http://researchspace.auckland.ac.nz

ResearchSpace@Auckland

Copyright Statement

The digital copy of this thesis is protected by the Copyright Act 1994 (New Zealand).

This thesis may be consulted by you, provided you comply with the provisions of the Act and the following conditions of use:

- Any use you make of these documents or images must be for research or private study purposes only, and you may not make them available to any other person.
- Authors control the copyright of their thesis. You will recognise the author's right to be identified as the author of this thesis, and due acknowledgement will be made to the author where appropriate.
- You will obtain the author's permission before publishing any material from their thesis.

To request permissions please use the Feedback form on our webpage. http://researchspace.auckland.ac.nz/feedback

General copyright and disclaimer

In addition to the above conditions, authors give their consent for the digital copy of their work to be used subject to the conditions specified on the Library Thesis Consent Form and Deposit Licence.
Intensity Modulated Radiotherapy
for
Skull Base Meningioma

Dr Vanessa Estall
BHBMBChB, FRANZCR

A thesis submitted in full for the degree of Doctorate of Medicine
The University of Auckland

March 2013
# CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>3</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>4</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>6</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>7</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>8</td>
</tr>
<tr>
<td>CHAPTER ONE: INTRODUCTION</td>
<td>10</td>
</tr>
<tr>
<td>CHAPTER TWO: THE ROLE OF DOSE ESCALATION IN MENIGIOMA</td>
<td>81</td>
</tr>
<tr>
<td>CHAPTER THREE: THE ROLE OF LINEAR ACCELERATOR BASED IMRT FOR SKULL BASE MENINGIOMA</td>
<td>100</td>
</tr>
<tr>
<td>CHAPTER FOUR: THE ROLE OF HELICAL TOMOTHERAPY FOR SKULL BASE MENINGIOMA</td>
<td>120</td>
</tr>
<tr>
<td>SUMMARY AND CONCLUSIONS</td>
<td>132</td>
</tr>
<tr>
<td>APPENDICES</td>
<td>151</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>161</td>
</tr>
</tbody>
</table>
ACKNOWLEDGEMENTS

I would like to thank my supervisory team of Prof Neil Burnet, Dr Rajesh Jena and Dr Sarah Jefferies for their advice, training, and wisdom for the duration of my fellowship and beyond. I would especially like to acknowledge Neil for the invaluable time he spent mentoring me as both a clinician and a researcher, and to thank him for his ongoing support and friendship.

I would like to thank my colleagues Dr Fiona Harris, Ms Kate Burton and Mrs Lorraine Muffett for making my working environment so enjoyable. Not only were they supportive and caring, I learnt much from working with such experienced clinicians.

I would like to thank the physics and radiotherapy team members Mr Jamie Fairfoul, Mr David Eaton and many others who provided their time, knowledge and expertise to assist me in my clinical and research ventures.

I would also like to acknowledge Siemens Oncology OCS who provided the funding for my 2yr clinical research fellowship. They were always supportive, professional and encouraging in all my projects.
LIST OF FIGURES

Figure 1. Common sites for meningioma in the CNS.

Figure 2. Age-specific incidence of meningioma per 100,000. (Graph derived from Leland et al 2007, using data from Claus et al 2005 and the Central Brain Tumour Registry of the United States).  

Figure 3. Recurrence-free survival following surgery alone for meningioma. Note long follow up duration of 20yrs, and continued risk of relapse with time. Graph sourced from Adegbite et al 1983.  

Figure 4. Kaplan–Meier curve of estimated recurrence-free survival (RFS) by WHO tumour grade, compiled from a series of 643 patients from studies by Perry et al 1997 and 1999. Results are similar to those reported by Palma et al 1997.  

Figure 5. Cumulative relapse free survival curve for patients treated with radiotherapy at Addenbrooke’s Hospital (Estall et al 2009).  

Figure 6. Local control based on extent of resection (Simpson’s Classification Grade I, II or III) for 175 patients (taken from Condra et al 1997).  

Figure 7. Results according to treatment group, showing that outcomes are similar for total excision versus subtotal excision + post operative radiotherapy (taken from Condra et al 1997). Note: graph (a) - Local Control, graph (b) - Cause Specific Survival, TE alone – total excision alone, SE+RT – subtotal excision followed by radiotherapy, SE alone – subtotal excision alone.  

Figure 8. Schematic representation of sigmoid distribution of TCP and NTCP dose response curves, illustrating therapeutic ratio (Barnett et al 2009). Note that for individual tumours and normal tissues, the slope and position of the curves vary.  

Figure 9. Example of a TCP curve demonstrating sigmoid relationship between tumour call kill and dose of radiation. The slope of the curve indicates the degree of inherent sensitivity to radiation ($\gamma_{50}$) (Graph taken from lecture series Nahum et al 2007).  

Figure 10. This graph shows cancer rates (1958 –1994) in atomic-bomb survivors relative to those for the unexposed control group (Top). The dose–response curve approximates a linear function of dose up to about 2Sv (Bottom). The low-dose region is expanded to show that some low-dose points tend to be above the linear extrapolation from higher doses. (Graph taken from Hall et al 2006, re-drawn using data from Pierce et al 2000).  

Figure 11. This data represents whole body, low dose, high dose rate exposure, and therefore not always be a true reflection of the risk from therapeutic irradiation. It remains difficult to quantify this risk, and there may be differences in risk based on low dose regions, high dose regions and the type of tissue irradiated. This data relates to estimated risks in the normal population, and therefore overestimates the risk to a sub-population of older patients such as those with meningioma.
Figure 12. Illustration of the dose–response relationship for radiation induced carcinogenesis in humans (Hall et al 2003).

Figure 13. Axial view of an extensive cavernous sinus lesion plan, following surgical resection. CTV green, PTV50 red, and PTV60 black. Optic nerves (green) and their corresponding PRV's (yellow), brainstem (blue) with corresponding PRV (yellow).

Figure 14. Axial, saggittal and coronal views of a lateralised petrous apex lesion planned for radiotherapy alone.

Figure 15. Schematic representation of the progression of radiotherapy over time from 2D planning producing a symmetrical box like dose distribution, to ultra-conformal therapy, where the dose distribution begins to mirror the actual shape of the target. (Fig courtesy of Prof Neil Burnet)

Figure 16. Possible radiotherapy dose response relationship for non-benign meningioma, based on 3 small studies finding an improved local control with doses delivered above 50Gy, 53Gy and 60Gy (Goldsmith et al 1994, Milosevic et al 1996 and Hug et al 2000).
LIST OF TABLES

**Table 1.** The different histological meningioma variants grouped by WHO 2007 grade (Louis et al 2007).

**Table 2.** WHO 2007 criteria for meningioma grading (Louis et al 2007).

**Table 3.** Simpson Grade of resection and prognosis, based on relapse rates following surgery alone (Simpson et al 1957).

**Table 4.** Departmental dose constraints we use for normal tissue limits when planning skull base radiotherapy for benign meningioma.

**Table 5.** Retrospective series documenting effect of dose escalation on local control for atypical and malignant meningiomas.

**Table 6.** Summary of high dose radiotherapy technologies available for skull base treatment.
LIST OF ABBREVIATIONS

CTV  Clinical Target Volume
D<sub>max</sub>  Maximum dose delivered to a volume
D<sub>mean</sub>  Mean dose delivered to a volume
D<sub>min</sub>  Minimum dose delivered to a volume
EORTC  European Organisation for Research and Treatment of Cancer
EUD  Equivalent Uniform Dose
GTR  Gross Total Resection
GTV  Gross Target Volume
HT  Helical Tomotherapy
IGRT  Image Guided Radiotherapy
IMRT  Intensity Modulated Radiotherapy
LC  Local Control
NTCP  Normal Tissue Complication Probability
OAR  Organs at Risk
OS  Overall Survival
PFS  Progression Free Survival
PRV  Planning Organ at Risk Volume
PTV  Planning Target Volume
SRS  Stereotactic Radiosurgery
STR  Sub Total Resection
TCP  Tumour Control Probability
VMAT  Volumetric-Modulated Arc Therapy
WHO  World Health Organisation
ABSTRACT

Meningioma is a primary central nervous tumour (CNS) affecting mostly adults. Skull base meningiomas cause morbidity (and occasionally mortality) by compressing adjacent critical organs, and the aim of treatment is to optimise and preserve CNS function. Radiotherapy is an effective treatment for meningioma, with doses of 50-54Gy in conventional fractionation schedules resulting in long-term local control rates of 80-90%. However, local recurrence is unacceptably high in aggressive histological subtypes (WHO G2 and G3), and these patients have a poor outcome following standard dose regimens. In recent years Intensity-Modulated Radiotherapy (IMRT) has been developed, and can deliver highly conformal dose distributions with sharp dose gradients, making dose escalation a possibility for many tumours, including those located in the skull base.

The aim of this thesis was to address two issues pertaining to the role of radiotherapy for skull base meningioma. Firstly the goal was to investigate the potential role of dose escalation above 54Gy for meningioma and secondly, to assess the feasibility/practicality of delivering high doses to the skull base region. Due to the long duration of follow up required to document treatment response in this condition, an assessment of clinical endpoints (i.e. local control, survival) was not within the scope of this work, and will not be presented.

Chapter One consists of a literature review of meningioma and its management, including details about Intensity-Modulated Radiotherapy (IMRT), as a background to support the proceeding work. The role of dose escalation is addressed in Chapter Two, in which a retrospective review of a large cohort of patients in our department is presented. This data is discussed with reference to other series, and confirms that there is a role for dose
escalation to at least 60Gy for G2 and G3 meningiomas. The role of IMRT to deliver this
dose is presented in Chapter Three. Using a retrospective CT database, a series of
planning studies were performed in which cases were re-planned using IMRT,
investigating the impact of parameters such as MLC width and number/position of fixed
beams etc on dosimetry. Plans were compared using both physical and biological
parameters and the results analysed for differences to identify an optimal planning
solution. The results show that not only is it possible to deliver 60Gy to skull base
meningiomas safely using fixed field IMRT, a statistically significant and practical
planning class solution has been identified. Chapter Four presents the results of a planning
study comparing the role of another form of highly conformal radiotherapy, helical
tomotherapy (HT). A comparison of IMRT and HT plan dosimetry showed that the two
treatment systems are equivalent in their ability to escalate dose to 60Gy in the skull base,
with HT demonstrating a clear advantage with regard to reduced monitor units and ‘on-
beam’ treatment times, making this form of IMRT the preferred option if available.

After considering of the results of this body of work within the clinical context, the
following can be concluded; dose escalation to 60Gy or more is indicated for high-grade
meningioma to maximise CNS function preservation. This dose can be achieved with
IMRT using fixed field linear accelerator based or helical arc (HT, VMAT) technology
using published planning class solutions. Therefore, all appropriate patients should be
considered for dose escalation and have access to these technologies, even if it means
referral to a metropolitan centre. Furthermore, in this climate of rapid radiotherapy
technology development, planning studies to asses the dosimetric and practical aspects of
emerging techniques as described here, are vital to ensure not only that the best modality
available is being utilised, but also that it is being operated to its optimal capacity.
CHAPTER ONE: INTRODUCTION

1.1. Background 11
1.1.1 Demographics 12
1.1.2 Classification and histological subtypes 13
1.1.3 Natural History and prognosis 15

1.2. Management 19
1.2.1 Surgery 20
1.2.2 Radiotherapy 22
1.2.2.1 Post operative 22
1.2.2.2 Radiotherapy alone 25

1.3. Fundamentals of skull base meningioma IMRT 27
1.3.1 Therapeutic index and dose escalation 28
1.3.2 Dose constraints to Organs at risk (OAR) 32
1.3.2.1 Optic Pathways 35
1.3.2.2 Brainstem 37
1.3.2.3 Retina 39
1.3.2.4 Lens 40
1.3.2.5 Brain tissue 40
1.3.2.6 Hypothalamic-Pituitary Axis 43
1.3.3 Treatment induced carcinogenesis: IMRT specific implications 45

1.4. Immobilisation 59

1.5. Volume delineation: Tumour 60
1.5.1 Gross Target Volume (GTV) 60
1.5.2 Clinical Target Volume (CTV) 63
1.5.3 Planning Target Volume (PTV) 65
1.5.4 Organs at Risk (OARs) 66

1.6. Planning 71

1.7. Plan comparison 76
1.7.1 Physical parameters 76
1.7.2 Biological parameters – Equivalent Uniform Dose (EUD) 77

1.8. Treatment delivery 79

1.9. Verification 80
1 CHAPTER ONE: INTRODUCTION

1.1. Background
Meningioma’s are common primary central nervous system tumours in adults, and arise from the arachnoid cap cells lining the surface of the arachnoid villi, and/or meningotheelial progenitor cells.

They grow along the dural lining of the venous sinuses of the brain and skull base, locations where arachnoid cells are most plentiful. Therefore, meningiomas occur at the sphenoid ridge (16%), convexity (14%), cerebellopontine angle (13%), parasellar (12%), parasagittal (11%), posterior fossa (8%), olfactory groove (8%), falx (7%), foramen magnum (3%), orbit (3%), and other (6%) (Condra et al 1997).

Figure 1. Common sites for meningioma in the CNS.
1.1.1 Demographics

Meningiomas account for 25-30% of all primary central nervous system tumours in adults and are one of the most common primary central nervous system tumours diagnosed (Claus et al 2005). In our department, they account for 10% of new patient neuro-oncology referrals. They can be asymptomatic and maybe diagnosed incidentally following imaging for other indications, and otherwise present with focal symptoms resulting from tumour compression, or more generalised symptoms such as headache, cognitive dysfunction or seizure. Studies indicate that 35%-62% of cases are diagnosed based on imaging alone, and 2.3% of autopsies reveal a previously undiagnosed lesion (Disbase et al 2004, Flickinger et al 2003).

The risk of developing meningioma increases with advancing age (Adegbite et al 1983, Claus et al 2005, Perry et al 2007). Meningioma rarely occurs in the paediatric population except in the setting of NF2 (Perry et al 2001), which is a genetically inherited condition associated with bilateral vestibular schwannoma, ocular abnormalities and an increased risk of meningioma.
Meningiomas occur more frequently in females with a female/male ratio of approximately 2:1 (Goldsmith et al 1998, Longstreth et al 1993). Progesterone receptors have been found in 30%-70% of cases (Perry et al 2007), and there have been reports of increased tumour growth and symptoms during pregnancy, as well as an association with breast cancer (Wahab et al 2003).

1.1.2 Classification and histological subtypes
Classification of meningioma is by the World Health Organisation 2007 criteria (Louis et al 2007), based on histopathological features including abnormal cytology and morphology.
Table 1. The different histological meningioma variants grouped by WHO 2007 grade (Louis et al 2007).

<table>
<thead>
<tr>
<th>Meningiomas with low risk of recurrence and aggressive growth (WHO grade 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningothelial meningioma</td>
</tr>
<tr>
<td>Fibrous (fibroblastic) meningioma</td>
</tr>
<tr>
<td>Transitional (mixed) meningioma</td>
</tr>
<tr>
<td>Psammomatous meningioma</td>
</tr>
<tr>
<td>Angiomatous meningioma</td>
</tr>
<tr>
<td>Microcystic meningioma</td>
</tr>
<tr>
<td>Secretory meningioma</td>
</tr>
<tr>
<td>Lymphoplasmacyte-rich meningioma</td>
</tr>
<tr>
<td>Metaplastic meningioma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Meningiomas with greater likelihood of recurrence and/or aggressive behaviour (WHO grade 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical meningioma</td>
</tr>
<tr>
<td>Clear-cell meningioma</td>
</tr>
<tr>
<td>Chordoid meningioma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Meningiomas with high likelihood of recurrence and/or aggressive behaviour (WHO grade 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaplastic (malignant) meningioma</td>
</tr>
<tr>
<td>Rhabdoid meningioma</td>
</tr>
<tr>
<td>Papillary meningiomas</td>
</tr>
<tr>
<td>Meningiomas of any type or grade with a high proliferative index and/or brain invasion</td>
</tr>
</tbody>
</table>

Other pathological features with prognostic significance include the presence of necrosis, brain or bone invasion and a high MIB 1% (Perry et al 1999, Gabaeu-Lacet et al 2009), and these are used to grade meningiomas for clinical aggressiveness.
Table 2. WHO 2007 criteria for meningioma grading (Louis et al. 2007).

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign meningioma (WHO grade 1)</strong></td>
<td>Histological variant other than clear-cell, chordoid, papillary or rhabdoid</td>
</tr>
<tr>
<td></td>
<td>Lacks criteria of atypical and anaplastic meningioma</td>
</tr>
<tr>
<td><strong>Atypical meningioma (WHO grade 2) (any of three criteria)</strong></td>
<td>Mitotic index ≥ four mitoses/ten high-power fields (HPF)</td>
</tr>
<tr>
<td></td>
<td>At least three of the five following parameters</td>
</tr>
<tr>
<td></td>
<td>- Increased cellularity</td>
</tr>
<tr>
<td></td>
<td>- High nuclear/cytoplasmic ratio (small cells)</td>
</tr>
<tr>
<td></td>
<td>- Prominent nucleoli</td>
</tr>
<tr>
<td></td>
<td>- Uninterrupted patternless or sheet-like growth</td>
</tr>
<tr>
<td></td>
<td>- Foci of spontaneous necrosis (i.e. not induced by embolisation or radiation)</td>
</tr>
<tr>
<td></td>
<td>Brain invasion</td>
</tr>
<tr>
<td><strong>Anaplastic (malignant) meningioma (WHO grade 3) (either of two criteria)</strong></td>
<td>Mitotic index ≥ 20 mitoses/10 HPF</td>
</tr>
<tr>
<td></td>
<td>Anaplasia (sarcoma, carcinoma or melanoma-like histology)</td>
</tr>
</tbody>
</table>

1.1.3 Natural History and prognosis

Meningiomas are generally a local problem, with relapse occurring at the site of the original lesion in almost all cases. Leptomeningeal spread via the cerebrospinal fluid or haematogenous metastases are extremely rare, and associated with rapid disease progression and mortality (Chamberlain et al. 2005, Teague et al. 2005).

Overall, meningiomas are considered to be benign in nature, with low relapse rates after therapy. However, Adegbite et al. challenged this concept in 1983, when they published long-term follow up results post-surgical resection.
Figure 3. Recurrence-free survival following surgery alone for meningioma. Note long follow up duration of 20yrs, and continued risk of relapse with time. Graph sourced from Adegbite et al 1983.

This graph shows the cumulative proportion of patients free of recurrence against the number of years since surgery. With prolonged follow up, it becomes clear that the relapse rate could be as high as 40%, which is an important consideration for patients expected to survive longer than 10 years and those in whom repeat surgery would be increasingly hazardous.

Prognostic factors impacting on the risk of local relapse have been identified, and include tumour grade, which is also an important factor in the overall survival rates for patients
with meningioma. Benign meningiomas (WHO Grade 1) account for the majority of cases (70-85%), and following treatment the long-term prognosis is favourable with a progression free survival (PFS) at 10 years of 75-90% (Claus et al 2005). However, atypical (WHO Grade 2) and anaplastic or malignant meningioma (WHO Grade 3), have a much poorer progression free survival (PFS) and overall survival (OS). In series investigating this group, recurrence rates post resection at 5 years can reach 52% and 84% for atypical and anaplastic meningioma respectively (Palma et al 1997).

Figure 4. Kaplan–Meier curve of estimated recurrence-free survival (RFS) by WHO tumour grade, compiled from a series of 643 patients from studies by Perry et al 1997 and 1999. Results are similar to those reported by Palma et al 1997.
In our department (Estall et al 2009), we found an overall local control (LC) rate of 85% at 5.3 years, with 93% LC if disease was G1, 45% for G2 and 82% for G3 disease. This unexpected better outcome in the G3 group was most likely biased due to the very small number of these patients in our cohort (n=6). The Kaplan-Meier survival curve is shown below for comparison with the Perry data, and the better G3 outcome was most likely biased due to very small numbers of G3 patient in our cohort (n=6).

![Survival Functions](image)

**Figure 5.** Cumulative relapse free survival curve for patients treated with radiotherapy at Addenbrooke’s Hospital (Estall et al 2009).

Note the difference between G1 and G2 disease in our cohort, consistent with other series. The survival of patients with non-benign histology is also noted to be poor in other series, with a 4.6 fold increase in the risk of death for patients with grade 2/3 disease (Kallio et al
1992). Other major prognostic factors include extent of surgical resection and possibly radiation dose, which we discuss in detail later in the chapter.

1.2. Management

Clinicians have been debating the most appropriate treatment for meningioma for many years, with most recommendations based on individual interpretation of retrospective data and expert opinion. The initial decision required is whether the patient will need treatment at all. In the skull base region, disease is often benign, with a long natural history of slow growth, and possible compression of surrounding critical structures with time. Lesions may be found incidentally, as typically these tumours do not become symptomatic for several years. Sughrue et al published a literature review which indicated that tumours <2.5cm are unlikely to cause symptoms for at least 5 years, and for those with tumours measuring 2.5-3cm, only 17% developed symptoms if they were managed conservatively (Sughrue et al 2010). Therefore, the decision to put the patient through treatment with surgical resection, radiotherapy or both relies on careful individual risk analysis, considering patient, tumour, and treatment factors. Treatment is recommended for patients with symptomatic tumours or those which are likely to become symptomatic in the future, tumours causing function loss or those which have the potential to do so (e.g. blindness, difficulty swallowing), tumours progressing either clinically or radiologically, non-benign lesions and recurrent lesions. In general, the pattern of relapse in meningioma is one of local recurrence; hence treatment strategies focus on surgery and radiotherapy.

Patients should be expected to have a reasonable life span, and should not have significant life threatening co-morbidities. For an example, the clinician may treat an elderly frail patient with an asymptomatic small vertex meningioma differently to a middle-aged well patient with a lesion in the cavernous sinus. Once a decision to treat is made, the choice of
modality will be dependent on the individual risk versus benefit assessment for either resection or radiotherapy.

1.2.1 Surgery

Surgery is usually the local treatment of choice for meningioma, provided the lesion can be removed without significant risk of treatment-related functional morbidity. Surgical series indicate that the extent of resection is prognostic for relapse, and in the late 1950’s, Donald Simpson described the ‘Simpson Grade’ of resection, a prognostic tool allowing clinicians to predict the likelihood of relapse following surgery alone (Simpson et al 1957). He assessed 265 surgical patients and identified relapse rates associated with varying extent of resection, illustrated in the table below.
Table 3. Simpson Grade of resection and prognosis, based on relapse rates following surgery alone (Simpson et al 1957).

<table>
<thead>
<tr>
<th>Simpson Grade</th>
<th>Extent of resection</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Gross total resection of tumour, dural attachments and bone</td>
<td>9%</td>
</tr>
<tr>
<td>II</td>
<td>Gross total resection of tumour, coagulation of dural attachments</td>
<td>19%</td>
</tr>
<tr>
<td>III</td>
<td>Gross total resection of tumour without coagulation or resection of dural attachments or extra-dural extensions (e.g. invaded or hyperostotic bone)</td>
<td>29%</td>
</tr>
<tr>
<td>IV</td>
<td>Partial resection</td>
<td>44%</td>
</tr>
<tr>
<td>V</td>
<td>Simple decompression (e.g. biopsy)</td>
<td>NA</td>
</tr>
</tbody>
</table>

In the 1990’s, Kinjo et al (Kinjo et al 1993), proposed an additional Simpson Grade 0, which was defined as gross total removal of the tumour, dural attachments and any hyperostotic bone with a 2cm margin. They reported outcome in 37 patients and showed a Grade 0 resection resulted in 100% local control at 5 years and no morbidity. The limitation of this approach, is that selection of patients for such an extensive resection is dictated by tumour location and surrounding anatomy, and therefore in many cases it is not possible. Other surgical series have clearly demonstrated that subtotal resection of tumour is associated with a significant increase in local relapse rates compared to a gross total resection (Stafford et al 1998, Condra et al 1997) confirming both Simpson’s and Kinjo’s findings.
Figure 6. Local control based on extent of resection (Simpson’s Classification Grade I, II or III) for 175 patients (taken from Condra et al 1997).

1.2.2 Radiotherapy

1.2.2.1 Post operative

The addition of post-operative radiotherapy usually follows a subtotal resection (STR), particularly if repeat surgery for progression would be overly hazardous. In this setting local control is similar to that following gross total resection, i.e. 85-97% (Chondra et al 1997, Debus et al 2001).
Figure 7. Results according to treatment group, showing that outcomes are similar for total excision versus subtotal excision + post operative radiotherapy (taken from Condra et al 1997). Note: graph (a) - Local Control, graph (b) - Cause Specific Survival, TE alone – total excision alone, SE+RT – subtotal excision followed by radiotherapy, SE alone – subtotal excision alone.
Based on these results, treatment of skull base meningioma with STR to preserve function followed by post-operative radiotherapy is a common approach, as it offers an excellent risk versus benefit ratio.

The role of adjuvant radiotherapy following a gross total resection is less defined and certainly limited in patients with WHO grade 1 tumours. Series indicate that local control outcomes are very good with gross total resection alone in benign disease, with local control rates of 98% reported in some studies (Debus et al 2001). As gross total resection of G1 lesions results in good local control rates of greater than 90% (Simpson Grade I resection), the addition of adjuvant radiotherapy is unlikely to be warranted when considering the risk: benefit ratio.

This may not be the case when dealing with atypical and anaplastic meningioma, where the risk of relapse is significantly increased. Here, based on first principles, it may be reasonable to consider treatment of microscopic residual disease in an attempt to reduce the risk of local relapse. Unfortunately, there is little data reported in the literature due to rarity of this condition. Goyal et al reported on 22 patients with atypical meningioma treated with gross total resection (GTR) and radiotherapy (Goyal et al 2000). They were unable to show that postoperative radiotherapy to a median dose of 50Gy had a significant impact on local control, although the extent of resection did. It may be that in this case, the dose delivered was insufficient; as small studies indicate that a higher dose may be required to control grade 2/3 lesions (See below).
Another potential indication for adjuvant radiotherapy is following surgical resection for a first relapse. A small series has indicated that in this setting, both local control and overall survival are improved (Taylor et al 1988).

1.2.2.2 Radiotherapy alone

Radiotherapy alone is appropriate for patients who are surgically or medically inoperable. Surgical in-operability occurs when the size and/or location of the tumour makes meaningful resection unlikely, or is contraindicated due to an unacceptable level of risk to normal function. Medical inoperability may be due to poor anaesthetic risk and/or medical co-morbidity, resulting in a poor risk to benefit ratio. Multiple series have shown that local control with radiotherapy is excellent in this setting. The evidence is usually derived from studies including both post operative and radiotherapy alone cases. Milker-Zabel et al (Milker-Zabel et al 2006) reported on 57 patients with cavernous sinus meningioma: 29 received radiotherapy as primary treatment, 10 following surgery and 18 patients were irradiated for recurrent disease. Results after 6.5 years showed a 100% local control rate overall. Debus et al also reported on 189 patients receiving fractionated radiotherapy for benign cavernous sinus meningioma. The median dose delivered was 56.8 Gy, and local control at 3 years was 98.3% (Debus et al 2001).

Patients with atypical or anaplastic meningioma unfortunately fair poorly in comparison. Milosevic et al reported on 59 cases of atypical and malignant meningiomas, following treatment with mean dose of 50 Gy (Milosevic et al 1996). The majority of cases were post-operative, and local control at 5 yrs was only 44%. 5 yr cause specific and overall survival was 34 and 28% respectively. This inferior outcome is consistently documented in the literature and consistent with the findings from our own department (Estall et al
It is difficult to establish from the literature whether radiotherapy alone is equivalent or better in controlling benign meningioma compared to complete surgical resection. Glaholm J et al reviewed 186 patients treated at the Royal Marsden Hospital between 1963 and 1983 with radiotherapy (Glaholm et al 1990). 10yr cause specific survival was 67% overall, with disease free survival 61%. Those who underwent a subtotal or partial tumour resection followed by radiotherapy did better than those who had radiotherapy alone. In the case of surgery and radiotherapy, cause-specific survival was 77% compared to 46% for those receiving radiotherapy alone. Multivariate analysis indicated that extent of surgical resection was an independent prognostic variable along with histological subtype and performance status. In contrast, Mendenhall et al investigated the outcomes of 101 patients with benign skull base meningioma treated between 1984 and 2001 (Mendenhall et al 2003). Sixty-six patients received radiotherapy alone, while 35 had treatment following subtotal resection. Long-term control was 95% at 5 years and 92% at 15yrs. Absolute survival was 86% and 62% at 5 and 15 years respectively. Multivariate analysis showed no parameter influenced the local control and survival; in particular, there was no discernable difference in the groups treated with radiotherapy alone compared to those receiving combination treatments. However, there was increased toxicity in those receiving surgery, and the authors concluded that although in some situations debulking of the tumour might be advantageous, it was associated with an increased risk of functional deficit, while still not obviously improving local control. This is an incredibly important point when discussing treatment options with patients, and highlights the need for a
multidisciplinary approach by a specialised group of clinicians when managing this disease.

Other retrospective analysis suggests that local control following radiotherapy is dependent on the tumour volume treated. Milker-Zabel et al showed a volume difference in response rate (15% >60cm³ and 4.5% <60cm³) for benign meningiomas (Milker-Zabel et al 2006). This suggests that if tumours are large (i.e. >4cm in diameter), appropriate management may be surgical de-bulking followed by radiotherapy to maximise local control.

The best way to establish the optimal local treatment for meningioma would be a randomised controlled trial. However, this would be unlikely due to the length follow up required and significant treatment selection bias likely to occur, making accrual to such a trial problematic. It would be reasonable then to treat benign meningioma with gross total resection where possible, and where the risk of significant morbidity is low. Where this is unlikely, either radiotherapy alone, or subtotal resection followed by radiotherapy would be acceptable treatment options. In the setting of atypical or anaplastic meningioma, the outcomes are significantly poorer, and it would be reasonable to consider aggressive local therapy with maximal de-bulking followed by radiotherapy, with the extent of surgery limited by functional constraints.

1.3. **Fundamentals of skull base meningioma IMRT**

Radiotherapy is a form of anticancer treatment, which has an important role in local management of both benign and malignant tumours. The radiobiology of tumour control and normal tissue damage is complex and is affected by multiple factors, which are beyond the scope of this work and therefore will not be discussed in detail. Radiobiologists such as Hall and Steel have widely investigated this, with their work identifying and
characterising fundamental concepts by which clinical radiation oncologists can work (Hall et al 1978, Steel et al 1993). Essentially, the clinical aim of therapy is to achieve tumour control or cure by eliminating all tumour clonagenic cells, and simultaneously to maintain normal organ structure and function.

