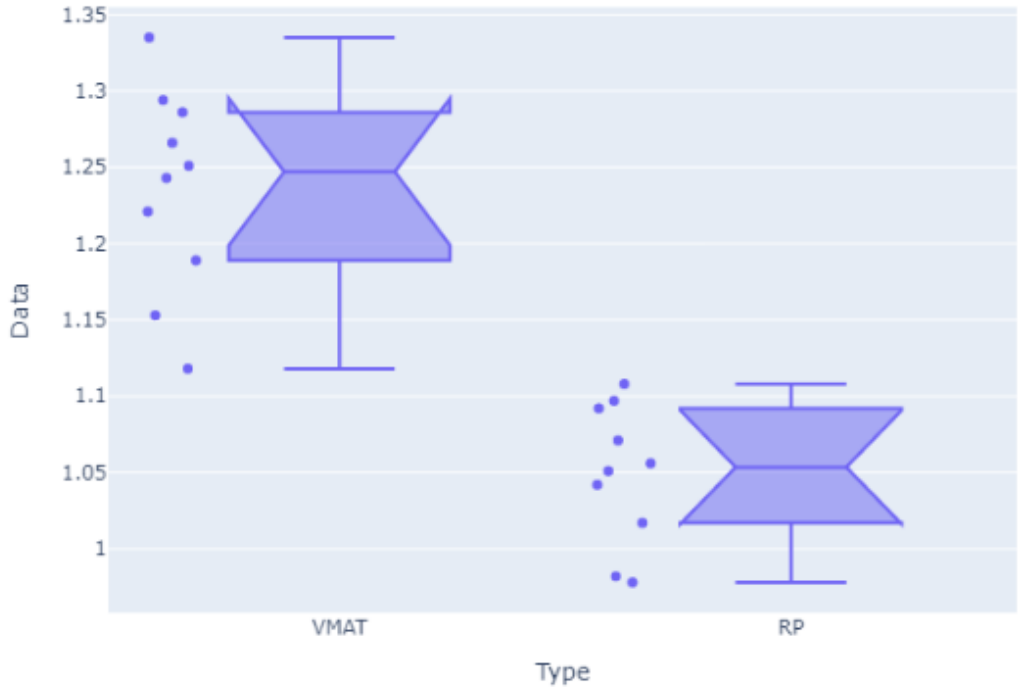

Figure 4-1: Comparison of CI95% for the PTV of VMAT and RP plans. Box plots illustrate the distribution of CI95% across the two planning approaches, highlighting variability and median differences between VMAT and RP plans.

4.5 Discussion

The findings of this study underscore the potential of knowledge-based planning (KBP) to expedite treatment planning for patients with DMG of the brainstem without compromising plan quality. This advantage holds true for planners with and without paediatric expertise. The results indicate a significant reduction in planning time when employing the RP model compared to traditional VMAT, which is critical given that the presentation of patients is often a medical emergency with the need for urgent treatment in this aggressive malignancy(4).

The median planning time for RP was markedly lower than that for VMAT with a median difference of 35 minutes for planner 1 and 23 minutes for planner 2 (see table 4-1). This reduction is particularly significant in a clinical context where time is critical, where delays in radiotherapy can lead to disease progression and worsening of symptoms. Streamlining planning without compromising quality can thus improve patient outcomes and optimize resource allocation within radiation oncology departments. The difference observed was more marked in the senior planner (non-paediatric specialist radiation therapist). This model allows for senior radiation therapists with less experience in planning paediatric cases to rapidly produce a high-quality plan in a shorter

time. This is important as an experienced paediatric radiation therapist may not be available when emergencies present.

This study uses the dose fractionation of 54Gy in 30 fractions. An advantage of using a Rapid plan model is that it can easily be adapted to other dose fractions. For example, the hypofractionated regimen of 39 Gy in 13 fractions which has been in use for around a decade in some centres around the world (6-8), with significant advantage in completing treatment in a much shorter time frame. Studies indicate that patients receiving this regimen typically experience mild to moderate skin erythema, but no grade 3 or 4 toxicity from radiotherapy. The use of well-tolerated hypofractionated regimens reduces the treatment burden on patients by allowing them to complete treatment more quickly. The development of a RP model with this dose fractionation can easily be developed and add to further efficiencies for planning in these cases. In addition, the development of a Rapidplan model for re-irradiation can be readily produced.

Knowledge-based planning (KBP) has been widely implemented in radiotherapy, utilizing anatomical measurements and geometric relationships to create predictive models(9, 10). These models analyse structural relationships and predict dosimetric outcomes, including dose-volume metrics and spatial radiation dose distributions. While commercially available tools like Rapidplan exist, challenges persist in developing comprehensive models, particularly for paediatric cancers with limited patient populations. Despite potential limitations in sample size, our model demonstrated robust performance when compared to standard volumetric modulated arc therapy (VMAT) planning, with potential for further refinement through additional case inclusion.

KBP has been used more widely in adult radiotherapy offering the advantages of improved planning efficiency with reduction in planning time(11) , enhanced plan quality and improved conformity of plans by standardising treatment plan quality(12, 13). The results of our study are consistent with these findings, with decreased planning time and improved PTV conformality. Despite the reduction in planning time, the treatment plans generated using RP remained clinically acceptable. Both RP and VMAT plans achieved the prescribed target coverage, with mean PTV coverage being comparable (98.1% for VMAT vs. 97.2% for RP). Notably, RP plans demonstrated superior conformity, as evidenced by the significantly lower conformity index (CI95% 1.05 for RP, 1.24 for VMAT). This improved conformity suggests that the RP model may better spare surrounding healthy tissues particularly important for a paediatric population.

While no statistically significant differences were found in the doses received by organs at risk, a trend toward lower mean doses for the pituitary gland was observed in the RP plans (35.4 Gy vs. 39.5 Gy for VMAT). Although this difference did not achieve statistical significance the decrease in pituitary dose seen in this study is likely to benefit some patients and the addition of increased patient numbers to the model may lead to further improvement in the dosimetry for the organs at risk.

Implementation of a RP model requires a structured quality assured commissioning process, including governance approval, medical physics/radiation therapist/radiation oncologist quality assurance review, followed by controlled clinical rollout and re-evaluation. The model should be

introduced with defined clinical indication specific to DMG in the brainstem and integrated into planning workflows. Early two-plan comparative audits and ongoing review of model performance including outlier tracking and re-training triggers are essential for reliable clinical use. The model could be adopted by other centres, provided they complete local import, independent validation on representative cases and peer review of initial plans, ideally supported through a formal research collaboration or data-sharing agreement.

Integrating RP into routine clinical practice could address several challenges associated with treating DMG. The rapid generation of high-quality treatment plans not only enhances efficiency but may also improve the overall treatment experience for patients and their families by reducing anxiety associated with prolonged waiting times for treatment initiation that is able to optimally cover the tumour and planning volumes.

Limitations and Future Directions

This study is limited by its retrospective design and small sample size. Incorporating additional DIPG cases into the model is likely to enhance organ at risk dosimetry and further improve plan conformity and target dose coverage.

4.6 Conclusion

In conclusion, the application of the RP model for the treatment of paediatric DMG facilitates the rapid generation of treatment plans with improved conformity, allowing for the timely initiation of urgent treatment.

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4.7 Strengths and Impacts

This study is the first to publish a validated RP model for DMG. It demonstrated that KBP can substantially improve plan consistency, reduce planning time, and minimise inter-planner variability for DMG cases. The model was able to generate plans of comparable or superior quality to expert-produced plans in significantly shorter timeframes. Notably, this chapter showed that KBP models are feasible within real-world clinical workflows, including urgent or time-sensitive scenarios. This has important implications for centres treating paediatric patients, where experience and planning capacity may vary. The methods used demonstrate that even for rare cancers, KBP models can be developed and successfully integrated into clinical practice—laying the groundwork for future tumour-specific models tailored to paediatric and AYA patients. This work contributes to the broader aim of the thesis of improving workflow efficiency and reducing variability through model-based planning approaches.

Chapter 5 Implementation of a Formal Planning Quality Assurance Checkpoint with Multi-Disciplinary Team Review for Radiosurgery

This chapter consists of the manuscript:

Salkeld AL, Sykes J, Nahar N, Hau EKC, Moodie T, Wang W, Thwaites DI. Implementation of a Formal Planning Quality Assurance Checkpoint with Multi-Disciplinary Team Review for Stereotactic Radiosurgery. 8th Annual Crown Princess Mary Cancer Centre Symposium. Sydney. 2019

Oral Presentation at Conference: November 16th, 2019

Part of this work was also presented as a poster: ESTRO 2018

Salkeld AL, Sykes J, Nahar N, Hau EKC, Moodie T, Wang W, Thwaites DI. EP-2175: Improvement in radiosurgical plan dosimetry with implementation of a quality assurance program. ESTRO 37. Barcelona. 2018. *Abstract available Radiotherapy and Oncology. Volume 127, Suppl 1, S1201-S1202*

The poster and abstract are in Appendix B

5.1 Abstract

The aim of this study was to determine if implementation of a formal dosimetric QA checkpoint in radiosurgery (RS) for brain metastasis led to an improvement in RS plan quality. Consecutive brain metastases RS cases were planned using a formal dosimetric QA checkpoint (scorecard) and compared to historic RS plans. There was a significant improvement in dose conformity and organ at risk doses with the introduction of the QA checkpoint. The introduction of a dosimetric QA checkpoint early in the planning process, ensures optimal standardisation of RS plans and improvement in RS plan quality.

5.2 Introduction

Cranial radiosurgery demands rigorous attention to all aspects of treatment planning and treatment delivery. The high doses used, coupled with small margins, has the potential for a higher rate of errors than conventional radiotherapy, as well as increased severity of adverse clinical events. Although radiosurgery (RS) planning has become increasingly automated, there is still significant subjective human input into the planning process. This can lead to inconsistent plan

quality and the potential for sub-optimal plans being delivered with potential compromise in patient care(1).

Large variations in plan quality have been reported both among different planners(2) and between institutions(3, 4). Whilst inverse planning has led to an improvement in plan quality, the multiple iterative steps that still require subjective clinician, physicist and radiation therapist/planner input means that plan quality remains variable. New planning software is using increasingly complex technology to address this issue using automated rule implementation and reasoning, multi-criteria optimisation and knowledge-based planning solutions(5, 6,7). However, these systems still require significant human decision making throughout their process and often rely on initial plan quality to drive the system.

Quality improvement is defined as systematic, data-guided activities designed to bring about direct improvement in health care delivery in particular settings(8). The aim of quality improvement interventions is to improve existing practices or to prevent potential adverse events(8). Quality assurance (QA) checkpoints are vital to ensure high-quality treatment of brain metastases with RS. There is very little published data in radiation oncology on specific departmental quality improvement interventions and their measured impact on radiotherapy quality (9), particularly in the field of cranial stereotactic radiosurgery.

As part of an institutional upgrade of cranial radiosurgery, a committee comprising radiation oncologists, medical physicists and radiation therapists was formed to review RS practice standards. It was recognised that RS plan quality was variable and that assessment of plan quality with formalized multi-disciplinary input early in the process may improve plan quality.

The purpose of this 18-month study was to determine if implementation of a formal dosimetric QA checkpoint early in the planning process, with a joint clinician/physicist/radiation therapist liaison led to standardisation of RS plans and improvement in RS plan quality.

