STEREOTACTIC RADIOTHERAPY - ITS
OPTIMISATION AND WIDER
APPLICATION

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Doctor of Medicine
at the University of Leicester

by

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<tr>
<td>ALARA</td>
<td>as low as reasonably achievable</td>
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<tr>
<td>AVM</td>
<td>arteriovenous malformation</td>
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<td>BED</td>
<td>biologically effective dose</td>
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<td>BEV</td>
<td>beam's eye view</td>
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<td>BRW</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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</tr>
<tr>
<td>CLB</td>
<td>conformal lead blocks</td>
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</tr>
<tr>
<td>cm</td>
<td>centimetre(s)</td>
<td></td>
</tr>
<tr>
<td>cm³</td>
<td>cubic centimetre(s)</td>
<td></td>
</tr>
<tr>
<td>⁶⁰Co</td>
<td>radioactive cobalt</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>computerised tomography</td>
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<tr>
<td>3-D</td>
<td>three-dimensional</td>
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<td>DSRS</td>
<td>dynamic stereotactic radiosurgery</td>
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<tr>
<td>DVH</td>
<td>dose volume histogram</td>
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<tr>
<td>EORTC</td>
<td>European Organisation for Research on Treatment of Cancer</td>
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<tr>
<td>GTC</td>
<td>Gill-Thomas-Cosman</td>
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<tr>
<td>GTV</td>
<td>gross tumour volume</td>
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<tr>
<td>Gy</td>
<td>Gray</td>
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<td>HSRT</td>
<td>hypofractionated stereotactic radiotherapy</td>
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<td>IBED</td>
<td>integral biologically effective dose</td>
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<tr>
<td>ICRP</td>
<td>International Commission on Radiological Protection</td>
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<td>IRT</td>
<td>interstitial radiotherapy</td>
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<td>KPS</td>
<td>Karnofsky performance status</td>
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ABBREVIATIONS CONTINUED

kV kilovoltage
LiF lithium fluoride
linac linear accelerator
MLC multileaf collimator
mm millimetre(s)
MRI magnetic resonance imaging
MV megavoltage
PET positron emission tomography
PTV planning target volume
RBE relative biological effect
RMH Royal Marsden Hospital
RTOG Radiation Therapy Oncology Group
SCRT stereotactically-guided conformal radiotherapy
SD standard deviation
SRS stereotactic radiosurgery
SRS/T stereotactic radiosurgery/therapy
SRT stereotactic radiotherapy
Sv Sievert
TLD thermoluminescent dosimetry
vs versus
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To Susan, Stephen, Paul, Frank and Muriel
CHAPTER 1
INTRODUCTION, BACKGROUND AND
HISTORICAL PERSPECTIVE

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1.1 Introduction

Stereotactic radiosurgery/therapy (SRS/T) using either a gamma knife or a linear accelerator (linac) has become an established technique for functional neurosurgery, the treatment of inoperable intracranial arteriovenous malformations (AVM) and the management of benign and malignant brain tumours. SRS/T has been developed and continues to be evaluated in oncology as a non-invasive means of accurate and precise delivery of localised irradiation to target volumes within the brain with two major goals in mind. First, it is hoped that focused radiation will improve tumour control by allowing higher doses of radiotherapy to be given safely without increasing normal tissue toxicity. Second, that the application of stereotactic technology to optimise treatment delivery will reduce the morbidity of conventionally delivered curative radiotherapy schedules.

The term stereotactic radiosurgery (SRS) is used to describe the delivery of a large single fraction of radiotherapy, classically as a functional neurosurgical procedure or to obliterate an AVM. Essentially it is a non-invasive neurosurgical technique and should be regarded as such. In this setting the treatment rationale is to deliberately induce late damage in the target volume receiving high dose to achieve the desired therapeutic effect.

The pathological mechanism of AVM obliteration starts with radiation damage to the intima of the blood vessels inducing hyperplasia of the lining endothelial cells, thickening of the vessel wall and extravasation of fluid. Histopathological
features include vascular thickening, perivascular fibrosis, fibrin and calcium deposition, fibrin exudation, chronic inflammatory cell infiltrates and coagulation necrosis (1,2). Subsequent thrombotic obliteration of the vessels as a consequence of these changes achieves the desired therapeutic outcome. Focal radionecrosis of a small volume of brain tissue will result if an end arteriole has been occluded. Late radiation damage occurs from four months onwards and has usually developed by two to three years (3), the point at which complete obliteration and complication rates for AVM series are usually reported.

Angiographic complete obliteration rates two years after SRS of over 80% are typically reported for AVM with diameters up to 25mm, in conjunction with a 3-5% incidence of neurological morbidity (4,5,6,7,8). The probability of successfully obliterating larger lesions is considerably lower and carries twice the risk of neurological complications (8,9,10).

Stereotactic radiotherapy (SRT) describes the use of stereotactic technology to deliver a fractionated course of therapeutic radiation. The treatment of primary malignant and benign brain tumours typically involves schedules comprising multiple small fractions of radiotherapy, with the intention of exploiting the intrinsic radiobiological differences between tumour and normal neural tissues. In this way the biological capacity of late reacting normal neural tissues to repair sublethal cellular damage is fully utilised, minimising the risk of late radiation damage developing.
How much primary brain tumours retain the radiobiological characteristics of their tissue of origin is variable. High grade gliomas usually have a high proliferative index and consequently their radiobiological behaviour more closely resembles that of early reacting normal tissue, whilst low grade gliomas can grow slowly for years and react like the glial cells from which they derive when irradiated. Benign meningiomas, pituitary adenomas and acoustic neuromas typically have a very low proliferative index. Laboratory investigations have documented proliferative indices of less than 5% for acoustic neuroma cells (11), but this is still in excess of normal neural tissue and a potential difference that would be exploited by a fractionated course of radiotherapy (12).

Clinical experience has shown that high dose SRS can be tolerated provided the volume of normal brain irradiated is small, non-critical and that there is a rapid fall off in dose with distance from the target (8,13,14,15,16). A gamma knife by design or an adapted linac using isocentric, multiple, noncoplanar, arcing circular beams can each accurately deliver a small, precisely defined isosphere of high dose radiation. Consequently the ideal target volume is spherical or near spherical when using either of these techniques.

In practice most target volumes are irregular and anatomical relationships and radiobiological tolerances usually restrict the use of single isocentre radiosurgery to those with a maximum dimension of 4 centimetres (cm) (8,15). It has been shown that modern SRS is a particularly effective and safe alternative to surgical interventional treatment when the AVMs
are in critical cerebral locations and their volume is less than 4 cm$^3$ (4,5,17). Work by Engenhart and colleagues at the University of Heidelberg showed that no serious complications occurred if a maximum dose of less than 25 Gray (Gy) was applied to treatment volumes of less than 33.5 cm$^3$, up to 4 cm in maximum dimension (8). Beyond this size the probability of successful obliteration is considerably lower and carries twice the risk of neurological complications (8,9,10).

The scope for treating irregular target volumes with the gamma knife using a single isocentre is limited. Blocking individual sources can change the treatment isodose from spherical to mildly elliptical to help avoid sensitive structures within the brain (18).