This work specifically investigates the technique of dose escalation to enhance clinical outcome, by using external beam radiotherapy delivered in a fractionated regimen using IMRT. Other modalities of treatment such as proton therapy, radiosurgery or cobalt therapy i.e. Gamma Knife Radiotherapy will not be discussed in detail. The following sections outline some of the fundamental concepts of radiotherapy, and how they relate specifically to IMRT.

1.3.1 Therapeutic index and dose escalation

Radiotherapy, like other anti-cancer treatment modalities, aims to exploit the therapeutic window between tumour control and side effects, the two outcomes of delivering a certain dose of treatment to a patient. Tumour control probability (TCP) and normal tissue complication probability (NTCP) are related to dose and follow a sigmoid distribution. The aim is to deliver a dose resulting in the most optimal TCP and minimal NTCP, with as much separation between the curves as possible. This will achieve the best outcome for the patient for the cost of complication, thus the best therapeutic ratio.
Figure 8. Schematic representation of sigmoid distribution of TCP and NTCP dose response curves, illustrating therapeutic ratio (Barnett et al 2009). Note that for individual tumours and normal tissues, the slope and position of the curves vary.

The exact shape and relative positions of these curves depend on multiple factors including inherent target and normal tissue sensitivity, dose and fractionation delivered, dose homogeneity and volume treated. Many NTCP and TCP models estimate these values (Nahum et al 2001, El Naqa et al 2006, Holthusen et al 1936), although these models have multiple limitations and assumptions associated with them. TCP represents the probability of long-term tumour control, which is the goal of therapy. Using the usual sigmoid curve of TCP with increasing dose, the $D_{50}$ (dose at which 50% of cells are killed) and $\gamma_{50}$ (proportional to the slope of sigmoid curve at level of $D_{50}$, representing inherent sensitivity of the target) can be established.
Figure 9. Example of a TCP curve demonstrating sigmoid relationship between tumour call kill and dose of radiation. The slope of the curve indicates the degree of inherent sensitivity to radiation ($\gamma_{50}$) (Graph taken from lecture series Nahum et al 2007).

The $\gamma_{50}$ is a useful parameter, which describes the slope of the TCP curve, and indicates inherent tumour sensitivity to radiation. It is defined as the percentage increase in TCP for a 1% increase in radiation dose as the 50% TCP level. The arbitrary level of 1.5 is quoted in the literature for many tumour types, and is based on modelling of data from in-vitro and in-vivo animal and clinical studies. This means that for many tumour types, a 1% increase in dose should increase the probability of tumour control by 1–2% (Suit et al 2001, Horiot
et al 1992). Thus, a dose increase of 20% could achieve a 20–40% increase in tumour control. Such radiation dose escalation is likely to have a positive effect on overall survival, as illustrated by the observation that one breast cancer death is prevented for every four local recurrences prevented with radiotherapy (Clarke et al 2005). By contrast, a dose reduction of 20% in radiation-sensitive normal tissue could significantly reduce the risk of serious treatment-related complications in some settings.

Techniques such as IMRT can produce a steep dose gradient allowing a tumouricidal dose to tumours, while simultaneously sparing normal tissue more effectively. This can allow dose escalation, which can improve tumour control (i.e. SCC head and neck) and/or improve the side effect profile following high dose radiotherapy i.e. salivary gland sparing and reduced xerostomia following radiotherapy for SCC head and neck (Nutting et al 2011). Some researchers and clinicians would always consider dose escalation (within the confines of normal tissue sparing) to be advantageous to the patient, even though we may not be able to prove the benefit in individuals based on population studies (Suit et al 2001). This is particularly relevant for rare tumours such as meningioma, as it is often difficult or impossible to obtain good clinical data to demonstrate these concepts.

NTCP can be very difficult to model, with the majority of normal tissue response data coming from the work done by Emami and colleagues in 1991 (Emami et al 1991). This data is retrospective, based on 2D planning and is in the setting of conventional radiotherapy prescriptions of 1.8-2.0Gy/fraction. The shape of the NTCP curve and organ sensitivity to radiation can be very complex, with total dose, dose per fraction, volume
irradiated and type of tissue organisation being important factors. A major review of normal tissue response data, the QUANTEC review, was published in 2010 in a set of papers, each focusing on a specific tissue; these will be referred to below (Bentzen et al 2010). Normal tissue response is currently being investigated in ongoing prospective studies, and may aid in modelling of the normal tissue response to radiation under different circumstances more easily.

TCP and NTCP can be used to compare multiple radiotherapy treatment plans, adding a new dimension to the physical parameters usually used such as dose and dose-volume histogram data. In addition, development of biological planning functions can allow these parameters to drive IMRT planning optimisation processes. However, these parameters rely on clinical data which in many settings is limited e.g. NTCP. As a result, these biological parameters should be used cautiously and in addition to physical plan parameters such as dose volume histograms and isodose distributions. In general terms however, the concept of using techniques to widen the distance between the two dose response curves for tumour and normal tissue is one used in almost all aspect of cancer therapy. This may be achieved with radiotherapy by increasing the dose delivered to the tumour and/or decreasing the dose delivered to the normal tissues, by using more conformal planning and delivery techniques i.e. IMRT.

1.3.2 Dose constraints to Organs at risk (OAR)

In the treatment of skull base lesions, the dose-limiting factor is the tolerance of surrounding normal tissue to radiotherapy. The organs at risk include the optic tracts
(optic nerves, optic chiasm, and posterior optic tracts), eye (retina), lens, hypothalamic-pituitary axis, brainstem, and normal surrounding brain tissue, in particular the temporal lobes and cerebellum.

The risk of damage to organs for a given dose can be estimated by the TD5/5 (the dose in Gy resulting in a 5% incidence of a pre-defined endpoint within 5 years of radiotherapy) and the TD50/5 (the dose in Gy resulting in a 50% incidence of a pre-defined endpoint within 5 years or radiotherapy). Estimates of TD5/5 and TD50/5 have been made from analysing animal models and clinical data, much of which has come from old studies where 2-dimensional radiotherapy was used and reflecting ‘conventional’ dose fractionation schedules of 1.8-2.0Gy/# (Emami et al 1991). Therefore, although they are important and form the basis of most of our dose limitations for normal tissue when planning radiotherapy, they may not be representative of the normal tissue response from more modern techniques such as altered fractionation schedules, concurrent chemoradiotherapy, IMRT, brachytherapy or proton therapy. The investigators from the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) Group have recently published updated models using more recent outcome and toxicity data in an attempt to more accurately predict normal tissue tolerance (Bentzen et al 2010). In general these reviews are very helpful, indicating both what is known and what is not known about normal tissue tolerance. The data is also structured in a clinically useful way, making it a practical tool when considering the risk: benefit ratio of treatment for individual patients. It must also be noted that for most cases, the endpoint in question is stochastic in nature, and represents a ‘complete loss’ of organ function e.g. optic neuropathy causing blindness, and may not always give information regarding more subtle or sub-clinical damage which could affect quality of life. For example, the endpoint for TD5/5 for brain tissue is necrosis. Thus, the tolerance dose chosen when planning an
individual case may result in a low risk of necrosis, but could still be associated with a significant risk of function loss through cognitive effects of radiation, which occur at lower doses. The volume of normal tissue irradiated may also be important, with some tumours being more sensitive to low volumes of damage (i.e. serial organ such as the brainstem) whole others may be relatively resistant until a critical volume of organ is damaged (i.e. cognitive failure from brain tissue dose). Therefore, when assessing an individual plan, and deciding appropriate tolerance doses for normal tissues, we need to take into account the context in which the treatment is being planned.

In terms of clinical context, certain indications and tumours my have different consequences if under-treated, and the desired end result for the patient can inform what level of risk of organ damage the clinician (and patient) are prepared to take. A life-threatening tumour such as a squamous cell carcinoma or sarcoma can be planned using very different tolerances for surrounding normal tissue, compared to a benign or non-cancerous lesion. In radical treatment for naso-pharyngeal cancer for example, tumouricidal doses may result in high doses to the brain stem and temporal lobes, acceptable in this setting, where a lack of tumour control will result in the rapid death of the patient. In contrast, a compressive non-functioning pituitary adenoma is not (normally) a life threatening condition. Tolerance doses to the optic pathways and brainstem are conservative and in most cases considered an absolute dose limitation. For example, it would not be acceptable to treat a patient with this condition using a plan where the optic chiasm received a dose above 50Gy/30#.
In the specific setting of skull base meningioma, clinicians must consider the goal of treatment, which is usually maintenance of function. The treatment of meningioma aims to prevent the tumour damaging or destroying adjacent critical organs, and therefore patient selection for specific treatment modalities must be a balance of the risk of morbidity without treatment and the risk of morbidity with treatment. This is equally true when considering patients for surgery or radiotherapy. Therefore, when treating meningioma with radiotherapy, for the most part it is appropriate to use conservative tolerance doses, which result in the lowest risk of functional morbidity, to ensure the patient is getting the best result possible from treatment, i.e. the best therapeutic ratio. Exceptions where higher tolerances may be considered acceptable may be in situations of recurrence where other modalities are not appropriate and the risk of morbidity from uncontrolled tumour growth outweighs that of radiotherapy. The tolerance of critical structures in the skull base will now be reviewed, based on clinical data to date.

1.3.2.1 Optic Pathways

The optic pathways comprise the optic nerves, chiasm, and posterior optic tracts. They contain retinal ganglion cell axons, which are myelinated except for the intraocular portion. Functional subunits are arranged in series, meaning even small volumes of damage resulting from exposure to high dose can cause significant late toxicity. The level of incapacity is dependent on which region of the pathway is damaged i.e. right optic nerve damage will result in right eye blindness, while optic chiasm damage is likely to result in homonomous visual loss.
The mechanism of radiation-induced injury is believed to be ischemia with neuronal atrophy resulting from small vessel endothelial damage. Radiation-induced optic neuropathy is a serious toxicity resulting in permanent visual loss with a mean time of onset 2-5 years following irradiation. Tolerance doses have been derived from retrospective series, which included patients planned with 2D therapy, and are TD5/5 (tolerance dose resulting in 5% or patients suffering end point) 50Gy and TD50/5 (tolerance dose resulting in 50% of patients suffering endpoint) 65Gy, with the end point defined as blindness (Emami et al 1991). Parsons et al investigated the incidence of optic neuropathy in patients receiving therapeutic radiation based on the total dose and dose per fraction received. The clinical endpoint was a decrease in visual acuity (VA) to 20/200. They found no neuropathy if the anterior optic tracts received less than 59Gy. In patients where the anterior optic tracts received greater or equal to 60Gy, the 15yr actuarial risk of neuropathy was 11% in those who had <1.9Gy/#, but as high as 47% in those receiving doses of equal to or greater than 1.9Gy/# (Parsons et al 1994, Parsons et al 1996). Other series that are more recent have also demonstrated that total dose, dose/fraction, and diabetes are significant predictors of toxicity (Debus et al 2001). Stereotactic radiosurgery series have further illustrated this, with one series of patients receiving gamma knife surgery showing that in 50 patients, there was no incidence of optic neuropathy if the cavernous sinus received 10Gy or less. However, if nerves received 10-15Gy the incidence of measurable damage was 27%, and even higher for doses >15Gy at 78% (Leber et al 1998). Similar results have been found in other radiosurgery series, further supporting the finding that anterior optic tracts have a low incidence of damage below 10Gy in a single fraction (Stafford et al 2003).
With the development of 3D conformal CT based radiotherapy, the incidence of neuropathy has decreased, and other studies have demonstrated that even more conformal techniques such as IMRT are associated with very low rates of neuropathy despite delivery of high doses to intracranial targets such as the paranasal sinus and nasopharynx (Daley et al 2007). Goldsmith et al performed a literature review, finding only once case of optic neuropathy from 49 patients treated with post-operative radiotherapy for skull base meningioma. Prescribed doses ranged from 45Gy to 59.4Gy, and at least one optic nerve was in the field in all cases (Goldsmith et al 1992).

The QUANTEC group reviewed more recent data and noted that there remains a paucity of dose-volume response data. They have reiterated that the risk of optic neuropathy increases significantly when total dose exceeds 60Gy in 1.8Gy/# or 12Gy in a single fraction, and with dose/# greater than 2Gy (Mayo et al 2010).

Based on this data, a safe dose limit to the optic pathway is 50Gy/30#, and consider this an absolute constraint when treating patients with benign meningioma. If higher doses are required to control tumour (i.e. G2/3 meningioma) we would consider increasing this constraint to 54Gy, counselling the patient that there may be a slightly increased risk of optic neuropathy at 2-3yrs. Pre and post treatment ophthalmology assessments should be done, and specific follow up of visual function should be carried out for the long-term.

**1.3.2.2 Brainstem**

The brainstem is the lower extension of the brain, connecting to the spinal cord and containing white matter tracts and cranial nerve ganglia. It is responsible for controlling involuntary life-maintaining functions such as breathing and cardiovascular function, and is the pathway for all fibre tracts connecting the central nervous system to the peripheral nervous system. As these organ’s functional subunits are arranged in series, even a small
volume of radiation-damaged tissue can have severe consequences. Radiation damage is vascular and associated with demyelination, necrosis, and atrophy. There is less data in the literature regarding radiation effect on the brainstem compared to brain or spinal cord, and Emami et al estimated tolerance doses to be TD 5/5 50 – 60Gy depending on volume irradiated and TD 50/5 65Gy with an endpoint of necrosis and infarction (Emami et al 1991). Debus et al reported brainstem toxicity in a cohort of 367 patients treated with conformal radiotherapy for chordoma. Brainstem toxicity occurred in 4.6% (17 patients), which was fatal in three patients. Total dose, dose/# and volume of brainstem receiving >60Gy were predictors of late toxicity. There was a statistically significant increase in risk of toxicity if >0.9cc of brainstem was irradiated to above 60Gy (Debus et al 1997). This indicates that improved dose conformation around the brainstem to reduce the maximum dose and volume irradiated is an important consideration in radiotherapy planning.

The QUANTEC group reviewed more recent data and again identified no robust dose-volume response data. The commented that most studies reporting brainstem toxicity were small (<100 patients) and there was no data available to characterise the effect of does of >60Gy to small volumes of the brainstem or the effects of hypo-fractionated treatment. The investigators concluded that the entire brainstem can safely be treated to a dose of 54Gy using conventional fractionation, and smaller volumes (1-10ml) could be treated up to 59Gy in conventional fractionation. However, the risk of significant brainstem injury increased markedly above 64Gy (Mayo et al 2010).

When treating benign skull base meningioma, an absolute dose limitation of 54Gy/30# for the brainstem is appropriate. For other indications such as nasopharynx squamous cell carcinoma, where patient survival is dependent on PTV coverage, small hotspots of up to
60Gy maximum are acceptable in the brainstem surface. These should be <1cc in volume, and the patient should be counselled when obtaining informed consent that there may be a small risk of brainstem necrosis.

1.3.2.3 Retina

The retina is a complex structure consisting of neural, glial, and vascular elements. A rich network of choroid capillaries derived from the retinal artery, vascularises the photoreceptor cells, located on the outermost layer of the retina. Radiation damage to the endothelium of small vessels results in ischemia and atrophy, and ultimately vascular retinopathy. As the photoreceptors are arranged in parallel, the volume of retina receiving radiotherapy is important, and the clinical visual loss corresponds to the area of retina irradiated. Tolerance data from Emami et al indicate a TD5/5 45Gy and a TD 50/5 of 65Gy with endpoint as blindness (Emami et al 1991). Parsons et al demonstrated a dose effect with a steep rise in toxicity from 45 to 55Gy, as well as a dose/fraction effect with doses >1.9Gy/# associated with increased toxicity (Parsons et al 1994.) A dose-volume effect has been shown in one series with an increased risk of retinopathy associated with >60% of the retina receiving >50Gy (Takeda et al 1999). In the treatment of orbital tumours, the retina is an important dose-limiting structure when treating meningioma in other parts of the skull base.

When treating skull base meningioma, we apply a constraint of no more than 45Gy to be delivered to the retina to minimise the risk of significant retinopathy. This is especially important for patients with an increased risk of retinal toxicity, such as those with diabetes, uncontrolled hypertension or known retinopathy.
1.3.2.4 Lens

The lens is a transparent structure posterior to the pupil of the eye responsible for light refraction. Epithelial cells lining the lens are sensitive to radiotherapy and damage can result in cataract formation several years after treatment. Tolerance doses noted by Emami et al are TD5/5 10Gy and TD50/5 18Gy (Emami et al 1991). The lens should have virtually no risk of cataract after receiving a dose of 5-6Gy spread out over 30 fractions. There is a 50% incidence of cataract formation after a dose of 15Gy (Henk et al 1993). However, due to the ability to treat cataracts surgically with good effect, the lens is not usually considered to be a dose-limiting organ.

1.3.2.5 Brain tissue

Brain tissue can sustain damage from irradiation via demyelination and vascular ischemia (Hopewell et al 1999, van der Kogel et al 1986). Clinically, effects can be characterised as acute (oedema, encephalopathy), sub acute (somnolence syndrome) or late (necrosis, infarction). There appears to be a dose and dose volume response and tolerance doses have been described as TD5/5 50-60Gy and TD 50/5 60-75Gy depending on volume irradiated (Daley et al 2007). As well as total dose and volume irradiated, dose/# is also a significant prognostic factor for toxicity. The clinical impact depends on the area of radio-necrosis, and toxicity can be significantly morbid and/or fatal.

The QUANTEC group reviewed more recent data and noted that the incidence of brain necrosis is 5% at a biological equivalent dose (BED) of 120Gy and increases to 10% with BED of 150Gy. The median duration of onset is 1-2 years and the risks are increased with
larger doses per fraction i.e. >2.5Gy (Lawrence et al 2010). Assessment of radiotherapy plans requires attention to these tolerances and awareness of potential regions of high dose within the brain tissue. A reasonable approach would be to limit hotspots to a max dose of 66Gy to prevent brain necrosis.

Another endpoint (which is hard to quantify but still important for quality of life) is the effect of radiotherapy on cognition. Loss of intellectual function is likely to be the result of demyelination of white matter and generalised cerebral atrophy from vascular changes. Cognitive dysfunction is most pronounced in children < 4 years old, as myelination of the white matter is usually not complete until this age (Jannoun et al 1990, Maire et al 1987). Volume irradiated is also a factor, with deterioration being significant in children treated for full brain or supratentorial irradiation for primary brain tumours (Mulhern et al 1992). Merchant et al prospectively assessed 78 children receiving radiotherapy for low grade glioma, and identified tumour location and volume, extent of resection, dose and volume of radiation delivered and patient age as being significant factors in cognitive effects of radiotherapy 5 years after treatment (Merchant et al 2009). There has been evidence more recently that adults are also affected, following data from survivors of small cell lung cancer who had prophylactic whole brain radiotherapy (Lee et al 1986) and those treated for primary brain tumours (Gregor et al 1996).

The actual mechanism of cognitive decline and specifically memory impairment is poorly understood. Research has identified that radiotherapy induced depopulation of neural stem cells may be a possible cause for treatment related memory impairment. Barani et al have
shown that the neural stem cells located in the sub-ventricular zone adjacent to the lateral ventricles, and the sub-granular zone in the dentate gyrus of the hippocampus are sensitive to ionising radiation. These cells are responsible for neurogenesis and are capable of self-renewal and can differentiate along multiple cell lines. Doses lower than 2Gy have been shown to deplete this cell population by up to 90%, thereby impairing normal neurogenesis (Barani et al 2007). The clinical impact of this is being investigated, mainly using rat models, but efforts to minimise treatment to these sites may prove useful in avoiding functional memory deficits in patients receiving therapeutic irradiation. It is therefore important to consider the risk of intellectual decline following skull base treatment in very young patients or patients with an increased risk of cognitive deficit i.e. elderly patients with underlying cognitive impairment. It is not possible at this time to apply an absolute dose constraint in this setting, but it may impact on our decision to treat with radiotherapy or not. In any case, patients must be informed of the potential for risk even though it is poorly quantified, and efforts should be taken to minimise the volume of normal brain treated. Further research may further inform us about dose responses and specific anatomical areas of the brain which should be avoided.

Radiotherapy can damage small and medium sized blood vessels, but the risk of cerebrovascular accidents (CVA) as a result of radiation damage is poorly understood. This may be a result of both small vessel atrophy and growth hormone deficiency. Brada et al have reported on large series of patients previously treated for pituitary adenoma, finding that in these patients, the relative risk of a CVA compared to the general population was increased to 4.1. Prognostic factors which may have contributed to risk, included being female, having extensive surgery, and having radiotherapy delivered in the 1980’s
prior to CT based planning (Brada et al 1999). The same investigators further assessed the mortality of these patients, finding that in these patients receiving irradiation, the relative risk death from CVA was 1.58 compared to the normal population (Brada et al 2002). The risk may be an overestimation now, when considering that these patients were treated with 2D planning techniques, and dose distributions in the modern era are known to be superior. However, this research does demonstrate that radiotherapy can have significant effects on normal brain, which could result in significant morbidity or even mortality. It would seem sensible to ensure normal brain tissue is spared as much as possible, with attention also paid to vascular structures within the cranium.

1.3.2.6 Hypothalamic-Pituitary Axis

The hypothalamic-pituitary axis is central to the function of multiple hormonal systems, and controls the secretion and regulation of growth hormone (GH), gonadatrophins (LH and FSH), adrenocotical hormone (ACTH), thyroid stimulating hormone (TSH), and prolactin. Radiotherapy can damage the cells of the structures directly and affect the microcirculation. The hypothalamus is more sensitive to radiation damage, which can cause growth hormone deficiency (GHD) in both children and adults at low doses (18-24Gy). A recent retrospective review of the incidence of endocrinopathy was performed by Bahl et al, and investigated children treated for ependymoma and medulloblastoma in the CT planning era. They reported an overall incidence of endocrine toxicity of 71% at 5 years for children receiving cranio-spinal radiotherapy, an incidence considerably higher compared to children treated with focal irradiation only (18%) (Bahl et al 2009). This clearly indicates that the volume of normal CNS tissue irradiated is an important factor. Dose-volume data from other investigators indicates that the dose to 90% of the structure is
predictive of endocrinopathy in children and following levels >35Gy, GHD occurs in 90% (Schmiegelow et al 1999). Merchant et al also showed a positive dose-volume relationship with <20Gy associated with a low incidence of GHD (Merchant et al 2002). Data for adults following high dose RT to the skull base indicate a high incidence of GHD following 50Gy to the HPA of 60% although it needs to be noted that at the time of this study, 2D radiotherapy planning was the standard of care (Samaan et al 1982). The usual dose constraints for the pituitary gland in adults is <45Gy, but the hypothalamus is rarely outlined or the dose estimated. With the use of IMRT, it may be possible to limit the dose to the anterior pituitary gland and hypothalamus to <30-40Gy, which should result in a lower incidence of endocrinopathy and may have an impact on long-term quality of life and possibly survival.

The table below shows the dose constraints we used for IMRT planning, based on literature documenting the effect of doses delivered as fractionated regimens in 2Gy/#, and result in a very low risk of significant functional morbidity. Alternative dose constraints may be considered when treating different pathologies, where disease is considered malignant or life threatening, and therefore a higher level of late toxicity is considered a reasonable compromise for better tumour control.
Table 4. Departmental dose constraints we use for normal tissue limits when planning skull base radiotherapy for benign meningioma. (PRV is the ‘planning organ at risk volume’, an expansion around the critical serial organs at risk to allow for the uncertainty of possible intra and inter-fraction motion. This is discussed in detail on P66).

<table>
<thead>
<tr>
<th>Organ at Risk</th>
<th>Tolerance (Dmax)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>&lt;54Gy</td>
</tr>
<tr>
<td>Brainstem PRV</td>
<td>&lt;56Gy</td>
</tr>
<tr>
<td>Optic tracts</td>
<td>&lt;50Gy</td>
</tr>
<tr>
<td>Optic tracts PRV</td>
<td>&lt;54Gy</td>
</tr>
<tr>
<td>Brain</td>
<td>&lt;66Gy</td>
</tr>
<tr>
<td>Eye/retina</td>
<td>&lt;45Gy</td>
</tr>
<tr>
<td>Lacrimal gland</td>
<td>&lt;30Gy (Dmean)</td>
</tr>
<tr>
<td>Hypothalamic/pituitary axis</td>
<td>&lt;45Gy</td>
</tr>
</tbody>
</table>

1.3.3 Treatment induced carcinogenesis: IMRT specific implications

An important toxicity is that of radiation-induced carcinogenesis. The risk of a normal cell becoming cancerous in this way is unknown and difficult to define. Multiple factors are likely to play a role, including treatment factors (total dose, dose rate, organ and tissue type irradiated, volume of tissue irradiated), patient factors (age, genetic susceptibility for cancer) and co-factors, which can also enhance the risk from irradiation (i.e. hormonal factors, viral exposure, lifestyle factors such as obesity, smoking or alcohol intact). Here we will consider the overall impact of therapeutic irradiation on second malignancy risk and the impact of IMRT in particular on this phenomenon.
The diagnosis of a radiation-induced malignancy can be made using criteria outlined by Cahan (Cahan et al 1998). The second malignancy should be within the field of previously irradiated tissue, and should be of a different pathology. There should also be appropriate time from the initial treatment to the development of the second tumour, generally greater than 10 years for a solid tumour, and 5-7 years for a haematological malignancy such as lymphoma or leukaemia. However, it is still often difficult to be sure of the aetiology of a cancer in a patient who has had previous radiotherapy, with confounding factors such as inherent patient risk and presence of lifestyle risk factors often making the diagnosis uncertain. It is likely that in many situations second malignancy is over or under diagnosed, and this makes an accurate estimation of risk difficult to quantify. The accurate diagnosis of radiation-induced malignancy is important, if we are to estimate the risk to individual patients of developing this toxicity for a specific course of treatment. In some patients this risk may greater than the perceived benefit from radiotherapy.

When considering meningioma, concern has been raised on two fronts regarding the potential risks of radiotherapy as a treatment option. Firstly, there is a theory that the use of high dose radiation may cause malignant progression of an initially benign meningioma. However, this has never been confirmed either clinically or pathologically. It is now more widely believed that malignant degeneration of benign meningioma is related to the natural history of a subgroup of meningiomas, which act more aggressively.

Another concern is the risk of a secondary malignancy such as a new meningioma or glioma because of high dose radiation treatment for benign lesions of the CNS such as meningioma, acoustic neuroma, or pituitary adenoma. The central nervous system has
long been recognised to be a sensitive site, especially in the setting of cranial irradiation in children, with authors reporting on cases of secondary malignancy because of childhood cranial radiotherapy (Ron et al 1988). Using a large database Lundell and Holm summarised the Swedish experience on carcinogenesis after radiotherapy in very early childhood to a number of different sites. They showed an increased relative risk (RR) for cancer induction of 1.2 for breast cancer, of 1.42 for CNS tumours and of 1.97 for thyroid cancer; for all other tumours the incidence was not influenced by irradiation (Lundell et al 1995). The risk of developing a secondary meningioma after therapeutic radiotherapy has been estimated to be 0.53% at 5 years and 8.18% at 25 years (Strojan et al 2000). In addition, data from the Royal Marsden Hospital revealed an increased incidence of brain tumours after the irradiation of pituitary adenomas with a latency period as long as 20 years and a cumulative relative risk of 2.4% (Brada et al 1992). Muracciole and Regis examined second malignancy following radiosurgery for benign CNS lesions (Muracciole et al 2008). They report two cases as well as noting three cases of radiotherapy-associated glioblastoma and five cases of allegedly transformed vestibular schwannoma related to radiosurgery previously reported in the literature. In 2006 Neglia et al investigated the risk of second malignancy in patients surviving childhood CNS malignancy. They found that adult survivors had at least a doubling of the incidence of radiation induced CNS tumours, including meningioma and glioma, from 8.7/100 000 in the general population to 19.3/100 000. Glioma appeared to be more likely to be associated with higher doses of radiation delivered and had an earlier onset at 8 years, while meningioma took longer to develop and were more common in patients treated with lower doses (Neglia et al 2006). This study illustrates the importance of the age of the patient and the dose delivered to the brain, as prognostic factors for treatment induced carcinogenesis.
As previously noted, multiple factors are likely to play a role in carcinogenesis. Some cannot be minimised i.e. age of patient and inherent genetic susceptibility. Lifestyle factors such as smoking could be altered with the co-operation of the patient. Treatment factors are very important, and in some situations treatment could be optimised to provide the lowest risk possible. It would be helpful for clinicians to have guidelines to help with radiotherapy planning, where dose constraints could be placed on certain tissues to minimise cancer risk from therapeutic radiation. Unfortunately, there is little or no robust data to inform us of such threshold doses, and we rely on extrapolation of a small amount clinical and laboratory data.

The identification of a dose response for radiation-induced carcinogenesis has been difficult. Knowledge of radiation-induced cancer comes from the atomic-bomb survivors, from radiation accidents, and from individuals medically exposed, which includes patients who have developed second cancers after radiation therapy. The figure below illustrates the data for radiation-induced solid cancers in the atomic-bomb survivors (Pierce et al 2000).
Figure 10. This graph shows cancer rates (1958–1994) in atomic-bomb survivors relative to those for the unexposed control group (Top). The dose–response curve approximates a linear function of dose up to about 2Sv (Bottom). The low-dose region is expanded to show that some low-dose points tend to be above the linear extrapolation from higher doses. (Graph taken form Hall et al 2006, re-drawn using data from Pierce et al 2000).

A linear relation may exist between the development of cancer, and dose from about 0.1Sv up to about 2.5Sv. This data represents the gold standard for our knowledge concerning radiation-induced cancer. The cancers consist principally of carcinomas in the lining cells of the body, such as the digestive tract or lung, or tumours in tissues hormonally controlled, such as the breast. The table below includes data taken from National Council on Radiation Protection and Measurements (NCRP) report 116, and shows the relative probabilities (% per Sv) of developing second malignancies by organ (NCRP Report 116).
This data represents whole body, low dose, high dose rate exposure, and therefore not always be a true reflection of the risk from therapeutic irradiation. It remains difficult to quantify this risk, and there may be differences in risk based on low dose regions, high dose regions and the type of tissue irradiated. This data relates to estimated risks in the normal population, and therefore overestimates the risk to a sub-population of older patients such as those with meningioma.

Hall et al has attempted to review the clinical literature, and model possible dose response relationships by extrapolating available data in both low dose and high dose regions (Hall et al 2003).
Figure 12. Illustration of the dose–response relationship for radiation induced carcinogenesis in humans (Hall et al 2003).