5.3 Materials and Methods

Patient Selection and Planning

Over an 18 month period from January 2015, consecutive brain metastases RS cases were planned using a formal dosimetric QA checkpoint (scorecard). For historic comparison, 12 months of RS plans (January 2014 to December 2014) for brain metastases prior to the introduction of the QA program were reviewed with the same scorecard. Fractionated radiosurgery and tumour resection cavity lesions were excluded from both groups.

Evaluation of Treatment Plans

A formal scorecard (see appendix 4-1) was developed to provide qualitative analysis of RS plans based on cumulative dose-volume histograms with analysis of target coverage, dose conformity and organ at risk doses. Dose conformity for the metastasis planning target volume (PTV) was

assessed using both the Radiotherapy and Oncology Group conformity index(10) ($RTOG_{PITV}$) and the Paddick Conformity Index(11) (CI_{Pad}). Organ at risk doses, including to normal brain, optic nerves, optic chiasm and brainstem, were assessed. Table 5-1 lists the assessment criteria.

The simple scorecard was available to the planner for initial plan development, with each plan's compliance with QA measures assessed and categorised as acceptable/minor deviation/major deviation (see Table 5-1 for assessment criteria). Once the plan was completed by the planner, the plan and scorecard were formally reviewed by the multi-disciplinary QA team prior to plan approval. This was performed in real-time with physicist, radiation therapist and radiation oncologist present and built into the workflow as a formal step. Plans were subsequently either accepted or re-planned based on the advice of the multi-disciplinary team.

Statistical Analysis

Statistical analysis was performed in Microsoft Excel 2013 using the students t-test to test the significance of the difference in the means of the measured plan quality metrics before and after the introduction of the MDT review.

Table 5-1: Dosimetric parameters used for plan assessment and comparison. RTOG PITV = Radiation Therapy and Oncology Group prescription dose to target ratio; CI_{Pad} = Paddick conformity index;

Measure	Method	Description and Reference Range
Dose Conformity	$RTOG_{PITV}$ (12) is the prescription isodose volume(PI) volume divided by the target volume (TV) PITV = PITV	Should be kept as close to 1.0 as possible. <2 = acceptable 2-2.5 = minor deviation >2.5 or <0.9 = major deviation
	CI_{Pad} (13) is defined as: $CI_{Pad} = (TV_{PV})^2 / (TVxPV)$ where the TV_{PV} is the TV within the prescribed isodose surface, TV is the target volume and PV the prescription volume	A perfect plan has a CI_{Pad} of 1. <0.62 = deviation >0.62 = acceptable
Normal Brain	V_{5Gy} (%)	Measures the volume of low dose wash and aim to keep as low as possible
	V_{12Gy} (%)	<5-10cm^3(14)
Brainstem	Maximum	<12.5Gy(14)
Optic Nerve and Optic Chiasm	Maximum	<12Gy (15)

5.4 Results

Following implementation of the multi-disciplinary QA checkpoint, 30 consecutive patients with brain metastases were planned over an 18-month period. There was a total of 58 metastases, with a mean PTV volume of 3.9cm^3 (range, 0.4-12.7 cm^3) and each received a single fraction of radiosurgery (16Gy – 20Gy dose range). For historical comparison, a total of 10 consecutive patients with 19 metastases treated in the 12 months prior were identified with a mean PTV volume of 4.7 cm^3 (range, 0.6-12.5cm^3). Prescribed dose ranged from 14.25Gy to 20Gy delivered in a single fraction. All plans that went through the new QA checkpoint and scorecard had modifications made following review by the multi-disciplinary team.

The RTOG prescription isodose to target volume ratio (PITV) and Paddick conformity indices (CI_{pad}), showed a better conformity after the implementation of the program (see table 5-2). The mean PITV was 2.06 (SD ± 1.02) before the QA checkpoint and was 1.46 after (SD ± 0.47). CI_{pad} was 0.35 (SD ±0.17) prior to the introduction of the dosimetric QA and increased to 0.70 (SD ± 0.15). While the improvement in both conformity indices was statistically significant using a paired sample t-test *($p<0.05$)* the increase in Paddick CI was highly significant *($p<10^{-7}$)*. The distribution of CI_{pad} scores is shown in Figure 5-1. For the normal brain, the $V5_{Gy}$(%) mean improved from 13.1 (SD ± 8.2) to 8.2 (SD± 7.4) with $p < 0.05$; the V12Gy(%) mean improved from 1.8 (SD±1.4) to 1.1 (SD ± 1.3) and $p<0.005$.

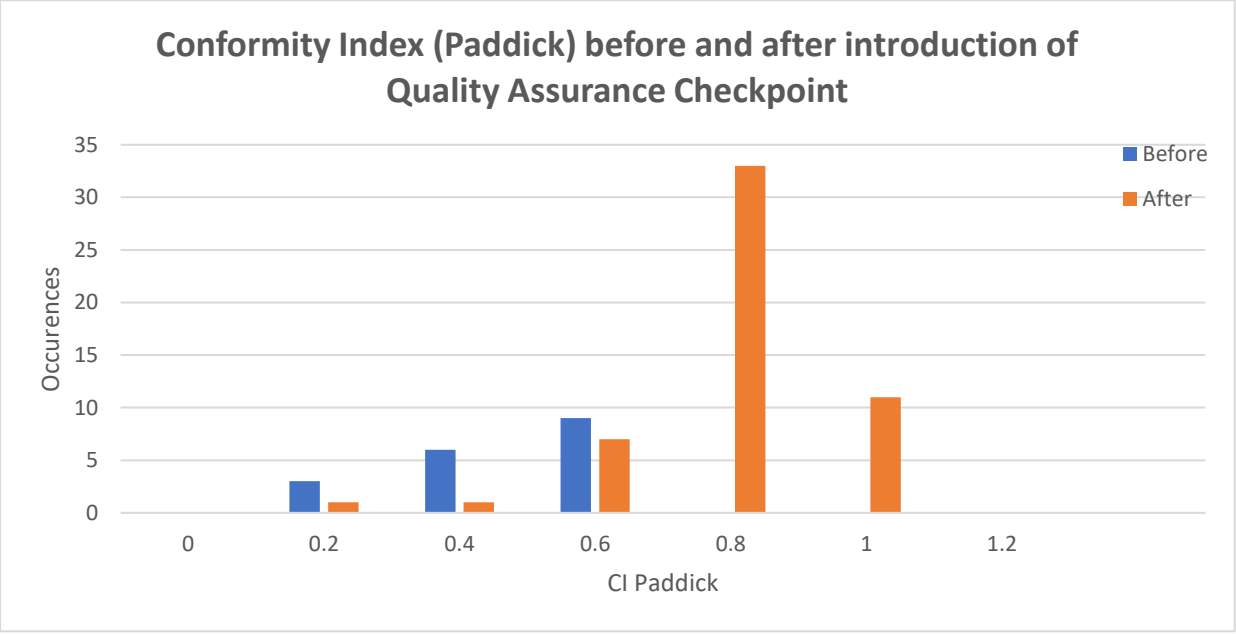

Figure 5-1: Histogram of Paddick Conformity index (CIpad) before and after the introduction of the QA checkpoint. A perfect score being 1, with acceptable being >0.62.

Table 5-2: Mean dosimetric parameters for the planning target volume and organs at risk before and after implementation of the dosimetric QA checkpoint.

	Mean ± SD prior to dosimetric quality assurance program Implementation	Mean ± SD after dosimetric quality assurance program implementation	P-value (no-difference in means)
PITV	2.06 (± 1.02)	1.46 (± 0.47)	0.023
CI_{Pad}	0.35 (± 0.17)	0.70 (± 0.15)	<0.001
Normal Brain			
V_{5Gy} (%)	13.1 (± 8.4)	8.2 (± 7.4)	0.021
V_{12Gy} (cm^3)	1.8 (± 1.4)	1.1 (± 1.3)	0.003

5.5 Discussion

Despite modern planning systems utilising inverse and knowledge-based approaches, there is significant variability of plan quality output in radiotherapy. There is a lack of universally accepted criteria in defining what is an 'optimum plan' and no straightforward mathematical solution to assess if a plan produced is optimal for a given clinical situation. The accepted plan represents a compromise of tumour coverage with adequate dose and minimisation of organ at risk late toxicity. Physician preference for planning goals is shaped by their training, experience and the individual patient consultation (where tumour control and toxicity are discussed, and patient preference solidified). Communication of these goals to the planning team throughout the planning process is vital to optimise plan quality and for teams to produce consistent high-quality plans.

Multiple data-driven solutions/planning tools have been developed to improve plan consistency, quality and efficiency. Knowledge-based planning systems are expert-based and aim to capture clinician knowledge and experience in terms of rules and algorithms(16) . The development of more sophisticated systems aims to generate clinically acceptable plans automatically. A recent review by Ge et al(15) found that the number of knowledge-based planning related studies has increased over the past seven years, but studies are still largely retrospective or use small data-bases. These solutions are often expensive, not available on all planning platforms, and require significant time and resource investment in-order to 'train the system'. The quality of the plans is also based on the quality of plans that have been used to build or train the system.

This study demonstrates that, with minimal staff and time resource or other costs, implementation of a dosimetric quality assurance step significantly improved PTV coverage and dose conformity with a significant improvement in both the Paddick and RTOG conformity indices. The doses to normal structures were also reduced, including the low dose to normal brain (represented by the

V5Gy) and the normal brain receiving high dose (V12Gy), thereby reducing the risk of radionecrosis. The low conformity scores for the PTV prior to the QA program implementation, reflects a diversity of planner experience in radiosurgery. With increasing and widespread use of radiosurgery, improvement and standardisation of plan quality are important for optimum patient care and outcomes, equally so for centres with high or low volumes of patients. Given the improvements observed following implementation of the QA checkpoint and low patient numbers, all eligible patients were included during the study period to show the overall benefit of the checkpoint rather than limiting the comparison to a matched cohort design. This is acknowledged as a limitation of the study.

Introducing the QA checkpoint required an initial investment of time to develop the program; however, as it was integrated into the existing real-time review process it required no additional staff or software. Plan reviews took only 5 minutes, and the spreadsheet developed during the project was adopted by planners to support optimisation. The checkpoint improved conformity and OAR sparing, representing a low-cost, high impact intervention without increasing resource demands.

The improvement in plan quality was largely driven by structured communication of clinical information, planning goals and technical issues within the multi-disciplinary team. This often compensated for planners with less experience, as well as making it clear what the clinician's major treatment goals were and the 'trade-offs' in dose to normal structure and PTV coverage that the clinician was willing to accept for each specific patient. Introducing this early in the planning process, improves efficiency, as additional time is not spent on a clinically unacceptable plan.

5.6 Conclusion

The introduction of a formal dosimetric QA checkpoint early in the planning process, with review by a multi-disciplinary team including clinician, radiation therapist and physicist ensures optimal standardisation of RS plans and improvement in RS plan quality. This work formed the basis for the development of standard departmental radiosurgical planning protocols currently used within the network. Although the checkpoint data are now incorporated into the updated planning system, a multi-disciplinary QA meeting/Checkpoint is performed prior to plan delivery. These reviews complement the standard independent medical, radiation therapy and physics checks and continue to reinforce a culture of shared learning and continuous quality improvement.