Multiple isocentre planning is commonly used to improve conformation of the prescription isodose and no-one has exemplified this better than Flickinger and colleagues, who have published detailed analyses on the series of patients treated for acoustic neuroma using the gamma knife at the University of Pittsburgh (16,19). Their painstaking work to optimise long-term outcomes after SRS for newly diagnosed, residual or recurrent acoustic neuromas less than 3 cm in extra-canalicular diameter, utilised radiosurgical treatment plans with multiple isocentres. In the majority of patients the 50% isodose line was shaped to just encompass the full extent of the tumour, which was defined by computerised tomography (CT) until the advent of magnetic resonance imaging (MRI). The superiority of MRI over CT for accurate definition of the tumour and the maximal exclusion of normal tissue from the high dose volume was quickly established (20,21).
Serial evaluation of acoustic, trigeminal and facial nerve function in the patients with CT-defined target volumes who received doses of 12-20 Gy to the 50% isodose line demonstrated some degree of hearing preservation in 71% of patients, but with a 30% actuarial incidence of cranial nerve damage (22). Further study of the data clearly demonstrated that the degree of risk correlated with the length of cranial nerve irradiated (23). Stepwise small reductions in the initial average dose of 18-20 Gy at the tumour periphery (24) to 16-18 Gy and subsequently 14-16 Gy, resulted in a fall in trigeminal and facial neuropathy to below 7% for extra-canaliculcar and less than 2% for intra-canaliculcar tumours whilst maintaining over a 95% long term control rate (16,21). These improved outcomes were achieved in conjunction with technical developments, notably the use of MRI scans for tumour definition and meticulous treatment planning utilising multiple small isocentres (16,20,21).

A total of 49 patients with long term follow up received radiation doses of up to 15 Gy at the tumour margin and the same high rate of control of tumour growth was observed, indicating that the radiation doses initially thought to be necessary for tumour response were too high (24). Radiobiological studies showed that this lower dose range results in tumour regression in human xenograft models (25).

Further patient data analysis demonstrated that the risks of developing trigeminal, facial and acoustic neuropathies following acoustic neuroma radiosurgery can be predicted from the transverse tumour diameter and the minimum tumour dose using dose-diameter response curves (26). By comparing
these curves they showed that the acoustic nerve is the most and the facial nerve the least sensitive to doses of 12-16 Gy.

A single institution non-randomised study from the Netherlands of 129 patients with vestibular schwannoma compared SRS using 10-12.5 Gy at the 80% isodose with hypofractionated SRT (HSRT) giving 20-25 Gy at the 80% isodose in five fractions over one week (27). No statistically significant differences were seen in five year local control or cranial nerve preservation probabilities except for trigeminal nerve function, which was just better maintained with the HSRT schedule. However, this is unlikely to represent a clinically significant difference and one would not expect HSRT schedules to be able to improve the therapeutic ratio when there are subtle differences in proliferation rates and repair capacity between tumour and normal tissue. Debate continues as to whether a conventionally fractionated treatment schedule would result in a further therapeutic gain, by exploiting the small excess proliferative capacity of vestibular schwannoma cells over the adjacent normal tissue (12).

From the foregoing discussion it is clear that large dose inhomogeneities will result within the AVM or tumour target volume when prescribing to the 50% or 80% isodose line. For example when 15 Gy is delivered to the 50% isodose line enclosing an AVM or acoustic neuroma, a minimum of 30 Gy will be received by the volume of tissue enclosed by the 100% isodose line. Even greater inhomogeneity can result with multiple isocentre planning due to overlap between adjacent sets of isodose lines. Conventional radiotherapy dogma would consider such dose variations within the target volume
clinically undesirable but provided the higher dose regions are confined to the AVM or tumour, poor homogeneity could be advantageous by increasing the probability of AVM obliteration or tumour cure.

Conversely if eloquent normal brain tissue is in close proximity to or included in the high dose volume, inhomogeneities can cause overdosage which result in radionecrosis. The size, volume and irregularity of the lesion, its location in the brain, the volume of any normal tissue included in or abutting the treatment volume, the treatment plan, prescription isodose line, total radiation dose and fractionation schedule are all factors which influence the risk of late damage.

A common method of quantifying the effect of a fractionation scheme is to calculate the equivalent dose in infinitely small fractions. This is known as the biologically effective dose (BED) (28). The BED can be used to compare the likely effects of different fractionation schemes. To quantify the effect of a dose distribution on normal tissue involves the calculation of an integral biologically effective dose (IBED), which is the sum of elemental BED values throughout a structure, each weighted by the fractional volume receiving that BED, obtained from a dose volume histogram (DVH) (29). The IBED serves as an indicator of relative damage to an organ when the dose distribution or fractionation scheme is varied. It does not attempt to calculate absolute values of normal tissue complication probability or to account for the effects of partial organ irradiation, as there are large
uncertainties involved due to the lack of radiobiological data and understanding of effects on organ function (30).

In contrast to the gamma knife, further modifications of the basic single isocentre multiple arc linac technique allow different degrees of shaping of the dose distribution to conform more accurately to non-spherical target volumes. These include using different sizes of circular collimators, arc lengths and doses for the different arcs when treating elongated targets (31,32), elliptical collimator apertures (33) and the use of adjustable rectangular collimation in addition to the basic circular collimators (34,35).

For larger irregular target volumes it is now well established that isocentric, multiple, noncoplanar, conformal fixed fields deliver a homogeneous radiation dose to the tumour and spare more normal tissue than multiple arcs (36). This is achieved by each noncoplanar fixed field being conformally shaped to its beam's eye view of the tumour, thus minimising the volume of normal brain included in the high dose isoenvelope. Isocentric technique ensures homogeneity of dose throughout the target volume and noncoplanar beam arrangements avoid or minimise any overlap between the exit dose from one beam and the entrance dose from another.

The recognition that non-spherical lesions are better treated in this way has lead to the development of stereotactically-guided conformal radiotherapy (SCRT) (37,38,39,40,41). This technique combines the high precision of stereotactic irradiation with the advantages of fractionation and conformal field shaping, which should enable the delivery of higher treatment doses with more effective sparing of
normal tissue. Theoretically this should result in improved rates of local control with an equivalent radiation side effect profile. Alternatively, treating with SCRT and using conventional, established dose fractionation schedules could reduce the incidence of side effects.

1.2 Background and historical perspective

1.2.1 The gamma knife

The gamma knife is a dedicated SRS facility, initially developed by Leksell and colleagues at the Karolinska Institute in Stockholm to enable closed stereotactic neurosurgery to be performed (42). Initial attempts at SRS used multiple collimated 300 kilovoltage (kV) x-ray beams convergent on a common focus (43,44). Subsequently multiple radioactive cobalt (60Co) sources were used, placed in a hemispherical distribution around the patient's head and focused onto a small central point (45). The 201 individual 60Co sources that comprise the radiation source in commercially available equipment (the gamma unit or gamma knife) are contained within a hemispherical cast steel shell (Plate 1). Each source is 1 millimetre (mm) in diameter and 20 mm in length and is aligned radially towards the isocentre. Each 60Co source undergoes primary collimation within the casting through a two-stage tungsten collimator, the second of which is sloped, opening to a beam 7.2 mm in diameter (46). Final collimation is achieved through one of four helmets each containing 201 circular holes of uniform diameter, which when docked align precisely with the 60Co sources (Plates 1 & 2; Figure 1.1).
Plate 1: Leksell gamma unit and collimator helmet.
Plate 2: Patient fitted into collimator helmet prior to treatment.
In the Leksell gamma knife, the central ray is inclined at an angle of 55 degrees to the patient treatment table. The patient’s head is supported in an inner helmet (D), docked to the source array (A), within a hemispherical shield (C). The sources extend over a ±48-degree angle along the cephalocaudal direction and ±80 degrees along the right-to-left direction. The outer structure (B) and retractable shutter (E) provide shielding from the gamma radiation for medical personnel.
The irradiated high dose volume is near spherical and its size is governed by the diameter of the holes in the collimating helmet which correspond to projected field sizes of 4, 8, 14 or 18 mm. As the gamma knife has no moving parts, once the patient, helmet and source assembly have been locked into place, the mechanical precision of the isocentric focus is ±0.3 mm (47).