The atomic-bomb data represents the “gold standard,” that is, the best quantitative data over a dose range from about 0.1 to 2.5Gy. Considerable uncertainty exists above and below this dose range. At doses below this range, standards organizations, such as International Commission on Radiological Protection or National Council on Radiation Protection and Measurements, recommend a linear extrapolation from the high-dose data; however, the possibility of a bystander effect and the potential existence of radiosensitive subpopulations would suggest that this procedure may underestimate risks, whereas phenomena such as adaptive response suggests that a linear extrapolation may overestimate risks at low doses. Equal uncertainty exists concerning the dose–response relationship at high doses characteristic of radiation therapy. Does the risk continue to rise as a linear function of dose, does it plateau, or does the risk fall at higher doses because of cell killing?
When considering protracted low dose exposure, a situation more consistent with fractionated radiotherapy schedules, investigators have considered data from radiation workers (Cardis et al 1995, Ashmore et al 1998, Sont et al 2001) and adult and child data from radiotherapy delivered for non-malignant conditions (Ron et al 1988, Ron et al 1995). Data suggests a threshold dose of approximately 100mSv for an increased risk of radiation-induced malignancy, although in some cases it could be as low as 50mSv. Some radiobiologists feel it is reasonable to consider that a linear relationship exists, although they acknowledge there are likely to be factors, which could under or over estimate the risk using this model including adaptive responses and the ‘bystander effect’ (Brenner et al 2003). Therefore, as modelled by Hall et al (graph above) the dose response relationship below 0.1Sv could be linear with no threshold dose below which carcinogenesis will not occur, it could have a threshold of 0.1Sv below which carcinogenesis is unlikely to occur, or there could be a region of hypersensitivity to carcinogenesis below 0.1Sv due to the bystander effect. It is possible that all models are correct under certain conditions, with other factors (hormonal co-factors, genetic susceptibility, lifestyle risk factors, type and volume of organ irradiated or dose rate) affecting the risk.

High doses of radiation to normal tissue are also an important factor, as dose escalation is becoming increasingly possible with new techniques. In prostate and cervix cancer, doses in the order of 70Gy can be delivered to organs such as the bladder and rectum. This has been shown to result in improved cancer survival of the initial disease for patients. However, the risk of carcinogenesis at these higher doses has been reported with follow up data maturing for long term survivors, contradicting the theory that second malignancy is unlikely at high doses because of increased cell death.
Hall et al have postulated three possible dose response relationships for higher radiation doses. First is the traditional model of cancer risk decreasing with dose because of cell death, a phenomenon seen in animal studies. However, this has not been demonstrated with clinical data, which shows that the risk of rectal and bladder cancer is increased in patients treated radically for prostate and cervix cancer (Brenner et al 2000, Boice et al 1985). Brenner has postulated that one of the reasons the carcinogenic risk has not decreased with increasing dose, is that stem cells, both normal and those potentially damaged by radiation, undergo accelerated re-population as a result of radiation induced damage. Second, the dose response could plateau after 4-8Gy, a phenomenon indicated by some human observational studies such as data from women receiving pelvic radiotherapy for endometrial cancer having an increased risk for leukaemia which plateaus after 4-6Gy (Curtis et al 1994). Thirdly, an intermediate case could be considered. Women receiving therapeutic radiotherapy for cervix cancer have an increased risk of leukaemia, but the dose response relationship is very complex. The risk increases linearly up to 4Gy, and decreases at doses higher than this, but at a much slower rate than that assumed by increased cell death as a result of increased dose (Boice et al 1987).

Therefore, it remains unclear what a ‘safe’ dose of ionising radiation is either to the whole body, or to individual organs when considering carcinogenic risk. There may be no dose limit below or above which carcinogenesis is not possible, and there is likely to be several different mechanisms. It is reasonable in this setting to aim with radiotherapy planning to reduce the dose as much as possible, both to the whole patient, and to specific organs, which could be at more risk (i.e. bone marrow, gastrointestinal tract, bladder, breast, lung).
One area of potential concern in the application of IMRT in the clinical setting is the impact of increased low dose to larger volumes of tissue on the risk of carcinogenesis. As noted earlier in the chapter, the relationship between dose to normal tissue and radiation-induced cancer is a complex one, and needs to be considered when deciding on a treatment approach for individual patients. Threshold doses of 5mSv in a single fraction or 50-100mSv in a protracted course have been identified as levels associated with a known risk of radiation-induced cancer. The dose-response relationship is much less clear at lower or higher dose levels, but it cannot be assumed that these doses are insignificant; in fact, there is concern that the carcinogenic risk following IMRT compared to 3D-CRT is higher.

Sources of increased risk include:

**Increased whole body dose.**

This is the result of increased monitor units required to achieve the required modulation. As a result, ‘beam on’ time is considerably increased in IMRT plans, and this can result in an increased whole body dose to the patient due to machine leakage. In the case of high energy photons (>10MV) increased neutron production, although most IMRT plans utilise 6MV and neutron production is not a factor in whole body dose. Studies have demonstrated this increased whole body dose and estimates of increased carcinogenesis risk have been made based on the increase of monitor units required. In the late 1990’s Verellen et al estimated the increase in secondary malignancy risk to be high following use of IMRT versus a 2D conventional treatment technique for Head and Neck malignancy, because of a higher number of monitor units for the IMRT technique (Verellen et al 1999). They estimated whole body equivalent doses of 242mSv (conventional) and 1969mSv (IMRT), and gave an increased risk for second malignancy with a factor of eight for the more complex IMRT techniques. Kry et al also used monitor units to estimate the
increased risk of secondary malignancy for IMRT plans. Using published risk coefficients and out-of-field dose equivalents to multiple organ sites, they estimated a conservative maximal risk of fatal secondary malignancy for a number of IMRT and one 3D conformal planning solution for prostate cancer. Depending on treatment energy, they showed that IMRT treatments required 3.5-4.9 times as many monitor units compared to the conventional plan. The conservative maximal risk of fatal second malignancy was 1.7% for conventional radiation, 2.1% for IMRT using 10MV photons, and 5.1% for 18MV photons (Kry et al 2005).

Followill et al investigated the impact of photon beam energy in more detail. They estimated the dose to patients from photons and neutrons outside the radiation fields with beam intensity modulation conformal therapy is given. Photon and neutron leakage was estimated for IMRT using 6MV, 18MV, and 25MV X-ray energies. Whole body dose equivalents were determined using leakage measurements reported in the literature and treatment parameters derived for two IMRT techniques. Risk values recommended by the National Council on Radiation Protection and Measurements (NCRP) were used to estimate the resulting risk of fatal radiation induced cancer for 70Gy. The computed worst case risks for secondary cancer increased in the range from 1.0% for 6MV X-rays to 24.4% for 25MV X-rays, a result of increased neutrons in the higher energy plans (Followill et al 1997). These results indicate that total beam on time is an issue as it can increase the dose to the patient because of increased machine leakage of photons and neutrons.

**An increased volume of normal tissue irradiated to lower doses.**

Generally for IMRT plans, more beams are used to ‘re-distribute’ dose away from dose limiting critical organs i.e. brainstem. In order to escalate dose to targets close to serial
OARs, the Dmax to these organs must be reduced to below tolerance. This is achieved using more beams placed through other angles in the body, so although the Dmax is easily reduced to certain points in the patient, the cost is a higher volume of normal tissues being irradiated to low dose levels. This dose is unlikely to cause clinical deficits in the patient, but sub-clinical damage is not easily quantified and could include DNA damage resulting in a second malignancy. As previously noted, doses as low as 50mSv are probably significant, and the effect of lower doses is not clear.

**Increased dose to adjacent organs as a result of dose escalation**

IMRT allows dose escalation in many cases as Dmax to serial critical organs can be decreased. However, due to redistribution of dose, other organs may get higher than usual doses, which may be considered clinically acceptable if these dose levels are below those traditionally thought to cause functional damage. In addition, it is likely that there is an increase in scatter within the patient from the treatment volume because of increased dose. This is postulated to be of high significance in children where the smaller size of the body could be significant (Hall et al 2003). As noted earlier in the chapter, Brenner and Hall have both postulated that there is still likely to be a cancer risk at high dose levels, although this is difficult to quantify or model and is likely to be related to specific organ tissue sensitivity. Therefore, the impact of higher doses to adjacent organs because of dose escalation is unknown but potentially significant.

**Integral dose might be increased (or decreased) with IMRT.**

Another concept, which has become more widely considered is that of integral dose to the patient because of different treatment techniques, and is controversial in the setting of IMRT. This is defined as the sum of the product of a given dose (Di) and the volume of
tissue receiving that dose \((Vi)\) and the density of the tissue volume \((\rho_i)\) as represented by the following equation:

\[
\text{ID} = \sum_{i} D_i \times V_i \times \rho_i,
\]

where the volume of normal tissue excludes the target volume (Followill et al 1997, Schneider et al 2006). Some investigators consider ID likely to be consistent across different planning solutions, as the ID is related to the total dose delivered to the patient rather than to the planning solution used.

D’Souza et al investigated the effect of ID of differing beam number when the dose prescribed was the same. They found that there was little impact of beam number on ID, as optimisation resulted in redistribution of the same dose delivered to the patient and target. This supports the concept that plan optimisation can reduced \(D_{\text{max}}\) to certain points, by finding the best distribution of dose, not by reducing the energy imparted (D’Souza et al 2003).

However, in the setting of dose escalation, the ID is likely to be increased for IMRT compared to 3D-CRT, if this is the reason for its implementation. Pirzkall et al compared IMRT and 3D conformal therapy in nine cases, showing an improved target coverage and conformity for the IMRT solution by 36% and 10% respectively. This improvement in target coverage, which has been widely reported with IMRT, is important because it may in itself improve local control. Where dose escalation was a goal, IMRT increased mean dose by 4-6Gy and target coverage by 19%. They investigated both rotational IMRT and fixed field IMRT and in both cases, integral dose was increased compared to 3D conformal
treatment (Pirzkall et al 2000). Hermanto et al assessed the impact of IMRT versus 3D conformal therapy in 2007, and found a different result. They aimed to determine whether IMRT increased the total integral dose of non-target tissue relative to conventional 3D conformal therapy, for high-grade glioma. Twenty patients were reviewed and a dosimetric comparison carried out between the two techniques using a conventional prescription for glioblastoma of 60Gy/30#. In all 20 cases, IMRT maintained equivalent target coverage, improved target conformity, and enabled dose reductions to normal tissues. This was achieved without increasing the total non-target ID by greater than 0.5%. Overall total integral dose was reduced by 7-10% with IMRT (p<0.001) (Hermanto et al 2007). ID is a concept that is not fully understood, and may be impacted on by multiple factors. Its potential link with carcinogenesis has not been quantified, but it is a useful general marker of dose exposure to normal tissue, and many would agree that any attempt to minimise non-tumour dose is warranted.

Tubiana has suggested an alternative view to that proposed by Hall et al regarding carcinogenesis and IMRT, in a recent review of the literature (Tubiana 2009). He argues that it has been shown that sensitive tissues exposed to a dose/fraction of less than 120-150mGy are unlikely to develop a second malignancy, and that the incidence of second cancers gradually increases with dose and is low for cumulative doses up to 3.5Gy. Suit et al have also performed a recent review and they suggest that a reduction in volume of normal tissue receiving more than 3.5Gy (cumulative) could diminish the risk (Suit et al 2007). This is made more possible with IMRT as a planning and treatment technique, therefore giving an example where the use of this treatment could decrease the second cancer risk.
Although the impact of new technologies on carcinogenesis risk remains unclear, it seems plausible that the risk of carcinogenesis may be increased in a patient receiving IMRT rather than 3D-CRT for a number of reasons. This risk is difficult to quantify and needs to be balanced within the context of tumour control, which is increased if more dose can be delivered in many cancers, something achievable with IMRT. If it is deemed necessary, IMRT planning should not only take into account Dmax and Dmean to OARs, but should aim to minimise the risk of second malignancy. When planning, low dose regions should be monitored, and where possible the dose to sensitive organs (bone marrow, gastrointestinal tract, breast) should be kept below a cumulative dose of 3.5Gy. Total monitor units, ‘beam on’ times and ID should be considered and minimised where possible. Where planning cannot be optimised further, a decision needs to be made assessing the risk: benefit ratio for the specific treatment plan and patient, to ensure the balance between benefit and harm is favourable.

1.4. Immobilisation

Immobilisation is important to prevent patient movement between (interfractional) and during (intrafractional) radiotherapy treatment. It must be individualised, comfortable, and be accurately reproducible on a daily basis. Movement of soft tissue within the bony cranium is minimal. Immobilisation techniques include a thermoplastic shell, relocatable stereotactic frames using a bite block, or rigid stereotactic frames for radiosurgery. The accuracy and tolerance of each technique informs the required PTV margin e.g. thermoplastic shell may need a PTV margin of 5mm, while a relocatable stereotactic frame could require less i.e. 2-3mm (Burton et al 2002).
Volume delineation: Tumour

1.5.1 Gross Target Volume (GTV)

Delineation of the tumour and identification of both the Gross Target Volume (GTV) and Clinical Target Volume (CTV) need to be performed as accurately as possible. GTV is defined as the gross visible tumour identified with imaging, and for meningioma is currently identified, using T1 weighted MRI scans with Gadolinium contrast. However, there are some limitations. MRI has poor resolution between bone and soft tissue, and in areas, there is uncertainty regarding the edge of the tumour in relation to the bony anatomy. In addition, another area of significant uncertainty is at the ‘dural tail’. This is identified as an area of contrast enhancement along the dural plane at the edge of the main bulk of the tumour. The inclusion of this ‘dural tail’ in the treatment volume is controversial, mainly due to the uncertainty surrounding its aetiology. It is postulated that the ‘dural tail’ may include neoplastic cells, and resection of a margin of circumferential dura around this region should be considered (Kinjo et al 1993, Borovich et al 1986). This is technically possible for convexity dura, but frequently these “tails” extend along the skull base in proximity to neural foramina where cranial nerves exit and major blood vessels pass. Resection of these extensions along the dura with a margin can carry significant potential morbidity (Newman 1994). In theory the radiation field should encompass the “dural tail” if this is proven to harbour neoplastic cells, but the proximity of these extensions to sensitive normal tissue structures may limit or modify the radiation dose possible.

Proving the true nature of the ‘dural tail has been difficult. The pathological and clinical significance of the dural tail’ sign as identified by gadolinium enhanced T1 MRI is unclear, and is complicated by the fact its aetiology is most likely multifactorial. Most
Histopathological studies show that this abnormal area on imaging is characterized by connective tissue congestion in almost all cases, which may be the result of impaction of tumour cells in dural vessels at the very edge of a tumour mass. The presence of abnormal meningeal tumour cells within this imaging abnormality is less consistent, but two of the largest series of cases indicated that tumour invasion was present in the abnormal enhancing tail in 62-64% of patients (Sekiya et al 1992, Hutzelmann et al 1998). Unfortunately, the current data is very limited making it difficult to draw firm conclusions. Although in most cases, venous and connective tissue congestion is present indicating a potential mechanical obstruction, there does seem to be a proportion of cases where the abnormal imaging also corresponds with the presence of tumour invasion at a significant distance from the macroscopic tumour edge. An accurate assessment of the risk of tumour invasion associated with abnormal MRI imaging would be useful. Until then, clinicians need to decide on an individual case-by-case basis the significance of this finding, and whether or not it should be included in the GTV. It may be reasonable to include dural enhancement if the region is also enlarged or expanded, and have a lower threshold for inclusion if the tumour is G2 or G3. In post-operative specimens, dural enhancement may be treatment related and pre-operative scans could be useful in deciding this. In our department, current practice is to include dural extensions if they are associated with dural swelling, or if the pathology is not benign. Post operatively we compare with pre-treatment imaging and include if clinical suspicion is high.

The use of more targeted imaging, which can differentiate between abnormal vascular and connective tissue congestion and dural invasion of meningioma cells, could be very helpful. Positron Emission Tomotherapy (PET) provides functional information, and has potential for use in oncology in diagnosis, staging, treatment planning and as an
assessment of treatment response. $^{68}$Ga-DOTA-Octreotate PET-CT is a novel-imaging tool with a possible role in the management of meningioma. These tumours express high levels of somatostatin receptor type 2 on their cell surface. Therefore, a somatostatin analogue labelled with gallium can be utilised as a PET tracer, and can be a useful diagnostic tool as well as providing improved information regarding their extent (Henze et al 2001, Nathoo et al 2007). One group has utilised this imaging as part of radiotherapy planning for patients with intracranial meningioma, showing that target delineation was ‘improved’, and significant alterations were made in 73% of cases (Milker-Zabel et al 2006). Therefore, $^{68}$Ga-DOTA-Octreotate PET-CT could be a more sensitive and specific test for the presence or absence of tumour cells in abnormally enhancing dura adjacent to meningioma. It may also prove useful in differentiating between MRI dural Gadolinium enhancement because of postoperative reaction versus tumour invasion. Our experience is limited at present to a single case because of lack of tracer availability, but the PET scan did alter outlining of the GTV in the inferior component, where the bone: soft tissue interface was difficult to interpret. We also found that the $^{68}$Ga-DOTA-Octreotate PET-CT could potentially be used to assess tumour activity and response to radiotherapy. We showed in one case that the volume of tracer uptake as well as the max SUV level was both reduced 6 weeks post radiotherapy to a dose of 50Gy in 30#. This data was reported in poster form at the 2008 AAPM ASM (Estall et al 2008).

Other aspects of tumour delineation also include contouring accuracy and inter-observer variation. There has been little or no work investigating this in the setting of meningioma contouring, but work has been done with outlining of GBM gross target volumes using Gadolinium enhanced T1 weighted MRI scans. Our group investigated the difference in contouring volumes between four clinical oncologists, and found significant inter-observer
variation in regions where MRI findings were uncertain and difficult to interpret i.e. in post-operative beds where enhancement could represent surgical change or tumour. Where lesions were not resected, and there was obvious differentiation between the edge of a mass and normal tissue, the contouring volumes were considerably more uniform (Burton et al 2008). It is clear, that more accurate imaging of tumour can improve consistency of contouring between clinicians, minimising the effect of this on outlining error/uncertainty.

1.5.2 Clinical Target Volume (CTV)

The CTV margin required to treat subclinical microscopic spread of disease is also poorly defined in the setting of meningioma. As noted above, the extent of spread along the dura is not well understood, and may be different depending on tumour grade.

It is unknown whether potentially neoplastic or progenitor cells exist beyond the enhancing margin of the tumour on MRI. In a study by Borovich et al, arachnoid cell “rests” more common in dura adjacent to meningiomas than normal cadavers (Borovich et al 1986). Arachnoid cell “rests” can be detected up to 5-10 cm from tumour margin. However the significance or proliferative potential of these “rests” is unknown. Only three series have reported the distance between the macroscopic tumour edge and the invasion along the dural tail, with maximal distances ranging from 14-45mm (Nakau et al 1997, Sakai et al 1993, Sato et al 1998). In cases where there is no dural tail visible, tumour cells were identified up to 25-30% of specimens, although authors did not stipulate to what distance from the edge of the macroscopic tumour this occurred (Hutzelmann et al 1998, Hutzelmann et al 1997).
Clinical data indicates a significant relapse rate following surgery of up to 30% at 15yrs, even following a GTR (Claus et al 2005). This implies that microscopic residual disease is significant, and can contribute to future relapse, which may be responsible for significant patient morbidity, and in some instances can decrease survival. Although in many cases such relapses can be easily salvaged, in other situations, a local relapse could result in permanent morbidity, and prevention of such an occurrence is desirable.

An alternative view is that even if there is microscopic disease in the dura beyond what is visible on imaging, evidence does not indicate it is particularly significant or needs to be treated. In the majority of cases, benign lesions do not recur and salvage therapy is possible in most cases. Use of stereotactic radiosurgery (SRS) without CTV margins to treat macroscopic residual disease only following partial resection has reasonable results although actual patterns of relapse are rarely reported (Kondziolka et al 1998, Liscak et al 1999).

Therefore, the best initial management of this microscopic residual disease is not well defined, with uncertainty surrounding the timing of further local treatment, and the optimal surgical margins and/or radiotherapy margins required to maximise local control and simultaneously minimise patient morbidity. Current practice is variable and there is a paucity of evidence to guide clinicians. The recommendations for CTV margins vary from 0 to 2cm and to complicate this issue further, relapse of meningioma may occur very late i.e. after 10-15 years, making active prospective research difficult. There is also likely to be a difference in the extent of dural spread for atypical and anaplastic meningiomas, which seem to act more aggressively, prompting one to consider the use of wider CTV margins, although there is no clinical evidence to support this or inform what margins
should be in this setting. It may be reasonable to expand GTV margins by 1-2cm along the dura, especially in the setting on non-benign disease, taking into account the potential increased toxicity of increasing the irradiated volume. Meningioma does not usually invade brain or skull, therefore it is not necessary to expand the GTV volume in this direction, unless there is specific pathological evidence suggesting these areas are at higher risk i.e. known bone invasion. This means the volume expansion cannot be automated and is not volumetric in the 3D plane, creating unusual target volumes and shapes that can be difficult to treat.

1.5.3 Planning Target Volume (PTV)

The planning target volume (PTV) refers to the margin expanded around the CTV to allow for geometric uncertainties during radiotherapy (ICRU Report 50 1993, ICRU Report 83 2010, BIR 2003). The required size of this margin is dependent on many factors including inter and intra-fraction motion of the target. The main components of this geometric uncertainty are internal motion i.e. of the target isocentre in relation to the bony anatomy, and external set up errors, i.e. the bony anatomy in relation to the treatment room coordinate system. In both cases these errors can be systematic (the same deviation from the planned position for each fraction) or random (deviations varying from fraction to fraction). Specific uncertainties for each patient are unknown, so standard deviations describing these geometric errors in patient groups are used to give $\Sigma$ (standard deviation of systematic errors) and $\sigma$ (standard deviation of random errors). Once these standard deviations have been established, they can be used to calculate a standard PTV margin which will account for 3 dimensional motion using the margin recipe $\text{PTV} = 2.5\Sigma + 0.7\sigma$ (BIR 2003), which will ensure that 95% coverage of the PTV is achieved in at least 90% or more of the patients treated.
When considering skull base lesions, immobilisation to minimise set up error and patient movement during treatment, is vital as often critical structures are only a few millimetres away from the target, and therefore very close to regions of high dose. This can usually be achieved with thermoplastic shells or stereotactic frames, and due to the bony cranium and anatomy of the skull base, intra-fractional target motion is not a significant issue. In our department, the movement variation of the two immobilisation techniques mentioned has been investigated, and factored into PTV margin calculations. Therefore we have a PTV requirement of 5mm when using a thermoplastic mask, and 3mm when using a relocatable stereotactic frame to allow for systematic and random set up and treatment error (Burton et al 2002). This margin results in greater than 90% of patients having 95% or more coverage of the PTV during treatment.

1.5.4 Organs at Risk (OARs)

As well as contouring the target volume, the clinician also needs to outline the critical structures. In most cases in the brain and skull base, these structures can be well identified with a combination of CT with IV contrast and MRI imaging. Areas of difficulty include the hypothalamus, temporal lobes, and optic chiasm, which are important structures to identify, as doses in excess of 50Gy have the potential to result in significant morbidity. When dealing with critical dose limiting structures where functional subunits are arranged in series, some advocate expanding these beyond what is visible on imaging to create a Planning organ at Risk Volume (PRV) (ICRU Report 62, ICRU Report 83). The PRV can be calculated in a similar way to PTV. Both inter-fractional (systematic or random) and intra-fractional motion can occur, with movement during treatment of the skull base minimised by rigid immobilisation devices and the lack of normal movement of organs within in the cranium. As for PTV margins, the values of Σ and σ can be estimated from
the standard deviations in movement of the treatment isocentre in relation to the OAR volume. Movement of the target isocentre during treatment in relation to the patient can be in the anterior – posterior, cranial – caudal or left – right directions. The value of Σ corresponds to the systematic error, which is repeated in the same direction each time the patient is treated. Therefore the size of this value for the OAR of interest will depend on whether the movement of the target isocentre in relation to the OAR is one direction or more, potentially putting the OAR in danger of over-dosage from more than one direction.

In contrast, the PTV margin is always considered three dimensional, and aims to cover the target for movement in all directions to ensure the target is not under-dosed. As a result of this concept the margin for geometric uncertainty for organs at risk may be smaller than for the PTV in some situations, and a different value of the constraint for systematic error can be used in the margin recipe i.e. Σ1.3 to Σ2.5 depending on the number of directions where the high dose distribution is found. Based on standard deviations of movement errors derived from a number of cases, McKenzie et al suggest using values of Σ of 1.3, 2.1 and 2.5 to calculate PRV margins, for cases where the OAR’s are likely to be affected by movement of the target isocentre in one, two or three directions respectively. For random errors, they suggest values of 0.5σ to - 0.5σ (McKenzie et al 2002). Another group investigated PRV margins for serial organs at risk such as the optic chiasm, and acquired values of 1.2-1.8 Σ for the spinal cord and 2.1 Σ for the optic chiasm (Stroom et al 2006). These values were similar to those derived by McKenzie et al. The larger value of Σ for the chiasm is a reflection of these small serial organs being almost completely encircled by regions of high dose in some situations, and therefore affected by movement in every direction. In contrast, the spinal cord is more likely to be affected in on direction only i.e. anterior - posterior or left – right depending on the position of the PTV in relation to the cord and therefore a smaller Σ can be used to calculate a PRV margin.
Figure 13. Axial view of an extensive cavernous sinus lesion plan, following surgical resection. CTV green, PTV50 red, and PTV60 black. Optic nerves (green) and their corresponding PRV’s (yellow), brainstem (blue) with corresponding PRV (yellow).

In this skull base example, an extensive cavernous sinus lesion has been contoured, with the CTV (green), the PTV designated to receive 50Gy (PTV50) (red) and the PTV designated to receive 60Gy (PTV60) (black) margins outlined. A two phase shrinking volume technique has been used to dose escalate the tumour (PTV60) and avoid critical structures, which include the optics (green) and the corresponding optics PRV (yellow), and the brainstem which is outlined (blue) along with the corresponding brainstem PRV (yellow). Where the PTV50 and critical structures overlap, a dose of 54Gy (but no higher) is acceptable. The PTV60 specifically avoids the critical structures and the PRV volumes, as this represents a volume at risk of damage if doses exceed 50Gy, accounting for movement of critical structures into the high dose region during treatment. In this case, it
is apparent that if the target isocentre moved during treatment as a result of systematic error, in either the anterior posterior, right - left or superior - inferior direction, the PTV60 volume (black) is at risk of overlapping critical structures. To prevent this occurring, a PRV margin expanded around the critical structures could ensure that such movement will not result in unacceptable morbidity. In this case a three dimensional solution is required to reflect the effect movement in any direction could have on the dose to critical structures. Using a larger Σ value such as 2.5 Σ, and using the margin recipe as per McKenzie et al, we calculated an appropriate PRV margin, which in our department would be 3mm in all directions.

In another example, the PRV margin could be calculated differently. Below is another case, but here the meningioma in question is well lateralised.
Figure 14. Axial, sagittal and coronal views of a lateralised petrous apex lesion planned for radiotherapy alone.

In this example, the GTV (light blue), CTV (dark blue), PTV50 (red) and PTV60 (black) are outlined. The critical structure at most risk is the brainstem lying directly adjacent to the tumour. The PTV50 overlaps the brainstem but this is acceptable as the dose constraint for this organ is 50Gy. However, when trying to dose escalate, the PTV60 must not overlap the brainstem and is edited to reflect that. In this example, it is apparent that if the target isocentre moves in relation to the patient during treatment, the only direction in which this would affect the brainstem is in the left-right direction. In this case, when calculating the PRV for the brainstem, a one-dimensional solution using a small value for Σ is appropriate (i.e. 1.3 Σ) giving a different PRV margin from that calculated in the first case.
For the purpose of skull base radiotherapy planning, the organs at risk include the optic chiasm, optic nerves, and brainstem. These are all serial organs whose damage results in significant morbidity if overdosed. In situations where dose escalation is desired, techniques that result in a high level of conformality, and a high dose gradient must be employed (i.e. IMRT). This could result in regions of high dose being deposited very close (i.e. within millimetres) to OAR. Therefore the impact of systematic error becomes very significant. In this setting the ICRU Reports 62 and 83 recommend using a PRV to minimise the risk of over-dosage. We use a value of 2.1Σ as derived from McKenzie to calculate the PRV margin for our serial OARs, which is 3mm when using a stereotactic relocatable frame. We accept this is a very conservative margin, which in some situations may be an over-estimation of what is actually required, such as where the PTV is well lateralised and isocentre motion is likely to impact the OAR of interest in one dimension only. However, we feel this is a safe margin resulting in a minimal risk to the patient from systematic error, which is appropriate if the tumour being treated is benign i.e. G1 meningioma.

1.6. Planning

Once the target and organs at risk volumes have been defined, radiotherapy planning can begin. The construction of an optimised plan can be enhanced by manipulation of various steps during the process. The goal of radiotherapy planning is to create an arrangement of beams that delivers the prescribed dose to the tumour while minimising the risk of serious complications.

In the past, 2D planning methods were used yielding dose distributions, which were unable to conform well to complex shaped targets. CT planning allowed the use of forward
planned 3D conformal therapy, where multiple fields from non-opposing directions were used, with portal shapes created by making beam blocks or using MLC technology. Three dimensional forward planning techniques attempt to achieve this goal through a manual iterative process, where a planner chooses and alters the number of treatment beams, their orientations, their energies, and the dose intensity of the beam using wedges and compensators and their relative weights.

In the last 20 years, the development of MLC technology has allowed even more conformal distributions, by manipulating not only the portal shape, but also the dose intensity or fluence within that portal shape. Intensity Modulated Radiotherapy (IMRT) is now used for the treatment of sites where dose escalation and/or critical structure avoidance is of significant benefit i.e. head and neck cancer.

Figure 15. Schematic representation of the progression of radiotherapy over time from 2D planning, producing a symmetrical box like dose distribution, to ultra-conformal therapy, where the dose distribution begins to mirror the actual shape of the target. (Fig courtesy of Prof Neil Burnet)
The diagram above illustrates the progression of radiotherapy treatment and planning over time, from 2D planning giving a ‘square’ dose distribution, 3D conformal therapy improving the dose distribution from a ‘square’ to a ‘sphere’, and IMRT which produces dose distributions with concave shapes, in keeping with the true shape of the target.