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Appendix

Stereotactic Radiosurgery QA

Patient Plan Quality Assurance

Fractions	3
Number of Mets	1

	Met 1	Met 2	Met 3	Met 4	Met 5
Dose [Gy]	24				
Location	Lt Frontal				
GTV Volume [cm³]	7.22				
PTV Volume [cm³]	12.693				

PTVs

Homogeneity Indices	$D_{2\%}$	31.07				
	$D_{98\%}$	25.7				
	D_{median}	29.2				
	HI	**0.184**				
	D_{max}	31.22				
	MDPD	**1.30**				

MDPD <1.25, 1.25-1.5, >1.5

Conformity Indices	Prescribed Isodose Vol [cm³]	17.15				
	PITV	1.35				
	Target Volume receiving PD	12.632				
	Paddick CI	**0.733**				
	D_{min}[Gy]	21.69				
	RTOG Coverage	**0.91**				

Dose Conformity [PITV <2, .2-2.5, >2.5]
Paddick CI >0.62, <0.67
RTOG Coverage <0.9, major <08.

OARs

Whole Brain - PTVs	D_{max}	29.9				
	V_{1Gy} [%]	28				
	V_{5Gy} [%]	7.9				
	V_{10Gy} [%]	2.3				
	$V_{19.5Gy}$ [%]	0.6				
	$V_{19.5Gy}$ [cm³]	9.5				
	$V_{19.5Gy}$ per Met]	9.5				

	D_{Max}
Rt Eye	0.19
Lt Eye	0.29
Rt ON	0.89
Lt ON	3.42
Chiasm	3.28
Brainstem	3.57

5.7 Strengths and Impacts

This study represents one of the first comprehensive evaluations of a multi-disciplinary QA checkpoint for radiosurgical cases. It demonstrated measurable improvements in plan quality at a time when limited QA capabilities were built into the planning system. Through the involvement of medical physicists, radiation oncologists, and radiation therapists in formal joint discussions, a structured framework was provided for plan discussion and optimisation. This improved communication between disciplines and, importantly, laid the foundation for developing standardised departmental radiosurgical protocols. While modern radiosurgical planning systems have many of these metrics built in, this study continues to influence the structure of departmental QA meetings, which are based on interdisciplinary communication and case review. This chapter offers a model for other departments to establish a framework of enhanced interdisciplinary communication and structured, team-based radiotherapy quality assurance. These findings support this thesis's overarching objective of improving treatment accuracy for complex CNS radiotherapy through systematic QA.

Chapter 6 Quality assurance and other challenges in paediatric radiotherapy: Accurate delivery of cranial-spinal radiotherapy

This chapter consists of the manuscript:

Salkeld AL, Sykes J, Fernandez J, Murphy L, Chard J, Thwaites DI. Quality assurance and other challenges in paediatric radiotherapy: Accurate delivery of cranial-spinal radiotherapy. Journal of Medical Imaging and Radiation Oncology. 2025. 69(3):388-394. doi: 10.1111/1754-9485.13721

Accepted for Publication: May 25th, 2024

The First page of the manuscript is included in Appendix A.

6.1 Introduction

Craniospinal radiotherapy (CSI) is a complex treatment technique used frequently in centres treating paediatric and adolescent/young adult (AYA) patients. It is used in the curative treatment of central nervous system (CNS) malignancies that commonly spread through the craniospinal fluid, such as medulloblastoma, disseminated ependymoma, non-germ cell tumours and embryonal tumours(1-3).

The planning and delivery of CSI remains challenging for all treatment modalities (VMAT, IMRT, protons, 3Dconformal). For both adult and paediatric patient set-up, immobilisation, simulation and treatment is difficult due to the complex needs of patients with primary brain tumours. This is further complicated for paediatric and AYA patients, with a variety of different patient needs across different age groups such as the need for general anaesthesia, play therapy, post-operative complications such as cerebella syndrome or the need for shunting. Considering the general issues for paediatric and adolescent young adult (AYA) patients, the QUARTET group (Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials) has recently published international guidelines to improve quality standards in radiotherapy and imaging for this patient group(4).

There is limited data within the literature on positional variation of children and adolescent/young adult patients (AYA) during CSI and the impact on dose delivered to target volumes and organs at risk(5). The aim of this study was to assess the set-up changes of both older and younger paediatric and AYA patients receiving CSI. The impact of these changes on target volume and organs at risk (OARs) were assessed.

6.2 Methods

Patients

The study was conducted as a single centre retrospective analysis of paediatric and AYA patients aged 4–25 treated with VMAT CSI between 2016 and 2022. 10 consecutive patients treated with standard departmental immobilisation and planning techniques were analysed. Patient age, demographics, diagnosis, prescribed CSI dose, fractionation, number of isocentres and complications during radiotherapy treatment were recorded through retrospective review of patient notes (see Table 6-1). The study proposal was submitted to Western Sydney Local Health District review and ethics committee with approval number 2303-15-QA.

Simulation and treatment planning

Patients were CT simulated with 2.5 mm slices in a supine position with arms by their side, with an individual neck mouldcare cushion, vacbag and thermoplastic head and neck mask using a SOMATOM go.OPEN PRO, (Siemens, Munich). Diagnostic MRI, both pre-operative and post-operative from a variety of imaging providers, were fused to the planning CT to aid contouring, including contrast and non-contrast T1 and T2, T2 flair and diffusion weighted images. The CSI Clinical Target Volume (CTV CSI) comprised the CTV Brain (including coverage of the cribriform plate and base of skull foramen), CTV C spine, CTV T Spine, CTV LS spine. Contours were completed as per the SIOPE consensus guidelines on CSI target delineation(6). CTV to planning target volume expansions were PTV = CTV brain +5 mm, PTV C spine = CTV C spine +5 mm, PTV T spine = CTV T spine +5 mm, PTV LS spine = CTV LS spine +8 mm, with all volumes then combined to make a PTV CSI. All planning target volumes were optimised using a commercial treatment planning system, Eclipse version 13.7 or 16.1 (Varian Medical Systems, Palo Alto, CA, USA).

Treatment positioning and verification

For treatment, patients were immobilised and set up in the simulated position. The reference marks on the patient's mask and body were then aligned in all three planes at each level as per the original CT simulation. Orthogonal kV paired images were taken at each isocentre starting from the most superior/head and neck isocentre. A match with 0 mm tolerance was made at the head/neck/most superior isocentre. The spinal isocentre/s paired images were taken and if each spinal isocentre was within an acceptable match tolerance of 3 mm, treatment commenced. If the spinal isocentre/s were not within the 3 mm acceptable match, the patient was adjusted and re-imaged at each spinal isocentre before treatment was delivered. This was repeated, or the patient completely re-set-up, if the match remained unacceptable. Departmental protocol is not to correct for z direction changes in the spinal fields to avoid changing the planned junction dosimetry. All image registrations were performed by a senior radiation therapist and verified by a second radiation therapist. Weekly CBCTs or extended CBCTS are taken for further review of matching offline in the 'Offline review' module in eclipse. The review of match is performed by an independent senior radiation therapist.

Retrospective review of inter-fraction geometric patient setup and dosimetric effect

A retrospective review of patient position was performed for all fractions of all patients in the study, following similar procedures to those used in the verification process. For each patient all treatment verification images (daily kV orthogonal images and any weekly CBCT's or additional CBCT's taken on treatment) were compared to the planning position at simulation. Two specialist paediatric radiation therapists and a paediatric radiation oncologist reviewed the changes between the planned position and treated position using the offline image review module (v16.1). The shift magnitude and direction of the spinal isocentres were recorded in the anterior–posterior, superior–inferior and lateral directions, evaluating the post-shift residual error. Reviewers were asked to annotate any perceived trends for patients.

To evaluate the dosimetric effects of changes in the treatment position for each fraction, the original plan was copied with the isocentre shifts applied for each fraction and recalculated using the treatment planning system. The same beam configuration and same total monitor units were used with the different treated isocentre positions. The dose for all treated fractions with included set-up errors was summed to estimate the delivered dose distribution. Plan quality metrics were then assessed for the delivered dose and compared to the original planned dose.

Statistical Methods

Population systematic and random errors and margins were calculated following the On Target 2 formulation(7). For each patient the range of variability between the planned and delivered treatment was assessed, considering the differences between planned and delivered doses to CTV, PTV and OAR for minimum, maximum, mean and median doses. OARs were assessed for clinically relevant endpoints.

6.3 Results

Patient characteristics for the study cohort are provided in Table 6-1. Half of the patients were pre-pubertal, and half were post-pubertal. 6 patients were treated with a single isocentre and 4 patients with two spinal isocentres. All but one patient was treated with either 23.4Gy in 13 fractions (5 patients) or 36Gy in 20 fractions (4 patients). One patient was treated with a 26Gy in 20 fraction protocol for a pineal tumour. The most common tumour type treated was medulloblastoma, in keeping with this being the most common indication for CSI in this age group. Clinical conditions impacting treatment are shown in Table 6-1 including, neurodevelopmental or learning disorders, hearing loss, emergency shunt placements, sepsis and cerebellar syndrome.

Table 6-1: Patient Characteristics.

Patient Number	Age	Gender	Diagnosis	CSI Prescription(Gy)	Number of Spinal isocentres	General Anaesthesia	Clinical conditions impacting treatment
1	14	Male	Medulloblastoma	36 in 20 Fractions	2	Yes	Neurodevelopmental disorder
2	19	Male	Relapsed Germ Cell Tumour	23.4 in 13 Fractions	2	No	Neoadjuvant ifosfamide / carboplatin/ etoposide. Significant radiotherapy associated nausea and vomiting, multiple transfusions through radiotherapy required
3	7	Male	Medulloblastoma	23.4 in 13 Fractions	1	Yes	Cerebellar syndrome
4	17	Male	Pineal Tumour	36 in 20 Fractions	2	Yes	Hydrocephalus with emergency presentation and Shunt insertion mid treatment
5	9	Female	Medulloblastoma	23.4 in 13 Fractions	1	No	Developmental learning disorder and hearing impairment
6	7	Male	Medulloblastoma	23.4 in 13 Fractions	1	Yes	Nil
7	10	Male	Medulloblastoma	36 in 20 Fractions	2	No	Unilateral upper limb and lower limb weakness using a wheelchair, significant anxiety requiring medication
8	12	Female	Medulloblastoma	36G in 20 Fractions	1	No	Hydrocephalus with shunt placement in the week starting radiotherapy. Uncomfortable in treatment position with shunt
9	6	Female	Medulloblastoma	36 in 20 Fractions	1	No	Rhinovirus with sepsis requiring admission
10	4	Female	Medulloblastoma	23.4 in 13 Fractions	1	Yes	Emergency shunt placement 2 days prior to radiotherapy starting. Panick attacks

Analysis of patient setup errors showed the overall population mean error was less than 1mm in all directions (see Table 6-2). The population systematic error was 0.5mm, 1.1mm and 1.6mm in the left-right, anterior-posterior, and cranial-caudal directions respectively with random errors approximately 0.5mm. This would lead to a CTV-PTV margin of 1.7mm, 3.2mm and 4.3mm, calculated using the van Herk formula(8, 9). This margin only accounts for setup error and

including uncertainties arising from delineation, dose calculation and intra-fraction motion would increase the required CTV-PTV margin.

Table 6-2: Population systematic (S) and random setup errors (s) calculated across all fractions for the patient cohort in the left-right (L-R), anterior-posterior (A-P) and cranial-caudal (C-C) directions. The margin calculation only includes patient setup error. Average Differences in setup for patients treated with and without general anaesthesia.