The dose distribution produced by using all 201 sources together has the shape of a sphere minimally elongated in the craniocaudal or z dimension. In this way different size spherical target volumes can be conformed to, whilst minimising dose to surrounding normal tissue. To treat targets larger than 20 mm it is necessary to add together dose distributions from two or more isocentres, resulting in additional dose inhomogeneity due to both overlap and underlap.

The base ring of the gamma knife is rigidly fixed to the patient's skull for immobilisation during imaging and treatment. Both procedures are usually performed on the same day, although it is possible to leave the base ring attached to the patient for up to six days, enabling a short fractionated radiotherapy schedule to be given (48). The right-to-left (x), anteroposterior (y) and craniocaudal (z) stereotactic coordinates of the target are determined by imaging the patient with a stereotactic frame attached to the base ring. The frame is then removed and treatment planning undertaken to calculate the coordinates of the isocentre(s). For treatment the base ring is fitted to the inner helmet of the gamma knife through adjustable arms that contain slide-adjustable socket bearings
(Plate 2). The socket bearings accept the trunnions (axis rods) of the collimator helmet and the sockets are adjusted to set the \( y \) and \( z \) coordinates. The \( x \) coordinate is set by adjusting the trunnions (19,49). The desired isocentre of the target is now positioned at the centre of the collimator helmet which, when docked with the hemispherical source array, is the focal point of the gamma-ray beams (Figure 1.1).

1.2.2 The linear accelerator (linac)

The potential for using the linac to produce a small precise isosphere of high dose radiation suitable for radiosurgery was recognised and developed by a number of groups including Betti's in Buenos Aires (50), Colombo's in Vicenza, Italy (51), Sturm and Schlegel's in Cologne and Heidelberg (52,53) and others (54,55).

The horizontal axis of gantry rotation intersects the vertical axis of couch rotation and is defined as the isocentre. The intersection of the radiation beam central axis with the mechanical isocentre over the full 360° range of gantry and 180° of couch rotational movement has a standard tolerance of \( \pm 1.0 \) mm. By using the highest mechanical precision components for the couch and gantry bearings and the wall and ceiling mounted lasers and by ensuring that rigorous quality assurance is maintained throughout the production and installation process, as well as on a regular routine basis and prior to each treatment session, the isocentric tolerances can be improved to \( \pm 0.5 \) mm (56). Such measures bring the mechanical accuracy and precision of linac SRS/T very close to the \( \pm 0.3 \) mm of the gamma knife.
The challenge in linac-based SRS/T has been the accurate positioning of the target isocentre at that of the treatment machine. This has been approached in two different ways.

The first is the use of a floor stand which attaches to the turntable assembly of the linac couch (54,57). The floor stand supports a machined plate on a three-dimensional (3-D) orthogonal rectilinear positioning device, which is used to accurately place the calculated isocentre of the target at the linac isocentre in stereotactic space (Figure 1.2). The stereotactic localisation coordinates would have been obtained earlier in the day, from imaging the patient in a rigidly fixed neurosurgical base ring and stereotactic localiser in much the same way as for the gamma knife. Next the patient is comfortably positioned supine on the linac couch with the base ring still fitted and their head supported. The couch height and position is adjusted to precisely align the base ring fixed to the patient's skull flush with the floor stand plate. The base ring is clamped to the plate attached to the floor stand, positioning the intracranial target isocentre accurately at the mechanical/radiation isocentre of the linac ready for treatment (Plate 3). A sophisticated mechanical interlock system is now activated, vital with floor mounted systems to avoid the catastrophic consequences of independent couch movement once the patient is clamped in position. Figure 1.3 illustrates how multiple, noncoplanar arc RS would be given.
The Brown-Roberts-Wells floor stand attaches directly to the turntable assembly that controls couch rotation (60). The floor stand is equipped with three-dimensional rectilinear (xyz) positioning capability. The head ring is bolted to a machined plate. R/L, right to left; A/P, anteroposterior; C/C, caudocephalad.
Plate 3: Patient ready for treatment with base ring clamped to floor stand plate. Note the base ring is pinned to the outer table of the skull.
Figure 1.3: Patient receiving multiple noncoplanar arc radiosurgery using the floor mounted system.

Illustration of the multiarc linac method of radiosurgery. The patient is rigidly attached to the head ring, which is attached to the floor stand. The floor stand is in turn attached to the turntable, which drives the couch rotation. For each fixed couch/turntable angle, the accelerator head travels in an arc in a vertical plane. The beam's central ray traces a path on the patient's head while directed toward the target located at the isocenter. Tracings are indicated showing the path of the central ray for several turntable angles.
The second is to use a couch-mounted head frame system, an approach adopted by a number of groups (52,55,58). This has several advantages including simplicity, a shorter time to convert a linac from routine to stereotactic use, less restriction of the maximum angle of gantry rotation, avoids the need for a complex interlock system and is considerably less expensive.

The development of non-invasive stereotactic frames with a relocation accuracy of ±1 mm has enabled localisation and treatment to be performed in separate sessions and fractionated radiotherapy schedules to be used. In addition they have made sequential multiple imaging with accurate repositioning practical.

The Gill-Thomas-Cosman (GTC) non-invasive relocatable head frame was initially developed for multiple imaging and stereotactic biopsy. It is based on the Brown-Roberts-Wells (BRW) system (59) and its potential for immobilising patients for SRT was recognised and assessed (60). Plate 4 shows Mr Steven Gill wearing the prototype Gill-Thomas stereotactic head frame which he developed with Professor David Thomas at the Institute of Neurology, Queen Square, London. Further adaptation resulted in a robust system suitable for routine clinical use (61).
Plate 4: Mr Steven Gill wearing the prototype Gill-Thomas stereotactic head frame and mouth bite with fiducial rod system attached.
The commercial GTC frame is probably the most commonly used relocatable system worldwide. The standard frame is individualised for each patient by selecting the appropriate size dental tray, mount plate and occipital pad support (Plates 5 & 6). Relocation is achieved via an individually moulded impression of the upper dentition made using a suitable dental impression material. This step is crucial for subsequent precise, accurate frame relocation and it should be undertaken in a dental clinic/laboratory by a practitioner experienced in dental impression work. Plate 7 shows the fully assembled GTC frame being fitted using firm upward pressure, having accurately located the dental impression onto the upper dentition. In edentulous patients a sufficiently good impression is usually obtained to enable the GTC frame to be fitted with adequate precision. The patient in Plate 8 is lying on the linac couch with the GTC frame fitted and located into a couch-mounted support bracket ready for treatment with SCRT. Note the Cerrobend conformal block attached to the end frame for the tertiary collimation of the linac photon beam.