Intensity Modulated Radiotherapy (IMRT) is a system of treatment planning and delivery that can improve significantly the ability to deliver radiotherapy to complex shaped targets, as well as minimising dose to surrounding critical structures. It has two primary components; inverse planned computerized iterative treatment plan optimization, and the use of intensity-modulated radiation beams. In the second component, the planner as for 3D conformal therapy chooses beam number, orientation and energies. In addition, the individual beam fluences are optimised using an inverse optimisation and utilising movable MLC technology.

IMRT can be delivered by a number of methods. Conventional linac and standard or micro-MLC technology can be used, as well as rotational arc therapy such as volumetric modulated arc therapy (VMAT) or helical tomotherapy (HT). In all cases the beam intensity is modified by segmenting the beam, then depositing dose in an inhomogeneous manner across the field, to allow tight sculpting of dose to the target and away from the OAR. This can be achieved by standard MLC, micro-MLC or rotational beamlets via helical tomotherapy, but always with the pattern of segmentation defined by the plan, created using a reverse iterative process.
Dosimetry studies of IMRT for skull base tumours have shown improved target coverage and potential for dose escalation, with a simultaneous reduction in dose to critical structures (Baumert et al 2003). Although follow up data is not long enough to document a clinical benefit, individual plan optimisation using IMRT is significantly improved, and this may translate to improved outcomes in the long term. The clinical impact of IMRT in terms of tumour control and normal tissue sparing can only be evaluated by following a group of patients over a suitable time. In the case of meningioma this would require a median follow up of 10-15 years, which is difficult to achieve, and during which significant changes in surgical and radiotherapy techniques are likely. This is an issue for other slow growing tumours and can make the implementation of IMRT in these settings controversial in the absence of clinical outcome data. However, its not unreasonable to assume a clinical benefit in any setting where the therapeutic ratio for a given treatment can be improved, and more recent literature reviews have been published discussing this specifically (Williams et al 2010, Ahmad et al 2012, Staffurth et al 2010, Veldman et al 2008).

In the setting of skull base meningioma, the ability to spare critical structures such as optic pathways and cranial nerves is very attractive, as is the potential to escalate dose if appropriate i.e. for non-benign meningioma. Limitations of IMRT include increased planning and treatment delivery time, increased QA requirements, increased patient immobilisation and verification requirements and in some sites, increased integral dose.

With regard to physical planning techniques, the number and arrangement of beams used could influence the dose distribution achievable. The number of beams and how they are arranged around the patient could influence the quality of plans achieved using inverse
planning techniques. Although this has not been specifically investigated in skull base radiotherapy planning, there have been some reports of techniques used in other sites. Das et al investigated five different prostate planning techniques (Das et al 2003). An automated beam selection process was used, and the Equivalent Uniform Dose (EUD) was used in the inverse planning process as part of the objective function. The study found that 3-5 non-coplanar beam arrangements gave similar dose distributions (target coverage and OAR sparing) to co-planar equidistant, unselected plans using a large number of beams (i.e. 15 coplanar). This suggested that a non-coplanar beam arrangement could allow fewer beams to be used, if they are placed optimally, making it easier for planning systems to meet planning constraints. This would also be expected to minimise treatment time, and possibly integral dose to the patient. Other studies have investigated automated algorithms to aid beam placement, utilising biological objective functions or traditional planning procedures such as beam’s eye view (BEV) techniques (Pugachev et al 2001). These studies used non-coplanar beam arrangements, and did not attempt to compare non-coplanar and coplanar beam arrangements. In the region of the skull base, it is not clear from current literature if there is benefit to using non-coplanar techniques compared to coplanar. Another aspect of IMRT is the degree of intensity modulation in each beam. This can be influenced by the size of the MLC leaves used, with smaller width leaves presumed to result in a more conformal dose distribution. This has been demonstrated in a number of small studies, showing better PTV coverage, organ at risk sparing and better conformity of high dose around a complex shaped PTV (Nill 2005, Fiveash et al 2002, and Monk et al 2003). This indicates that the higher the level of dose intensity modulation, the better the dose distribution, although the cost of this is likely to be a longer beam on time and increased uncertainty with the high level of segmentation required. These factors are
considered in Chapter Three where planning class solutions for IMRT for skull base meningioma are identified.

1.7. Plan comparison

1.7.1 Physical parameters

Conventionally, plan quality is assessed using physical planning parameters, such as tumour and OAR $D_{\text{max}}$, $D_{\text{mean}}$, $D_{\text{min}}$, volume of PTV and OAR receiving prescribed dose (i.e. $V_{90}$, $V_{95}$, $V_{100}$), and tumour and OAR DVH and dose distribution analysis. These have been, and remain useful tools when assessing plans for safety and efficacy, and for the comparison of one plan against another. Each parameter gives specific and useful information, but must be interpreted in context. In most cases, all these parameters need to be considered to build up an overall picture of a specific plan, and how it may or may not be appropriate for a specific patient.

These parameters are limited, in that they relate only to dose and total dose delivered to a patient, i.e. the ‘physical’ component of treatment response. They do not account for the complex ‘biological’ factors, which are important also. The differential responses of certain tumours and tissues to specific doses and dose fractionation schedules are becoming more apparent. Biological parameters such as TCP and NTCP are becoming more prevalent as planning tools, both as a means to assess and compare plans, but also as potential plan optimisation functions. However, these require underlying biological models containing parameters that are not well defined. Specific to IMRT is the concept of equivalent uniform dose, which is discussed below. This has the advantage of not containing biological assumptions, requiring only one parameter to describe the effect of dose variation.
1.7.2 Biological parameters – Equivalent Uniform Dose (EUD)

The equivalent uniform dose (EUD) for tumours is defined as the biologically equivalent dose that, if given uniformly, will lead to the same cell kill in the tumour volume as the actual non-uniform dose distribution (Niemierko et al 1997). This concept has been expanded to apply to normal tissue as well (Niemierko et al 1999). EUD can be a useful end when comparing treatment plans with non-uniform dose distributions, which is a particular feature of IMRT. EUD has been used in this role in our department.

Generally, most IMRT optimisation systems use dose-volume information for objective functions. However, this may not accurately reflect the non-linear response of tumours or normal structures to dose, especially in the setting of in-homogenous dose distributions. Since the development of the concept of EUD, some researchers have investigated its role in IMRT plan optimisation. Wu et al in 2002 proposed an objective function based on EUD for IMRT plan optimisation, and compared it to corresponding plans optimised with dose volume criteria. They found that EUD-based optimisation provided improved sparing of normal tissues for the same or higher target dose in patients with head and neck or prostate cancer (Wu et al 2002). Thomas et al in 2005 compared plans for intra-hepatic IMRT and 3D conformal therapy. The EUD was used to assess the dose across the PTV, which was superior in the IMRT plans resulting in safe dose escalation by 10-18Gy (Thomas et al 2005). Therefore, initial investigation suggests EUD may have a role in individual plan optimisation for patients undergoing IMRT.
The original definition of EUD was derived based on mechanistic formulation using a linear-quadratic cell survival model. Niemierko has suggested single formulae for both tumour and normal tissue.

\[ EUD = \left( \frac{1}{N} \sum_i^{N} D_i^a \right)^{\frac{1}{a}} \]

- \( N \) number of voxels in anatomical structure of interest
- \( D_i \) dose to voxel \( i \)
- \( a \) parameter defining dose volume effect

The value \( a \), is the defining parameter which has to be assigned for the equation, and relates to the importance (or lack of) dose volume effects i.e. cold spots = under-dosing in tumour, or hotspots = over-dosing in normal tissue.

The above formulation of EUD is based on a power law dependence of the response of a complex biologic system to a stimulus. EUD as represented by the above equation is the ‘generalised mean’ of the non-uniform dose distribution. For \( a = \) infinity the EUD is equal to the maximum dose. For \( a = -\) infinity, the EUD is equal to the minimum dose. For \( a = 1 \) EUD is equal to the arithmetic mean and for \( a = 0 \) the EUD is equal to the geometric mean. For tumours, parameter \( a \) will attain large negative values for malignant tumours indicating the importance to outcome of covering the PTV with an appropriate dose i.e. minimising hot spots. Skull base chordoma clinical outcome data reliably suggests that the value of \( a \) for this tumour is -15, supporting this concept (Terahara et al 1999, Niemierko...
personal communication). For normal serial structures such as the spinal cord, large positive values of $a$ will reflect the critical importance of hotspots to functional outcome. For organs with parallel architecture, $a$ will be closer to 0 as the dose response is more related to the mean dose than to hotspots. For normal tissue, parameter $a$ can be related to $n$ (as $a=1/n$) defined by the Lyman model based on original Emami dose-volume response data.

In tumours affecting the skull base, EUD used as a plan optimisation tool could significantly improve dose distribution to the tumour and normal structures. In situations where dose escalation is desirable, this could influence individual plan optimisation. It is a relatively new concept, and warrants further investigation. As well as ongoing studies assessing its usefulness as a planning tool, long-term clinical endpoints such as normal tissue dose response and tumour control could be examined as a function of the EUD of both the target and the normal tissues.

1.8. Treatment delivery

IMRT delivery is possible because of the development of moving MLC technology. Individual leaves of the MLC are positioned throughout the fraction in either a ‘step and shoot’ or ‘dynamic’ moving MLC method. In the case of meningioma, doses of at least 50Gy are used and conventionally prescribed over 30 or more fractions. The number of segments used in construction of the plan can influence the number of monitor units and therefore the beam on time. This could influence of factors such as integral dose to patient
and the practicality of delivering a highly modulated plan in a department. Consideration must be made for the practical implications and limitations in some settings.

1.9. Verification

In the setting of more conformal dose distributions and possible dose escalation, verification of dose and treatment portals is essential to ensure patients are not given more or less dose than is planned. Verification during treatment can include the use of PORT films, on line EPID, cone beam technology, helical CT imaging (i.e. Tomotherapy). Online, real time imaging using cone beam technology, has allowed patients to be treated with a new level of accuracy. Daily assessments and treatment shifts when required, mean that radiotherapy can be delivered to a target with a high level of precision, almost removing the uncertainty of inter-fractional motion in some settings (Burnet et al 2010). This can mean that PTV margins could be reduced, further improving our ability to dose escalate PTV volumes without compromising adjacent critical structures.

Dose quality assurance can be tested by phantom measurements of one fraction of the plan before treatment starts, and then during treatment via the use of TLD’s in the centre and/or edge of the field, and adjacent to OAR i.e. outer canthus of eye. It is a vital step in any treatment protocol, but of high importance when dealing with sharp gradients of dose and complex dose distributions.
CHAPTER TWO: THE ROLE OF DOSE ESCALATION IN MENIGIOMA

2.1. Preface 82

2.2. Publication: Pattern of relapse after fractionated external beam radiotherapy for Meningioma: Experience from Addenbrookes Hospital. 84

2.3. Discussion 85

2.3.1 Contribution and Significance 93

2.3.2 Literature following publication 97

2.3.3 Future directions 98
2  CHAPTER TWO: THE ROLE OF DOSE ESCALATION IN MENINGIOMA

2.1. Preface

Doses of 50-54Gy have been standard for the treatment of meningioma for decades, and retrospective studies show good long-term local control rates in this group of patients (Carella et al 1982, Glaholm et al 1990, Goldsmith et al 1994, Mirabell et al 1992, Nutting et al 1999, Pourel et al 2001, Vendrely et al 1999, Dufour et al 2001, Yamashita et al 1980). However, atypical (WHO Grade 2) and anaplastic or ‘malignant’ meningioma’s (WHO Grade 3), have a much poorer progression free survival (PFS) and overall survival (OS). These tumours rarely recur outside of the local site in the majority of series, and one strategy to improve local control (and therefore possibly survival) could include delivery of a higher dose of radiation to the tumour i.e. radiotherapy dose escalation.

As noted in Chapter One, radiation dose escalation is likely to have a positive effect on overall survival for many cancers, as illustrated by the observation that one breast cancer death is prevented for every four local recurrences prevented with radiotherapy (Clarke et al 2005). By contrast, a dose reduction of 20% in radiation - sensitive normal tissue could significantly reduce the risk of serious treatment-related complications in some settings. Population studies indicate that dose escalation in general (within the confines of normal tissue sparing) can be advantageous to patients, even though we may not be able to prove the benefit in individuals (Suit et al 2001).

The role for dose escalation in meningioma is currently not well evidenced compared some other examples, but we can attempt to answer the question of whether or not there is a dose response above a certain level using basic principles and the limited retrospective data
available. Although there is no robust pre-clinical or clinical dose-response data to inform us what the inherent sensitivity of G2 and G3 meningioma is, and therefore what an appropriate $\gamma_{50}$ should be for meningioma, it is reasonable to apply a level of 1.5. This level can be applied to many other tumours with similar relapse patterns, and could be particularly relevant for G2 and especially G3 meningiomas, which have a more aggressive natural history in keeping with malignant tumours. Based on this concept, when treating an aggressive meningioma with radiotherapy, a 20% dose escalation of 10Gy from 50Gy to 60Gy could be expected to result in an increase in TCP by 30% (See Figure 8, Chapter One). This means that the question of dose escalation in the management of this disease is a relevant one, regardless of its rarity.

Our department has added to this pool of data by publishing our own retrospective review of outcomes for meningioma patients treated with radiotherapy, in an attempt to further characterise the impact of radiotherapy dose on response.
2.2. Publication: Pattern of relapse after fractionated external beam radiotherapy for Meningioma: Experience from Addenbrookes Hospital.

The following section contains an unaltered reproduction of the article “Pattern of relapse after fractionated external beam radiotherapy for meningioma: Experience from Addenbrooke’s Hospital” published in the journal Clinical Oncology, 2009, Volume 21, Issue 10, Pages 745-752. Clinical Oncology is the official journal of the Royal College of Radiologists, and covers research in the field of clinical oncology. Its emphasis is on practical clinical implication of up to date developments in cancer research and the journal had an impact factor of 2.846 in 2009, and a 5year impact factor of 2.386. This article has been cited in at least one recent article (See Appendix Three).
Original Article

Pattern of Relapse after Fractionated External Beam Radiotherapy for Meningioma: Experience from Addenbrooke’s Hospital

V. Estall†, S. J. Treece‡, R. Jena†, S. J. Jefferies†, K. E. Burton†, R. A. Parker‡, N. G. Burnet§

†Cambridge University NHS Hospitals Trust, Cambridge, UK; ‡Addenbrooke’s Hospital, Oncology Centre, Cambridge, UK; §The General Practice and Primary Care Research Unit, University of Cambridge, Cambridge, UK; Department of Oncology, Cambridge, UK

ABSTRACT:
Aims: Radiotherapy is an important treatment modality for meningioma. We aimed to review the clinical outcomes for meningioma patients treated with radiotherapy in the Addenbrooke’s Hospital Oncology Department.

Methods and methods: A retrospective chart review was carried out on patients with meningioma referred and treated in the department between 1 November 1996 and 31 October 2006. Patient details and outcomes were recorded and the results were analysed to assess survival outcomes. Survival data were confirmed by the Eastern Cancer Registration and Information Centre.

Results: In total, 174 patients were referred to the department for an oncology opinion. Of these, 128 proceeded to radiotherapy. The median follow-up was 5.3 years (range 2.1–11.9 years). Sixty-seven percent of the patients were older than 50 years, and the female: male ratio was 2.2:1. Overall survival was 78% at the time of follow-up, with death related to meningioma in 7% of the total cohort. Local control was 85% overall, 93% for grade 1 disease, 45% for grade 2 disease and 82% for grade 3 disease. Patients with non-benign disease were more likely to receive >50 Gy (27% of grade 1 lesions vs 65% of grade 2/3 lesions), but despite this local control remained poor, even with the higher dose delivered (local control 60% and 40% for grade 2 lesions treated with 50 and >50 Gy, respectively, and 100% and 73% for grade 3 lesions treated with 50 and >50 Gy, respectively).

Conclusions: Our cohort of patients had an overall local control and survival similar to those documented from other departments. Grade was an important prognostic factor. Patients treated with >50 Gy had worse local control outcomes, probably due to selection bias. Dose escalation may still be appropriate for high-risk disease, and may be more effective with more conformal techniques, such as intensity-modulated radiotherapy. Estall, V. et al. (2009).

Clinical Oncology 21, 745–752

© 2009 The Royal College of Radiologists. Published by Elsevier Ltd. All rights reserved.

Key words: Local control, meningioma, radiotherapy

Introduction

Meningioma account for 25–30% of all primary central nervous system tumours in adults [1], although they represent only 10% of all cases referred for an oncology opinion in our centre. They are thought to arise from the arachnoid cap cells lining the surface of the arachnoid villi, and/or meningotheial progenitor cells, and can be classified based on the World Health Organization (WHO) 2007 criteria [2]. Benign meningioma (grade 1) account for most cases (70–85%) and after treatment the long-term prognosis is favourable, with a progression-free survival at 10 years of 75–90% [1]. However, atypical (grade 2) and anaplastic or ‘malignant’ meningioma (grade 3) have a much poorer progression-free survival and overall survival. In series investigating this group, recurrence rates after resection alone at 5 years can reach 52% and 84% for atypical and anaplastic meningioma, respectively [3]. The survival of these patients is also considerably worse, with a 4.6-fold increase in the risk of death for patients with non-benign disease [4].

There is little real evidence available to guide clinicians regarding the most effective treatment for meningioma, but, in general, the pattern of relapse is one of local recurrence; hence, treatment strategies focus on surgery and radiotherapy. Surgery is considered by many to be the mainstay of treatment, especially if resection is possible without compromising the functional status of the patient. The extent of resection is prognostic, based on the work by Donald Simpson in the late 1950s, with complete resection
resulting in long-term local control of 92% [3]. Complete resection is often not feasible, however, due to the location of the tumour or medical inoperability, such as anaesthetic risk or co-morbid disease, and subtotal resection alone is associated with poorer local control of only 66% [3].

Radiotherapy is an effective therapy that can be used in conjunction with surgery or alone. The evidence is usually derived from studies including both postoperative and radiotherapy-alone cases and indicate local control rates at 5 years of 95% or more [6, 7]. Radiotherapy can also improve local control when given postoperatively after a subtotal resection, from 66% [3] to 85–97% [7, 8]. Its effect on local control after complete resection of grade 1 disease seems to be less significant, when considering that retrospective data indicate similar outcomes for complete surgical resection and partial resection plus radiotherapy [5, 7].

In these series the meningioma were usually grade 1 or 'benign' in nature, and in contrast, WHO grade 2 and 3 disease generally have inferior local control after radiotherapy. Local control at 5 years has been reported as 17–34% in two series where patients received doses of 50–54 Gy in 30–33 fractions [9, 10], doses generally resulting in local control rates of more the 90% in benign disease [8]. Dose escalation above standard doses of 60 Gy in 30 fractions may improve local control in the setting of grade 2 and 3 meningioma [9–11]. Table 1 summarises the retrospective data. To examine the question of dose and local control, a European Organization for Research and Treatment of Cancer study investigating dose escalation up to 70 Gy in these patients is being conducted.

Therefore, our indications for radiotherapy include its use for grade 1 lesions radically, or postoperatively if the disease is recurrent or resection is suboptimal and disease progression is considered likely. In grade 2 lesions, radiotherapy is indicated if there is subtotal resection, or disease recurrence after resection, and we would advocate adjuvant therapy after complete resection if the site involved is not amenable to repeat surgery. We would always consider radiotherapy to be indicated in grade 3 disease due to the high risk of local failure. In the setting of non-benign meningioma, we would consider using doses up to 60 Gy/30 fractions if this can be achieved without compromising dose tolerances of adjacent critical structures. In all cases, patient factors would also be considered, in particular competing risks for morbidity or mortality, including patient age, co-morbidity and performance status. The aim would be to select patients for radiotherapy who are at risk: benefit analysis is favourable.

The aim of this study was to retrospectively review the outcomes after radiotherapy delivered for meningioma in our department over a 10 year period. We sought to compare our results with those documented in published studies and to identify any possible correlations with prognostic factors. Specifically, we aimed to investigate, where possible, the effect of tumour grade, patient factors, extent of resection and dose delivered on outcomes.

### Materials and Methods

A retrospective review was carried out for all patients with meningioma referred and seen in the Oncology Centre between 1 November 1996 and 31 October 2006. Patient factors (age, gender), tumour factors (grade, location) and treatment factors (resection details, radiotherapy dose and fractionation), as well as outcomes (local relapse, survival) were recorded and analysed using Microsoft Excel and SPSS software. The surgical details were difficult to extract from both the neurosurgical and oncology patient files, and were limited to whether or not the patient had a biopsy or surgical resection vs no surgical intervention. It was not possible to quantify the extent of resection retrospectively from the resources available.

We calculated Kaplan–Meier survival curves for relapse-free survival and overall survival. Unfortunately, it was not appropriate to apply a Cox's proportional hazards regression model to the data because there was evidence for non-constant hazard ratios over time. Therefore, the data were analysed using a multiple logistic regression method, such that the recurrence up to a single specific time point was considered. The variable of interest was a binary variable recording recurrence of meningioma or death from disease up to (and including) the time point 1179 days after radiotherapy. Choosing a suitable time point at the analysis stage of a study can introduce bias. Therefore, in an attempt to reduce the potential for bias, a time point was randomly chosen in a suitable time interval of 500–1500 days after randomisation. The randomly chosen time point was 1179 days, corresponding to about 3 years after treatment. Logistic regression models were then applied to investigate significant predictors of recurrence among the variables gender, age, treatment, tumour grade and radiation dose.

With the exception of age (which was continuous), all these variables entered the logistic regression models as binary variables: gender (male, female); treatment (surgery, radiotherapy only); tumour grade (1, 2 or 3); radiation dose (50 Gy or less, more than 50 Gy). Because the numbers of patients with a tumour grade of 3 was very small, it was decided to group the grade 2 and 3 patients in the same category, as well as analysing separately. Forward model selection (with likelihood ratio

### Table 1 — Retrospective series indicating a possible dose response for grade 2/3 meningioma. The outcomes measured included progression-free survival (PFS), cause-specific survival (CSS) and local control (LC).

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. patients</th>
<th>Dose of radiation</th>
<th>Outcomes</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>[3]</td>
<td>23</td>
<td>&lt;53 Gy</td>
<td>5 year PFS 17%</td>
<td>0.01</td>
</tr>
<tr>
<td>[6]</td>
<td>59</td>
<td>&gt;50 Gy</td>
<td>5 year PFS 67%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 Gy</td>
<td>5 year CSS 42%</td>
<td></td>
</tr>
<tr>
<td>[7]</td>
<td>15 grade 2</td>
<td>&gt;60 Gy</td>
<td>5 year LC 0%</td>
<td>0.025</td>
</tr>
<tr>
<td>[7]</td>
<td>16 grade 3</td>
<td>&lt;60 Gy</td>
<td>5 year LC 0%</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥60 Gy</td>
<td>5 year LC 100%</td>
<td></td>
</tr>
</tbody>
</table>
testing) was used to find the 'best' or optimum model that balanced simplicity with goodness-of-fit. This model selection procedure adds variables to the logistic regression model in turn to test if the goodness-of-fit is significantly improved. If there is a significant improvement, the variable remains; otherwise the variable does not enter the final model.

The study was registered as a audit project with the hospital Audit Department, and overall survival data were obtained from the Eastern Cancer Registration and Information Centre.

Results
In the 10 year period investigated, 174 patients with meningioma were referred for consideration of radiotherapy treatment. Of these, 128 proceeded to therapeutic irradiation and were analysed. The median follow-up time was 5.3 years (range 2.1–11.5 years).

Demographics
The age of the patients ranged from 20 to 82 years. Sixty-seven per cent of patients were 50 years or older at the time of treatment, with 33% being younger than 50 years. The female to male ratio of patients was 2:2:1.

Planning and Treatment
In the 10 year period analysed, most patients were treated as per our departmental protocol with three-dimensional conformal therapy, which became standard practice in 1998. Target volumes (tumour and normal structures) were delineated with computed tomography: magnetic resonance imaging (MRI) co-registration from 2000 and the gross tumour volume was identified as the dural abnormality noted on T1 W MRI with gadolinium. The clinical target volume (CTV) was created by the addition of 0.3 cm along the dural planes in grade 1 disease and 1.0–1.5 cm in the setting of grade 2 or 3 disease. The planning target volume (PTV) was created by a volumetric expansion of the CTV by a margin defined by the immobilisation device used, and was 5 mm for a thermoplastic mask and 3 mm for our relocatable stereotactic frame, which is used for stereotactic conformal radiotherapy. External beam photon therapy (6 MV) was planned using three to five beams, usually in a non-coplanar arrangement with wedges to improve dose homogeneity where appropriate. For large target volumes, “field in field” techniques were used as a forward planned intensity-modulated radiotherapy (IMRT) solution to improve dosimetry. The doses prescribed and delivered ranged from 50 to 60 Gy in 1.67–2.0 Gy/fraction. Serial organs, such as the optic pathways and brainstem, were limited to a maximum dose of 50 Gy. Inverse planned IMRT using a microleaf multileaf collimator and helical tomotherapy became available after 2006 and therefore were not techniques used in this cohort.

Prognostic Factors
The location of the tumour was at the skull base in 54%, convexity in 22%, parasagittal in 15% and optic nerve meningioma in 9% of cases. Most of the tumours receiving radiotherapy for which we had histological confirmation of diagnosis (84% of all cases treated) were benign, with 79% WHO grade 1, 16% grade 2 and 8% grade 3. The 26% of patients overall who were treated based on radiological diagnosis were generally managed as grade 1 tumours and included optic nerve sheath tumours, difficult to access skull base tumours and tumours in patients considered not medically fit for surgery. All but two of these were located in the skull base or were optic nerve sheath meningioma. With regard to surgical management, 6% were biopsied only for diagnosis, 26% had no surgery or biopsy, and 68% had a resection. Thirty-five patients were treated without histological diagnosis and details of the extent of tumour resection were poorly documented in the case notes and a meaningful quantitative assessment of subtotal vs gross total resection was not possible. Therefore, 31% of cases were treated with radiotherapy alone, whereas 69% received radiotherapy postoperatively, after either total or subtotal resection. The dose delivered was 50 Gy in 1.67–1.8 Gy/fraction in 63%, and over 50 Gy in 1.67–1.8 Gy/fraction in 37%. Forty-five patients received 55 Gy; 23 were grade 1, 12 were grade 2 and six were grade 3. Five patients received 60 Gy; in all cases disease was recurrent after surgery, and sites were sphenoid wing in one case, parasagittal in two cases and convexity in the remaining two cases. Only one case was grade 1, with three cases grade 2 and one case grade 3.

Relapse Data
Of the 128 patients treated, 15% (19/128 patients) developed progressive disease. Therefore, 85% overall had sustained local control at the time of reporting, with a median follow-up of 5.3 years (Fig. 1). Treatment for relapse after radiotherapy included further surgery in eight patients, re-irradiation in four patients and both surgery and re-irradiation in four patients. Three patients were observed without active salvage therapy. Seven of the 16 patients treated for relapse (37%), recurred a second time. Of these, two received hydroxyurea, one had further surgery and a single fraction of palliative radiotherapy to disease eroding the scalp, one had re-resection and three were observed. The histological grade was WHO grade 2 in four cases, grade 3 in two cases and unknown in one case, as the lesion was diagnosed radiologically.

Survival Data
At the time of audit, 24/128 (18%) patients had died, giving an overall survival at the time reporting of 82% (Fig. 2). The Eastern Cancer Registration and Information Centre was able to confirm all deaths, meaning no patients were lost to follow-up in our cohort. Death was due to the disease in nine of the 24 patients (37%) and unrelated in 15 (63%). Of
the nine patients who died from disease, two were grade 1, three were grade 2 and four were grade 3, making most of the deaths (7/9; 78%) due to non-benign histology.

**Effect of Grade and Dose on Local Control**

After carrying out forward model selection at the 5% level of significance, only the grade variable appeared in the final logistic regression model. (The same result was also found after using backwards model selection.) The WHO grade was found to be a strongly significant predictor of recurrence or death from disease at the 5% level ($P < 0.0001$). The odds ratio of recurrence or death from disease for a patient with a grade 2 or 3 tumour relative to a patient with a grade 1 tumour was 16.79 (95% confidence interval 4.91–75.39). Therefore, the odds of recurrence or death from the disease is estimated to be about 17 times greater for patients with either grade 2 or grade 3 tumours relative to patients with grade 1 tumours. Patients with either grade 2 or grade 3 tumours seem to have a significantly higher risk of suffering from recurrence or death due to the disease. The fact that only the grade variable entered the final model shows that this variable dominates over all the other variables in predicting recurrence. None of the other variables had a significant effect on recurrence after adjusting for tumour grade. However, it should be noted that just because the other variables did not appear in the final model does not necessarily mean that in reality there is no relationship between these variables and recurrence. Lack of power is probably the main reason why the other variables were not significant. The number of variables in the model compared

with the sample size means that the power to detect significant effects (given that such significant effects exist) in this study is probably quite low. Any non-significant results should be interpreted cautiously.

Local control was 94% in the patients with benign disease, but reduced to 45 and 81% for grade 2 and 3 lesions, respectively (Table 2; Fig. 3). WHO grades 2 and 3 are strongly significant predictors of recurrence at the 5% level based on logistic regression modelling (Table 3).

In our cohort of 128 patients, we treated 63% with a conventional dose of 50 Gy, whereas 37% received more than 50 Gy. Typically, higher doses were given to tumours considered more aggressive, as long as doses to surrounding organs at risk could be maintained within tolerance. A higher proportion of grade 2/3 lesions were treated with doses of radiotherapy $>$50 Gy compared with grade 1 tumours. Dose escalation above 50 Gy was delivered in

<table>
<thead>
<tr>
<th>Grade</th>
<th>50 Gy (n)</th>
<th>$&gt;$ 50 Gy (n)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>70</td>
<td>27</td>
<td>97</td>
</tr>
<tr>
<td>Grade 2</td>
<td>8</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Grade 3</td>
<td>3</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>81 (63%)</td>
<td>47 (37%)</td>
<td>128</td>
</tr>
</tbody>
</table>
28% of grade 1 lesions, 60% of grade 2 lesions and 73% of grade 3 lesions. Local control was poor in the group receiving >50 Gy, despite the increased dose delivered (Fig. 4). However, this difference was not significant after logistic regression modelling. In patients receiving 50 Gy (of which the majority, 86%, had benign lesions), local relapse at the time of reporting was 7.4%. Of these six relapses, five had had an initial resection, which may indicate large volume lesions, and four were grade 2 lesions. In patients receiving >50 Gy, 28% relapsed. Of the 13 relapses, 11 had been treated initially with resection alone and nine were grade 2 or 3. Therefore, despite the dose delivered most relapses occurred after resection and/or in non-benign tumours. There were insufficient retrospective data to establish the volume of the initial tumours or the extent of resections carried out, which may have had some bearing on local control rates.