	CSI Setup Error (mm)		
	L-R	A-P	C-C
Overall Population Mean Error	-0.25	0.55	0.57
Population Systematic Error (S)	0.52	1.15	1.61
Population Random Error (s)	0.54	0.49	0.38
Absolute Maximum Setup Error	5.80	6.90	6.30
CTV-PTV margin (2.5 S +0.7 s)	1.69	3.21	4.29

The setup error overall is highest in the inferior spine (Figure 6-1) with most patients having a setup error of 3mm or less. In the superior spine the errors were 2mm or less for most patients. For the shorter patients with a single spinal isocentre, the setup error was 3mm or less for most of the patients. When retrospectively reviewed, all patients had some shifts outside of tolerance, with Figure 6-2 showing the frequency of absolute set-up errors for all patients across all fractions. The probability of the variance between patients receiving general anaesthesia and those that didn't as calculated by an F test was 0.88, 0.40 and 0.001 for the X, Y and Z. directions, respectively. The independent reviewers all independently documented a perceived 'flattening' or 'relaxation' in patients' shoulders and pelvis as treatment proceeded.

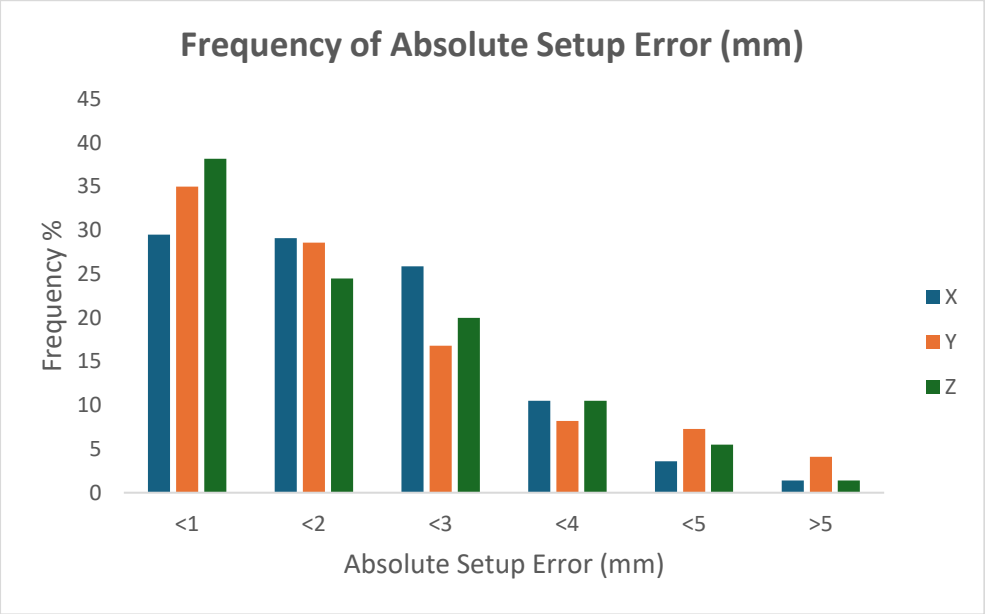

Figure 6-1: Frequency of absolute setup error in the X (left-right), Y (anterior-posterior) and Z (cranio-caudal) directions.

The mean change in coverage for CTV (as shown by change in minimum doses to the CTV in Table 6-3) was minimal. For the cohort, the mean minimum dose to all CTV's increased by 0.1Gy with a range of ± 0.5Gy. The changes in doses linked to clinically significant endpoints for the organs at risk are displayed in Table 6-4. For the parallel organs (Heart, kidneys, liver and lungs) the mean dose to the organs over the cohort was less than 0.15Gy (see table 6-4). The kidneys showed the biggest change. However, the maximum increase within all the patients was 0.83Gy. For the Oesophagus, the maximum point dose across the cohort increased by an average of 0.07Gy, with the highest increase in one patient being an increase of 0.53Gy.

Table 6-3: The CTV spine coverage for each patient showing the difference between planned and delivered dose across the delivered course in Gy. The bracketed results show the range over the patient group.

	No. Structures	**ΔMin**
All CTV	**26**	**0.1 [-0.5, 0.4]**
CTV C Spine	6	0.1 [-0.2, 0.4]
CTV T Spine	6	-0.1 [-0.5, 0.4]
CTV LS Spine	6	0.2 [0.0, 0.4]
CTV Spine	4	-0.4 [-0.2, 0.5]

Table 6-4: Changes in organ at risk dose (Gy) for all patients between the planned and delivered treatment, for doses linked to clinically relevant endpoints for each organ. Relative change is calculated based on prescribed dose.

	Absolute Change			Relative Change (%)		
	Average (Gy)	Minimum (Gy)	Maximum (Gy)	Average	Minimum	Maximum
Heart Mean	0.05	-0.08	0.26	-0.2	-5.1	1.1
Left Kidney Mean	0.14	-0.11	0.83	0.6%	-0.6%	2.7%
Right Kidney Mean	0.14	-0.17	0.51	1.0%	-1.1%	7.2%
Liver Mean	0.05	-0.07	0.20	0.4%	-0.2%	2.1%
Left Lung Mean	0.04	-0.16	0.31	0.1%	-0.7%	0.9%
Right Lung Mean	0.10	-0.12	0.3	0.5%	-0.3%	1.9%
Oesophagus Maximum	0.07	-0.49	0.53	-0.7%	-3.5%	5.1%

6.4 Discussion

The delivery of highly conformal paediatric and AYA CSI radiotherapy is complex with challenging planning, set-up and delivery of treatment across a variety of ages in patients with multiple medical comorbidities. PTV margins attempt to correct for this, but due to daily variation there can be extreme shifts outside of tolerance due to a number of factors. This study observed shifts of up to 6 mm in x, y and z directions. On any given day, a younger child may not tolerate the immobilisation mask despite multiple attempts at set-up and positioning. They may be restless and moving due to a co-morbidity such as upper respiratory tract viral infection or from anxiety; have difficulty understanding instructions due to hearing loss or learning difficulties; or be feeling unwell from chemotherapy. Compromises may need to be made on individual treatment days, with treatment outside of tolerance balanced against the risk of delays or not proceeding with treatment due to the extended set-up time. Taking multiple sets of kV images or cone-beam CTs for patient set-up may not be practical and may expose the patient to significant additional radiation. This study quantifies set-up error in real-world conditions in a paediatric and AYA radiation oncology department for a cohort of patients and assesses the impact of set-up errors on the dose to tumour volumes and OARs.

Traditionally, CSI involved treatment with opposed bilateral cranial fields matched to a posterior field with one or two spinal isocentres. However, modern techniques like VMAT, tomotherapy or proton therapy offer advantages such as a more comfortable supine position, better position reproducibility, easier anaesthesia management and reduced radiation exposure to organs at risk. Despite these benefits, the small margins between the clinical target volume (CTV) and planning target volume (PTV) (5–8 mm) allow little room for error.

This data analysis, for 10 VMAT paediatric and AYA CSI patients, indicated that some significant shifts outside of departmental tolerances were present during treatment on individual days (see Figs 6-1, 6-2). The largest shifts were seen in the lumbo-sacral spine, in keeping with previous published data. Within this patient cohort, shifts were observed with set-up errors exceeding departmental tolerances. These were accepted based on individual patient complications on given days. The data in Table 6-2 demonstrates that the median errors are mostly <1 mm but with a range that extends up to 6 mm. Comparing patients treated with and without general anaesthesia (as given by the F test), there was little difference in the X and Y direction; however, a significant difference was seen in the Z direction ($p = 0.001$) When using multiple isocentre VMAT CSI, there is no correction in the z direction to avoid over- or underlapping of field junctions leading to hot and cold spots. The changes in 'z' direction may be related to changes in patient position as they become more comfortable in the treatment position and less anxious through treatment with relaxation of the pelvis and shoulders as treatment days progress.

This study has shown that despite some such significant set-up shifts during daily treatment of CSI in paediatric and AYA patients this had little impact on the overall coverage of CTV as shown in Tables 6-3 and 6-4. There was very little change in the minimum dose to CTV across the cohort and no clinically significant changes to the doses to OAR. The relative change in OAR doses was minimal at 1% or less. This is shown in Table 6-4 where doses linked to clinically relevant endpoints (maximum or mean dose) are displayed for thoracic and abdominal organs at risk. The mean change in coverage for CTV (as shown by change in minimum doses to the CTV) was minimal. For the cohort, the mean minimum dose to CTV increased by up to 0.1Gy across all CTV volumes with a range of ±0.5Gy (see Table 6-3). These mean minimal doses to CTV represent an average of the minimum point doses across all fractions and are not clinically significant.

Paediatric and AYA patients present with a variety of challenges for accurate set-up for daily treatment of CSI radiotherapy. For example, the patient may become uncomfortable or irritable during treatment because of post-operative pain or nausea particularly with chemotherapy, fidgeting due to age or cerebella syndrome. Table 6-1 demonstrates that all but one patient had clinical conditions that impacted their treatment. These complications are common within this population due to tumour location in the posterior fossa, use of chemotherapy and a need to start radiotherapy quickly after surgery. This study demonstrates, that over a course of cranial spinal radiotherapy changes in coverage are minimal and are largely averaged out over the shifts where appropriate PTV margins are used.

All patients in the current study had some shifts outside of tolerance/PTV, which were accepted and treated on, for the reasons discussed above. Shifts for patients were in some cases in the same direction over several fractions. Despite this, the dosimetric differences were compensated for with daily movement across all fractions of radiotherapy and with rigorous set-up on other treatment days. This was the same for doses to OARs with dosimetric changes being not clinically significant.

The departmental PTV margins are comparable to those in the limited literature available(6). A recent paper by the St Jude group (10) analysed the set-up uncertainty of paediatric brain tumour patients receiving proton therapy but excluded CSI patients. This prospective study of cranial set-up uncertainty demonstrated that the 95th percentile can be reduced to approximately 1 mm with daily CBCT guidance and the treatment isocentre being located near the CTV centroid. CSI technique was not assessed. (Ps 6.1) Novak et al. evaluated CSI set-up and reproducibility for 10 patients undergoing tomotherapy-based CSI (11). They demonstrated that the mean set-up deviation in the AP plane was 2.49 mm at the sella, 3.40 mm at T1 and 3.83 mm at L5. The mean lateral set-up error was 2.86 mm, 4.02 mm and 5.46 mm at the sella, T1 and L5, respectively. The effect on dose was not analysed. The recommendation of the authors was for a 10 mm PTV margin to be used in the spine. These patients were all adults, with only one patient having a primary CNS malignancy. In addition, the immobilisation methods did not include standard cranial immobilisation techniques such as a thermoplastic mask. Immobilisation was with an Aquaplast mask over the arms. An older study by Al-Wassia et al.(12) showed that the mean patient shifts in the medial-lateral, cranial-caudal and anterior–posterior direction were 0.5 ± 2.1 mm, 1.0 ± 2.7 mm and 0.7 ± 1.1 mm, respectively. They recommend a PTV margin of 3 mm. The effect on dose was not analysed. Gupta et al.(13) evaluated the three-dimensional set-up errors using image-guided IMRT radiotherapy for CSI. They reported the mean displacements in the lateral, longitudinal and vertical directions as ±1.21, ±1.36 and 1.38 mm; ±1.25, ±0.34 and 0.65 mm; and ±1.47, ±2.78 and 0.22 mm for the brain; upper spine; and lumbar spine, respectively. The effect on dose was not analysed. (Ps 6.2)

This study demonstrates that departmental PTV margins compensated for occasional shifts outside tolerance during CSI radiotherapy. The shifts were not systematic in nature and appeared to cancel each other out across the entire course of CSI. However, there is a risk that shifts may become systematic for a patient in a particular direction, with trends not identified if different staff are treating or performing offline review on different days. We are currently developing a prospective daily monitoring system with alerts used to assess all shifts over all fractions, to identify systematic shifts for individual patients and evaluating the use of daily CBCT for use in CSI.