Proponents of floor mounted systems quote the marginally superior mechanical tolerances (±0.5 mm versus ±1.0 mm for couch-mounted systems) as sufficient justification for their use. Whilst there may be some potential clinical benefit in functional and AVM SRS, there is no evidence that such small differences have clinical relevance in oncology, particularly in view of the inherent uncertainties in determining tumour extent from imaging compared with localising an AVM using stereotactic orthogonal film angiography (62).
Plate 5: Components of the commercial GTC stereotactic head frame prior to assembly. Different combinations of head support, mouth bite plate and tray enable the system to be individualised to fit each patient.
Plate 6: Assembled GTC stereotactic head frame.
Plate 7: The GTC stereotactic head frame is fitted by the individual dental impression being pulled firmly upwards onto the upper dentition using the velcro head straps.
Plate 8: Patient in position on the linac couch with the GTC frame fitted and located into the couch-mounted support bracket ready for treatment with SCRT.

Note the Cerrobend conformal block attached to the end frame for tertiary collimation of the linear accelerator treatment beam.
Classical linac SRS uses multiple noncoplanar arcing circular beams shaped by collimators of appropriate diameter to produce a high dose isosphere to envelop the target at the linac isocentre. For each arc in turn, the turntable which controls the orientation of the treatment couch and head support is set to a specific angle according to the treatment plan. The linac photon beam is switched on and treatment delivered at an appropriate dose rate, as the gantry rotates around the isocentre in an arc from the calculated start to finish points. The dose delivered or beam weight for each arc is a proportion of the total treatment dose. Individual arcs may be equally weighted or deliver a different proportion of the total dose depending on how the plan has been optimised and whether the rotational lengths, the total number of degrees each arc comprises, are the same or vary.

A wide variety of techniques have been used, ranging from a single transverse to a combination of eleven noncoplanar arcs (50,63). A single arc treats a cylindrical volume and results in excessive dose to surrounding normal tissue. It has been shown that 3 to 5 arcs give the best dose distribution for the treatment of spherical volumes, in terms of minimizing the volume of normal tissue receiving ≥ 50% of the prescribed dose (64). Dose delivered (beam weight), rotational length and circular or elliptical collimator size may be individualised for each arc to improve conformation of the treatment isodose when the target volume is elliptical or elongated. Further refinement is possible by using different sized collimators for different sectors of the same arc. For more irregular volumes,
static or dynamic rectangular and multileaf collimation can be used with arc therapy.

Dynamic stereotactic radiosurgery (DSRS) involves modification of the standard linac controls to allow simultaneous rotation of the gantry and treatment couch (55,65). The radiation arc produced is not restricted to a single plane in the patient, avoiding parallel beam opposition at and beyond 180° (Figure 1.4). Consequently the gantry rotation extends over a 300° angle and the arc is repeated as often as required to deliver the prescribed dose. The use of the single arc in DSRS restricts the volume of normal tissue irradiated compared with the standard multiple arc technique, as this function is proportional to the total number of distinct degrees of treatment arc. However, because the total integral dose to the cranial tissues is the same, DSRS will irradiate this smaller volume of normal tissue to a somewhat higher dose (66). Whether such differences have clinical relevance is unknown.

The isodose surfaces produced by DSRS follow the shape of the surface of an open cone, folded and focused on the isocentre. The 90% isodose surface is approximately spherical but the lower isodoses are non-spherical shapes (67,68). The unusual dose distribution generated by DSRS in conjunction with dynamic rectangular field shaping can be used to produce cylindrical dose distributions of any orientation (69).
Figure 1.4: In DSRS the gantry rotation extends over a 300° angle and the arc is repeated as often as required to deliver the prescribed dose.

In dynamic stereotactic radiosurgery, the linac head and the couch are rotated simultaneously. The beam central ray traces a path that does not lie in a single plane.
1.2.3 Proton and heavy ion radiosurgery

Cyclotron generated protons or heavy charged particles as an alternative means of localised therapeutic irradiation was first discussed in 1952 (70) and a clinical programme was begun in the mid-1950s by J. H. Lawrence and colleagues at Berkeley (71,72,73). Heavy particle accelerators use the distinct physical properties of helium ions or proton beams to achieve a sharply defined dose distribution. A heavy-ion particle beam causes dense ionisation over a short distance at a depth in tissue, known as the Bragg peak (Figure 1.5), determined by the energy of the entrant beam particles and the energy-absorption characteristics of the tissue. Compared with megavoltage photons, the entrance dose is lower and the exit dose is zero, if scattered radiation is excluded. The depth of the Bragg peak is determined by the particle energy, which can be decreased by placing an appropriate material in the path of the beam before it enters the tissue. The favourable dosimetry, fixed range with increased ionisation in the stopping region, of charged-particle beams over photon beams makes them an attractive modality for treatment with one or a few fractions (74).
Figure 1.5: The Bragg peak.

Depth-dose distributions for a helium-ion beam (65) compared with that from a conventional 4-MV photon (x-ray) beam. The x-ray beam dose distribution exhibits an initial build-up region of approximately 1 cm in extent, then falls exponentially at the rate of about 7% per centimeter, including the effect of beam divergence. The monoenergetic helium-ion beam dose distribution increases slowly with depth in the “plateau” region, until a depth of about 2 cm less than the nominal range of the beam is reached. The dose then increases rapidly with depth to a peak (Bragg peak), then decreases precipitously. To treat a target of thickness of 2 to 4 cm, the helium-ion beam must be energy modulated, which results in an extended Bragg peak. The height of an extended Bragg peak is decreased relative to the plateau as compared with the nonextended Bragg peak.
Initial work in Sweden used a narrow, high-energy proton beam from a synchrocyclotron to produce precise lesions in experimental animals (75) and was the basis for the subsequent treatment of a small number of patients with stereotactic proton-beam irradiation by the same group (13). In Boston a cyclotron was subsequently adapted for clinical radiosurgery, utilising the Bragg peak of the proton-beam dose distribution (76). Later still, the group at Berkeley started to use their synchrocyclotron to treat AVMs with Bragg peak helium ion beam radiosurgery (77,78,79).

All of the above three facilities were located in physics research departments supported by a high level of scientific and technical infrastructure and expertise. The major resource implications of basing a cyclotron or synchrocyclotron in a hospital and their limited clinical application has resulted in very few such facilities being developed. The best known is probably the proton treatment centre at Loma Linda University in California (80). In the United Kingdom (UK) the only proton facility currently available for patient treatment is the Douglas Cyclotron at the Clatterbridge Centre for Oncology. The proton energy is 60 MeV equating to a maximum range of 3 cm which essentially limits its clinical use to the treatment of rare tumours of the anterior chamber of the eye and ocular melanomas. There is general agreement that a UK national centre of radiotherapy excellence based around a high-energy proton facility should be established, to enable the treatment of appropriate deep seated tumours as well as research and development (81,82). Such a centre would provide the opportunity for the UK to build on and develop its own
expertise in this field and put into clinical practice the well
documented potential benefits of proton beam radiation therapy
(83,84,85), the economics of which continue to reduce with the
increasing interest and facilities developing worldwide (86).