Table 3 — Local control after radiotherapy based on the dose delivered and grade. Note that patients receiving >50 Gy seemed to have a poorer local control compared with those receiving 50 Gy. This may be due to selection bias, with those being prescribed higher doses of radiotherapy as a result of a worse predicted prognosis.

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>50 Gy</th>
<th>&gt;50 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>93%</td>
<td>97%</td>
<td>85%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>45%</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>82%</td>
<td>100%</td>
<td>75%</td>
</tr>
</tbody>
</table>

**Effect of Surgery on Local Control**

In this study, local control was better for patients where treatment was with radiotherapy alone as the primary therapy (Fig. 3), although this finding was not significant after logistic regression modelling. It is unclear why this may be the case, but one explanation could be selection bias. It is possible that the cases treated with surgery followed by radiotherapy may have been a poorer prognosis group, with postoperative radiotherapy indicated after partial debulking of a large tumour and/or if histology confirmed a higher grade. In contrast, radiotherapy alone was more likely to be prescribed for smaller tumours and tumours in the skull base, which were less amenable to primary resection, but are often slow growing and benign. In our case, this included optic nerve sheath meningioma, resulting in 100% control at the time of follow-up for this group, comparable with other reported series [12]. Therefore, those cases selected for radiotherapy alone may have been in a lower risk group at the time the management decision was being made.

**Effect of Age on Local Control and Death due to Meningioma**

There seems to be little effect of age on local relapse or death from meningioma (Fig. 6). Local relapse occurred in 14% of patients aged 50 years or less, and in 15% of patients aged over 50 years. Death due to meningioma occurred in 4.8% of patients aged 50 years or less, and in 4.7% of patients aged over 50 years.
Effect of Gender on Local Control and Death due to Meningioma

Local relapse was assessed by patient gender, and there seems to be an increased risk for relapse in men compared with women, despite the higher incidence in women overall. In our sample, 30% of men relapsed, whereas only 8% of women relapsed (Fig. 7), although this difference was not significant after logistic regression analysis. There was also an increase in the proportion of men (10%) vs women (3-4%) dying from meningiomas. This was probably the result of the difference in gender in our cohort between the proportions of non-benign meningioma. Of the male patients treated, 35% had grade 2 or 3 disease, whereas for the females treated, only 19% had non-benign histology.

Discussion

In this retrospective study, we report our experience of outcomes when treating meningioma patients with radiotherapy. With a median follow-up of just over 5 years, we achieved an overall local control rate of 85%, an overall survival of 78% and an approximate death rate from meningioma of 7%. For grade 1 lesions, local control was 93%, which is in keeping with other published reports, indicating that our treatment approach for this group of patients has been appropriate. As expected, the rate of local control dropped in the case of non-benign histology, which in our case was more prevalent in male patients. We were unable to identify an association between patient age and treatment outcomes, and although patient gender seemed to be prognostic, this was most probably due to the confounding factor of a different distribution of histological grades between the gender groups. Statistical analysis was not performed but can be useful in future studies.
difficult due to the small number of events, but based on our modelling using a multiple logistic regression method, we found that grade was statistically significantly prognostic of relapse. Other variables, such as dose, were not statistically significant, which could be a result of under-powering of the study due to small numbers.

An important limitation of this retrospective study was the lack of detail regarding the extent of surgical resection, particularly as it is a known prognostic factor for local control. We attempted to quantify the extent of resection, but were unable to do this in a way that we could be satisfied was robust and meaningful. As a result of this finding, we will attempt to prospectively document surgical resection details at the time of initial consultation, which will require good lines of communication with surgical colleagues.

Because of the nature of relapse of meningioma, we would recommend continuing follow-up in these patients for at least 10 years. Our policy is to see patients on a yearly basis, with MRI scans at 1, 2, 5 and 10 years after treatment to ensure we can diagnose, treat and document relapse, although this protocol is not based on any published studies showing an improvement in outcomes.

In this cohort, local control was less in those selected for dose escalation, compared with those we chose not to treat with more standard doses of 50 Gy in 30–33 fractions. This was a reflection of the poor prognosis of this group, which prompted the selection for dose escalation, rather than an indication that the higher dose used was in itself detrimental. There was no statistically significant difference found based on our analysis, but this was limited due to small numbers of events. When clinically assessing patients, we consider adverse prognostic factors, such as higher tumour grade, multiple recurrences and very large tumour volumes and, if feasible, attempt to deliver up to 60 Gy to the tumour in an attempt to improve local control. Unfortunately, despite this, our results for these patients remained poor, prompting us to question whether our treatment approach has been appropriate, and to postulate that possibly even higher doses may be required to control these locally aggressive cases. Alternatively, this could be because the dose delivered to the PTV was not sufficient, principally because the dose achieved using three-dimensional conformal therapy was not adequate as a result of normal tissue tolerance limits in the region of the skull base. We have typically used conservative dose limits for our critical structures in the brain when treating meningiomas, limiting $D_{\text{max}}$ to less than equal to 50 Gy for the brainstem and optic pathways. This can make it difficult to deliver high doses of radiotherapy to a sufficient proportion of the PTV, i.e. limit the volume of the PTV receiving 95% or more of the prescribed dose.

There is no clinical information regarding improved clinical outcomes when using different techniques such as IMRT for meningioma patients at this stage, but dose distribution and the ability to dose escalate have been shown to be superior in planning studies [13,14]. It may be that using more advanced radiotherapy techniques to allow radiotherapy dose escalation could improve the clinical outcomes, and be beneficial in the setting of non-benign histology, as indicated in some series. IMRT using linear accelerators and multileaf collimator technology [13,14], helical tomotherapy [15,16] and proton therapy [17] have all been investigated and have been shown to result in improved physical dose distributions, and are techniques we are interested in exploring in the treatment of non-benign meningioma. The clinical effect of dose escalation has been difficult to quantify as data are limited to small series, but the European Organization for Research and Treatment of Cancer are currently attempting to answer this question with a randomised controlled trial [18].

Other improvements to radiotherapy that may improve clinical outcomes for these patients include improved imaging techniques to identify the gross tumour volume, such as computed tomography/positron emission tomography using somatostatin analogue-labelled isotopes, or improved understanding regarding the spread of non-benign meningiomas through the dura, which could more accurately inform our CTV margins. Image-guided radiotherapy might also allow a decrease in PTV margin, facilitating safe dose escalation [19]. Of course, systemic therapies are limited in the setting of aggressive meningioma, and further investigation of new agents is warranted, especially as these conditions are not only locally devastating, but can also result in the death of the patient. As a result of these findings, and those reported in other published studies, it seems that 50 Gy in conventional fractionation is an adequate dose for good local control of WHO grade 1 tumours accepting a relapse rate of 6% overall. However, grade 2 and 3 lesions do poorly locally, and although our results did not show an improvement in outcome, we would still postulate that higher doses to the PTV are warranted if they can be delivered safely without compromising the normal surrounding structures. This is more likely to be successfully achieved as planning and treatment techniques become more advanced, allowing better dose distributions to this difficult treatment site.

Conflict of interest

V. J. Estall is a Clinical Research Fellow funded by Siemens Oncology OCS, through an unrestricted educational grant, in collaboration with Addenbrooke's Hospital Oncology Centre and Cambridge University Department of Oncology.

Acknowledgements. V. J. Estall is supported by Siemens OCS, R. Jene by the Health Foundation UK and N. Burnett by the NIHR Cambridge Biomedical Research Centre. Special thanks for input from the Eastern Cancer Registration and Information Centre.

Author for correspondence: V. Estall, Cambridge University NHS Hospitals Trust, Cambridge, UK; Tel: 01223-368008; Fax: 01223-63120; E-mail: vjestall@hotmail.com

Received 3 March 2009; received in revised form 10 August 2009; accepted 12 August 2009
References


2.3. Discussion

2.3.1 Contribution and Significance

Radiotherapy dose response data for meningioma is restricted to small retrospective reviews of longitudinal cohorts of patients; however, there is limited evidence that doses above 50Gy could be beneficial with regard to improved local control in non-benign meningioma. Milosevic et al reported on 59 patients with atypical or anaplastic meningioma, treated with 3D conformal radiotherapy to a median dose of 50Gy, following or as an alternative to surgical resection. Local control was low overall at 34%, with 5 year actuarial overall and cause-specific survival of 28% and 34% respectively. They found that doses delivered above 50Gy were associated with a statistically significant improved local control on both univariate and multivariate analysis (Milosevic et al 1996). Hug et al analysed outcomes for 31 patients with non-benign meningioma treated with 3D conformal external beam radiotherapy using photons alone, or a mixture of photons and protons (Hug et al 2000). They identified a statistically significant improvement in local control with doses of radiotherapy ≥60Gy for both atypical (p=0.025) and anaplastic meningioma (p=0.0006). Goldsmith et al reported on 23 patients with WHO Grade 2 or 3 meningioma, who had been treated with radiotherapy with a median dose of 54Gy, as an adjunct to subtotal resection (Goldsmith et al 1994). They found that the 5 year PFS was significantly improved when a dose of ≥53Gy was administered in contrast to a dose <53Gy (67% vs. 17% p=0.01). Coke et al reported an improved survival in 17 non-benign meningioma patients treated with post-operative radiotherapy to a median dose of 61Gy (Coke et al 1998). Three of 5 (60%) patients treated with less than 54Gy died of meningioma within the follow up period (median 87 months) in comparison to only one of 12 (8.3%) patients dying of recurrent disease in the group treated with more than 54Gy.
A crude dose response curve can be constructed from the 3 external beam radiotherapy studies indicating a possible dose response relationship for non-benign meningioma. However, it must be emphasised that the basis of this information is a limited number of small, longitudinal cohort series, and we cannot claim statistical significance with current levels of data.

Figure 16. Possible radiotherapy dose response relationship for non-benign meningioma, based on 3 small studies finding an improved local control with doses delivered above 50Gy, 53Gy and 60Gy (Goldsmith et al 1994, Milosevic et al 1996 and Hug et al 2000).

Dose response data may also be derived from stereotactic radiosurgery (SRS) patient cohorts, which in some cases suggest a higher dose to the tumour may improve local control. Stafford et al reported on 21 atypical or malignant meningioma patients treated with SRS at the Mayo Clinic (Stafford et al 2000). A median maximal dose of 32Gy was administered with a range of 20Gy-60Gy, depending on the tumour volume. The observed
5 year local control was 68% for atypical, and 0% for anaplastic meningioma (p<0.0001), but interestingly they found that tumour margin doses >16Gy were associated with a significantly improved local control on univariate analysis. Ganz et al also noted that in their series of meningioma patients receiving SRS, a minimum tumour dose of 10Gy or less was associated with a higher risk of treatment failure, whereas a dose of at least 12Gy resulted in improved local control (Ganz et al 1993). Subsequently, many authors now recommend tumour margin doses of at least 12-16Gy when treating meningiomas with SRS (Morita et al 1999).

In contrast to the above positive findings, there have also been series showing no difference in outcome based on dose delivered. Goyal LK et al investigated a cohort of 22 patients with atypical meningioma, who had been treated with post-operative radiotherapy to a median dose of 50Gy (Goyal et al 2000). They were unable to identify a difference in local control bases on doses above or equal to 50Gy, although in their series, extent of resection was found to be a significant prognostic factor.

The following table summarises some of the retrospective data supporting this (Goldsmith et al 1994, Milosevic et al 1996, Hug et al 2000) and includes the addition of our department’s data.
Table 5 Retrospective series documenting effect of dose escalation on local control for meningiomas.

<table>
<thead>
<tr>
<th>Authors</th>
<th>No of patients</th>
<th>Radiation dose</th>
<th>Outcomes</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldsmith 1994</td>
<td>23</td>
<td>&lt;53Gy</td>
<td>5yr PFS 17%</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥53Gy</td>
<td>5yr PFS 67%</td>
<td></td>
</tr>
<tr>
<td>Milosevic 1996</td>
<td>59</td>
<td>&lt;50Gy</td>
<td>5yr CSS 0%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥50Gy</td>
<td>5yr CSS 42%</td>
<td></td>
</tr>
<tr>
<td>Hug 2000</td>
<td>15</td>
<td>&lt;60Gy</td>
<td>5yr LC 0%</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥60Gy</td>
<td>5yr LC 90%</td>
<td></td>
</tr>
<tr>
<td>Hug 2000</td>
<td>16</td>
<td>&lt;60Gy</td>
<td>5yr LC 0%</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥60Gy</td>
<td>5yr LC 100%</td>
<td></td>
</tr>
<tr>
<td>Estall 2009</td>
<td>128</td>
<td>50Gy</td>
<td>5yr LC 93%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;50Gy</td>
<td>5yr LC 72%</td>
<td></td>
</tr>
</tbody>
</table>

In our retrospective review, we were able to demonstrate similar local control and overall survival rates to other series. In our department, patients receiving >50Gy did poorly and included patients with large G1 tumours (n=23), G2 tumours (n= 12) and G3 tumours (n=3) and all were recurrent after initial resection. The radiotherapy technique during the time of this series was conventional 3D conformal treatment, and therefore limited in its ability to deliver high doses to the tumour without overdosing surrounding structures. A modest dose escalation was attempted but not successful in most cases with only 3 patients...
achieving doses of 60Gy while maintaining acceptable doses to critical structures. This suggests to us that high-risk patients (e.g. recurrent disease, large volume disease, G2 or G3 disease) were undertreated with conventional fractionation schedules in our department.

We feel this retrospective review highlights the importance of achieving dose distributions of good enough quality to ensure high enough doses are being delivered to aggressive tumours, without damaging normal tissue. As a result of this study, our department questioned our standard approach and moved to treat G2 and G3 lesions to a standard dose of 60Gy (1.8-2Gy/#) using more conformal techniques (IMRT, Tomotherapy).

2.3.2 Literature following publication

Chan et al from Harvard School in Boston published data from a dose escalation protocol in 2012 (Chan et al 2012). They enrolled 6 patients with G2 or G3 meningioma onto a prospective dose escalation trial between 1997 and 1999. Using a photon/proton mixed plan at the Harvard Cyclotron Laboratory/Massachusetts General Hospital, the team were able to achieve mean total doses of 68.4Gy to G2 tumours and 72Gy to G3 tumours, while maintaining safe doses to surrounding tissue. They showed that this treatment was tolerable with no significant acute reactions, and acceptable late toxicity (one patient developed G1 late eye dryness, 2 patients developed late grade 2 hypothyroidism and 2 patients developed late grade 2 hypogonadism). There was no documented late grade 3-5 toxicity. Only one patient relapsed at the local site during the follow up period (median 145 months) giving a local control rate of 83%. For the 5 patients with controlled disease at the treated site, 3 went on to develop a second meningioma at a distant site within a median of 25 months. The median survival was 145 months for G2 tumours but only 28...
months for G3 tumours. Despite having only a small number of patients, these investigators did demonstrate that dose escalation to doses higher than 60Gy was able to achieve good local control, and produced excellent results when compared to historical series. It again suggests that part of the reason for treatment failure in the past may have been under dosing of the tumour. This improved local control may have impacted on survival in G2 tumours where the median survival was in the order of 145 months or 12 years. However, when treating aggressive meningioma, it must be noted that there is a significant risk of distant intracranial failure; local control of the primary lesion may have less impact on survival than expected due to the more disseminated nature of its spread. To date, this is the only published study documenting outcomes when using larger doses of radiation to treat G2 and G3 meningioma.

### 2.3.3 Future directions

The study published by Chan et al supports the concept of dose escalation for management of G2 and G3 meningioma, suggesting that doses of closer to 70Gy than 60Gy are required to maximise local control. This is considerably higher than standard doses of 50-54Gy, and it is not possible to deliver this using 3D conformal radiotherapy. This implies that we should be considering using more conformal techniques such as IMRT or Tomotherapy in these patients to improve their clinical outcomes.

Currently there is an EORTC protocol accruing patients in an attempt to answer this question more specifically. EORTC protocol 22042 – 26042 is a Phase II and observation study investigating the clinical outcomes following post-operative high dose radiotherapy for atypical and malignant melanomas (http://www.eortc.be/clinicaltrials/protocol22042).
Doses of 60Gy and 70Gy will be delivered to the postoperative bed depending on extent of resection and volumes requiring treatment. The study hopes to accrue approximately 80 patients by February 2013 and will be documenting toxicity, local control and survival outcomes. This is likely to be the largest series of patients to be investigated, so the results will be important in helping to define the optimal doses required to maximise survival and quality of life for patients. If as suspected it demonstrated that doses of 60-70Gy results in superior outcomes, a change is standard management is likely to be recommended. This will mean the role of conformal radiation therapy techniques to achieve this dose range will be needed including IMRT, Tomotherapy and other techniques such as the use of proton therapy.
CHAPTER THREE: THE ROLE OF LINEAR ACCELERATOR BASED IMRT FOR SKULL BASE MENINGIOMA

3.1. *Impact of MLC width on IMRT planned distributions in the skull base* 102

3.1.1 Preface 102

3.1.2 Publication: Impact of MLC width on IMRT planned dose distributions to the skull base. 103

3.1.3 Discussion 105

3.1.3.1 Contribution and Significance 105

3.1.3.2 Literature following publication 106

3.1.3.3 Future directions 106

3.2. Planning class solutions for Linac based IMRT can be identified and used to optimise the planning process and achieve safe dose escalation in the skull base 108

3.2.1 Preface 108

3.2.2 Publication: Intensity-Modulated Radiotherapy plan optimisation for skull base lesions: Practical class solutions for dose escalation. 108

3.2.3 Discussion 118

3.2.3.1 Contribution and significance 118

3.2.3.2 Literature since publication 118

3.2.3.3 Future directions 119
CHAPTER THREE: THE ROLE OF LINEAR ACCELERATOR BASED IMRT FOR SKULL BASE MENINGIOMA

IMRT is a useful modality when treating skull base tumours, as it can achieve moderate dose escalation when compared to 3D conformal treatment, which may improve clinical outcomes for G2 and G3 meningioma as well as for other pathologies. As outlined in Chapter 1, there are many factors to be considered when planning and delivering the most optimal radiotherapy plan in this setting. Tumour factors such as size and location of the tumour are important, as well as treatment factors including size of the multi-leaf collimator used, and the number and angles of beams. Investigators had previously shown improvements in dosimetry when using IMRT compared to 3D conformal treatment for skull base meningioma, but little work had been done to practically guide radiation oncologists in the most optimal combination of all of these elements. This new technology required some investigation to ensure that as clinicians we were in fact getting the best out of the planning systems, and providing the best treatment possible within the limitations of the hardware and software available. In this chapter we present 2 pieces of work aimed at providing a class solution for radiation oncologists, when planning IMRT in the skull base region. We specifically investigate planning methods to optimise treatment using a linear accelerator based IMRT system and further characterise the role of MLC width, which has practical and resources implications for a department.
3.1. **Impact of MLC width on IMRT planned distributions in the skull base.**

3.1.1 **Preface**

MLC width is an important component in planning IMRT in this region. It has been demonstrated that a small width MLC (<10mm) results in a higher degree of dose modulation, allowing better PTV coverage for the same amount of OAR sparing compared to 10mm MLC (Fiveash et al 2002, Monk et al 2003, Nill et al 2005). This improvement in PTV coverage can be assessed by the volume of PTV receiving 95% of the prescribed dose (V95%) and is approximately 20% better for the 2.5mm MLC compared to 10mm MLC, based on other work we have done, which is presented later in this thesis (Estall et al 2008). This implies that an increased amount of dose intensity modulation can result in tighter dose conformation around a target with a sharper dose ‘drop off’ at the margins.

However, here are practical limitations to the use of micro-MLC widths, with these plans usually requiring an increased number of segments, monitor units and consequent ‘beam-on’ times. An increase in treatment time can have a number of potential adverse effects including a greater risk of intra-fractional motion, increased whole body dose due to machine leakage a poorer and less comfortable experience for the patient and an increase in the use of limited resources (Followill et al 1997). In addition, many linear accelerators have standard MLC widths of 5 or 10mm, meaning that micro-leaf MLC technology is unavailable. Therefore, the use of micro-leaf MLC in practice must be justified by a clinically significant improvement in dose distributions, in settings where dose escalation is considered an important factor in tumour control. An intermediate MLC width of 5mm had not been assessed in the setting of external beam IMRT for small skull base lesions, and we aimed to compare this width with a micro-leaf MLC and our standard MLC with
regard to the ability to increase dose to lesions in this area, while keeping doses to critical structures at a safe level.

3.1.2 Publication: Impact of MLC width on IMRT planned dose distributions to the skull base.

The following section contains an unaltered reproduction of poster ‘Impact of MLC width on IMRT planned dose distributions in the skull base.’ published in abstract form in the journal Medical Physics: The International Journal of Medical Physics Research and Practice, Volume 36, Issue 6, Page. 2557 and presented in poster form at the American Association of Physicists in Medicine (AAPM) Annual Scientific Meeting, July 26-30, 2009 Anaheim USA. Medical Physics is the official journal of the AAPM and covers research in the field of medical physics, and publishes extensively on new technologies and their applicability in the field and had an impact factor of 2.704 in the year of publication and has a 5yr impact factor of 3.095.
SU-FF T-163: Impact of MLC Width On IMRT Planned Dose Distributions in the Skull Base

V Estall¹, R Jena¹, and N Burnet¹,²
¹Cambridge University Hospitals NHS Foundation Trust, Cambridge, Cambridgeshire, GB
²University of Cambridge, Cambridge, Cambridgeshire, GB

Abstract

Purpose: This study aimed to investigate the impact of MLC width on dose distributions for tumours in the skull base. Methods and materials: Five cases of skull base meningioma were planned using IMRT to an escalated dose of 60Gy/30#. 4 IMRT plans were calculated for each case, using 2.5mm, 5mm, and 10mm MLC widths and helical tomotherapy (HT) with a beamlet width of 1mm. Organs at risk (OAR) were not permitted to exceed clinically relevant dose tolerance levels. PTV coverage was assessed using Dmin, Dmax, V90, V95 and V100. Results: OAR doses were maintained below safe threshold levels in all cases. Average Dmax, Dmin, Dmean and Dmed were similar, with a trend to higher values for the 2.5mm MLC. Average V90, V95 and V100 improved as the MLC width got smaller, the V95 increasing from 65.4% to 80.1% to 89.2% for the 10mm, 5mm and 2.5mm MLC respectively. HT produced similar PTV coverage to the 2.5mm MLC (V95 85.6%). It appears that the magnitude of difference between the MLC widths was greater if the PTV was particularly complex and touching OAR. The number of segments required increased as the MLC width decreased and on average was 35, 47 and 58 for the 10mm, 5mm and 2.5mm MLC respectively. Discussion: Our findings indicate that MLC width does impact on the ability of an IMRT plan to achieve excellent PTV coverage for skull base lesions, which are generally difficult to dose escalate due to the proximity of OAR. As MLC width reduces, the degree of dose intensity modulation improves, allowing tighter conformation of high dose around the edge of the PTV. There may be no benefit to MLC smaller than 2.5mm, as the outcomes are similar to HT.

Conflict of Interest: Clinical fellow funded by Siemens OCS Ltd.

© 2009 American Association of Physicists in Medicine
3.1.3 Discussion

3.1.3.1 Contribution and Significance

This work showed that the MLC160 provides excellent coverage of the high dose PTV60, while maintaining a low dose to critical structures, and our work confirmed findings from other researchers. Based on other work from our department we knew that 2.5mm MLC could give significantly better dose distributions compared to 10mm MLC, but the advantage over 5mm MLC (which is becoming more common as part of modern linear accelerators) was unknown. As predicted, the degree of dose intensity modulation for the 5mm MLC is intermediate between the small 2.5mm MLC and the more standard 10mm MLC. The difference between the PTV coverage for the 2.5mm and 5mm MLC may be less when lesions are laterally located and a distance from OAR, but there may be a small clinically important benefit with a 2.5mm MLC if the lesion is particularly complex and close to critical structure. This is an observation we had already noted in our department when planning these lesions, but can now confirm. Of course, any dose distribution benefit of the micro-MLC must be balanced with the increased number of segments and increased treatment time. When selecting patients appropriate for this treatment technique (2.5mm vs. 5mm MLC), it should be appreciated that treatment times are likely to be in the region of 2-3mins longer per fraction. It may be that there are specific situations where this longer treatment time is warranted by a potential benefit in improved tumour control (i.e. G2 or G3 meningioma), in which case the micro-leaf MLC can be considered a useful tool when treating tumours of the skull base.
3.1.3.2 Literature following publication

There has been little published since 2009 on the impact of micro-MLC compared to 5mm or 10mm MLC. Wu et al’s team from Duke University published a study the same year investigating the impact of collimator width as one of the parameters compared in planning a cohort of approximately 70 patients (Wu et al 2009). The showed that a fine leaf MLC (2.5mm) significantly improved OAR and normal tissue sparing particularly for small, complex and concave lesions supporting our findings.

An interesting question is whether or not MLC <2.5mm width could provide further improvements. A 1mm MLC is not clinically available for IMRT unless part of a radiosurgery system. The best comparator would therefore be Helical Tomotherapy, which utilises 1mm MLC with fields. We specifically addressed this with a planning study comparing Helical Tomotherapy with IMRT using 2.5mm MLC and this is presented later in the thesis.

3.1.3.3 Future directions

MLC technology in the past concentrated on reducing the width of the leaves to optimise dosimetry, but the technical limits of this have now been reached at a MLC width of 2.5mm. The technology has now progressed to result in the development of dynamic MLC (dMLC) arc therapy. In the setting of ‘fixed beam’ IMRT, MLC’s can either be ‘dynamic’ where the beam is continuous and is delivered as the MLC’s move, or ‘step and shoot’ where the beam delivery is interrupted and delivered in a stepwise manner only after the MLC’s have moved into place (LoSasso et al 1998). Now there is a new form of IMRT where the dynamic MLC’s move while the beam is on, and at the same time, the
beam/field moves delivering treatment as an arc. This is called Volumetric Arc Radiotherapy (VMAT) and has been extensively investigated in recent years. Chen et al published a treatment planning comparison of VMAT vs. fixed beam ‘static’ IMRT therapy in 2012. They compared dose distribution, monitor units and radiation delivery time, and found both systems resulted in similar target coverage, homogeneity and conformity (Chen et al 2012). For skull base cases in particular, VMAT generated less hot spots in the PTV (i.e. delivered a more homogeneous dose) while at the same time reduced the dose to the optic chiasm by 10Gy (p value 0.026). There was also a reduction in the MU’s of 70% for a VMAT plan compared to a static fixed field plan and a significantly shorter (73%) treatment time. This would not only allow skull base lesions close to the central critical structures to potentially be dosed to a higher volume, it can impact on the integral dose delivered to the patient and improve the efficiency of a course of treatment which is an important issue for a radiation therapy department.

VMAT capable machines are becoming more accessibly worldwide, and are clinically in use in Australasia. They represent a progression in the technology of linear accelerator based IMRT which can result in not only very effective treatment, but also a more efficient and cost effective treatment when compared to earlier forms of IMRT. This progress has occurred rapidly over the last few years demonstrating the significant developments being made with regard to the technology of radiation therapy delivery.
3.2. Planning class solutions for Linac based IMRT can be identified and used to optimise the planning process and achieve safe dose escalation in the skull base

3.2.1 Preface
IMRT is a technique, which has been shown to improve PTV coverage when compared to 3D conformal therapy, especially in complex-shaped lesions close to critical structures (Baumert et al 2003). The number of beams and beam arrangement, the size of the multi-leaf collimator (MLC) leaves used and the tumour location and size all influence the dose distributions possible using IMRT. Our department was interested in identifying a class solution for IMRT planning in this region; as we had previously been unsuccessful in our attempts to dose escalate tumours of the skull base. We hypothesize it is possible to identify an evidence based IMRT class planning solution, which would maximise plan quality and efficiency. This solution could then be applied to all patients requiring high dose radiotherapy for tumours in the skull base from a number of different pathologies, and we hoped to use the results of such investigations to formulate a departmental dose escalation protocol. This was an attempt to devise a practical solution, which could be applied to individual patients, maximising the potential of the technology we had available, as well as streamlining and making our practice more time and cost efficient.

3.2.2 Publication: Intensity-Modulated Radiotherapy plan optimisation for skull base lesions: Practical class solutions for dose escalation.
The following section contains an unaltered reproduction of the article “Intensity-Modulated Radiotherapy Plan Optimisation for Skull Base Lesions: Practical Class Solutions for Dose Escalation” published in the journal Clinical Oncology, Volume 22,
Issue 10, Pages 313-320. Clinical Oncology is the official journal of the Royal College of Radiologists, and covers research in the field of clinical oncology. Its emphasis is on practical clinical implication of up to date developments in cancer research and at the time of publishing the journal had an impact factor of 2.294, and has a 5 year impact factor of 2.386. Since publication this article has been cited in 4 published works in the field (See Appendix Three).
Original Article

Intensity-Modulated Radiotherapy Plan Optimisation for Skull Base Lesions: Practical Class Solutions for Dose Escalation

V.J. Estall *, D. Eaton †, K.E. Burton †, S.J. Jefferies ††, R. Jena ††, N.G. Burnet †‡

*PeterMac Cancer Centre, East Melbourne, Australia
†Medical Physics Department, Royal Free Hampstead NHS Trust, London, UK
††Oncology Centre, Addenbrooke’s Hospital, Cambridge University Hospitals NHS Trust, Cambridge, UK
‡University of Cambridge Department of Oncology, Oncology Centre Addenbrooke’s Hospital, Cambridge, UK

Received 19 October 2009; received in revised form 19 December 2009; accepted 3 February 2010

Abstract

Aims: To identify practical intensity-modulated radiotherapy planning solutions when attempting dose escalation in the skull base. Materials and methods: Twenty cases of skull base meningioma were re-planned using a variation of beam number (three, five, seven and nine), beam arrangement (coplanar vs non-coplanar) and multileaf collimator (MLC) width (2.5 mm vs 10 mm) to 60 Gy/30 fractions. Plan quality and planning target volume coverage was assessed using planning target volume \(V_{95}\), equivalent uniform dose (EUD) and integral dose. Results: Critical structures were maintained below clinical tolerance levels. The 2.5 mm MLC achieved an average improvement in \(V_{95}\) by 22.8% \((P = 0.0003)\), EUD by 3.7 Gy \((P = 0.002)\) and reduced the integral dose by 13.4 Gy \((P = 0.0001)\). \(V_{95}\) and the integral dose improved with five vs three beams and seven vs five beams, but did not change with nine vs seven beams. There was no effect of beam number on EUD. There was no difference in \(V_{95}\) \((P = 0.54)\), integral dose \((P = 0.44)\) or EUD \((P = 0.47)\) for beam arrangement used. Segments per plan increased by a factor of 1.5 with each addition of two beams to a plan, and by a factor of 2.5 for 2.5 mm MLC plans vs 10 mm MLC plans. Conclusions: We present evidence-based planning solutions for skull base intensity-modulated radiotherapy, and show that 2.5 mm MLC and five to seven beams can achieve safe dose escalation up to 60 Gy. This must be balanced with an increase in segmentation, which will increase treatment times.