6.5 Conclusion

The current study demonstrates that robust PTV margins can compensate for occasional shifts outside of tolerance during CSI radiotherapy for paediatric and AYA patients. However, the use of large PTV margins would lead to increased irradiation of normal tissue, increasing the late toxicity in paediatric and AYA patients. The concern is that if shifts become systematic and the pattern is not picked up by treating teams due to rotating staff members that these may lead to decreases in coverage of the CSI volumes or increases in organ at risk doses To counter this, it is recommended that off-line review is performed at appropriate intervals to ensure systematic errors are identified, with appropriate action levels to ensure planning dose tolerance is not exceeded for OARs or the CTV dose coverage compromised.

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Postscripts

Ps 6.1: Novak et al. evaluated CSI set-up and reproducibility for 10 patients undergoing tomotherapy-based CSI (11). They demonstrated that the mean set-up deviation in the AP plane was 2.5 mm at the sella, 3.4 mm at T1 and 3.8 mm at L5. The mean lateral set-up error was 2.9 mm, 4.0 mm and 5.5 mm at the sella, T1 and L5, respectively. The effect on dose was not analysed. The recommendation of the authors was for a 10 mm PTV margin to be used in the spine. These patients were all adults, with only one patient having a primary CNS malignancy. In addition, the immobilisation methods did not include standard cranial immobilisation techniques such as a thermoplastic mask. Immobilisation was with an Aquaplast mask over the arms. An older study by Al-Wassia et al.(12) showed that the mean patient shifts in the medial-lateral, cranial-caudal and anterior–posterior direction were 0.5 ± 2.1 mm, 1.0 ± 2.7 mm and 0.7 ± 1.1 mm, respectively. They recommend a PTV margin of 3 mm. The effect on dose was not analysed. Gupta et al.(13) evaluated the three-dimensional set-up errors using image-guided IMRT radiotherapy for CSI. They reported the mean displacements in the lateral, longitudinal and vertical directions as ±1.2, ±1.4 and 1.4 mm; ±1.3, ±0.3 and 0.7 mm; and ±1.5, ±2.8 and 0.2 mm for the brain; upper spine; and lumbar spine, respectively. The effect on dose was not analysed

Ps 6.2: Although set-up variations of 0.5-6.2mm were observed, these produced minimal dosimetric impact, and margins of 3mm (cranial) to 8mm (lumbo-sacral) appear appropriate provided robust immobilisation, daily image guidance, consistent verification and tracking of shifts over a course of treatment are maintained.

6.6 Strengths and Impacts

The CSI dose-delivery and set-up accuracy study provided a detailed quantification of uncertainties for the delivery of CSI in children and AYA patients. This added to other published studies by producing real-world data studying the impact of daily shifts on dosimetry. By analysing set-up variations and their dosimetric impact, this work highlights the variability in day-to-day set-up and the challenges of paediatric CSI, and offers guidance on margin selection. Additionally, this study underscores the importance of developing real-time monitoring of shifts throughout radiotherapy to ensure they are not systematic. This chapter offers practical insights into one of the most technically demanding treatments in paediatric radiotherapy and helps guide clinical practice in Australia. The work strengthens the overarching theme of improving treatment accuracy for complex CNS radiotherapy.

Chapter 7 Discussion and Conclusions

7.1 Overall Discussion

Together, these studies examine the steps of the radiotherapy pathway for CNS adult and paediatric tumours. The studies demonstrate that potential errors and variations arise at multiple points – from imaging and anatomic changes during planning, through planning consistency and quality assurance processes, to setup and treatment delivery. As modern techniques become increasingly complex, with more steps, small deviations in any step can affect overall treatment accuracy. This section integrates the findings from chapters 3-6, demonstrating how each component contributes to understanding and optimising the radiotherapy process and to improving the quality of treatment across the entire pathway.

The overall aim of this thesis was to optimise CNS radiotherapy through (i) stronger image integration, (ii) improved planning efficiency nd consistency, (iii) strengthened workflow and quality assurance processes in planning and (iv) improved accuracy and robustness of radiotherapy treatment delivery for CNS tumours. Taken as a whole, the thesis evaluates the radiotherapy pathway as an integrated clinical system. By examining each stage of the pathway, the thesis focused on clinically relevant steps, leading to strategies that can have an immediate impact on the quality of radiotherapy treatment for CNS tumours. This thesis developed clinically feasible strategies to enhance CNS radiotherapy, improving safety, accuracy, quality, and the timely delivery of treatment. CNS radiotherapy was the focus of the thesis because it is one of the most technically demanding and clinically difficult areas of radiation oncology, playing a large role in the curative treatment of these tumours in adults and children. Including paediatric patients adds to the body of knowledge in paediatric oncology where they have historically been underrepresented.

Whilst non-clinical studies, including modelling and dosimetric simulations, have been key to advancing radiotherapy techniques, they are often conducted under theoretical or ‘perfect’ conditions. Radiotherapy in clinical practice is shaped by patient anatomy, workflow pressures, staffing, technology availability, resource constraints and patients who are often unwell. The studies in the thesis, therefore, prioritise real-world clinical data to understand how processes perform within a department and to identify achievable practice-ready improvements.

Although the individual studies examine different components of the workflow, they are unified by several key themes: the importance of high-quality, timely imaging, the need for planning approaches that remain robust under clinical urgency and variable expertise, and recognition that patient and tumour factors may lead to anatomic shifts or geographic misses in planning or treatment. Structured quality assurance is integral to improvements at both the system and individual patient levels. Together the studies form a coherent body of work that strengthens the entire radiotherapy process for CNS tumours across diverse clinical contexts.

Each study makes a progressive contribution to the overarching aim of optimising CNS radiotherapy. Chapter 3 strengthens the theme of imaging-integrated target definition by demonstrating, for the first time, that clinically significant volumetric and geometric changes in CNS lesions can occur within days (Study Aim 1); this finding directly supports the need for timely imaging and informs re-planning strategies. Chapter 4 advances the theme of improving planning efficiency and consistency by developing the first validated RapidPlan model for DMG (Study Aim 2); this study shows that KBP markedly reduces planning variability, improves OAR sparing, and shortens planning time—highlighting a robust transferable framework for rare paediatric and AYA tumours. Chapter 5 contributes to workflow optimisation and departmental QA by evaluating a formal multidisciplinary planning checkpoint (Study Aim 3); the work demonstrates improved plan quality and reduced deviations, showing the value of systematic QA structures embedded within routine planning. Chapter 6 characterises the real-world set-up uncertainties in craniospinal irradiation (Study Aim 4); this study provides one of the few paediatric/AYA real-world CSI datasets, defines the magnitude and distribution of positional variation, assesses its impact on dosimetry, and informs recommendations for robust margin selection. Together, these strengthen the evidence base for more accurate, efficient and consistent CNS radiotherapy.

Chapter 3: Anatomical dynamics and the central role of imaging in target accuracy

Chapter 3 delivered one of the earliest and most detailed quantitative assessments of volumetric and geometric changes in brain metastases across the short interval between diagnostic MRI and simulation. A key achievement of this was demonstrating that clinically meaningful alterations in tumour/cavity size and shape can occur within only a few days, changes substantial enough to require replanning. By providing clear, measurable evidence of this variability, the study strengthened the need for imaging to be as accurate and close to treatment delivery as possible, and it provides impetus for refining planning pathways to ensure rapid, accurate planning. This influenced both local policy and international discussions within the radiotherapy community.

This study highlights the importance of accurate and timely image integration into the radiotherapy pathway and clarifies why the workflow must be designed to minimise the time between imaging and treatment, whilst maintaining planning consistency, quality assurance, and delivery robustness in CNS radiotherapy.

Chapter 4: Achieving Planning Efficiency and Consistency Through Knowledge-Based Planning

The second study developed and validated the first published KBP model for DMG, a tumour where clinical urgency and variability in planner experience create difficulty. Its strength lies in demonstrating that the KBP can deliver high-quality plans with improved OAR sparing, but at the same time showing a substantial reduction in planning time and inter-planner variability. The consistent performance across the patient plans and with both experienced and less experienced paediatric radiotherapy planning staff underlines its importance and the potential for broader adoption in rare paediatric and AYA CNS tumours.

These achievements add to the overall thesis by improving planning efficiency, reproducibility and

access to high-quality radiotherapy. By demonstrating that complex CNS plans can be standardised without a detriment to dosimetry, the study shows that KBP can reduce workflow pressure, support junior planners and enhance departmental reliability. It builds on chapter 3, showing that after targets are accurately defined, planning can be completed efficiently and consistently through KBP - maintaining quality under urgent conditions.

Chapter 5: Structuring Departmental Quality Assurance to Reduce Variation and Improve Outcomes

The third study's primary achievement was the implementation and evaluation of a formalised multidisciplinary planning checkpoint—a structured QA process that demonstrated measurable improvements in plan quality and reductions in deviations across a diverse patient cohort. A key strength of this work is its real-world design: by embedding the checkpoint into routine practice, it demonstrated the practical benefits of oversight by a multidisciplinary team, early identification of planning issues, and greater standardisation of treatment. The study provides one of the most detailed descriptions of a departmental QA intervention applied prospectively in radiosurgery.

This study directly advances the thesis aim of robust QA through workflow-level interventions. It provides evidence that QA mechanisms do not need to be technology-heavy to be effective; rather, multidisciplinary communication, clear expectations, and structured review processes can systematically improve plan quality. The study builds on Chapters 3 and 4: once targets are accurately defined and efficiently planned, the checkpoint acts as a safeguard, ensuring those standards are upheld early in the planning process. This reinforces the aim of embedding robust, reproducible QA processes within the radiotherapy pathway. Beyond local impact, the study introduces a scalable QA model suitable for adoption within national and international radiotherapy networks (e.g. QUARTET, TROG, COG). In addition, it is suitable for low-resource settings, as technology outlay is minimal.

Study 4 (Chapter 6): Real-World Set-Up Variations and Implications for Treatment Delivery

The final study generated one of the few prospective datasets quantifying setup uncertainty in paediatric craniospinal irradiation, offering detailed insight into the magnitude and direction of positional variation across the brain and spine. A major strength is its practical focus: rather than relying on theoretical models or mixed adult–paediatric series, the study captures true clinical variability in a vulnerable patient group where immobilisation, age and treatment burden present unique challenges. The resulting data directly inform margin selection and highlight the components of CSI most susceptible to geometric inaccuracy.

These contributions align with the thesis themes by demonstrating how real-world delivery uncertainties must be incorporated into the design of earlier pathway stages. The study shows that even when imaging is current, optimisation is consistent and QA processes are robust, setup variability remains an inherent source of geometric risk that must be considered when defining margins and planning dose gradients. Chapter 6 builds on the earlier studies by demonstrating that treatment delivery is the final stage at which accuracy must be maintained.

Taken together, the four studies form a coherent and sequential body of work addressing each of the overarching aims.

- Aim (i): Strengthening imaging integration - Achieved through Study 1, which demonstrates rapid volumetric and geometric changes over short intervals, highlighting the need for timely imaging.
- Aim (ii): Improving planning efficiency and consistency - Achieved through Study 2 (KBP for urgent DMG cases) to reduce planning variability and time; and reinforced by Study 3 (structured QA reducing variability) which demonstrates improved plan consistency and quality through structured peer review.
- Aim (iii): Strengthening workflow and quality assurance - Achieved through Study 3 (multidisciplinary peer review) and Study 4 (real-world setup evidence supporting appropriate margins).
- Aim (iv) Improving the accuracy and robustness of radiotherapy treatment delivery – achieved through study 1 (accuracy) and study 4 which characterises real-world set-up uncertainty in CSI.