The different physical properties of heavy particle beams
make comparisons with photon techniques difficult since the
distribution of dose in the tissues is different and charged
particle beams have a higher relative biological effect (RBE)
than megavoltage photons, which varies with dose per fraction
(87,88). Although the techniques of dose delivery differ, the
methods of patient fixation and target localisation are similar
with each of the systems. The biological effects of photons and
protons are similar but for a small RBE difference of around
1.1 for protons (88,89,90). The proton beam RBE varies
along its path and is highest at the terminal part of the Bragg
peak, which can be modulated to spread out the region over
which the higher RBE occurs (88,91,92). This RBE value of
1.1 is used to convert proton radiotherapy absorbed dose in
Grays to the equivalent megavoltage photon dose and vice
versa, so that treatments can be compared.

A comprehensive review of the gamma knife, linac and
heavy-ion beams for stereotactic radiosurgery with respect to
dosimetry, radiobiology, treatment planning, cost, staffing
requirements and ease of use was undertaken by G. Luxton et
al. (93). They concluded that the linac provides the most
practical and versatile treatment facility.
CHAPTER 2

POTENTIAL WAYS OF OPTIMISING LINEAR ACCELERATOR-BASED STEREOTACTIC RADIOSURGERY/THERAPY (SRS/T) TREATMENT DELIVERY

2.1 Minimising whole body radiation dose 53

2.2 Optimal beam shaping for the treatment of small irregular target volumes 54

2.3 Hypofractionated SRT dose finding study for recurrent glioma 55
2.1 Minimising whole body radiation dose

This clinical thesis contains three distinct but interrelated components. The first addresses the optimisation of SRS/T treatment delivery by considering ways in which technical set up factors can be utilised to minimise radiation dose to the rest of the patient's body.

A typical arrangement for treating a spherical target volume, consisting of five noncoplanar arcing circular beams including a sagittal arc, was compared with one of four arcs in which the sagittal plane was avoided. Using lithium fluoride (LiF) thermoluminescent dosimetry (TLD), whole body measurements were carried out on an Alderson-Rando anthropomorphic phantom.

For the treatment of non-spherical lesions an arrangement of four or more static, noncoplanar, conformal fields may typically include one which exits down the long axis of the torso. Measurements were recorded using an ionisation chamber along several such exit paths, including one to assess the effect of traversing the long axis of a lung.

The results are discussed in the context of subsequent life time risk of radiation-induced malignancy, of particular relevance when treating AVMs or benign tumours in children and young adults.
2.2 Optimal beam shaping for the treatment of small irregular target volumes

The second examines the issue of optimal beam shaping for the treatment of small irregular target volumes with SCRT, comparing individually cast conformal lead blocks (CLB) with beam shaping using a multileaf collimator (MLC).

The aim of SCRT is to deliver the prescribed dose homogeneously to the defined target volume and minimise that received by normal neural structures beyond the treated lesion. Normal tissue sparing was globally assessed by dose volume histogram (DVH) profiles, which are 3-D dose distributions for the normal brain transformed into graphs of percentages of the brain's volume receiving a certain percentage of the isocentre dose, known as isodose bins. These were calculated in 10% dose increments up to 80%, above which 2% dose intervals were used. Global DVH profiles do not take into account the proximity of critical sensitive structures which must be considered when deciding upon the optimal treatment plan. Individual DVH profiles can be generated for specific eloquent structures, to check that the dose that they would receive from a proposed treatment plan would be within acceptable tolerance limits.

A commercially available standard tungsten MLC is a practical and rapid means of shaping fields which requires less time for preparation, quality assurance and delivery of treatment compared with CLB. However, beam shaping is less precise than with CLB because the projected width of each leaf at isocentre, known as the leaf pitch, is 10 mm. The techniques
of conformal blocking using CLB and conventional MLC were compared for a range of model spheroidal and conoidal targets of increasing size.

The hypothesis under test was whether a minimum target size could be defined, for which standard MLC field shaping approximates sufficiently accurately to that achieved with CLB to be clinically acceptable. Differences between the two methods were quantified by the DVH data from treatment plans. Six patient tumour volumes of different shapes and sizes were evaluated in the same way. The results and their potential implications for treating small brain lesions are presented and discussed.

2.3 **Hypofractionated SRT dose finding study for recurrent glioma**

The third comprises clinical data on a cohort of patients treated in a Phase II hypofractionated SRT dose finding study for recurrent glioma, having previously undergone a course of radical conventional external beam radiotherapy at primary diagnosis. The efficacy and toxicity of the regime is reported and discussed in the context of published clinical data for patients treated with the alternative focal treatment techniques of interstitial radiotherapy or SRS.
CHAPTER 3

WHOLE BODY DOSES FROM LINEAR ACCELERATOR BASED STEREOTACTIC RADIOTHERAPY

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3.1 Introduction

Stereotactic radiosurgery/therapy (SRS/T) using a linear accelerator has become a widely used technique for the treatment of intracranial AVM and malignancy. Focal irradiation is delivered with isocentric multiple noncoplanar arcing beams or fixed fields. The optimal arc arrangement has not been clearly defined and a wide variety of techniques have been reported ranging from a single transverse to a combination of 11 noncoplanar beams (50,63). There is little reduction in the volume of normal brain receiving greater than 50% of the isocentre dose outside the target volume, using more than four arcs to treat spherical targets from 10-55 mm diameter (64). Nevertheless, dose to critical structures and along beam exit paths can be reduced by increasing the number of arcs further. One possibility involves five evenly spaced 90° arcs, comprising a sagittal, two transverse, and an intermediate arc placed at 45° to the plane of each transverse and sagittal arc (94). However, this set up is suboptimal as the two transverse arcs are coplanar and consequently their entrance and exit dose paths traverse the same brain tissue.

A truly noncoplanar five arc arrangement is achieved by substituting the two transverse arcs with one at +70° (table angle +20°) and another at -70° (table angle -20°) to the sagittal arc and altering the angle between the intermediate arcs and the sagittal to +40° (table angle +50°) and -40° (table angle -50°) respectively (Figures 3.1 & 3.3b and Table 3.1).
Figure 3.1: Noncoplanar five arc arrangement including sagittal.
Concern over whole body doses from different beam arrangements, especially in children with a non-malignant condition, was the basis for comparing techniques, particularly with and without a sagittal arc.

For the treatment of non-spherical lesions four or more static, noncoplanar, conformal fields result in better sparing of normal brain compared to multiple arcs (36,95). Although the best practical beam arrangement is not defined, Sailer and colleagues used basic principles of solid geometry to define the tetrad (four field) and the hexad (six field) noncoplanar conformal treatment plans for irradiation of the prostate (96). They hypothesised that the most conformal optimised plan should result when radiation beams are maximally separated in three dimensions.

The tetrad beam arrangement is based on the methane molecule (Figure 3.2) and comprises two orthogonal pairs of fields. One pair enters the patient anteriorly and the other posteriorly with each of the four beam entrances maximally separated by 109.5°.