© 2010 The Royal College of Radiologists. Published by Elsevier Ltd. All rights reserved.

Keywords: Class solutions; IMRT; meningioma; skull base

Introduction

Skull base tumours, both benign and malignant, pose a challenging management problem for clinicians. Treatment modalities include surgical resection and radiotherapy, and in both cases treatment is limited by the often complex shape of the tumour, as well as its proximity to critical structures (OARs), such as the optic pathways, cranial nerves and brainstem. Radiotherapy dose escalation may improve local control, but must be balanced with normal tissue late effects. Generally, the prescribed dose is a compromise between tumour control and treatment-related morbidity.

Intensity-modulated radiotherapy (IMRT) is a technique that has been shown to improve planning target volume (PTV) coverage when compared with three-dimensional conformal therapy, especially in complex-shaped lesions close to critical structures. There are many factors to be considered during the IMRT planning process. The number of beams, beam arrangement, size of the multileaf collimator (MLC) leaves used and the tumour location and size all influence the dose distributions possible using IMRT. In addition, IMRT planning and delivery may also affect the practicalities of treatment, including increased time required for planning, quality assurance, patient set-up and treatment time.

Our department was interested in identifying a class solution for IMRT planning in this region, as we had previously been limited in our attempts to dose escalate skull base tumours. Our hypothesis was, that it was possible to identify evidence-based IMRT class planning...
solutions that would maximise plan quality and efficiency. This solution could then be applied to all patients requiring high-dose radiotherapy for tumours in the skull base, and we hoped to use the results of such investigations to formulate a departmental dose-escalation protocol.

**Materials and Methods**

The aim of this study was to investigate the effect of the following parameters on IMRT plan quality and efficacy achievable for skull base tumours: MLC width (10 mm vs 2.5 mm); beam number (three, five, seven or nine); beam arrangement (coplanar vs non-coplanar); tumour size and location.

Twenty skull base meningioma cases were retrospectively reviewed. These cases had been treated with radical radiotherapy between 2003 and 2006, with doses of at least 50 Gy in 1.67/1.8 Gy/fraction using a three-dimensional conformal technique delivered by a 6 MV linear accelerator.

The original gross tumour volume and clinical target volume were used in a planning study. The PTV margin was chosen as 3 mm, calculated from vector movement data for patients immobilised using a Gill Thomas Cosman relocatable frame in our department [2]. A full set of OARs was outlined for each patient, and a margin of 3 mm was added to serial organs to create a planning OAR volume. This value was extrapolated from our PTV data, allowing for coverage of three-dimensional systematic movement errors in 97% of cases [3], and represents a safe margin that overestimates the planning OAR volume margin required in situations where only one- or two-dimensional movement is probably relevant. The cases were planned using KonRad IMRT planning software (Siemens Oncology Care Systems, Concord CA, USA), using 10 discrete intensity levels. The MLC widths compared were 10 mm (measured at the isocentre) as the standard and 2.5 mm using the MODULEAF mini-MLC device and a Siemens 6 MV linear accelerator (Siemens OGS), reflecting the equipment used in our department. The algorithm used was the same for both the 2.5 and 10 mm MLC plans. Initially, 18 plans were generated per case, to assess the effect of beam number, beam arrangement and MLC width on plan quality (Table 1). Plans were generated using three, five, seven and nine fields for coplanar and non-coplanar arrangements. Coplanar plans were developed with equidistant beams and with beam one at 0° to allow entry between the eyes. Non-coplanar arrangements were chosen based on individual patient anatomy and conventional beams eye view beam placement techniques.

An interim analysis was carried out after 15 cases had been planned. Large statistically significant differences were identified between three- and five-field plans, with three-field plans significantly inferior. It was felt by the investigating team that these findings were strong enough to make a conclusion about the three-field vs five-field techniques. The next five cases were planned excluding three-field beam arrangements to save resources, resulting in a cohort of 15 cases to assess the differences between three- and five-field plans, and 20 cases to assess the differences between five-, seven- and nine-field plans (Table 1).

Cases were prescribed 60 Gy/30 fractions to the ICRU dose reference point based on our usual IMRT prescription method at the time. Planning aimed to achieve coverage of the PTV by the 95% isodose line. Plans were optimised in the first instance to ensure the OAR doses were kept within clinically acceptable tolerance limits for meningioma (Table 2). The PTV coverage was then maximised within these tolerance constraints, and aimed to sculpt dose away from the OAR.

**Plan Evaluation**

To assess plan quality, both physical and biological parameters were measured and compared.

**Physical Planning Parameters**

PTV coverage was assessed by the volume of PTV (%) receiving 95% or 100% of the prescribed dose obtained from planning dose volume histogram data, i.e. $V_{95\%}$ and $V_{100\%}$. The dose to serial OARs was assessed as $D_{\text{max}}$, for parallel organs, i.e. lacrimal glands, $D_{\text{max}}$, values were used.

**Biological Planning Parameters**

Radiobiological assessments of the plan quality were made using the equivalent uniform dose (EUD), as defined by Niemierko [17]. This is the biologically equivalent dose that if given uniformly will lead to the same cell kill in the

| Table 1 |
| Beam arrangements evaluated – the first 15 cases including three-field plans and the next five cases excluding three-field plans |
| | Coplanar beam arrangement | Non-coplanar beam arrangement |
| | Three fields | Five fields | Seven fields | Nine fields | Three fields | Five fields | Seven fields | Nine fields |
| First 15 cases |
| 2.5 mm MLC |
| Plan 1 | Plan 2 | Plan 3 | Plan 4 | Plan 5 | Plan 6 | Plan 7 | Plan 8 |
| 10 mm MLC |
| Plan 9 | Plan 10 | Plan 11 | Plan 12 | Plan 13 | Plan 14 | Plan 15 | Plan 16 |
| Next five cases |
| 2.5 mm MLC |
| – | Plan 1 | Plan 2 | Plan 3 | Plan 4 | Plan 5 | Plan 6 | Plan 7 |
| 10 mm MLC |
| – | Plan 8 | Plan 9 | Plan 10 | Plan 11 | Plan 12 | Plan 13 | Plan 14 |

MLC, multileaf collimator.
Table 2

<table>
<thead>
<tr>
<th>Organ at risk</th>
<th>Tolerance (Dmax)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>&lt;52 Gy</td>
</tr>
<tr>
<td>Brainstem PRV</td>
<td>&lt;54 Gy</td>
</tr>
<tr>
<td>Optic tracts</td>
<td>&lt;52 Gy</td>
</tr>
<tr>
<td>Optic tracts PRV</td>
<td>&lt;54 Gy</td>
</tr>
<tr>
<td>Brain</td>
<td>&lt;66 Gy</td>
</tr>
<tr>
<td>Eye/retina</td>
<td>&lt;45 Gy</td>
</tr>
<tr>
<td>Lacrimal gland</td>
<td>&lt;30 Gy (Dmean)</td>
</tr>
<tr>
<td>Hypothalamic/pituitary axis</td>
<td>&lt;45 Gy</td>
</tr>
</tbody>
</table>

PRV, planning organ at risk volume.

Justification for the tolerance limitations is based on a review of published studies [4–16]. Tolerance doses indicate Dmax or Dmean using conventional fractionation, i.e. 2 Gy/fraction.

Three-dimensional conformal plans. There was no significant difference in the doses to OARs based on the planning technique used, including the brainstem and optic structures, which are the primary dose-limiting structures in this area.

Effect of Multileaf Collimator Width

Use of the 2.5 mm Moduleal MLC resulted in an average increase in V95% achievable by 22.8% (P < 0.0001) when compared with the standard 10 mm MLC (Fig. 1a). This improvement was consistent for all beam numbers and arrangements used. The V95% was also significantly better by an average of 28.2% (P < 0.001). There was also an increase in EUD for 2.5 mm MLC plans compared with 10 mm MLC plans by an average of 3.7 Gy (P < 0.001) (Fig. 1b).

Moduleal achieved a lowering of the integral dose by an average of 13.4 Gy kg (P < 0.01) compared with the standard width MLC (Fig. 1c), again a finding consistent for all beam numbers and arrangements used.

Effect of Beam Number

Three-, five-, seven- and nine-field coplanar and non-coplanar beam arrangements were compared for differences in V95%, integral dose and EUD. A significant improvement in V95% and EUD was seen when using five vs three fields, when using seven vs five fields, but not when using nine vs seven fields (Fig. 1a-c). The magnitude of difference was greatest for an increase of three- to five-field plans, with an average improvement of 10.8% (P = 0.01) in V95% with a further improvement of 3.6% (P = 0.04) if an additional two fields were added. If seven fields were increased to nine fields, there was only a non-significant increase in V95% of 1.2% (P = 0.5).

EUD was improved when fields were increased from three to five by an average of 6.27 Gy, but there was no significant difference if seven or nine beams were used.

There was no clinically or statistically significant difference in integral dose between three-, five-, seven- and nine-field plans.

These findings indicate that a minimum of five fields and a maximum of seven fields will be appropriate for most cases, resulting in the optimal V95%.

Effect of Beam Arrangement

Each case was planned using coplanar and non-coplanar beam arrangements, for comparison between the two methods. When assessing PTV coverage via V95%, there was no significant difference between non-coplanar and coplanar beam arrangements, when using the same number of beams. This was also true for the EUD and integral dose (Fig. 1a-d).

We compared five non-coplanar and seven coplanar arrangements specifically, as we noted during the study that there was little difference in dose distributions achieved, especially if lesions were well lateralised. There was three-dimensional conformal plans. There was no significant difference in the doses to OARs based on the planning technique used, including the brainstem and optic structures, which are the primary dose-limiting structures in this area.

Effect of Multileaf Collimator Width

Use of the 2.5 mm Moduleal MLC resulted in an average increase in V95% achievable by 22.8% (P < 0.0001) when compared with the standard 10 mm MLC (Fig. 1a). This improvement was consistent for all beam numbers and arrangements used. The V95% was also significantly better by an average of 28.2% (P < 0.001). There was also an increase in EUD for 2.5 mm MLC plans compared with 10 mm MLC plans by an average of 3.7 Gy (P < 0.001) (Fig. 1b).

Moduleal achieved a lowering of the integral dose by an average of 13.4 Gy kg (P < 0.01) compared with the standard width MLC (Fig. 1c), again a finding consistent for all beam numbers and arrangements used.

Effect of Beam Number

Three-, five-, seven- and nine-field coplanar and non-coplanar beam arrangements were compared for differences in V95%, integral dose and EUD. A significant improvement in V95% and EUD was seen when using five vs three fields, when using seven vs five fields, but not when using nine vs seven fields (Fig. 1a-c). The magnitude of difference was greatest for an increase of three- to five-field plans, with an average improvement of 10.8% (P = 0.01) in V95% with a further improvement of 3.6% (P = 0.04) if an additional two fields were added. If seven fields were increased to nine fields, there was only a non-significant increase in V95% of 1.2% (P = 0.5).

EUD was improved when fields were increased from three to five by an average of 6.27 Gy, but there was no significant difference if seven or nine beams were used.

There was no clinically or statistically significant difference in integral dose between three-, five-, seven- and nine-field plans.

These findings indicate that a minimum of five fields and a maximum of seven fields will be appropriate for most cases, resulting in the optimal V95%.

Effect of Beam Arrangement

Each case was planned using coplanar and non-coplanar beam arrangements, for comparison between the two methods. When assessing PTV coverage via V95%, there was no significant difference between non-coplanar and coplanar beam arrangements, when using the same number of beams. This was also true for the EUD and integral dose (Fig. 1a-d).

We compared five non-coplanar and seven coplanar arrangements specifically, as we noted during the study that there was little difference in dose distributions achieved, especially if lesions were well lateralised. There was
Fig. 1. Difference in (a) $V_{95\%}$, (b) equivalent uniform dose (EUD) and (c) integral dose based on multileaf collimator (MLC) width, beam number and beam arrangement. Note there is minimal difference between the non-coplanar (NC) and coplanar (C) beam arrangements, but a significant difference between 2.5 and 10 mm MLC. Also, the results for EUD seem to mirror the effect of planning parameters on planning target volume coverage as measured by $V_{95\%}$. In addition, when a 10 mm MLC was used, the number of beams did not affect the integral dose, but if a 2.5 mm MLC was used, there seemed to be a small reduction in integral dose if more fields, up to a maximum of seven, were used.

A minimal difference noted in average $V_{95\%}$, EUD and integral dose when comparing the two techniques. There was an increase of 2.4% overall in $V_{95\%}$ for seven coplanar vs five non-coplanar plans ($P = 0.04$). This improvement was larger if tumours were central and close to OARs ($P = 0.2$) compared with those well lateralised ($1\%, P = 0.2$). Examples of a well-lateralised lesion (Fig. 2a and b) and a more centrally located complex lesion (Fig. 3a and b) are given, showing representative dose distributions for the 2.5 and 10 mm MLC plans. It seems that the higher level of modulation of the 2.5 mm MLC width and the use of seven coplanar beams achieves a greater improvement in PTV coverage for the central complex lesions, which by nature are difficult to dose escalate.

Effect of Tumour Size

The volume of PTV treated ranged from 10.78 to 119.96 cm$^3$, with an average volume of 56.91 cm$^3$ and a median volume of 53.56 cm$^3$. The volume of PTV was
found to have no effect on plan dosimetry achieved as measured by V95\% for any of the MLC field widths or field orientation solutions. This indicates that small as well as large lesions can be treated to high doses effectively using these IMRT planning methods.

**Effect of Tumour Location**

We separated tumours into those that were typically well lateralised (petrous apex, sphenoid wing, cerebello-pontine angle: n = 8, average volume 85.7 cm$^3$), those that were mediolateral (cavernous sinus: n = 5, average volume 37.9 cm$^3$), and those that were centrally located (suprasellar: n = 7, average volume 37.7 cm$^3$). The use of a 2.5 mm MLC improved the V95\% in all locations compared with the 10 mm MLC, but to a greater magnitude if the lesions were central or mediolateral compared with those that were well lateralised (Fig. 4). This suggests that for very complex small lesions where dose escalation is especially problematic, a small MLC allows a greater level of intensity modulation, fundamental in achieving a more conformal dose distribution to a complex target.

**Plan Efficiency**

This was assessed by comparing the number of segments generated per plan, which was used to estimate beam-on time. This was in part a result of the inbuilt planning sequencer, for which we used 10 intensity levels based on other comparative IMRT studies reported [22]. The use of
the ModulLeaf MLC significantly increased the number of segments per plan, resulting in an increase, on average, from 20 to 50 segments for the three-field plans, 35 to 82 segments for the five-field plans, 49 to 125 segments for the seven-field plans and 63 to 159 segments for the nine-field plans. As expected, this was also increased by the number of beams used. As a result, beam-on time was potentially increased by a factor of 2.5 for plans using the ModulLeaf MLC vs the standard MLC with the same number of beams, and by a factor of 1.5 for every two beams added to a plan.

Discussion

It has been well documented that local control from radiotherapy is improved with dose escalation above 50 Gy in the setting of chordoma [23,24] squamous cell carcinoma [25], and non-benign meningioma [26–28], all of which may arise in the skull base. The practical use of dose escalation is limited at this site by the proximity of critical normal structures, and without strong evidence of efficacy and safety, many clinicians are reluctant to increase doses above 50–54 Gy. The advent of highly conformal radiotherapy via stereotactic radiotherapy, IMRT and proton therapy can now allow increased doses to be delivered safely, making dose escalation a more attractive possibility.

Planning studies of IMRT vs three-dimensional conformal radiotherapy for skull base tumours have shown improved target coverage and potential for dose escalation, with a simultaneous reduction in the dose to critical structures [1]. The limitations of IMRT include increased planning and treatment delivery time and, in some cases, an increased integral dose, which may increase the risk of radiotherapy-induced carcinogenesis [20,21]. We were motivated to find an evidence-based and practical class solution that could streamline and facilitate IMRT implementation for patients with skull base tumours in our department.

Although IMRT planning solutions have been investigated, there is a paucity of data in the literature regarding IMRT planning for dose escalation of skull base tumours specifically and not enough data, we felt, to provide us with specific guidance. For example, Wijgenraad et al. [29] recently reported a planning study comparing IMRT with dynamic arc therapy for 25 glioma or meningioma cases. The meningioma cases reflect our cohort, but as they planned to doses of 50–54 Gy only and did not assess the ability of the two techniques to escalate dose in the region, their outcomes are difficult to compare with our own. In fact, we could find no other skull base planning studies where linear accelerator IMRT plan doses were higher than the conventional 50–54 Gy.

MLC width has been investigated, showing that a smaller MLC width is associated with better intensity modulation and, therefore, better PTV coverage. Nil et al. [30] compared MLC widths of 10, 4 and 2.75 mm in a planning study of five patients (three intra-cranial, two extra-cranial). They found that the smallest beam width of 2.75 mm yielded the best PTV coverage, although the difference between 4 and 2.75 mm was small. Pivazh et al. [31] compared 10 mm with 5 mm MLC widths in three central nervous system lesions, showing improved conformity for the smaller MLC. Monk et al. [32] showed an improvement in PTV coverage if a 3 mm vs 5 mm MLC was used, but this benefit was small and of questionable clinical significance. Our results are very similar to these, corroborating our belief.
that a MLC width of 5 mm or less is required to maximise the benefit of IMRT at this site. However, many of these studies were small and not able to produce the level of statistical significance we could by investigating a large number of cases. This is of practical significance when assessing resource utilisation and requirements for a radiotherapy department. It provides a strong case for the use of appropriate technology (such as fine leaf MLC or tomotherapy) when a high level of intensity modulation is required to achieve safe, high-dose plans for patients. The primary limitation when using smaller MLCs is that any increase in modulation of a beam requires more segments to deliver the dose. By assessing the effect of MLC widths on the number of segments, we have been able to show that segment number increased by a factor of 2.5 for 2.5 mm vs 10 mm MLCs. This can give clinicians and planners an accurate indication of the effect of using small MLCs on the treatment time, which may have an effect on treatment decisions for individual patients. One concern regarding IMRT plans compared with conformal therapy is the possible effect of increased volumes of normal tissue receiving a low dose of radiation. The integral dose is one method of trying to estimate the dose delivered to normal tissue outside the tumour volume and, reassuringly in our study, using a greater degree of intensity modulation does not seem to increase this further. In fact, the average integral dose is less with the smaller MLC.

Regarding beam number, we identified the optimal number of fields for IMRT in this setting as being no less than five and no more than seven. This is a statistically significant finding, and ensures that inappropriately low or high numbers of beams are not used. Clearly, using the least number of beams possible is advantageous, which is why we looked closer at five-field non-coplanar plans and seven coplanar plans when we noticed a similarity in dose distribution. There was, in fact, little difference between the two techniques in regard to the ability to dose escalate the tumour within normal tissue constraints. This is supported by findings from Das et al. [33], who investigated five different prostate planning techniques. This study found that a modest, three to five non-coplanar beam arrangement gave similar dose distributions (target coverage and OAR sparing) to coplanar equidistant plans using a large number of beams (i.e., 15 coplanar). This suggested that a non-coplanar beam arrangement could allow less beams to be used, if they are placed optimally, making it easier for planning systems to meet planning constraints. Keller-Reichenbecher et al. [34] also noted a similarity between five-field non-coplanar plans and seven-field coplanar plans in their IMRT planning study, supporting our findings. A possible advantage to the seven-field coplanar plan is better PTV coverage for centrally located tumours, which are typically very difficult to plan, such as small suprajacent tumours. This advantage was small and not statistically significant, but supports the consideration of this particular arrangement for centralised lesions in close proximity to normal structures. It also seems to be a more simple and more sensible arrangement for a central small lesion. This would need to be balanced with the increased treatment time two additional beams would add, and a risk-benefit analysis for each patient should be made. We have confirmed that lateralised lesions could be just as effectively managed using a five-field coplanar or non-coplanar technique.

In addition to the physical planning parameters, which we can influence, we also confirmed that lateral lesions are easier to dose escalate, and this can be achieved with less intensity modulation and, therefore, fewer beams. Small MLCs are still advantageous here, but to a lesser degree, and what has not been documented before is an evidence-based, effective technique for treating the much more problematic central lesions.

As a result of the findings of this study, our department now has an IMRT planning protocol for dose escalation of skull base tumours. We use a seven-field coplanar beam arrangement and the Modulab 2.5 mm MLC for central lesions and a five-field non-coplanar or coplanar arrangement and Modulab/2.5 mm MLC for lateralised lesions. This offers the most advantageous balance between plan quality and treatment practicality for both the patient and the department. We acknowledge that the treatment time is probably two to three times longer per fraction, depending on the complexity of the plan and the resulting number of segments. This must be a consideration when selecting patients for this treatment, and balanced with the clinical need for dose escalation.

Our findings have indicated that it is possible to dose escalate safely in the region of the skull base, and we have achieved our goal in identifying a planning class solution for skull base lesions clinically appropriate for dose escalation.

Conflict of Interest

V. J. Estall was a Clinical Research Fellow funded by Siemens Oncology OCS during this research, through an unrestricted educational grant, in collaboration with the Addenbrooke's Hospital Oncology Centre and Cambridge University Department of Oncology. Modulab mMLC and the KonRad Planning system are Siemens OCS products.

Acknowledgements

V. J. Estall is supported by Siemens OCS Ltd, R. Jena by the Health Foundation UK and N. Burnet by the NHRR Cambridge Biomedical Research Centre, Special thanks to the radiotherapy staff at Addenbrooke's Hospital Oncology Centre, in particular Sue Tabor and June Dean.

References


3.2.3 Discussion

3.2.3.1 Contribution and significance

From a very practical point of view, this work has had a significant impact in our department. Firstly it was established that it was possible for us to treat skull base lesions (including high grade meningioma) to doses of 60Gy safely and effectively. Secondly, we identified the most time and cost effective method in which to apply our available technology in this setting. We have produced a robust and evidence based class planning solution for IMRT in the skull base using linear accelerator based IMRT, which is the most commonly available form of this treatment. This means that the basic principles we have identified can be applied to other departments, for example:

- 2.5mm MLC is recommended for complex central lesions adjacent to critical structures, 5-10mm appropriate for well-lateralised lesions.
- A 7 field co-planar beam arrangement is recommended for central complex lesions adjacent to critical structures, but a 5 field non-coplanar beam arrangement is adequate for well lateralised lesions.

3.2.3.2 Literature since publication

There has been little published since this study specifically addressing planning solutions for IMRT of the skull base. However, this work has been since been published articles regarding the role of IMRT and other highly conformal forms of radiotherapy for the management of skull base meningiomas, including a textbook on the radiosurgical management of meningioma (See Appendix Three).
3.2.3.3 Future directions

Linear accelerator based IMRT remains an excellent form of treatment for skull base meningioma, when dose escalation to 60Gy is desired. The delivery of these doses can also be safely given using other forms of IMRT including Helical Tomotherapy (HT) and Volumetric Modulated Arc Therapy (VMAT). The dosimetry of these techniques are very similar to those achievable from linear accelerator based IMRT as demonstrated by planning studies over the last few years and this is discussed further in the next chapter. It is unlikely that this current technology will be able to achieve safe delivery of >60Gy in the skull base region.

The next step will be to investigate the role of different radiotherapy modalities to deliver even more dose i.e. close to 70Gy. As noted in the previous chapter, there is some evidence that these doses are more likely to achieve durable local control in the setting of G2 and G3 meningioma. If planned prospective studies confirm this (i.e. the EORTC Phase II dose escalation trial currently accruing), then other treatment techniques which are more likely to be able to deliver these very high doses, (such as proton therapy) will need to be considered more seriously. This will have significant repercussions, as proton therapy is clinically available in a limited number of centres worldwide, with no centres in Australasia at this time. Other forms of photon based treatment delivery such as CyberKnife and GammaKnife may also have a more important role if dose escalation above 60Gy is shown to be of clinical benefit, with similar problems of accessibility likely to become significant, especially in Australasia where this technology is not readily available.
CHAPTER FOUR: THE ROLE OF HELICAL TOMOTHERAPY FOR SKULL BASE MENINGIOMA

4.1. Preface 121

4.2. Publication: Skull base meningioma – comparison of intensity-modulated radiotherapy planning techniques using the Moduleaf Micro-multileaf collimator and helical tomotherapy. 122

4.3. Discussion 129
   4.3.1 Contribution and significance 129
   4.3.2 Literature since publication 129
   4.3.3 Future directions 131
4  CHAPTER FOUR: THE ROLE OF HELICAL TOMOTHERAPY FOR SKULL BASE MENINGIOMA

4.1. Preface

In the skull base region, IMRT can allow a moderate dose escalation to the tumour while at the same time keeping critical structure dose to within tolerance levels. IMRT plans for skull base lesions generally require 5-7 beams in a coplanar or non-coplanar arrangement with many segments in each beam to achieve adequate modulation of beam intensity.

Helical Tomotherapy (HT) is an IMRT treatment technique, which uses small beamlets of photons delivered in continuous rotational treatment arcs. It can conform the dose to a complex shaped PTV extremely well, while at the same time reducing dose to critical structures. It has other advantages including CT imaging capability for soft tissue verification, and has the potential for adaptive radiotherapy in some settings. With regard to skull base lesions, one group has compared the dosimetry of 3D conformal radiotherapy/IMRT and HT in 10 patients (Soissen et al 2006). HT offered no significant advantage over other IMRT techniques other than a reduction in homogeneity within the PTV. However, the dose prescribed was 50-54Gy and no attempt was made to assess the ability of HT to allow higher dose escalation while maintaining dose to normal tissue to a tolerance level. Another group compared Linac based IMRT using 5mm MLC, HT and Proton therapy for a range of small brain tumours, prescribing doses of 50-60Gy. They found that proton therapy produced maximal critical organ sparing, while HT and Linac based IMRT plans were very similar in PTV coverage and critical organ dose sparing (Yartsev et al 2005).
It was our hypothesis that dose distributions for plans attempting to treat skull base lesions to a high dose are likely to be at least the same or better for HT compared to linear accelerator based IMRT using narrow MLC. This question was important to us as we had acquired one of the first clinical Tomotherapy units in the UK, and were developing clinical protocols for its use. We wanted these protocols to be evidence based and needed to compare the performance of this new technology with our standard of care, which was micro MLC linear accelerator based IMRT. In this study we aimed to compare the dose distribution and quality of IMRT plans for skull base lesions using a micro-multileaf collimator (mMLC) system in a conventional linac with that achievable from HT treatment, with particular reference to escalating dose. We also aimed to assess practical aspects of the planning and treatment regarding time and resource factors to help us identify a solution for the highest quality IMRT delivery technique.

4.2. Publication: Skull base meningioma – comparison of intensity-modulated radiotherapy planning techniques using the Moduleaf Micro-multileaf collimator and helical tomotherapy.

The following section contains an unaltered reproduction of the article “Skull Base Meningioma – Comparison of Intensity-modulated Radiotherapy Planning Techniques using the Moduleaf Micro-multileaf Collimator and Helical Tomotherapy” published in the journal Clinical Oncology, Volume 22, Pages 179-184. Clinical Oncology is the official journal of the Royal College of Radiologists, and covers research in the field of clinical oncology. Its emphasis is on practical clinical implication of up to date developments in cancer research and at the time of publishing the journal had an impact factor of 2.294, and has a 5year impact factor of 2.386. Since publication this article has been cited in 4 published works in the field (See Appendix Three).
Original Article

Skull Base Meningioma — Comparison of Intensity-modulated Radiotherapy Planning Techniques using the Moduleaf Micro-multileaf Collimator and Helical Tomotherapy

V. Estall *, J. Fairfoul †, R. Jena †, S.J. Jefferies †, K.E. Burton †, N.G. Burnet †§

1 PeterMac Cancer Centre, East Melbourne, Australia
2 Medical Physics Department, Addenbrooke’s Hospital, Cambridge, UK
3 Oncology Centre, Addenbrooke’s Hospital, Cambridge, UK
4 University of Cambridge Department of Oncology, Oncology Centre, Addenbrooke’s Hospital, Cambridge, UK

Received 19 October 2009; revised 21 December 2009; accepted 23 December 2009

Abstract

Aims: Therapeutic radiotherapy to lesions of the skull base is limited by complex target shapes and their proximity to organs at risk. Intensity-modulated radiotherapy (IMRT) using helical tomotherapy may result in improved dose distributions and safer dose escalation. The aim of this study was to compare plan efficacy and efficiency using image-based micro-multileaf collimator (mMLC) IMRT and helical tomotherapy.

Materials and methods: Five cases of skull base meningiomas, previously treated with three-dimensional conformal radiotherapy (50 Gy/30 fractions) were identified. They were re-planned to a dose of 60 Gy/30 fractions using IMRT with Moduleaf mMLC (2.5 mm) and helical tomotherapy. Plan efficacy was compared using measures of PTV93% coverage (D93, D95, V93, V95 and V100). Plan efficiency was assessed by comparing estimated beam-on times.

Results: The critical structure dose was limited to below predetermined tolerance levels in all cases, with similar doses obtained between techniques. The average PTV93% coverage D93, D95, D98, D99, V93, V95 and V100 across the five cases achieved were as follows: mMLC IMRT 64.5 Gy, 48.3 Gy, 60 Gy, 55.6 Gy, 95.4%, 88.8% and 69.2%, respectively; helical tomotherapy: 67.2 Gy, 50.3 Gy, 60 Gy, 59.8 Gy, 95.8%, 83.5% and 51.9%, respectively. The average treatment time per fraction was 18.4 min for IMRT with mMLC and 6.7 min for helical tomotherapy.

Discussion: This study shows that safe dose escalation to a dose of 60 Gy to skull base lesions can be achieved; using either mMLC- or helical tomotherapy-based IMRT. A plan comparison between the two solutions is difficult, but they seem to be similar in efficacy with any small differences being difficult to interpret and of questionable clinical significance. Helical tomotherapy has the advantage of a significantly decreased beam-on time.