Findings from one stage of the pathway inform the next, and together, they provide practical, evidence-based strategies that strengthen the entire radiotherapy process for adult and paediatric CNS tumours. CNS radiotherapy quality is maximised when imaging, planning, QA and delivery are improved to produce system-wide impacts.

7.2 Conclusions

This thesis presents investigations of methods to optimise the planning and delivery of radiotherapy for adult and paediatric tumours within the CNS. By addressing the complex steps in radiotherapy through the study of real-world patient data and producing data relevant to everyday practice, it provides solutions that can be implemented immediately into clinical practice. Whilst each chapter addresses a discrete step in the planning and delivery of radiotherapy, taken together, this work demonstrates that CNS radiotherapy is a complex system that can be improved through the study and improvement of each step.

Challenging issues in CNS radiotherapy addressed include changes in volumes for stereotactic radiotherapy treatment of brain metastasis, urgent planning solutions for DMG in children, setup accuracy in the delivery of CSI for paediatric and young adult patients and the implementation of multidisciplinary QA processes for CNS radiotherapy.

Temporal Changes in Brain Metastasis During Planning

Chapter 3 examined the temporal changes in brain metastasis and resection cavities during the radiotherapy process. Consecutive patients underwent a standard planning MRI as well as a second verification MRI immediately prior to RS. The volumetric change in the metastasis/resection cavities and the impact of target and organ at risk coverage were analysed.

This study found that brain metastasis and tumour resection cavities change within planning time and that these changes were both measurable and substantial resulting in alterations to radiotherapy treatment plans for a large proportion of patients. Specifically, 70% of patients with delays longer than 7 days between planning MRI and treatment required re-planning of treatment to avoid a geographic miss, highlighting the importance of rapid turnaround of planning and treatment delivery in patients with brain metastasis. This was the first study of its kind, which has been cited 62 times in the literature since its publication (google scholar citation search September 9th, 2025). This work also prompted a comment to the editor of the journal highlighting the quality of the study and linking the work to controversies in RS practice. It also commented that it is a stimulus for further research into the link between clinical outcomes and margins applied in rapidly growing lesions treated with RS.

Knowledge-based planning can be successfully implemented for rare paediatric CNS cancers

The development of KBP models with limited numbers of patients is possible for DMG, despite the rarity of the cancer, meaning that a limited number of patient cases were available for model development. This study (Chapter 4) showed that high-quality plans could be produced in a rapid time frame by both experienced and less experienced planners without compromising plan quality. This provides a pathway for the rapid generation of high-quality plans using VMAT and opens the possibility of future studies into developing radiotherapy approaches for DMG without compromising time between planning and treatment, e.g. dose escalation through simultaneous integrated boosts or escalated doses to small boost volumes using highly conformal techniques.

Multi-disciplinary QA review improves treatment plan quality

This study (Chapter 5) highlighted the value of team communication and a multi-disciplinary approach to highly conformal radiotherapy planning for CNS tumours. It was completed at a time when automated QA data and options were limited. However, many of the lessons learned can be directly implemented throughout the process of CNS planning. This study reinforces the value of structured team-based approaches to plan quality in sub-specialised techniques such as radiosurgery, having a widespread clinical impact using existing resources and knowledge.

Real-world paediatric and AYA CSI setup variations have limited dosimetric impact

This study (Chapter 6) demonstrated that relatively large measurable setup variations can be observed within paediatric and AYA patients needing CSI treatment, due to the complex treatment needs. The most pronounced shifts were in the cranial-caudal direction. However, these setup errors had minimal impact on coverage of target volumes and organ-at-risk doses across whole treatments in the studied cohort, given the random direction of the setup errors. It does, however, highlight the need for ongoing vigilance and systematic monitoring across the course of radiotherapy for each patient.

7.3 Impact

The work in this PhD makes several important contributions to CNS radiotherapy for adults and children with aggressive CNS cancers. It fills gaps in evidence by providing real-world data on setup errors, tumour and resection cavity changes during planning, and the feasibility of KBP for rare CNS tumours in children. These are all areas where published literature is limited – particularly in children and AYA patients. The studies presented in this thesis provide practical solutions that can

be implemented by radiotherapy departments. KBP models, structured communication, QA checkpoints, and workflow refinements can be easily and rapidly translated into clinical practice. The studies were designed with QI principles in mind, with each study optimising an individual step in the complex process of CNS radiotherapy planning and delivery to improve patient safety and departmental workflows. The results of these studies provide evidence for the development of more nuanced national guidelines for radiotherapy for CNS tumours, underlining the need for a structured approach to QI projects linked to clinical outcomes, as well as opening future directions for research into radiotherapy for aggressive CNS tumours in adults and children. This thesis strongly advocates for further clinically based radiotherapy studies into tumours of the CNS in both adults and child – where prognosis remains poor and tumours are often rare.

7.4 Future Directions

The work highlights the lack of quality improvement projects in paediatric CNS radiotherapy. There is a lack of evidence linking quality assurance to patient outcomes, such as recurrence-free survival and overall survival. Whilst the study of rare tumours is inherently more difficult, given the small patient numbers, it is important that collaboration on a national and international level occurs to improve the quality of radiotherapy treatment and outcomes.

The work carried out for this PhD thesis shows the lack of data examining how brain tumours and their cavities change during the radiotherapy planning process and throughout treatment. Using our departmental MRI scanner, I plan to study the tumour cavity dynamics of primary brain tumours in adults and paediatric patients. This will involve comparing imaging at diagnosis, post-resection and during radiotherapy. For tumours or cavities that reduce in size through the planning period, this could lead to a reduction in treatment volumes. For paediatric patients who are at increased risk of late toxicity, decreased doses to critical organs (such as the memory centres) may reduce late toxicity. Conversely, for high-grade tumours, imaging may show tumour enlargement and geometric changes that help explain areas that progress after radiotherapy. This work will add towards the development of an adaptive radiotherapy trial in CNS tumours.

DMG continues to be one of the most difficult to treat tumours with a poor prognosis. Currently, there are no effective surgical or systemic treatment options, rendering radiotherapy the only effective (yet rarely curative) treatment option. Building on the findings of the PhD, I am developing a research program focusing on imaging and optimisation strategies for radiotherapy for DMG with a current grant application submitted.

Patients with DMG tend to recur in the centre of the tumour (as opposed to the dose fall-off region or periphery). The first area of study is to identify areas of likely relapse by comparing diagnostic MRI, mid-treatment and post-treatment MRI studies of individual patients. MRI and functional MRI sequences will be used to characterise the tumour dynamics through treatment and after treatment to identify imaging features at diagnosis that represent radioresistant parts of the tumour.

One hypothesis for the radioresistance of DMG is that the tumour microenvironment is relatively hypoxic, rendering the tumour resistant to treatment. Traditionally, hypoxia has been studied using hypoxic tracers in PET and correlated with a biopsy of the identified hypoxic areas. This is not possible in DMG due to the inability to biopsy specific areas in tumours as well as the time-sensitive and urgent treatment requirements of children with these tumours, meaning that minimal additional imaging can be completed. To look for the presence of hypoxia in tumours, MRI sequences will be used, thus not exposing the child to additional interventions. These will be correlated with the areas of treatment failure in DMG.

Predicting areas of likely relapse allows the study of dose escalation through simultaneous integrated boosts or RS to small areas. Previous studies have been limited in their capacity to dose escalate given the inherent radiosensitivity of the brainstem to large areas at high doses. Identification of smaller areas provides a feasible pathway to safe escalation.

Furthermore, boosting small areas identified on diagnostic imaging as being likely to be resistant gives an opportunity to explore boosting these areas with particle therapy (e.g. protons or carbon ions). After identification of these areas, we will conduct a planning study to look at the dosimetry and safety of using focal boosts within the brainstem.

The cellular mechanism of radioresistance in DMG is also poorly understood. By collaborating with existing radiobiology labs looking at cell death, I am imaging DMG cells following different radiotherapy fractionation schedules to better understand the mechanism of cell death and cell evasion. The goal of this is to identify optimal treatment fractionation size for radiotherapy (particularly boost areas) and establish the alpha/beta ratio of DMG. Through this work I hope to identify more optimal fractionation schedules that balance maximising local control while minimising number of treatment fractions to be attended by children and their families.

A priority is to establish national radiotherapy guidelines for the treatment of DMG. Current DMG guidelines focus on outdated ‘field-based’ techniques and do not include the use of hypofractionated schedules which have become commonplace in Europe. The development of a national approach lends itself to the development of a collaborative platform to collect data (e.g. radiotherapy dosimetric data and outcome), allowing for the development of clinical and QI projects that can track outcomes on a national level. Furthermore, within Australia, all children with DMG are offered genomic sequencing (which includes radiotherapy response and resistance profiling). This would allow dosimetric data and imaging data to be correlated for patients with DMG, which is not currently possible. These initiatives were discussed at the national paediatric radiotherapy special interest group meeting (April 2025) with broad agreement for me to move forward with a project leading this initiative – starting with national DMG guidelines.

Collaboration is key to this work and partners that I have engaged with include researchers at the Children’s Medical Research Institute Westmead (radiobiology), Biologically targeted Radiation Therapy (The University of Sydney) and our local radiotherapy MRI group, neurosurgeons and paediatric oncologists.

In addition to these tumour-specific programs and collaborations, several broader research opportunities have arisen directly from the findings of this thesis. Expanding these ideas to other CNS tumour types, eg Atypical Teratoid/Rhabdoid Tumour (ATRT), Ependymoma or Medulloblastoma, allows for large multi-centre trial development in adaptive radiotherapy and in the integration of novel imaging techniques outlined below.

One of the most promising is the development of adaptive radiotherapy trials for paediatric CNS tumours, leveraging the anatomical and volumetric changes demonstrated in this work as well as the optimisation of planning and quality assurance programs to rapidly integrate changes into treatment. A multi-centre feasibility study could assess the use of mid-treatment MRI (e.g., at weeks 2 and 4 of radiotherapy) to trigger adaptive replanning for paediatric brain tumours (e.g. medulloblastoma, ependymoma and ATRT). Collaboration with existing international groups such as COG, SIOP and QUARTET would be essential to ensure adequate patient numbers and to harmonise to current international treatment protocols. Such a trial would evaluate not only the dosimetric benefits of reducing CTVs in shrinking cavities (reducing late side-effects) but also the workflow implications, the suitability of imaging intervals, and potential reductions in late toxicity to improve neurocognitive and endocrine outcomes. This approach aligns well with emerging international interest in adaptive radiotherapy.

Anatomical imaging alone is insufficient for predicting patterns of relapse in CNS tumours. A further research direction would be to investigate the integration of biological imaging into radiotherapy planning, to improve the identification of radioresistant tumour subregions that may be amenable to targeted dose escalation. This work could begin with prospective observational studies coordinated through existing international networks such as QUARTET, the Children's Oncology Group (COG), and SIOP. Advanced MRI techniques—including diffusion, perfusion, susceptibility mapping, and MRI-based hypoxia surrogates—could be used to identify biologically aggressive or radioresistant tumour subregions. Within the same framework, existing PET tracers, such as hypoxia-specific tracers, as well as the development of novel tracers, could be incorporated to further refine biological target definition. Given the low patient numbers at individual centres, an international observational study collecting serial biological imaging (for example, MRI and PET hypoxia tracers) at diagnosis, mid-treatment, and post-treatment would represent a pragmatic first step.