The hexad plan starts with two sets of three planar beams 120° apart in the anatomical transverse plane. The two sets of beams are then offset by 30° so that the beam entrances and exits are separated by 30° (Figure 3.3). Each beam entrance is then rotated 25° superiorly or inferiorly in an alternating fashion, resulting in one set of three beams angled 25° above and the other set angled 25° below the transverse plane. The end result is that each set of three beams, when viewed from a superior or inferior viewpoint are separated by 120° with a beam entrance or exit every 30°.
Figure 3.2: The tetrad beam arrangement is based on the methane molecule and comprises two orthogonal pairs of fields, represented by the pairs of hydrogen atoms.
Figure 3.3: The hexad plan starts with two sets of three planar beams 120° apart in the anatomical transverse plane, offset by 30° so that the entrances and exits are separated by 30°.
However, although the tetrad and hexad plans result in smaller irradiated volumes when compared to their respective planar four and six field counterparts, they did not show clear superiority with respect to improved normal tissue sparing based on DVH profiles for the bladder and rectum. Sailer concluded that the principle of maximum beam separation can be used as a starting point for noncoplanar 3-D planning but that individualisation of beam arrangements is likely to be required, depending upon the tumour site and the proximity and tolerance of adjacent normal tissue structures.

A possible practical field arrangement for irradiating an intracranial tumour may include a beam exiting through the length of the body. Under these circumstances the dose received by organs outside the brain may be an additional factor in deciding upon the most appropriate beam configuration.
3.2 Materials and methods

A comparison of the two multiple arc arrangements (Table 3.1) was performed on a 5MV Philips SL75/5 linac which was used for SRS/T until it was replaced by a 6MV Varian 600C. The measurements for the five arc arrangement were repeated on the 6MV Varian to assess a potential difference in whole body doses and provide a mid-thoracic axial dose distribution. Using LiF TLD, whole body measurements were carried out on a supine Alderson-Rando anthropomorphic phantom. For each experimental treatment exposure, dosimeters were placed in the coronal and sagittal planes on an axial grid of 3 cm separation. Four were taped in a position equivalent to the testes and covered with a sheet of wax to simulate the scrotum. Measurements were made on consecutive axial slices, which were numbered sequentially downwards from slice 1 at the top of the skull, at 2.5 cm separation to mid-thoracic level and at 7.5 cm slice separation for the remainder of the torso. The mid-thoracic axial dose distribution was recorded using a 3 x 3 cm grid of LiF dosimeters covering the area of slice 16. Readings were made on a Teledyne 7300 reader (Teledyne Isotopes, Westwood, New Jersey, USA).
Table 3.1: The 4 and 5 arc beam arrangements

<table>
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<tr>
<th>Technique</th>
<th>Table angle*</th>
<th>Gantry angle**</th>
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<td>Four arc rotation (Figure 3.3a):</td>
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<tr>
<td>Arc 1</td>
<td>20°</td>
<td>20° to 110°</td>
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<tr>
<td>Arc 2</td>
<td>65°</td>
<td>20° to 110°</td>
</tr>
<tr>
<td>Arc 3</td>
<td>-20°</td>
<td>-20° to -110°</td>
</tr>
<tr>
<td>Arc 4</td>
<td>-65°</td>
<td>-20° to -110°</td>
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| Five arc rotation (Figures 3.1 & 3.3b): |              |                |
| Arc 1                          | 20°          | 20° to 110°    |
| Arc 2                          | 50°          | 20° to 110°    |
| Arc 3                          | 90°          | 20° to 110°*** |
| Arc 4                          | -20°         | -20° to -110°  |
| Arc 5                          | -50°         | -20° to -110°  |

When standing at the foot of the table facing the gantry:

* Clockwise table rotation is positive, anticlockwise is negative.

** 0° = gantry vertical; 90° = left lateral; -90° = right lateral.

*** Long sagittal arc = 20° to 160°.
Fixed field and solitary 90° sagittal arc measurements were taken on the 6 MV Varian with the phantom upright (Plate 9). A Farmer graphite walled 0.6 cm$^3$ ionisation chamber and an electrometer (Farmer dosemeter 2570, Nuclear Enterprises, Reading, UK) were used to record central and off axis exit doses at slice levels 13, 16, 18, 21, 23, 25, 28 and 33. The chamber was securely fixed within a specially machined, 2.5 cm thick, body contoured perspex sheet which replaced the relevant slice to maintain a constant exit path length (Plate 10).

With the phantom supine, the isocentre of a spherical target volume situated in the midline in the middle of slice 2 (equivalent to a lesion in the corpus callosum) was positioned at the radiation isocentre using the isocentric localising lasers. A 20 mm and a 40 mm collimator (Radionics Inc, Burlington, Mass, USA) were used with the linac secondary collimating jaws set to a 5 x 5 cm field, to provide two sets of measurements for each arc arrangement. The collimator sizes were chosen to represent the range commonly used in clinical practice. All arcs were 90° long, except for one set of measurements where the sagittal arc was lengthened to 140° to assess the potential effect on the thyroid dose. Each degree of arc was equally weighted and an isocentre dose of 20 Gy was delivered during each experimental exposure, one for each different treatment scenario.
Plate 9: Fixed field and solitary sagittal arc measurements were taken on the 6MV Varian with the Alderson-Rando phantom upright.
Plate 10: The Farmer ionisation chamber fixed within the body-contoured perspex sheet, replacing the relevant slice in the phantom to maintain a constant exit path length.
The leakage radiation dose was determined for each linac using TLD in the humanoid phantom with the 4 arc arrangement (Table 3.1). A single 20 Gy fraction was delivered at the isocentre with secondary collimators fully closed and a lead block placed centrally on the lead tray. The measured leakage radiation dose as a percentage of the dose at isocentre was 0.02-0.03% for the 5MV Philips SL75/5 and 0.005-0.008% for the Varian 600C.

Fixed field measurements were taken with the phantom upright, gantry and couch at 0°, secondary jaws set to 5 x 5 cm, and the 40 mm circular collimator.

To determine the highest density fixed field exit path through the head, neck and thorax, the minimum dose position in the central sagittal plane just below the diaphragm (phantom slice 21) was located with the ionisation chamber. The treatment isocentre was situated in the middle of slice 2 along this vertical axis. The linac light field was used to position the ionisation chamber in the centre of the radiation field and isocentric localising lasers aligned with marks on the phantom ensured its correct relocation before each measurement.

A second set of measurements was recorded using the same set up but with a more anterior isocentre such that the beam exit passed through the pharynx, trachea, thyroid, and main upper airways.