Key words: IMRT; meningioma; tomotherapy; skull base

Introduction

Meningioma of the skull base poses a difficult clinical problem. Complete resection is usually impossible due to the proximity of normal critical structures and complexity of the local anatomy. Radiotherapy is a good treatment option, but optimal dose distributions are limited by the complex shape of the lesion and, again, the proximity of critical structures sensitive to radiotherapy damage. In cases of World Health Organization grade 2 and 3 meningioma, dose escalation may result in a clinical improvement in tumour control, but is limited by the tolerance of surrounding organs at risk (OARs) [1–4].

Comparisons of three-dimensional conformal techniques with intensity-modulated radiotherapy (IMRT) have shown that the latter technique can achieve improved dose distributions, especially if the planning target volume (PTV) is a complex shape [5]. Both OAR sparing and PTV dose and coverage are maximised, which is presumed to result in an improved clinical outcome for the patient. In particular, lesions abutting serial organs, such as the optic chiasm or brainstem, can potentially be treated to higher doses than the tolerance dose for these OARs, which in traditional three-dimensional conformal therapy generally limit the prescribed dose. Therefore, IMRT can allow a moderate dose
escalation to the tumour while at the same time keeping the critical structure dose to within tolerance levels. IMRT plans for skull base lesions generally require five to seven beams in a coplanar or non-coplanar arrangement, with many segments in each beam to achieve adequate modulation of beam intensity [6]. Quality assurance (QA), verification and patient treatment time are important aspects of treatment and can be time and resource intensive. These factors can be technically challenging in the clinical delivery of these plans.

Helical tomotherapy is a relatively new IMRT treatment technique that uses small beamlets of photons delivered in continuous rotational treatment arcs. Treatment is delivered through the full 360°, effectively using 51 different beam directions, with an approximate spacing of 7°. A single beamlet is defined as the radiation emitted through one open leaf of the multileaf collimator (MLC), at a specified gantry angle, during one rotation. It can sculpt the dose to a complex-shaped PTV extremely well, while at the same time reducing the dose to critical structures as the helical delivery typically allows many thousands of individual beamlets to be used. It has other advantages, including computed tomography imaging capability for soft tissue verification allowing image-guided radiotherapy, and has the potential for adaptive radiotherapy in some settings. Its clinical role is currently being developed.

With regard to skull base lesions specifically, one group has compared three-dimensional conformal radiotherapy (3D-CRT) and helical tomotherapy in 10 patients [7]. Helical tomotherapy offered no significant advantage over other IMRT techniques. However, the dose prescribed was 50–54 Gy and no attempt was made to assess the ability of helical tomotherapy to allow higher dose escalation while maintaining the dose to normal tissue to a tolerance level. Another group compared linac-based IMRT using 5 mm MLC, helical tomotherapy and proton therapy for a range of small brain tumours, prescribing doses of 50–60 Gy. They found that proton therapy produced maximal critical organ sparing, whereas helical tomotherapy and linac-based IMRT plans were very similar in PTV coverage and critical organ dose sparing [8].

It was our hypothesis that dose distributions for plans attempting to treat skull base lesions to a high dose are likely to be at least the same or better for helical tomotherapy than linac-based IMRT using narrow MLC. The aim of this study was to compare the dose distribution and quality of IMRT plans for skull base lesions using a micro-MLC (mMLC) system in a conventional linac with helical tomotherapy treatment, in particular in the setting of an escalating dose. We also aimed to assess practical aspects of the planning and treatment regarding time and resource factors to help us to identify a solution for the highest quality IMRT delivery technique.

**Materials and Methods**

A representative selection of previously treated base of skull meningiomas was identified from departmental records (Table 1). The original computed tomography datasets and volumes were used to create the plans. A shrinking dose technique was used with two PTV volumes outlined, a PTV<sub>50</sub> and a PTV<sub>95</sub> which excluded dose limiting structures such as the brainstem and optic chiasm. When treating a patient with cranial IMRT, we use a stereotactic relocatable frame with mouth bite.

For linac IMRT, a seven-field coplanar plan was developed using the Modulon mMLC (2.5 mm MLC width at the isocentre) fitted over the machine head, and the KonRad planning system (Siemens Oncology Care Systems). The field size for the Modulon system is 10 × 12 cm. This beam number and arrangement is based on our investigation of IMRT planning solutions for skull base lesions [6]. We found that a seven coplanar beam arrangement was able to achieve an excellent dose distribution when aiming to deliver 60 Gy to the skull base regardless of location, with the additional benefit of easier planning, quality assurance and treatment delivery compared with non-coplanar plans. The dose prescribed was 60 Gy/30 fractions to the International Commission on Radiation Units (ICRU) dose point for the mMLC plans, chosen as the centre of the PTV<sub>95</sub> volume. For dose calculations, we used an intensity level of 5 for the sequencing and a voxel size of 2.0 × 2.0 mm.

A helical tomotherapy plan was developed for each case using the TomoTherapy Inc Hi-Art planning system for comparison. For the helical tomotherapy plans, the median dose was set as the prescription dose to the PTV<sub>95</sub>, which was a different prescription to that used for the mMLC plans, but aided our optimisation process. We used a field width of 1.0 cm, a pitch of 0.287 and a planning modulation factor of 3.0. The plan calculation grid was set to "fine", giving a voxel size of 0.92 × 0.92 × 1 mm.

Absolute D<sub>max</sub> doses to the OAR were kept within clinically acceptable tolerance levels, as defined by published studies and in clinical use in our department (Table 2). These OAR dose constraints were given priority and considered absolute, with the PTV coverage as a secondary objective. This was to ensure that any plans generated would be able to be delivered safely in our department.

Plan quality was assessed based on PTV coverage (PTV<sub>95</sub> and PTV<sub>90</sub>, D<sub>95</sub>, D<sub>mean</sub>, D<sub>5cc</sub>, V<sub>95</sub>, V<sub>100</sub>, uniform effective dose), where V<sub>95cc</sub> and V<sub>100cc</sub> were defined as the volumes of the PTV receiving 95 and 100% of the prescribed dose, respectively; the uniform effective dose was calculated from dose–volume histogram data [22]. The biologically equivalent dose, if given uniformly, will lead to the

---

**Table 1** Site and volume of five skull base lesions used in a comparative planning study

<table>
<thead>
<tr>
<th>Site</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV&lt;sub&gt;95&lt;/sub&gt; volume (cm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>Cavernous sinus</td>
<td>Suprasellar</td>
<td>Suprasellar</td>
<td>Sphenoid wing</td>
<td>Petrous apex</td>
</tr>
<tr>
<td></td>
<td>67.27</td>
<td>47.69</td>
<td>18.43</td>
<td>80.67</td>
<td>116.15</td>
</tr>
</tbody>
</table>
same cell kill in the tumour volume as the actual heterogeneous dose delivered. This is useful as dose heterogeneity is a particular feature of IMRT.

An estimation of beam-on time was made to assess the efficiency of treatment delivery. For mMLC plans, we used the number of segments to make a beam-on time assessment, based on departmental phantom studies, which have shown that it takes on average 13 s to treat one segment using a 'step and shoot' technique. For the helical tomotherapy plans, the system calculated a beam-on time as part of the planning process.

**Results**

The five cases were individually planned and optimised, and were compared for plan efficacy. In all cases, OAR doses were minimised successfully to below absolute tolerance levels and, therefore, all plans were clinically acceptable for delivery in our department (Table 3).

PTV coverage was excellent in all cases. There was very little difference in the $D_{\text{max}}$, $D_{\text{med}}$ and $D_{\text{mean}}$ between the helical tomotherapy and mMLC plans (Fig. 1). $D_{\text{min}}$ was improved on average by 10.2 Gy in the helical tomotherapy plans. Coverage of the PTV$_{90}$ with 90% of the prescribed dose was the same for both methods. Coverage with 95 and 100% of the prescribed dose was on average 88.8 and 83.5% for helical tomotherapy and mMLC, and 52 and 60% for helical tomotherapy and mMLC. This indicates that there is little difference in the ability of the two planning and delivery systems to safely cover the target volume to high doses. Examples of a petrous apex case and a suprasellar case are shown in Figs. 2 and 3. These two cases were chosen to illustrate the two extremes seen in skull base radiotherapy from well-lateralised to complex centralised tumours.

**Discussion**

We compared two techniques for planning and delivery of IMRT, with the objective of dose escalation in the skull base in five patients. Safe delivery of high doses to the region is possible, using either helical tomotherapy or linac-based IMRT using an mMLC. In both cases, the dose to critical OAR can be minimised to below a predefined threshold, in our case a conservative 50 Gy to the optic pathways and brainstem, while simultaneously achieving a very high PTV$_{90}$ dose of up to 95%. The PTV coverage as measured by physical parameters was similar in both planning systems. It is clear that a high degree of intensity modulation is required to achieve the desired dose distributions, and this can be achieved with either mMLC or helical tomotherapy technology.

One major limitation of this study is the difficulty in comparing the two planning systems accurately, which we found to be challenging during this exercise. We used identical contours for both systems, but prescribed the dose differently using a 100% dose to the ICRU point as defined as the centre of the PTV$_{90}$ in the mMLC plans and a median dose in the helical tomotherapy plans. The different optimisation algorithms and management of overlapping structures between the two systems meant that using the same prescription method limited one or other of the planning methods. We decided to use the prescription
methods that would result in the best plan possible from each system, which was prescription to a point in the centre of the target in the mMLC plans and prescription to the median dose in the helical tomotherapy plans. These methods of dose prescription directly relate to our current clinical practice, producing results that are clinically relevant, if not truly comparable in every sense. It highlights some of the practical difficulties faced when comparing...
Fig. 3. (a) Suprasellar lesion helical tomotherapy plan dose distribution in the axial, coronal and sagittal planes (red = 60 Gy, orange = 50 Gy). (b) Suprasellar lesion micro-multileaf collimator plan dose distribution in the axial, coronal and sagittal planes (red = 60 Gy, orange = 50 Gy). Note that both plans sculpt the 60 Gy isodose tightly around the planning target volume despite its very unusual shape, minimising the dose to the optic chiasm located anteriorly and superiorly and the brainstem posteriorly and inferiorly. The hypothalamus (posterior/superior) is less well spared in the micro-multileaf collimator plan compared with the helical tomotherapy plan, which may be of clinical relevance in some settings.

treatment modalities and techniques, which can be especially problematic if the differences are small.

Not only were different dose points used, calculation algorithms, beamlet/segment and voxel size were also different, being considerably smaller for the helical tomotherapy plans. As the dose grids are not the same, and cannot be changed by the operator, it is very difficult to compare dose to volumes for very small structures. In the helical tomotherapy plans, extremely sharp dose gradients are produced, with less 'blurring' or spreading of the dose at the penumbra. It seemed to be much harder to cover the PTV95 with 100% of the prescribed dose, as very small hotspots, some not easily visible on the dose distribution maps, elevated the Dmax to the OAR to levels above our predetermined threshold. In order to meet the absolute OAR planning constraints, the high dose had to be moved further away from the critical structures, resulting in a slightly lower PTV95 coverage for the helical tomotherapy plans, as noted by a small difference in V100. In many cases, the volume of tissue exceeding the dose constraint was extremely small, i.e. only a few voxels, and may not have been of clinical relevance. Whether these very small hotspots are 'real' or clinically significant is currently unclear. Although V100 may seem to be slightly superior if using LINAC-based IMRT and mMLC, it is not clear whether this effect is 'true' due to the difficulty of interpreting very small differences between two different planning systems, or if it is of clinical relevance. This could possibly be measured by using film phantom studies to establish if the tiny hotspots are artefacts of the calculation algorithm or real dose distribution inhomogeneity.

One of the apparent advantages of helical tomotherapy over mMLC in our study was a possible improvement in treatment beam-on time. If this is a true difference, it has positive implications for the patient with regard to comfort and total body dose from machine leakage, and for a resource-limited busy department. In our cohort, the beam-on time for the mMLC was quite long, but was based on our in-department experience and time measurements when using our mMLC technology. Although these results may not be directly applicable to other departments, it illustrates the necessity to make estimations of treatment time based on phantom and time studies in addition to differences in dose distributions. This could vary between departments, and could affect treatment delivery significantly. Therefore, in our department, with other factors being equal or similar, helical tomotherapy is a good solution compared with mMLC for its ability to treat patients in much less time. Although helical tomotherapy may be an inefficient solution for the treatment of long targets
compared with mMLC IMRT, due to the axial scanning component, which does not treat all of the target all of the time, this may be less of an issue in the setting of small volumes such as those in the skull base.

In summary, we have shown that it is possible to achieve safe dose escalation of up to 60 Gy in the region of the skull base, by using high levels of dose intensity modulation with either mMLC IMRT or helical tomotherapy. We have not been able to show superiority of one technique over the other, and acknowledge that small differences between the two methods are hard to define, as a comparison of plans remains problematic and imperfect. For most departments, helical tomotherapy is unlikely to be an unrealistic option, and it is useful to confirm that IMRT with 2.5 mm MLC is able to produce similar results. This technology is generally more accessible, thus providing patients who clinically need treatment to a high dose to the skull base, a safe option for management. In addition, we have highlighted some of the practicalities and difficulties in implementing a new technology into a clinical department. Competition between manufacturers now means that new technologies that improve dose modulation are becoming more available. Comparing these techniques is important to ensure we are selecting the best treatment modalities for individual patients, as well as investing in appropriate, cost-effective technologies for our local communities. These challenges will continue to see more advanced techniques become available.

**Conflict of Interest Statement**

V. J. Estall was a clinical research fellow funded by Siemens Oncology OCS during this research, through an unrestricted educational grant, in collaboration with the Addenbrooke’s Hospital Oncology Centre and Cambridge University Department of Oncology. Modular mMLC and the IonRad Planning system are Siemens OCS products.

**Acknowledgements**

V. J. Estall is supported by Siemens OCS Ltd, R. Jena by the Health Foundation UK and N. Burnet by the NIHR Cambridge Biomedical Research Centre.

**References**


4.3. Discussion

4.3.1 Contribution and significance

This paper was one of the first to compare HT with linear accelerator based IMRT for skull base lesions when aiming to deliver dose escalated schedules, and has been cited in 4 articles discussing the management of skull base meningioma. It demonstrated that the tumour coverage and OAR sparing was very similar for the 2 techniques, with the main practical difference being the reduction of MU’s required and the more rapid treatment time for the HT plans. This suggests that both techniques are suitable for the treatment of skull base lesions where dose escalation is desirable, and are interchangeable. This is useful practical information as it aids clinician’s in their recommendations for where a patient should have treatment. HT technology is becoming more widely accessible, and would be the technique of choice for high dose radiotherapy of the skull base if available due to the reduction in treatment times. However, linear accelerator based IMRT using a fine leaf MLC is an appropriate alternative, and likely to be more available in most areas including Australasia.

4.3.2 Literature since publication

There have been no further planning studies comparing HT with linear accelerator based IMRT in the skull base region, and to date, our study is the only one to have specifically tested prescription doses of 60Gy.

There have been several clinical studies published in the last few years reporting early toxicity and outcome data for the use of HT for skull base meningioma, some of which cited our planning study (Gupta et al 2012, Tejpal et al 2012). Gupta et al reported
outcomes following treatment of 30 skull base tumours using HT. This included a range of tumours, but did include high-grade lesions in which 60Gy was prescribed and delivered, although the majority of patients were prescribed 50-54Gy. The overall control rate at 2yrs was 93%, however the authors did not report on the specifics of the patients treated with 60Gy and it’s likely the numbers would have been too small to comment on. In all patients the treatment was well tolerated with acceptable levels of toxicity.

Tejpal et al reported on 27 patients treated using HT to deliver a mean dose of 54Gy. At a median follow up of 19months, the 2-year clinico-radiological progression-free survival and overall survival was 93.3% and 100% respectively.

In 2011 Combs et al reported outcomes following HT for 12 patients with meningioma, with 5 patients G2 and 2 patients G3. They prescribed 60Gy to gross disease and reported no significant toxicity. At time of the publication, 4 of 12 patients had progressed (2, 4, 17 and 29m post radiotherapy). Two of these patients were G2 meningioma and 2 were G3, indicating that in this setting, 60Gy may still not be adequate to control disease locally (Coombs 2011).

In the same year Schiappacasse et al reported outcomes for 28 patients with meningiomas close to the optic pathway (Schiappacasse et al 2011). In this cohort the majority of patients had benign meningioma, which was inoperable or had gross disease post operatively. The patients were treated to preserve visual function, so doses of up to 54Gy were prescribed with HT used to minimise the dose to the optic apparatus. At 3yr follow up there was no reported late toxicity and no patients had developed radiotherapy related visual disturbance. There was also no reported disease progression. The authors here
utilised HT for its OAR capabilities as opposed to its ability to dose escalate which is of course an important endpoint. This indicates that this type of highly conformal treatment should also be considered when more modest doses are required for tumour control, but where there is also a desire to minimise dose to very sensitive structures. This may have important implications for re-treatment scenarios, and to avoid OAR not previously considered relevant i.e. the pituitary axis in a pre menopausal patient etc.

4.3.3 Future directions

Tomotherapy is now an accepted modality for the treatment of skull base meningioma, and it is being utilised to treat small skull base lesions to doses, which are not possible with 3D conformal treatment. In a short period of time, clinicians have reported results indicating that this technique is feasible and safe with regard to short and medium term toxicity, and effective at controlling tumour. However, the majority of series published show that clinicians are still using more modest ‘safe’ doses of 54Gy. As clinicians become more confident with using this technology, it may be that doses of 60Gy and above may be delivered more often, possibly with improved results.

It’s unlikely that the dosimetric capabilities of HT (or linear accelerator based IMRT) can be further improved. If the role of dose escalation is proven to be important in the setting of meningioma, and doses greater than 60Gy are found to be beneficial, then other forms of treatment may need further investigation i.e. proton therapy.
SUMMARY AND CONCLUSIONS

5.1. RATIONALE 133
5.2. THESIS FINDINGS 135
5.3. IMPLICATIONS FOR MANAGEMENT OF PATIENTS WITH SKULL BASE MENINGIOMA 139
5.4. IMPLICATIONS FOR CLINICAL IMPLEMENTATION OF NEW RADIOTHERAPY TECHNOLOGY 139
5.5. ISSUES NOT ADDRESSED IN THIS THESIS 144
5.6. CONCLUSIONS 147
5 SUMMARY AND CONCLUSIONS

5.1. RATIONALE

Skull base meningioma is a relatively rare, but important clinical issue. The fact that this condition is rare should not be a disincentive to investigating optimal methods to manage it. The RARECARE project (Surveillance of Rare Cancers in Europe) analysed the incidence, prevalence and survival of rare cancers (including malignant meningioma) in Europe over a period of 4 years, covering a mean population of 162,000,000 (Gatta et al 2011). They showed that the annual incidence rate of rare cancer in Europe was 108/100,000; 22% of all new cancer diagnoses. This represents a significant cancer burden on the population. They also reported that the 5-year overall survival of patients with a rare cancer was poor at 47% compared to 65% for common cancers. This evidence justifies ongoing research initiatives to improve outcomes for patients diagnosed with a rare cancer.

Despite being considered to be a ‘benign’ disease by many, meningiomas have the capacity to cause significant morbidity, and in some cases mortality. Although the majority of cases are slow growing with a low metastatic potential, their location close to critical neurological structures i.e. cranial nerves, brainstem etc, means that poorly controlled disease has a negative impact on quality of life and potentially can be fatal. Management decisions in this setting are often very complex requiring a multidisciplinary specialist approach, as treatment with surgery and/or radiotherapy is limited by the risk of treatment-related damage to the same critical organs at risk from the tumour. For these reasons, this condition should be managed by an experienced group of clinicians familiar with the specific issues, and careful consideration of all treatment options is imperative.
When radiotherapy is being used for this condition, local control for non-benign meningioma, i.e. G2 and G3 disease, is improved if doses of 60Gy can be delivered. 3D conformal techniques are appropriate to deliver doses of up to 54Gy, but this approach is inadequate if higher doses are required as the dose distributions are simply not conformal enough. Therefore, this justifies an investigation into techniques to optimize radiotherapy delivery to this location, and the results can be easily applied to any diagnosis in the skull base.

IMRT is a form of highly conformal radiotherapy, which can allow dose escalation to the tumour, while maintaining the dose to surrounding tissues to below tolerance. The planning process is significantly more complex than that for 3D conformal therapy, and a steep learning curve for radiation practitioners was evident when it was first introduced into clinical practice. It is important to spend time investigating techniques such as IMRT to ensure that patients are indeed receiving optimal treatment plans, paying close attention to maximizing the dosimetry of the treatment as well as the practical aspects of delivering the treatment, e.g. ‘beam on’ time etc. This concept has become increasingly important in recent years, following the rapid development of new technologies.

Therefore, the main aims of this thesis were:

- To investigate the potential role for dose escalation above 54Gy to treat meningioma of the skull base. This included a review of the outcomes from our unit.
- To investigate clinically available IMRT technology to identify planning class solutions, which will result in optimized IMRT plans in the skull base.
region. This would be in the context of safe dose escalation to the tumour, and the results can be applied to any lesion in the skull base requiring a higher dose than 54Gy. This included both fixed field IMRT and helical tomotherapy.

5.2. THESIS FINDINGS

A literature review and a retrospective review of the clinical outcomes following radiotherapy at Addenbrooke’s Hospital were conducted as part of this thesis. The following conclusions can be drawn from the work investigating the role of dose escalation for meningioma:

- Doses of 60Gy or more are clearly indicated for patients with G2 and G3 disease, and are likely to improve local control compared to doses of 50-54Gy.
- The evidence for a clinical benefit to dose escalation in the setting of G1 meningioma is less clear. However, it is still reasonable to use a highly conformal technique such as IMRT when aiming to treat to 50-54Gy in the skull base in certain settings for G1 disease i.e. re-irradiation.

A series of planning studies were then conducted using CT data from previously treated patients at Addenbrooke’s. Other investigators had already proven that IMRT produces significantly more conformal plans in the skull base compared to 3D conformal. However, it was not clear if there was an optimal planning class solution for IMRT to the skull base, and this was the question the planning studies aimed to answer. The following conclusions can be drawn from the work investigating fixed field IMRT plan optimisation:
• It is possible to safely dose escalate skull base tumours to doses of 60Gy using IMRT, using the same normal tissue constraints as for 3D conformal radiotherapy.

• A planning class solution has been identified, with the following methods resulting in the optimal dosimetry and optimal efficiency i.e. plans which have the best PTV coverage as well as acceptable MU and ‘beam on’ times

  o 2.5 – 5mm MLC
  o 7 field co-planar beam arrangement for central lesions
  o 5 field non-coplanar beam arrangement for lateralized lesions

When using linear accelerator IMRT, small MLC widths result in better conformation of dose around complex structures. We confirmed other reports that MLC widths of 2.5-5mm are required, with the smaller MLC’s perhaps providing a small further improvement in dose distributions for centrally located lesions close to optic tracts and brainstem. However, there are clinical limitations to using very small MLC widths, which need to be taken into account. Increased segmentation of the beam as a result of fine MLC width will increase considerably the ‘beam on’ time. This does not only have implications for treatment times and resource planning, but there is also some evidence that prolonged treatment times can increase the total dose to a patient from machine leakage and scatter. The clinical impact of this on the patient in the long term is unclear, but it is possible that this increased dose to patients could result in an increased risk of radiation-induced carcinogenesis. This question will only be answered definitively in the long-term after many years of treatment follow up. Until that time, it seems prudent to assume an increased risk, and reserve this treatment for
patients who are likely to gain a net clinical benefit. This could include patients who require dose escalation for tumour control (i.e. chordoma, malignant meningioma), or patients where dose reduction to normal tissues is needed (i.e. re-treatment scenarios).

We have also demonstrated that 5-7 beams in a co-planar or non-coplanar arrangement provide optimal dose distributions. We now use a 7 coplanar beam arrangement as our standard, but will consider a 5 field non-coplanar arrangement for well lateralised lesions, as in this setting the dose distributions are adequate and less beams have benefits with regard to treatment times. We have found this information to be very helpful in our clinical practice, and have used it to formulate a clinical protocol, where our planning technique has been justified by evidence based research.

IMRT has been in clinical use for some time despite a slow uptake in Australia, New Zealand, and the UK. But in recent years, there has been a significant increase in technology development. A number of new technologies have become available including helical tomotherapy (HT), which delivers dose in 1mm beamlets using a continuous helical arc. The same principles used to examine the clinical utility of IMRT for dose escalation in the skull base can be applied to Tomotherapy. As part of this thesis, a planning study was performed comparing the dosimetry and practical issues for the two techniques for dose escalation to the skull base. The following conclusions can be made from the work:

- Tomotherapy results in similar dose distributions to that of IMRT
- MU number and ‘beam on’ times are considerably less for helical tomotherapy
This work indicates that both systems are equally able to achieve dose escalation in the skull base, but helical tomotherapy has practical advantages, primarily a significantly reduced treatment time. It also has inbuilt CT imaging capabilities for image guided radiotherapy, another significant advantage.

One of the biggest lessons during this planning study was the difficulty we had in comparing the plans between the 2 systems. Differences in voxel size, planning algorithms, the way the systems dealt with overlapping structures, and how DVH data was stored made direct comparison difficult. However, when taking into account the plan statistics, DVH plots and isodose distributions, we were unable to show a clinically significant difference between the two planning techniques with regard to dosimetry. Of practical significance there was the difference in treatment time, with HT being at least half that of linear accelerator-based IMRT. This is an important consideration for both the patient’s comfort and safety, and resource management in a department. The possible risk of carcinogenesis could also be reduced by reducing beam on time. However, helical arc therapy can deliver low doses to a large volume of normal tissue in a ‘low dose bath’, and the impact of this phenomenon on carcinogenic risk is also unclear. As for other forms of IMRT, it is sensible to assume there could be an increased risk and ensure only patients in whom there is a clear clinical benefit are offered these treatment modalities. Of note, is that the integral dose is typically the same for both 3D conformal radiotherapy and IMRT, though the distribution of that dose is different.
5.3. IMPLICATIONS FOR MANAGEMENT OF PATIENTS WITH SKULL BASE MENINGIOMA

The findings of this thesis have the following clinical implications for patients with skull base meningioma:

- Patients who have indications for radiotherapy should be considered for high dose radiotherapy (60Gy or more) using a suitable technique i.e. IMRT, helical tomotherapy, VMAT especially for G2 and G3 tumours.
- Doses of 60Gy can be safely delivered to skull base lesions using the IMRT planning class solution described.
- Doses of 60Gy can be safely delivered using Tomotherapy with an advantage of a reduced treatment time. Integrated IGRT is also available.
- If patients meet the criteria for dose escalation, and an appropriate technique is not readily available locally, consideration should be given to referring the patient to a specialist centre with the required technological capacity.

5.4. IMPLICATIONS FOR CLINICAL IMPLEMENTATION OF NEW RADIOTHERAPY TECHNOLOGY

Both linear accelerator IMRT and helical tomotherapy have been discussed in some detail in this thesis. Other important modalities, which are clinically useful for the management of skull base tumours, include GammaKnife, CyberKnife (Adler et al 1997), and Volumetric-Modulated Arc Radiotherapy (Lagerwaard et al 2009). These machines are notable by their ability to provide excellent dose distributions, inbuilt imaging technology for imaged-guided and adaptive treatment and a reduction in monitor units and therefore ‘beam on’ treatment times.
Below is a table outlining and summarising the various technologies currently available, some of which have only been in clinical use in Australia and New Zealand for a limited period of time.
Table 6. Summary of high dose radiotherapy technologies available for skull base treatment.

<table>
<thead>
<tr>
<th></th>
<th>Fixed Field IMRT</th>
<th>Rotational IMRT (VMAT/RapidArc)</th>
<th>Tomotherapy</th>
<th>CyberKnife</th>
<th>GammaKnife</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Intensity modulated treatment using MLC technology delivered as multiple fixed angled beams.</td>
<td>VMAT delivers radiation by rotating the linac gantry through one or more arcs with the radiation continuously on. As it does this, beam parameters can be varied. These include: i) the MLC aperture shape, ii) the dose rate, iii) the gantry rotation speed and iv) the MLC orientation.</td>
<td>Intensity modulated treatment using 1mm beamlets delivered as a helical rotational arc. Helical IMRT combines a CT scanner with a radiotherapy delivery system (linac), enabling daily 3D imaging with radiation treatment as well as volumetric IMRT</td>
<td>Highly conformal treatment using an infinite number of small width pencil beams aimed from any angle at an isocentre using micro liner accelerators and robotic technology.</td>
<td>Highly conformal treatment using up to 201 small width pencil beams aimed at an isocentre using a low dose rate cobalt source with beams collimated by a specialised array in a heavily shielded lead helmet</td>
</tr>
<tr>
<td>Dosimetry</td>
<td>Excellent conformality with significant improvement in dosimetry beyond 3D conformal planning (<a href="#">Baumert et al 2003</a>)</td>
<td>Excellent conformality achievable with similar dosimetry to an 18F fixed IMRT plan (<a href="#">Lee et al 2010</a>).</td>
<td>Excellent conformality achievable with similar dosimetry to a 7F IMRT plan (<a href="#">Estall et al 2010</a>).</td>
<td>Excellent conformality achievable in the skull base (<a href="#">Collins et al 2006</a>).</td>
<td>Excellent conformality achievable in the skull base (<a href="#">Jang et al 2010</a>).</td>
</tr>
<tr>
<td>Dose escalation</td>
<td>Yes up to 60Gy</td>
<td>Yes up to 60Gy</td>
<td>Yes up to 60Gy</td>
<td>Yes to 60Gy, possibly higher</td>
<td>Yes to 60Gy, possibly higher</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Conformal dose distributions adequate for 60Gy plans</td>
<td>Highly conformal dose distributions Less MU required and reduced ‘beam on’ time compared to fixed field IMRT</td>
<td>Highly conformal dose distributions Less MU required and reduced ‘beam on’ time compared to fixed field IMRT + Integrated IGRT</td>
<td>Highly conformal dose distributions Excellent gating opportunities (not relevant for skull base lesions but important for other treatment sites including abdomen and chest) Good option for single fraction or hypo-fractionated therapy</td>
<td>Highly conformal dose distributions</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Requires a high number of MU and increase ‘beam on’ times, limiting its practicality and increasing overall dose to patient. This required MLC widths of 5mm or less.</td>
<td>Less opportunity for gating</td>
<td>Less opportunity for gating (not relevant for skull base lesions but important for other treatment sites including abdomen and chest)</td>
<td>Cannot treat around 360 circumference of bed, so patient may be required to lie prone Long ‘beam on’ times Limited practicality for children and palliative patients</td>
<td>Can treat CNS lesions only Requires a source to be replaced and disposed of Long ‘beam on’ times and limited practicality for children and palliative patients</td>
</tr>
<tr>
<td><strong>Role in skull base meningioma</strong></td>
<td>Standard of care for G2/3 meningioma requiring doses of 60Gy</td>
<td>Similar to that for fixed field IMRT Good for dose escalation at least to 60Gy and possibly higher</td>
<td>Similar to that for fixed field IMRT Good for dose escalation at to 60Gy but unlikely to achieve higher than that Can be using to deliver a</td>
<td>Standard fractionated regimens are better delivered using other modalities Can be using to deliver a single or</td>
<td>Standard fractionated regimens are better delivered using other modalities Can be using to deliver a single or hypo-fractionated</td>
</tr>
<tr>
<td>Availability in Australia/NZ</td>
<td>Can be using to deliver a single or hypo-fractionated course of treatment</td>
<td>single or hypo-fractionated course of treatment if needed.</td>
<td>hypo-fractionated course of treatment field IMRT if needed. Could be used for a re-treatment scenario or where dose escalation &gt;60Gy indicated</td>
<td>course of treatment field IMRT if needed. Could be used for a re-treatment scenario or where dose escalation &gt;60Gy indicated</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>85% of linacs in Australia are IMRT capable.</td>
<td>Clinically available at a limited number of centres in Australia since 2010, and NZ since 2012. 25% of Linacs in Australia are VMAT capable.</td>
<td>Clinically available at 3 sites in Australia since 2011. Not clinically available in NZ.</td>
<td>Not clinically available in Australia or NZ at this time. One centre in Australia has been approved for development.</td>
<td>Clinically available at one centre in Australia but not government funded.</td>
<td></td>
</tr>
</tbody>
</table>
There is unlikely to be a perfect machine, which can provide an optimal solution for every case. This table illustrates that there is a range of technologies worldwide, which can be utilised in this setting. For dose escalation schedules of 60Gy in 1.8-2.0Gy/fraction, fixed field linear accelerator based IMRT, helical tomotherapy and rotational IMRT provide equivalent dose distributions. However, the later two treatment systems have clear advantages with regard to a reduced number of monitor units and a reduced ‘beam-on’ time, which has implications for patients with regard to overall radiotherapy exposure, and to departments with regard to treatment efficiency and resource planning. Therefore, one would consider helical tomotherapy and rotational arc therapy to be the optimal solutions with regard to both treatment effectiveness and efficiency. These treatment solutions are likely to become more common in future years as more departments invest in this technology. However, fixed field IMRT with 2.5-5mm MLC leaves remains the most widely available solution at this time for the treatment of skull base lesions and is an appropriate alternative.