Following identification of biologically aggressive or radioresistant regions, the next step would be to correlate the imaging features with patterns of failure and survival that could then be integrated with broader molecular tumour studies, such as the ZERO-2 trial. This would enable linkage of radioresistant imaging phenotypes with underlying tumour biology. This approach may help identify rational targets for combined systemic and radiotherapy strategies.

Large-scale imaging data would lay the groundwork for future dose-painting or sub-volume boost trials, informed by biological imaging, which would ideally be studied as part of a multinational cooperative trial. These studies could evaluate the feasibility of delivering simultaneous integrated boosts or stereotactic boosts to MRI- or PET-defined subregions predicted to harbour radioresistant cell populations. A staged phase I/II design would allow assessment of safety—

particularly with respect to brainstem tolerance—followed by evaluation of patterns of failure, local control, and functional outcomes. Incorporating proton or carbon-ion boosts into these trials would provide an opportunity to explore the advantages of particle therapy in delivering highly conformal, biologically targeted escalation.

There is also scope for trials that integrate knowledge-based planning (KBP) and multi-centre planning quality assurance. A national planning registry for paediatric CNS tumours could allow the refinement and optimisation of KBP models across multiple CNS and non-CNS paediatric sites. This would also allow standardisation of planning in multi-centre trials, including those examining different systemic treatments.

Further, embedding prospective peer-review processes within such a registry would address the current evidence gap linking planning QA to clinical outcomes, and could serve as a platform for a future cluster-randomised trial comparing standard versus mandatory multidisciplinary plan review.

Finally, several collaborative trial concepts arise from the evidence gap regarding setup accuracy and margin optimisation in paediatric CNS radiotherapy. A prospective, multi-centre TROG-led study could combine daily image guidance data with serial MRI to better quantify anatomical and positional changes during treatment. This would inform margin refinement strategies and support the feasibility of adaptive techniques in routine paediatric practice.

In all of this work, embedding patient-reported outcomes and neurocognitive endpoints into these trials would ensure that radiotherapy innovations are measured not only by technical success but by meaningful improvements in long-term survivorship. This can link to existing large survivorship projects, such as those from the COG and St. Jude Children's Research Hospital, to enhance existing networks and further improve PENTEC data.

7.5 Final Reflections

CNS tumours remain one of the most devastating cancers for patients and their families. Radiotherapy plays a large role in the treatment of these tumours – often in a setting where limited treatment options are available. Rigorous attention to all steps of radiotherapy, research embedded with QI principles involving real-world data, and examining solutions that are accessible to most centres around the world treating patients with CNS tumours is important to continue to improve treatment outcomes for our CNS patients. Rarity of tumours or being a paediatric patient should not be a barrier to studying methods of improving radiotherapy treatment.

Appendices

Appendix A: First author publications and related work

The following pages are front page copies of manuscripts where I am the first author which have been used as chapters in this thesis:

Chapter 3. published in Internation Journal of Radiation Oncology Biology Physics.

Chapter 4. submitted for peer review Journal of Medical Imaging and Radiation Oncology.

Chapter 6. published in Journal of Medical Imaging and Radiation Oncology.

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Determining Disease Extent

Changes in Brain Metastasis During Radiosurgical Planning

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Summary

The time between planning magnetic resonance imaging (MRI) and radiosurgical treatment of brain metastases and tumor resection cavities is highly variable among centers. This prospective study performed a standardized planning MRI and a repeat verification MRI 24 hours before radiosurgery. Any change in management, including replanning based

Purpose: To determine whether there are any changes in brain metastases or resection cavity volumes between planning magnetic resonance imaging (MRI) and radiosurgery (RS) treatment and whether these led to a change in management or alteration in the RS plan.

Methods and Materials: Patients undergoing RS for brain metastasis or tumor resection cavities had a standardized planning MRI (MRI-1) performed and a repeat verification MRI (MRI-2) 24 hours before RS. Any change in management, including replanning based on MRI-2, was recorded.

Results: Thirty-four patients with a total of 59 lesions (44 metastases and 15 tumor resection cavities) were assessed with a median time between MRI-1 and MRI-2 of 7 days. Seventeen patients (50%) required a change in management based on the changes seen on MRI-2. For patients with 7 days or less between scans, 41% (9 of 22) required a change in management; among patients with 8 days or more between scans, 78% (7 of 9) required a change in management. Per lesion, 32 out of 59 lesions

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Radiation Oncology Original Article

Using Knowledge Based Planning to Shorten Planning Time for Diffuse Midline Glioma

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Additional Information

Research Topics

Radiation Oncology; Peadiatrics

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RADIATION ONCOLOGY—ORIGINAL ARTICLE

Journal of Medical Imaging and Radiation Oncology

Quality assurance and other challenges in paediatric radiotherapy: Accurate delivery of craniospinal radiotherapy

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Abstract

Introduction: Cranio-spinal radiotherapy (CSI) is used to treat central nervous system malignancies in paediatric, adolescent/young adult (AYA), and adult patients. Its delivery in the paediatric/AYA population is particularly challenging across different age groups. This study aims to assess the setup variations and dosimetric impact of CSI in paediatric and AYA patients.
Methods: This retrospective analysis included, 10 paediatric and AYA patients (aged 4–25) who underwent volumetric modulated arc therapy (VMAT) CSI between 2016 and 2022. Patient characteristics, diagnoses, prescribed CSI doses, and fractionation details were assessed. CT simulation and treatment planning followed standard protocols with setup errors were quantified by comparing daily treatment setup images with the planned position. The study evaluated the dosimetric impact on target volumes and organs at risk (OARs).
Results: The setup errors were identified, ranging from 0.5 to 6.2 mm in different directions, especially in the cranio-caudal direction. Despite these variations, there was minimal impact observed on the coverage of clinical target volumes (CTV) and doses to OARs (<1% relative change).
Conclusion: Ensuring precise setup in paediatric and AYA patients undergoing CSI is essential to maintain adequate CTV coverage. Although occasional substantial setup variations occurred during treatment, they had a limited impact on CTV coverage and OAR doses when infrequent. Appropriate planning target volume (PTV) margins can effectively compensate for occasional shifts. However, systematic errors could compromise treatment quality if undetected. Regular off-line review of patient set-up trends is recommended.

Key words: cranio-spinal radiotherapy; paediatric radiotherapy; peadiatrics; quality assurance; radiation oncology.

Introduction

Craniospinal radiotherapy (CSI) is a complex treatment technique used frequently in centres treating paediatric and adolescent/young adult (AYA) patients. It is used in the curative treatment of central nervous system (CNS) malignancies that commonly spread through the craniospinal fluid, such as medulloblastoma, disseminated ependymoma, non-germ cell tumours and embryonal tumours.[1–3]

The planning and delivery of CSI remains challenging for all treatment modalities (VMAT, IMRT, protons, 3D-conformal). For both adult and paediatric patient set-up, immobilisation, simulation and treatment is difficult due to the complex needs of patients with primary brain tumours. This is further complicated for paediatric and AYA patients, with a variety of different patient needs across different age groups such as the need for general anaesthesia, play therapy, post-operative complications such as cerebella syndrome or the need for shunting. Considering the general issues for paediatric and adolescent young adult (AYA) patients, the QUARTET group (Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials) has recently published international

Appendix B: First Author Poster

The following pages are front page copies of abstracts and posters where I am the first author which have been used as chapters in this thesis:

Chapter 5. poster presentation ESTRO 37 – Barcelona 2018

Improvement in radiosurgical plan dosimetry with implementation of a quality assurance program

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PURPOSE

Quality assurance (QA) check points are vital to ensure high quality treatment of brain metastases with radiosurgery (RS). The small margins used require rigorous attention to all clinical and technical steps contributing to treatment quality. Poor quality radiotherapy has been reported to impact overall survival and increase treatment failure(1, 2). In 2015, an internal audit of RS plans demonstrated that minimal dosimetric QA parameters were being formally reported or assessed during RS planning for brain metastases. The purpose of this 18 month study was to determine if implementation of a dosimetric QA checkpoint, with joint clinician/physicist/dosimetrist review and using a dosimetric QA program early in the planning process led to improvement in RS plan quality.

METHODS

A committee comprising a radiation oncologist, physicist and radiation therapist performed a literature review of RS practice standards and recommended reporting of conformity indices (see table 1), as well as organs at risk (including normal brain). A scorecard / template was developed indicating each plan's compliance with QA measures (acceptable/minor deviation/major deviation and this was built into the work-flow to streamline the process. The plan and scorecard were assessed by the planner during the planning process and reviewed by the multi-disciplinary QA team prior to plan approval. 12 months of RS plans (January 2014 to December 2014) for brain metastases were reviewed as a historical comparator. The QA program was introduced in January 2015. Fractionated radiosurgery and tumour resection cavity lesions were excluded from both groups.

RESULTS

For historic comparison, a total of 10 patients with 19 metastases were identified with a mean PTV volume of 4.7 cm3 (range, 0.6-12.5cm3). Prescribed dose ranged from 14.25Gy to 20Gy delivered in a single fraction. After implementation of the QA program 30 patients over an 18month period were evaluated. These had 50 metastases, with a mean PTV volume of 3.9cm3 (range , 0.4-12.7 cm3) and receiving a single fraction of radiosurgery (16Gy – 20Gy dose range).

There was an observed difference in both the RTOG prescription isodose to target volume ratio (PITV) and Paddick conformity indices (CIpad), showing a better conformity after the implementation of the program (see table 1). When assessing individual lesions for deviation to conformity indices (see Table 2), the PITV was assessed before and after QA program implementation as 58% vs 98%(acceptable), 21% vs 2%(minor deviation), 21% vs 0 (major deviation). For the CIpad 5% vs 74%(acceptable) and 95% vs 26%(deviation). The dose to normal brain was also lower with the V5Gy(%) normal brain historic vs post-implementation being 13.1(± 8.4) vs 8.2(± 7.4) and the V12Gy(%) being 1.8(± 1.4) vs 1.5(± 0.8).

Table 1. Dosimetric parameters used for plan assessment and comparison and mean dosimetric parameters for the planning target volume and organs at risk before and after implementation dosimetric QA check-point.

Measure	Method	Description and Reference Range
Dose Conformity	RTOG PITV (3)	*Should be kept as close to 1.0 as possible.* <2 = acceptable 2-2.5 = minor deviation >2.5 or <0.9 = major deviation
	CI_{Pad} (4)	*A perfect plan has a CI_{Pad} of 1.* <0.62 = deviation >0.62 = acceptable
Normal Brain	V_{5Gy} (%)	
	V_{12Gy} (%)	
	Mean ± SD prior to dosimetric quality assurance program implementation	**Mean ± SD after dosimetric quality assurance program implementation**
PITV	*2.06 (± 1.02)*	*1.46 (± 0.46)*
CI_{Pad}	*0.35 (± 0.17)*	*1.18 (± 0.27)*
Normal Brain		
V_{5Gy} (%)	13.1 (± 8.4)	8.2 (± 7.4)
V_{12Gy} (%)	*1.8 (± 1.4)*	1.5 (± 0.8)

RTOG PITV = Radiation Therapy and Oncology Group prescription dose to target ratio; CI_{Pad} = Paddick conformity index; SD = standard deviation .

Table 2. Number of lesions meeting acceptable conformity criteria or with deviation before and after implementation of dosimetric QA check-point.