A final set of readings was taken using a central beam axis 4.5 cm to the right of the first. This was sufficiently lateral to include the long axis of the right lung in the beam exit whilst minimising the effect of neck curvature on transmission.
At each fixed field exposure 500 monitor units were given as an applied dose and the ionisation chamber measurements converted to Gray using the relevant calibration factors. To provide a comparative data set 1000 monitor units (to ensure adequate chamber readings) were given using a single 90° sagittal arc and the 40 mm circular collimator to treat the first (maximum density path) and third (lateral) isocentres. A sagittal section isodose plot was generated at each isocentre from CT data of the phantom entered onto a GE Target 1 planning computer, and from these the percentage depth doses at each isocentre determined. For direct comparison with the solitary arc values the fixed field values were doubled. Both sets of results were divided by five to represent body dose values from treatment plans using 5 fixed fields or arcs, as negligible contribution to body dose from the four beams other than the sagittal had been noted in the planned 5 multiple arc experiments.
3.3 Results

3.3.1 Multiple arcs

Figures 3.4-3.7 display isodose plots in the sagittal and coronal planes for each arc arrangement and collimator on the 5 MV Philips linear accelerator. The contribution of the sagittal arc was most noticeable in the coronal plane, causing the isodose lines to penetrate much further along the central axis (Figures 3.4 & 3.6). By increasing the sagittal arc length from 90° to 140° the midline isodoses were less penetrant, thus reducing the thyroid dose (Figure 3.8). A greater reduction in thyroid dose was achieved by using a 4 arc arrangement without a sagittal arc (Figures 3.5 & 3.7), where two arcs exit through the shoulders avoiding the long axis of the body. There was a 3-4 times greater exit dose to the neck and superior mediastinum comparing the five arc with the four arc arrangement. The abdomen received less than 0.2% of the isocentre dose with the 5 arc and less than 0.1% with the 4 arc technique. The pelvis received less than 0.05% of the isocentre dose with either technique.
Figure 3.4a: Coronal isodose lines for a 20 mm collimator using the four arc technique on the 5 MV Philips SL75/5. Isodose line values expressed as a percent of isocentre dose.
Figure 3.4b: Coronal isodose lines for a 20 mm collimator using the five arc technique on the 5 MV Philips SL75/5. Isodose line values expressed as a percent of isocentre dose.
Figure 3.5: Midline sagittal isodose lines for a 20 mm collimator comparing the four and five arc techniques on the 5 MV Philips SL75/5. Isodose line values expressed as a percent of isocentre dose.
Figure 3.6a: Coronal isodose lines for a 40 mm collimator using the four arc technique on the 5 MV Philips SL75/5. Isodose line values expressed as a percent of isocentre dose.
Figure 3.6b: Coronal isodose lines for a 40 mm collimator using the five arc technique on the 5 MV Philips SL75/5. Isodose line values expressed as a percent of isocentre dose.
Figure 3.7: Midline sagittal isodose lines for a 40 mm collimator comparing the four and five arc techniques on the 5 MV Philips SL75/5. Isodose line values expressed as a percent of isocentre dose.
Figure 3.8a: Coronal isodose lines for a 40 mm collimator using the five arc technique with a 90° sagittal arc on the 5 MV Philips SL75/5. Isodose line values expressed as a percent of isocentre dose.
Figure 3.8b: Coronal isodose lines for a 40 mm collimator using the five arc technique with a 140° sagittal arc on the 5 MV Philips SL75/5. Isodose line values expressed as a percent of isocentre dose.
Repeating the measurements using the 5 arc technique on the 6MV Varian 600C gave similar isodose plots with the absolute dose 10-15% higher at thyroid level. The mid-thoracic axial isodose distribution measured using the 20 mm collimator is shown in Figure 3.9 and using the 40 mm collimator in Figure 3.10. A higher central axis exit dose and a greater effect of lung scatter were demonstrated for the 40 mm collimator, resulting in twice the mediastinal dose and a 30-40% greater lung dose.
Figure 3.9: Axial isodose lines at mid-thoracic level for a 20 mm collimator using the five arc technique on the 6 MV Varian 600C. Isodose line values expressed as a percent of isocentre dose.
Figure 3.10: Axial isodose lines at mid-thoracic level for a 40 mm collimator using the five arc technique on the 6 MV Varian 600C. Isodose line values expressed as a percent of isocentre dose.
The effect of a sagittal arc on dose to critical organs is summarised in Table 3.2, with doses expressed as a percentage of the isocentre dose. Each of the mean thyroid dose values was the average of two dosimeter readings, whilst each gonad dose value was derived from four. Lengthening the sagittal arc by 50° reduced the thyroid dose by 25% but it remained considerably higher than with the 4 arc technique.

Multiple repeat TLD powder measurements at thyroid and gonad levels using the 20mm collimator and five arc technique on both linacs were undertaken, to ascertain the errors associated with them. For this study the random errors associated with the TLD powder measurements were +/-3% standard deviation (SD) for the thyroid and +/-10% SD for the gonads, reflecting the different order of magnitude of the doses being recorded.

On the 5MV Philips SL75/5 the mean gonad dose measurements as a percentage of the dose at target isocentre were 0.01-0.02% for the 4 arc technique (Table 3.2). As the leakage radiation dose measured on this linac was 0.02-0.03% and due to the large distance from the isocentre, virtually all of the dose received by the gonads using the 4 arc technique can be accounted for by leakage radiation and to a lesser extent scatter.

Although the gonad dose values of 0.02-0.03% measured for the 5 arc technique on the 5MV Philips SL75/5 are also in the leakage radiation dose range, a contribution from the sagittal arc was detectable (Table 3.2).

The leakage radiation from the 6MV Varian 600C of 0.005-0.008% of the dose at isocentre contributed
approximately one third of the dose at gonad level, the majority being from the sagittal arc.

Table 3.2: Mean organ doses as a percentage of the dose at target isocentre

<table>
<thead>
<tr>
<th>Photon energy</th>
<th>5 MV*</th>
<th>6 MV**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ</td>
<td>Collimator</td>
<td>4 arcs</td>
</tr>
<tr>
<td>Thyroid</td>
<td>20 mm</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>40 mm</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>20 mm</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>40 mm</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testis</td>
<td>20 mm</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>40 mm</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 5MV Philips SL75/5.
** 6MV Varian 600C.
*** Mean organ dose with long sagittal arc length of 140°.
3.3.2 Fixed fields

The fixed beam exiting through the long axis of the phantom gave a tenfold greater dose at all levels including the gonads than the 90° sagittal arc (Figure 3.11).

An additional 30-40% dose increase to organs below the level of the diaphragm was recorded when the fixed beam or sagittal arc traversed the long axis of the right lung (Figure 3.12) or the pharynx and main upper airways of the phantom.

In figures 3.11 and 3.12 the isodose line values are each expressed as a percent of the dose at isocentre, when the 90° arc or fixed field is one of five equally weighted components of a treatment plan comprising five arcs or fixed fields respectively. These scenarios assume that the geometry of the other four arcs or fixed fields is such that they do not contribute to the long axis dose.
Figure 3.11: Coronal isodose lines for central and off-axis 90° sagittal arc using a 40 mm collimator. Isodose line values expressed as a percent of isocentre dose.
Figure 3.12: Coronal isodose lines for central and off-axis fixed field using a 40 mm collimator. Isodose line values expressed as a percent of isocentre dose.
3.4 Discussion

When the linear accelerator was first adapted to deliver SRS/T, a variety of techniques were developed involving up to eleven noncoplanar arcs of rotation. Currently four to six arcs are most widely used. Dose volume histogram analysis of the volume of brain receiving greater than 50% of the isocentre dose when treating a range of spherical targets has shown no advantage to support the routine use of more than four arcs (64). However, the use of five or more arcs will lower the exit dose from each and can help to reduce the dose to critical structures adjacent to the target volume.

Important considerations when deciding upon the optimal beam arrangement include tight conformation and homogeneity of target dose, as well as minimising dose to eloquent intracranial structures and to the rest of the brain. The issue of arc or fixed beam exit through extracranial structures is of less importance but should be considered when treating benign lesions in young patients with a normal or near normal life expectancy after SRS/T.