5.5. ISSUES NOT ADDRESSED IN THIS THESIS

The main aim of this thesis was to investigate optimal ways to use current IMRT technology to improve dose distributions to tumours in the skull base, with the ultimate goal of achieving dose escalation on the presumption that an improved therapeutic index will be of benefit to patients. The clinical benefit of dose escalation in the setting of meningioma is difficult to prove due to the rarity of this condition and the prolonged relapse times i.e. 10-15 years. It has been assumed based on Level IV evidence there is a rationale for dose escalation in this setting, but it is clear that there
are other pathologies in which dose escalation is proven i.e. squamous cell carcinoma or chordoma, and this work has unquestionable relevance for these conditions.

To definitively prove that outcomes i.e. local control and survival, can be improved for meningioma patients treated with IMRT to 60Gy, a clinical study with a minimum follow period of 15 years would be required and this is outside of the scope of this work. Our department is accruing patients to a prospective trial, but will not be able to report any survival outcomes for several years. In 2010 a review of the literature of 61 studies comparing IMRT and conventional radiotherapy for a range of conditions was published. The authors found evidence that IMRT reduced toxicity when treating head and neck cancer, prostate cancer and breast cancer, but none of the studies were able to demonstrate (or were powered to identify) survival differences (Staffurth et al 2010). Despite this, the improvement in toxicity is a good justification for the IMRT in these settings, to improve a patient’s experience, ensure they complete the course of treatment (reduction of acute toxicity) and reduce long term morbidity from late toxicities. The impact on survival outcomes may be difficult to show in many settings (including meningioma) unless very large studies with long term follow are conducted, and it would be difficult to withhold this treatment option from patients now based on lack of data for this endpoint alone.

As new technologies become available to clinicians, we will need to assess the clinical feasibility of these treatments to ensure they are appropriate with regard to both dosimetric and practical endpoints. In general, survival outcomes have been considered the most important endpoints to justify a treatment concept, but more novel endpoints need to be considered in situations where survival differences may be
difficult or impossible to demonstrate. This thesis illustrates the questions that need to be asked whenever a new technology is presented to us for clinical use, and provides a framework for clinicians to assess these new technologies:

1. Is there a clinical indication to use a highly conformal technique for a specific diagnosis, i.e. is dose escalation or OAR sparing indicated?
2. Can the new technology deliver the required dose distributions to achieve the desired clinical outcomes, and is this superior to standard techniques — is the treatment superior with regard to effectiveness?
3. Are the costs of treatment in terms of patient comfort, safety and time/cost effectiveness acceptable for the improved dosimetry gains — is the treatment superior with regard to efficiency?

The Australian Government Department of Health and Aging has commissioned the Trans Tasman Radiation Oncology Group (TROG) to develop and pilot an evaluation framework for the assessment of new radiation oncology technologies and treatments to address this specific issue. They now recognize that the standard survival endpoints are likely to be published in the next 12 months, and may result in a new paradigm for assessing the utility of new radiotherapy technologies.
5.6. CONCLUSIONS

Based on the work conducted for this thesis we can conclude the following about the role of IMRT for the management of skull base meningioma:

- Dose escalation for skull base meningioma is indicated for non-benign histology.
  - Following a review of the outcome data in our department and a literature review of other centres' experience, dose escalation to 60Gy is indicated for G2 and G3 meningioma. Data is limited to retrospective studies (Level IV), which include generally small numbers of patients, as this condition is rare. However, these series are consistent in their findings, and where data is limited and/or hard to obtain it is beneficial for teams treating these rare conditions to report on their outcomes and add to the collective knowledge. This is also in keeping with the fundamental concept of therapeutic index, which we can assume is likely to be improved whenever we are able to deliver a tumouricidal dose of radiotherapy while simultaneously minimising the dose to normal tissue. Randomised and comparative studies are challenging, although prospective studies of outcomes following management of patients with aggressive treatment i.e. dose escalation, should be encouraged.

- Fixed field IMRT using 2.5-5mm MLC produces dose distributions, which will allow safe dose escalation up to 60Gy in the skull base.
  - Prior to the work performed for this thesis, studies of IMRT for skull base tumours only investigated dose escalation up to 54Gy, which is generally possible with 3D conformal treatment. This was the first
A body of work to document that the delivery of 60Gy to small, complex volumes in the skull base is an achievable goal.

- A majority of skull base tumours treated with fixed field IMRT can be planned using a planning class solution
  - This work has produced a set of evidence based guidelines to optimise the planning process and ensure optimal dose distributions and the most efficient use of the machine time
  - This was the first study of skull base radiotherapy to document such a planning class solution and has been practise-changing for our department. This data is not only important for radiation oncologists who specialise in treating skull base lesions, but is also an excellent resource for clinicians working in less specialised practices who may need to treat these patients occasionally. A robust, evidence-based planning technique which has been shown to result in optimal treatment plans will save time and allow the clinician to have confidence that appropriate treatment is being delivered.

- Helical tomotherapy can produce dose distributions, which will allow safe dose escalation up to 60Gy in the skull base.
  - The results of a planning study as part of this thesis were the first to be published documenting the feasibility of helical tomotherapy for dose escalation in the skull base. Although other investigators had previously documented that helical tomotherapy dose distributions are superior to 3D conformal techniques up to dose of approximately 54Gy, this work was the first to confirm that doses to 60Gy were achievable and safe using this technique.
This work has been cited in other retrospective series of patients treated with this technique, suggesting that clinician’s consider the results of this study to justify the use of helical tomotherapy for this indication.

- Helical tomotherapy will result in similar dose distributions to that achievable for fixed field IMRT when dose escalation to small complex lesions in the skull base is the goal. It has the added advantage of significantly reduced beam on times. Therefore, it can be concluded that if dose escalation of 60Gy is required to the skull base region, helical tomotherapy should be considered as the ideal treatment solution if it is readily available. If not, fixed field IMRT is a reasonable alternative.

Although not specifically identified as an aim for this thesis, the process of completing the work presented here has demonstrated an important aspect of radiation oncology. This has been recognised in response to the explosion of new technology onto the market in recent years. Systematic assessment of the feasibility of new technologies in treating specific conditions is imperative, and in the first instance must include a comparison of dose distributions between the standard available techniques and the new technology. These feasibility studies should include an estimation of practical factors such as beam-on time and if possible, should identify planning class solutions to ensure patients get the most optimal treatment plans delivered to them from the outset. This concept is relatively new, but as clinical outcome data can take some time to collect, and the progress with regard to radiotherapy technologies is rapid, the need to make quick assessments about whether or not a certain technology has relevance for a certain group of patients is paramount.
This process allows clinicians and other health provision leaders to make informed and evidence based decisions about which patients may benefit from what technology, ensure that the technology is being utilised to its maximal effect, and aids health providers to decide on which technologies should be acquired to meet the wider community’s needs. This is well demonstrated by a large number of planning and feasibility studies which have been published since this work, across a large number of treatment sub-sites, indicating that radiation oncologists now recognise the importance of this type of planning research. The results presented here illustrate an important principle that the optimisation of new technology can deliver improvements in dose distributions likely to result in improved patient outcomes.
APPENDICES

6 APPENDICES

6.1. APPENDIX ONE: Poster Presentations associated with this Thesis 152
6.2. APPENDIX TWO: List of publications associated with this Thesis 159
6.3. APPENDIX THREE: List of publications citing work from this Thesis 160
6.1. **APPENDIX ONE: Poster Presentations associated with this Thesis**

AAPM  July 27-31, 2008  Houston, USA
“Improved target volume delineation and early assessment of radiotherapy for skull base meningioma using 68Ga DOTA-Octreotide PET-CT.”

AAPM  July 27-31, 2008  Houston, USA
‘The impact of intensity levels and number of segments on skull base IMRT plan quality and efficiency.’

ESTRO27  September 14-18, 2008  Goteburg, Sweden
‘IMRT plan optimisation for skull base lesions: planning solutions.’

RANZCR59  October 4-7, 2008  Melbourne, Australia
‘Tomotherapy versus IMRT for skull base meningioma: a planning comparison.’

UKRO  April 6-8, 2009  Cardiff, UK
‘Skull base meningioma – comparison of IMRT and Tomotherapy planning techniques.’

AAPM  July 26-30, 2009  Anaheim, USA
‘Impact of MLC width on IMRT planned dose distributions in the skull base.’
68Ga-DOTA-Octreotate PET-CT: Does it have a role in the assessment of radiotherapy response in patients with meningioma?

VJ Estall, R Jena, N Early, W Waddington, NG Burnet

Addenbrooke’s Hospital, Oncology Centre, Cambridge, United Kingdom
Addenbrooke’s Hospital, Dept of Medical Physics, Cambridge, United Kingdom
University College London Hospital, Dept of Nuclear Medicine, London, United Kingdom
University of Cambridge Dept of Oncology, Cambridge, United Kingdom

Aim
To assess 68Ga-DOTA-Octreotide PET-CT as a potential marker of early treatment response following radiotherapy for skull base meningioma.

Background
- Radiotherapy is an effective treatment for intracranial meningioma.
- Treatment response is difficult to assess using standard imaging and usually requires several years of follow up to establish.
- Most meningiomas express surface somatostatin receptors, which can be imaged using somatostatin analogues linked with PET tracers.
- Ga68-DOTA-Octreotate(DOTATOC)PET is a recently developed imaging tool with a specific role in meningioma.
- This gallium labelled somatostatin 2 analogue binds to meningioma cell surface receptors, providing a specific tool for imaging tumour extent, helpful in radiotherapy planning.
- It has been postulated in one small series that radiotherapy causes an early loss of these cell surface receptors, which may be correlated to late clinical tumour response.

Methods
- A patient with a recurrent right sphenoid wing meningioma (WHO Grade 1) was referred for radiotherapy.
- She received 50Gy/30Fx over a period of 6 weeks, and had pre and post treatment (6 weeks) imaging with 68Ga-DOTA-Octreotate PET-CT.
- SUV calculations were performed to assess the impact of the radiotherapy delivered on:
  - The volume of PET tracer uptake
  - The maximum and average SUV values

Results
- The patient tolerated the treatment and the two PET-CT imaging procedures well.
- The pre-treatment imaging showed the meningioma was identified well using 68Ga-DOTA-Octreotide.
- Using a ‘Volume of interest’ SUV growth limit of 1.6 (based on correlation of anatomical and functional imaging findings), the tumour was found to have a Max SUV of 6.8, an Average SUV of 3.1 and a volume of 4.2cc before treatment was delivered.
- At 6 weeks following delivery of radiotherapy, the lesion showed an response on imaging to radiotherapy, with a reduction in Max SUV to 4.0, a reduction of Average SUV to 2.4, and an reduction in tumour volume to 3.9cc. (See Table 1)

Conclusions
- In this case, all parameters measured were reduced 6 weeks following radiotherapy. (Max SUV, Average SUV and tumour volume.)
- The use of this tracer specifically targeted to the tumour cell surface improved our identification of the lesion for treatment planning.
- In addition, we were able to demonstrate a response to radiotherapy at a molecular level, much earlier than can currently be achieved with standard CT and MRI imaging.
- The clinical implication of this early response indicator is unknown at this stage, and will require several years of follow up to establish.

Table 1. Pre and Post radiotherapy SUV values and tumour volume

<table>
<thead>
<tr>
<th></th>
<th>Max SUV</th>
<th>Average SUV</th>
<th>Tumour volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre 50Gy</td>
<td>6.8</td>
<td>3.1</td>
<td>4.2cc</td>
</tr>
<tr>
<td>Post 50Gy</td>
<td>4.0</td>
<td>2.4</td>
<td>3.9cc</td>
</tr>
</tbody>
</table>

Acknowledgements
VJ Estall is funded by Siemens OCB - Oncology Research Fellowship.

Contact VJ Estall: vanessa.estall@addenbrookes.nhs.uk
Skull Base IMRT: The impact of intensity levels and number of segments on plan quality and efficiency.

VJ Easal, R Jena, K Barton, NG Burnett

Addenbrooke’s Hospital, Oncology Centre, Cambridge, United Kingdom
University of Cambridge, Department of Oncology, Cambridge, United Kingdom

Aim
To investigate the impact of the number of intensity levels and segments on plan quality and efficiency, when planning IMRT for skull base lesions.

Background
- IMRT is an important technique for treating complex shaped skull base lesions in close proximity to critical organs.
- IMRT plans can be achieved allowing safe dose escalation.
- Higher intensity levels usually result in more conformal plans, but at the cost of a higher number of segments.
- A pragmatic clinical solution was sought for the optimum number of intensity levels for use in a skull base IMRT solution.

Methods
- 5 previously treated skull base meningioma cases were retrospectively assessed in a planning exercise.
- The cases were chosen to represent the most common locations likely to be treated and included suprasellar, cavernous sinus and sphenoid wing lesions.
- Cases were re-planned using KonRad IMRT planning software and Moduleaf, with dose 60Gy/30F prescribed to ICRU60 point. 7-9 coplanar beam arrangements were used.
- Plans aimed to achieve at least 90% coverage of PTV, while maintaining dose to critical structures to clinically tolerant levels.
- For each case, 3 plans were generated, using 5, 10 or 15 intensity levels.
- Plan quality was assessed using PTV V95% (Volume of PTV receiving 95% of prescribed dose), EUD (equivalent uniform dose), TID (integral dose to normal tissue) and organ at risk Dmax.
- An an analysis of TID was used to calculate EUD to reflect the growth pattern of G1 meningioma.
- Plan efficiency was assessed by number of segments required to generate the plan, and estimated beam on time.

Results
- In all cases, critical structure dose was maintained within clinical tolerance.
- The average V95%, V95% and V100% was 90.2%, 93.3% and 84.8% respectively.
- The average EUD achievable was 52Gy.
- There was no statistically significant difference in plan quality when using 5 versus 10 versus 15 intensity levels in the planning process.

Table 1. Plan Quality achieved across the 5 cases by intensity level used

<table>
<thead>
<tr>
<th></th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>Average</th>
<th>Std Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>V95%</td>
<td>90.6</td>
<td>90.7</td>
<td>90.4</td>
<td>90.5</td>
<td>0.3</td>
</tr>
<tr>
<td>V95%</td>
<td>91.4</td>
<td>91.4</td>
<td>91.4</td>
<td>91.4</td>
<td>0.3</td>
</tr>
<tr>
<td>V100%</td>
<td>90.9</td>
<td>90.9</td>
<td>90.9</td>
<td>90.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Dmax</td>
<td>47.8</td>
<td>47.8</td>
<td>47.8</td>
<td>47.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Dmax</td>
<td>47.8</td>
<td>47.8</td>
<td>47.8</td>
<td>47.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Oxygen Dose</td>
<td>67.7</td>
<td>67.7</td>
<td>67.7</td>
<td>67.7</td>
<td>0.3</td>
</tr>
<tr>
<td>TID</td>
<td>15.8</td>
<td>15.8</td>
<td>15.8</td>
<td>15.8</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Conclusions
- Safe dose escalation was possible in all 5 cases.
- There was no clinically significant difference in plan quality depending on intensity level used.
- There was a slight increase in V100% with and increase in intensity level with a standard deviation of 2.5% - this is unlikely to be clinically significant.
- The use of greater than 5 intensity levels increased the number of segments and therefore estimated beam on time by a factor of 2, resulting in plans not suitable for delivery.
- Resulting treatment times of greater than 30 minutes were deemed clinically suboptimal due to patient scheduling and also because of patient tolerability.
- As a result of these findings, IMRT plans using KonRad planning software and Moduleaf are performed using an intensity level of 5, to produce the most clinically appropriate plans.

Acknowledgements
The author VJ Easal is funded by Siemens Medical Oncology Research Fellowship.

Contact VJ Easal: vanessa.easal@addenbrookes.nhs.uk

Figure 1: Average plan parameter values assessed over 5 cases

Table 2. Plan efficiency achieved across the 5 cases by intensity level used

<table>
<thead>
<tr>
<th>Intensity Levels</th>
<th>5</th>
<th>10</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of segments</td>
<td>98</td>
<td>171</td>
<td>238</td>
</tr>
<tr>
<td>Estimated beam on time (30 beams)</td>
<td>16.6</td>
<td>37.1</td>
<td>61.6</td>
</tr>
</tbody>
</table>
IMRT plan optimisation for skull base lesions: planning solutions.

VJ Estall1, R. Jen4, D. Eaton4, S. Jeffery3, K. Burton4, NG Burnel1

1Addenbrooke’s Hospital, Oncology Centre, Cambridge, United Kingdom
2Addenbrooke’s Hospital, Dept of Medical Physics, Cambridge, United Kingdom
3University of Cambridge Dept of Oncology, Cambridge, United Kingdom

Aim
To identify optimal IMRT planning solutions for treatment of skull base lesions.

Background
- IMRT can allow for indirect dose escalation when treating skull base lesions, sculpting high dose away from serial organs at risk, and improving the therapeutic ratio.
- The optimal planning technique in the setting has not been previously assessed.
- We have investigated these factors and how they may affect the plans generated, in an attempt to identify potential clinical solutions to optimise plan quality and efficiency in our department.

Methods
- The original planning CT data sets of 10 patients with skull base meningioma were used to generate 16 IMRT plans for each case.
- The plans used a variation of beam number (3, 5, 7, and 9), beam orientation (coplanar vs non-coplanar) and MLC width (2.5mm Moduleleaf vs 10mm MLC) (See Table 1).
- 60Gy/30Fr was prescribed to the ICRU 60 point, and dose to organs at risk were limited to safe levels based on standard tolerance doses.
- Plan quality was assessed using physical PTV V95%, organ at risk Dmax(mean)) and biological parameters (PTV EUD, integral dose-ID).
- Plan efficiency was assessed using the number of segments required to produce the plan, and an estimated beam on time
- Differences were considered statistically significant if the p value (paired, 2 tail student t-test) was <0.05.

Table 1. Planning techniques assessed

<table>
<thead>
<tr>
<th>Beam MLC</th>
<th>Coplanar</th>
<th>Non-coplanar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plan 1</td>
<td>Plan 2</td>
<td>Plan 3</td>
</tr>
<tr>
<td>Plan 4</td>
<td>Plan 5</td>
<td>Plan 6</td>
</tr>
<tr>
<td>Plan 7</td>
<td>Plan 8</td>
<td>Plan 9</td>
</tr>
<tr>
<td>Plan 10</td>
<td>Plan 11</td>
<td>Plan 12</td>
</tr>
<tr>
<td>Plan 13</td>
<td>Plan 14</td>
<td>Plan 15</td>
</tr>
<tr>
<td>Plan 16</td>
<td>Plan 16</td>
<td>Plan 16</td>
</tr>
</tbody>
</table>

Results

Beam Number
- PTV V95% and ID was improved with the use of 5 vs 3 beams and 7 vs 5 beams, but was not improved further with the use of 9 beams.
- EUD was not changed with beam number.

Beam arrangement
- There was no difference in V95%, ID or EUD if coplanar or non-coplanar beam arrangements were used for the same number of fields.
- 7F coplanar and 5F non-coplanar arrangements resulted in similar PTV coverage.
- There was a small improvement in PTV V95% in the setting of centrally located lesions close to OAR with 7F coplanar arrangements (5%), but this was not significant.

Results

MLC width
- Moduleleaf MLC (2.5mm) resulted in superior plan quality compared to 10mm standard MLC.
- V95% was increased by average 22.3% (p value 0.04)
- ID was decreased by average 14.3Gy (p value 0.0001)
- EUD was increased by average 4.52Gy (p value 0.002)

Conclusions

IMRT using Moduleleaf, 5-7 fields and coplanar or non-coplanar field arrangements can achieve safe dose escalation in the skull base.
The optimal planning solution should be individualised to achieve the optimal therapeutic ratio.

Acknowledgements
VJ Estall is funded by Siemens Medical - Oncology Research Fellowship.

Contact VJ Estall: vanessa.estall@addenbrookes.nhs.uk
Tomotherapy versus IMRT for skull base meningioma: a planning comparison.

VJ Estall1, R Jena1, NG Burnet2

1Addenbrooke’s Hospital, Oncology Centre, Cambridge, United Kingdom
2University of Cambridge Dept of Oncology, Cambridge, United Kingdom

Aim
To compare plan quality for skull base tumours using helical tomotherapy versus IMRT for dose escalation to 60Gy.

Methods and Materials

- 5 skull base meningioma cases previously treated with conformal radiotherapy (50-54Gy/30-33F) were identified to represent the range of skull base locations seen clinically.

- These cases were re-planned using helical tomotherapy (HT) or linac based IMRT using a MultiLeaf Collimator (MLC) (2.5mm).

- A ‘shrinking volume’ technique was used, with a PTV50 and PTV60 (PTV50=serial organs at risk) outlined.

- 60Gy/30F was prescribed to the PTV60 as the median dose for the HT plans, and to the ICcRUs dose point (middle of PTV60) for the mMLC IMRT plans.

- Critical structures (optic pathways/brainstem) were limited to predetermined tolerance levels of 50Gy.

- The ability of each planning solution to close escalate was assessed by the extent of PTV60 coverage with the prescribed dose of 60Gy.

Results

- All plans maintained organ at risk doses to acceptable levels.

- The average values for the PTV60Gy were as follows for the HT and the mMLC plans respectively:

  - Omin: 42.9Gy and 41.9Gy
  - Omax: 67.7Gy and 64.9Gy
  - Omean: 59.4Gy and 59.4Gy
  - Omed: 59.9Gy and 60.1Gy
  - V/50%: 88.9% and 94.4%
  - V/95%: 80.0% and 88.6%
  - V/100%: 53.2% and 64.5%

Figure 1. Average PTV60 coverage for HT versus mMLC

Figure 2. Dose distribution for HT (2a) versus mMLC (2b) plans for petrous apex lesion. Note similar PTV60 coverage and sculpting of dose away from brainstem.

Figure 3. Dose distribution for HT (3a) versus mMLC (3b) plans for suprasellar lesion. Note similar PTV60 coverage and sculpting of dose away from brainstem and optic tracts.

Conclusions

- Excellent plans were produced by both systems, allowing safe dose escalation up to 60Gy.

- Comparison of plan quality between the systems was difficult due to differences in planning algorithms, dose points and overlap priorities.

- The clinical superiority of one planning solution over the other could not be established by this study.

Acknowledgements

VJ Estall is funded by Siemens OCB - Oncology Research Fellowship.

Contact VJ Estall: vanessa.estall@addenbrookes.nhs.uk
Skull base meningioma – comparison of IMRT and Tomotherapy planning techniques.

**Introduction**
- Therapeutic radiotherapy to lesions of the skull base is limited by targets which are complex in shape, and close to the serial organs at risk (brainstem, optic pathways).
- IMRT using helical tomotherapy (HT) may result in improved dose distributions.
- The aim of this study is to compare plan efficiency and efficacy using 3D conformal, IMRT using 10mm or 2.5mm MLC and HT.

**Methods and Materials**
- 5 skull base meningioma cases previously treated with conformal radiotherapy (50-54Gy/30-33W) were identified to represent the range of skull base locations seen clinically.
- They were re-planned using 7F coplanar IMRT with 10mm and 2.5mm MLC and HT.
- A ‘shrinking volume’ technique was used, with a PTV50 and PTV60 (PTV50-serial organs at risk) outlined.
- 60Gy/30F was prescribed to the PTV60 as the median dose for the HT plans, and to the ICRU dose point (middle of PTV60) for the IMRT plans.
- Critical structures (optic pathways/brainstem) were limited to predetermined tolerance levels of 50Gy.
- The ability of each planning solution to dose escalate was assessed by the extent of PTV60 coverage with the prescribed dose of 60Gy.

**Results**
- All plans maintained organ at risk doses to acceptable levels.
- The average values for the PTV60Gy V90%, V95% and V100% were as follows for the HT and IMRT plans:
  - 10mm IMRT: 80.3%, 71.8% and 51.9%
  - 2.5mm IMRT: 95.7%, 93.6% and 94.6%
  - HT: 82.6%, 76.1% and 69.2%
- Average treatment time per fraction was 9.5mins for the 10mm IMRT plan, 18.2mins for the 2.5mm IMRT plan and 6.6mins for the HT plans.

**Figure 1.** Average PTV60 coverage across the 5 cases as assessed by Dmin, Dmax, Dmedian, Dmean, V90%, V95% and V100%, for the 3 different planning techniques.

**Figure 2.** Dose distribution and DVH for HT (2a) versus 2.5mm MLC (2b) and 10mm MLC (2c) plans for a petrous apex lesion. Note similar PTV60 coverage and sculpting of dose away from brainstem for the 2.5mm and HT solutions.

**Conclusions**
- Excellent plans were produced by the 2.5mm mMLC IMRT and HT systems, allowing safe dose escalation up to 60Gy.
- Comparison of plan quality between the systems was difficult due to differences in planning algorithms, dose points and overlap priorities.
- The clinical superiority of one planning solution over the other could not be established by this study.
- One significant advantage of HT over 2.5mm mMLC IMRT plans is a considerably shorter ‘beam-on’ time.

**Acknowledgements**
- VJ Estall is funded by Siemens CRUK – Oncology Research Fellowship.
- Contact VJ Estall: vanessa.estall@addenbrookes.nhs.uk

157
Impact of MLC width on IMRT planned dose distributions in the skull base.

VJ Extall¹, RJ Jen¹, NG Burne²

¹Addenbrooke’s Hospital, Oncology Centre, Cambridge, United Kingdom
²University of Cambridge Dept of Oncology, Cambridge, United Kingdom

Aim
This study aimed to investigate the impact of MLC width on dose distributions for tumours in the skull base.

Methods and Materials
• 5 skull base meningioma cases previously treated with conformal radiotherapy (50-54Gy/30-33 fractions) were identified to represent the range of skull base locations seen clinically
• These cases were re-planned using IMRT to an escalated dose of 60Gy/30W
• A ‘shrinkering volume’ technique was used, with a PTV50 and PTV90 (PTV50=satellite organs at risk) outlined
• 4 IMRT plans were calculated for each case, using 2.5mm, 5mm and 10mm MLC and a 7F coplanar technique, and helical tomotherapy (HT).
• Critical structures (optic pathways/brainstem) were limited to predetermined tolerance levels of 50Gy
• The ability of each planning solution to dose escalate was assessed by the extent of average PTV90 coverage across the 5 cases by Omean, Dmax, V90, V55 and V100.

Results
• All plans maintained organ at risk doses to acceptable levels.
• Average Omean, Dmax, Omean and Dmedian were similar with a trend to higher values for the 2.5mm MLC.
• Average V90, V55 and V100 improved as the MLC got smaller, the V55% increasing from 65.4% to 89.2% for the 10mm, 5mm and 2.5mm MLC respectively.
• HT produced similar PTV coverage to the 2.5mm MLC IMRT plans.
• It appears that the magnitude of difference between the MLC widths was greater if the PTV was a particularly complex shape and touching critical organs.
• The number of segments required increased as the MLC width decreased and on average was 36, 47 and 58 for the 10mm, 5mm and 2.5mm MLC respectively.

Conclusions
• Our findings indicate that MLC width does impact on the ability of an IMRT plan to achieve excellent PTV coverage for skull base lesions when aiming for dose escalation.
• As MLC width reduces, the degree of dose intensity modulation increases, allowing tighter sculpting of high dose around the edge of a complex shaped PTV and away from critical structures.
• There may be no benefit to an MLC width smaller than 2.5mm, and the outcomes seem similar to those achievable with HT.

Acknowledgements
VJ Extall is funded by Siemens OCM - Oncology Research Fellowship.
Contact VJ Extall: vanessa.extall@addenbrookes.nhs.uk
6.2. **APPENDIX TWO: List of publications associated with this Thesis**


6.3. **APPENDIX THREE: List of publications citing work from this Thesis**


REFERENCES


without previous surgery: is there an alternative to aggressive tumour removal? Neurosurgery 48:285-94.