	Lesions (%) before dosimetric QA program implementation	Lesion (%) after dosimetric QA program implementation
RTOG PITV		
Acceptable	11 (58%)	49 (98%)
Minor deviation	4 (21%)	1 (2%)
Major deviation	4 (21%)	0
CI_{Pad}		
Deviation	18 (95%)	13 (26%)
Acceptable	1 (5%)	37 (74%)

RTOG PITV = Radiation Therapy and Oncology Group prescription dose to target ratio; CI_{Pad} = Paddick conformity index

CONCLUSIONS

Implementation of a multi-disciplinary dosimetric QA program with scorecard early in the planning process showed a significant improvement in RS plan quality with improvements in plan conformity and decreased dose to normal brain.

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EP-2175
Physics track: Implementation of new technology, techniques, clinical protocols or trials (including QA & audit)
Alison Salkeld
Poster presented at: ESTRO 37
PosterSessionOnline.com

EP-2174 Fabrication of three-dimensional printed customized bolus for the irregular shape of the outer ear

M. Baeza Trujillo[1], G. Gomez[2], J.C. Mateos[3], J.A. Rivas[2], S. Velazquez[2], J. Simon[3], D. Mesta Ortega[4], M.A. Flores Carrión[4], M.J. Ortiz Gordillo[4], T. Gómez-Cía[5], J.L. Lopez Guerra[4]

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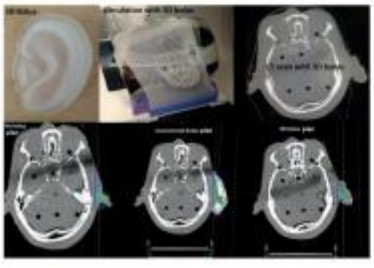
Purpose or Objective

The skin-sparing effect of megavoltage-photon beams in radiotherapy reduces the target coverage of superficial tumours. Consequently, a bolus is widely used to enhance the target coverage for superficial targets. Commercial bolus cannot easily be applied on irregular surfaces. A three-dimensional (3D)-printed customized bolus (3D bolus) can be used for radiotherapy application to irregular surfaces. This study examines the possibility of the fabrication of a 3D customized bolus for an irregular surface.

Material and Methods

We fabricated a bolus using a computed tomography (CT) scanner and evaluated its efficacy. The head of an Alderson Rando phantom was scanned with a CT scanner. A 3D bolus of 5-mm thickness designed to fit onto the ear was printed with the use of a Stratasys Objet260 Connex3 with the use of PolyJet technology (Stratasys Ltd., Eden Prairie, MN, USA) with the malleable 'rubber-like' printing material, Agilus (Stratasys Ltd.). CT simulations (Figure 1) of the Rando phantom with and without the 3D and a commercial high density bolus (eXaSkin©) were performed to evaluate the dosimetric properties of the 3D bolus. The ear was delineated as the target (15 cc). Radiotherapy plans with two beams were generated in the Oncentra Masterplan v4.1 radiotherapy treatment planning system with the use of the enhanced collapse cone algorithm. The prescription dose was normalized for 95% of the prescribed dose to cover 90% of the target volume in the plan without bolus. The plans with the bolus were normalized to ensure that the target dose lie within 95% and 107% of the prescription dose. The following dosimetric parameters were estimated for all cases: maximal dose (Dmax), mean dose (Dmean), minimum dose (Dmin), V95% (volume receiving at least 95% of the prescription dose), V90%, and homogeneity index (HI) proposed in ICRU-83.



Results

We fabricated the customized 3D bolus, and further, a CT simulation indicated an acceptable fit of the 3D bolus to the ear (Figure 1). Due to the irregular shape of the outer ear anatomy, there was some air gap between the bolus and the phantom surface with both the commercial and the 3D bolus. Figure 1 shows the isodose lines corresponding to the plans with and without the bolus. We observe that the target coverage is better with the bolus and it is similar between the commercial and the 3D bolus. Table 1 summarizes the relevant dosimetric parameters for the three plans.

Parameter	No bolus	3D bolus	Commercial bolus
Dmax (%)	123.27	110.09	105.43
D98(%)	8	94.38	97.77
Dmean (%)	109.10	105.77	101.93
Dmin (%)	8	83.64	96.08
D2(%)	121.82	108.34	104.73
D95(%)	77.64	97.5	98.47
V95(%)	79.19	97.58	100
V90(%)	79.19	97.58	100
V98(%)	75.35	94.55	100
Homogeneity index	Non-calculable	0.13	0.07

Conclusion

We successfully fabricated a customized 3D bolus for an irregular surface using a CT scanner. The fabrication process was simple and fast. The bolus, made of the malleable material Agilus, suitably fitted the surface, and the surface dose was sufficiently enhanced. Thus, we believe that the use of malleable materials can be seriously considered for the fabrication of customized boluses.

EP-2175 Improvement in radiosurgical plan dosimetry with implementation of a quality assurance program.

A.L. Salkeld[1,2], W. Wang[1], N. Nahar[1], E.K.C. Hau[1], N. Nahar[1], J.R. Sykes[2,3], T. Moodie[1], D.I. Thwaites[1,2]

[1]*Sydney West Radiation Oncology Network, Radiation Oncology, Westmead, Australia*
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Material and Methods

A committee comprising a radiation oncologist, physicist and radiation therapist performed a literature review of RS practice standards and recommended reporting of conformity indices (see table 1), as well as organs at risk (including normal brain). A scorecard / template was developed indicating each plan's compliance with QA measures (acceptable/minor deviation/major deviation and this was built into the work-flow to streamline the process. The plan and scorecard were assessed by the planner during the planning process and reviewed by the multi-disciplinary QA team prior to plan approval. 12 months of RS plans (January 2014 to December 2014) for brain metastases were reviewed as a historical comparator. The QA program was introduced in January 2015. Fractionated radiosurgery and tumour resection cavity lesions were excluded from both groups.

Results

For historic comparison, a total of 10 patients with 19 metastases were identified with a mean PTV volume of 4.7 cm^3 (range, 0.6-12.5cm^3). Prescribed dose ranged from 14.25Gy to 20Gy delivered in a single fraction. After implementation of the QA program 30 patients over an 18month period were evaluated. These had 50 metastases, with a mean PTV volume of 3.9cm^3 (range , 0.4-12.7 cm^3) and receiving a single fraction of radiosurgery (16Gy - 20Gy dose range).

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Normal Brain	V_{5Gy} (%)	
	V_{12Gy} (%)	
	Mean ± SD prior to dosimetric quality assurance program implementation	**Mean ± SD after dosimetric quality assurance program implementation**
PITV	2.09 (± 1.02)	1.49 (± 0.49)
CI_{pad}	0.35 (± 0.17)	1.18 (± 0.27)
Normal Brain		
V_{5Gy} (%)	13.1 (± 8.4)	8.2 (± 7.4)
V_{12Gy} (%)	1.8 (± 1.4)	1.5 (± 0.8)

RTOG PITV = Radiation Therapy and Oncology Group prescription dose to target ratio; CI_{pad} = Paddick conformity index; SD = standard deviation.

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Deviation	18 (95%)	13 (26%)
Acceptable	1 (5%)	37 (74%)

RTOG PITV = Radiation Therapy and Oncology Group prescription dose to target ratio, CI_{pad} = Paddick conformity index

Conclusion

Implementation of a multi-disciplinary dosimetric QA program with scorecard early in the planning process showed a significant improvement in RS plan quality with improvements in plan conformity and decreased dose to normal brain.

EP-2176 Compatibility test of a newly-designed patient transfer system with a 1.5T MR-simulator

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Purpose or Objective

Patient transfer system using hover technique has been introduced to accommodate the use of MRI for patient positional verification prior to each radiotherapy treatment fraction. The previous design of such a system isolates all electronics outside the MRI scan room, and only the hose passes through the MRI scan room and connects to the hover board. Recently, a new design integrates the electronics and power button at the hose end in the MRI room for better user friendliness and efficiency, while raising a potential concern on its possible influence on MRI-sim image quality due to electromagnetic interferences. In this study, we aim to test the compatibility of this newly-designed patient transfer system with a 1.5T MR-simulator (MR-sim) and assess whether this new design would affect the MR-sim image quality due to electromagnetic interferences.

Material and Methods

An ACR MRI phantom was scanned 5 times each under two settings: with the new-designed electronics-integrated hose connected to the hover board laid on the patient table of the MR scanner (hose-in), or leaving all the new-designed system outside the MR scan room (hose-out). Sagittal localizer (TE/TR = 20/200ms), axial T1 (TE/TR = 20/500 ms) and T2 scans (TE1/TE2/TR = 20/80/2000ms) were acquired (NEX = 1). Percent-signal ghosting (PG) and image intensity uniformity (PIU) were conducted following ACR guidelines. SNR was calculated using the image of the homogeneous portion of the phantom. The radiofrequency noise images were also acquired 5 times for each setting (by setting a 4-channel and a 18-channel array coils at receive only mode for 6 minutes). The noise image was inspected to look for the noticeable artifacts such as streaks, dots or patterns. A rank-sum test was performed to compare PG, PIU and SNR difference between the two settings.

Results

Similar PG, PIU and SNR were obtained between the hose-in and hose-out settings (PG: 0.023±0.003 (hose-in), 0.024±0.010 (hose-out), p=0.69; PIU T1: 91.0±0.4 (hose-in), 90.8±1.0 (hose-out), p=0.84; PIU T2=90.8±0.5 (hose-in), 90.7±1.0 (hose-out), p=1; SNR T1: 310±57 (hose-in), 323±44 (hose-out), p=0.42; SNR T2: 361±37 (hose-in), 342±55 (hose-out), p=0.69). No noticeable artifacts were observed for all noise images.

Conclusion

No degrade in image quality and no RF interference were noted when the newly-designed electronics-integrated hose in the MR scanner room. The newly-designed patient transfer system is compatible with 1.5T MR-simulator, and may smooth the procedure of patient transportation.

EP-2177 dosimetric evaluation of carbon-ion beam grid therapy of brain tumors

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Purpose or Objective

Radiotherapy with beam grids has been performed on a small scale for more than a century. Research on grid therapy using arrays of minibeams or microbeams have been carried out during the past two decades. In the pre-clinical trials made for this kind of grid therapy, it has been found that the normal tissue is tolerating irradiations up to remarkably high peak doses if the valley doses in-between the beam grid elements are maintained at low levels. It has been hypothesized that such a micro- and mini-beam grid therapy could be useful for CNS treatments. In this study, we made a dosimetric evaluation with Monte Carlo simulations of different irradiation geometries of potential use for carbon-ion grid therapy of brain tumors.

Material and Methods

The PHITS Monte Carlo code was used for the simulations. Beam elements of different widths in the interval 0.5-3.0 mm were used to build the grids. A beam element width of 0.5 mm has been considered for minibeam therapy in the past, whereas a width of 3.0 mm could be produced and delivered with more technical ease, while still providing a certain increase in the tolerance doses of the risk organs.

Appendix C: Co-author related works

Paediatric Radiotherapy

Cant I, Sykes J, Surjan Y, Beldham-Collins R, Murphy L, Fernandez J, **Salkeld A**. Comparison of Auto-Contouring Tools for Delineation of Normal Organs at Risk in Paediatric Patients Undergoing Radiotherapy.J Med Radiat Sci. 2025 Jun 29. doi: 10.1002/jmrs.893. Online ahead of print.PMID: 40583224

Murphy L, Cantwell J, Chard J, Cheuk R, Harrington C, Hindson B, **Salkeld A**, Saran F, Wheeler G, Wiltshire K, Ahern V.Quality improvement in paediatric radiation oncology through peer review. J Med Imaging Radiat Oncol. 2020 Oct;64(5):697-703. doi: 10.1111/1754-9485.13092. Epub 2020 Jul 27.PMID: 32715642

Paediatric Neuro-Oncology

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Quality Improvement in Radiotherapy

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