The Alderson-Rando anthropomorphic phantom and LiF TLD provides an in vitro method for the measurement of radiation dose received by different parts of the body. Potential errors need to be quantified for the particular system used as these are variable. For this study the random errors associated with the TLD measurements were +/-3% SD for the thyroid and +/-10% SD for the gonads, reflecting the different order of magnitude of the doses being recorded.
The results of the whole body dose measurements show significantly higher values throughout the length of the torso when a sagittal arc is used. This was most striking in the thyroid gland dose, which was three to four times higher with five rather than four arcs. The four arc technique with beams exiting through the shoulder girdle is clinically preferable, as this avoids irradiating the thyroid gland and other centrally placed organs in which relatively low doses of radiation can induce benign tumours or carcinomas (97,98,99,100). The risk of sarcoma induction in the soft tissues or bones of the shoulders is likely to be extremely low, as a high radiation dose is probably required (101,102). However, there may be an issue with respect to carcinoma induction in the axillary tail of the breast in women (102).

Central dose can also be reduced by using a higher number of longer arcs (103). When it is of clear benefit to include a sagittal or near sagittal arc in a treatment plan, an alternative to increasing the number and length of arcs would be to interrupt the sagittal arc over the higher risk exit region. The 355°-5° apical sector was noted to deliver more than 95% of the body dose and could be excluded in clinically appropriate situations.

Lengthening the sagittal arc also reduced the central dose but this required the gantry to rotate into the undercouch position, which may not be possible with stereotactic techniques in which the head is supported on a floor stand separate from the treatment couch (54).

Four to six fixed conformal fields may provide the optimum way of minimising the volume of normal brain
irradiated to more than 50% of the isocentre dose outside the target volume for larger non-spherical targets (36,95). The static beam measurements recorded show the importance of considering the path of a beam which exits down or near to the long axis of the body and the radiation dose delivered along it. The dose to thyroid and the rest of the body should be taken into account in appropriate cases when deciding upon the optimal treatment plan.

The primary reason for considering dosimetry outside the brain is the risk of radiation-induced second malignancy. The most likely site for such tumours following SRS/T would be intracranially, although so far no cases have been reported. This absence probably reflects the relatively short follow up of the majority of this patient group and over the next 10-20 years the risk may become apparent. The combination of smaller target volumes and steep dose fall off may result in a lower incidence than described following fractionated radiotherapy for pituitary adenomas (104,105).

Brada reported on a cohort of 334 patients with pituitary adenoma who received fractionated radiotherapy between 1962 and 1986 at the Royal Marsden Hospital (RMH), most of whom had undergone neurosurgical biopsy or debulking beforehand (104). The median dose of radiotherapy was 45 Gy in 25-30 daily fractions and treatment was delivered using a three field technique with an anterior oblique and two lateral fields. A breakdown of the cohort showed that 7 patients received less than 40 Gy, 104 patients 40-44 Gy, 146 patients 45-49 Gy and 77 patients 50 Gy or more. The start date of radiotherapy was designated as the date of entry into the study and there were a
total of 3760 person years of follow up, with over three quarters of the cohort being at least 5 years and over a half at least 10 years out from treatment. Five patients developed a second intracranial tumour; two an astrocytoma, two a meningioma and one a meningeal sarcoma. Three of these tumours were diagnosed 5-9 years, one 10-19 years and one over 20 years after radiotherapy to the pituitary. The cumulative risk of developing a second brain tumour over the first 10 years after radiotherapy was 1.3% (95% confidence interval [CI] 0.4% to 3.9%) and over 20 years was 1.9% (95% CI 0.7% to 5.0%). The relative risk of a second brain tumour compared with the risk of a brain tumour in the normal population was 9.38 (95% CI 3.05 to 21.89). There was insufficient information to provide evidence of either an increasing or a decreasing trend in risk by time since radiotherapy. However, both astrocytomas occurred relatively soon after treatment (six and seven years respectively) whereas the meningeal tumours occurred later.

Tsang reported the experience of the Princess Margaret Hospital in Toronto using a similar retrospective cohort study, in which four of 305 patients irradiated for pituitary adenoma developed gliomas, a relative risk of 16 for a second brain tumour (105). In conjunction with the data from RMH there seems to be a small but definite risk of developing a second brain tumour following radiotherapy for pituitary adenoma.

However, no such incidence of second brain tumour was seen in the cohort of 296 patients treated with pituitary irradiation in Edinburgh between 1962 and 1990, reported by Bliss (106). From 1962 to 1986, the treatment received by 221
patients comprised 35 Gy in 15 daily fractions using 4 MV photons delivered using two lateral opposed fields. After 1986 a three field technique, an anterior and two opposed laterals, was used and the dose fractionation schedule changed to 45 Gy in 25 daily fractions. There was a total of 2527 patient years follow up with a median of 8 years (range 1 to 28 years). In one patient a 5 mm benign meningioma was diagnosed one year after pituitary irradiation but considered to be an incidental finding and not related to treatment. A second patient developed central nervous system lymphoma, six years after chemotherapy for stage III mixed cellularity Hodgkin's disease, which presented six months after radiotherapy for pituitary adenoma. This case was also unrelated to the pituitary irradiation. It is likely that with continuing follow up cases of second brain tumour will be diagnosed in this cohort, as the number of events reported in the other two studies is small and the confidence intervals wide.

When ionising radiation interacts with matter energy is absorbed, mainly by the process of ionisation. The mean energy imparted by ionising radiation per unit mass at a point in the body is known as the absorbed dose in tissue. The unit of absorbed dose is the gray, which is one joule per kilogram.

Radiation energy absorbed in living tissues initiates physical and chemical reactions which result in biological changes. When relating the absorbed dose to specific radiation-induced health effects, it is important to identify the particular body tissues of interest in which the absorbed doses have occurred.
To be able to compare the effect of absorbed dose in different tissues, a quantity is required which reflects the modifying effects of different types of radiation and the relative radiosensitivity of the irradiated tissues and organs. This quantity is defined as the absorbed dose weighted by a radiation weighting or quality factor, which depends on the type and energy of the radiation incident upon the body. For low linear energy transfer radiation such as photons, electrons and gamma rays this quality factor is unity. This quantity is then further weighted by a tissue weighting factor, which represents the relative contribution of the tissue or organ detriment to the total detriment, as if the whole body were uniformly irradiated. This doubly weighted absorbed dose is called the effective dose. The unit of effective dose is the sievert (Sv) which is one joule per kilogram (100).

There is probably no threshold of absorbed dose for the initiation of some deleterious biological changes. Consequently, even small absorbed doses in tissues may increase the risk of cancer and small absorbed doses in the gonads may induce mutations or chromosomal changes. These types of effect are known as stochastic. The probability of their occurrence increases with the absorbed dose, whereas the severity of the effect is independent of the dose (100).

Thyroid malignancy is well established as a late complication of thyroid irradiation and the principle of 'as low as reasonably achievable' (ALARA) should be applied where practical (97). Exposure before the age of five years may result in three times the risk of thyroid cancer than following exposure in adulthood, due to the long latency associated with
radiation-induced cancers (98,99,100). Females are two to three times more likely to develop both naturally occurring and radiation-induced thyroid cancers (98,99). Applying these risk coefficients to a general population comprising equal numbers of both sexes of adults and children, and using an absolute risk estimate of 2.5 cases per $10^4$ person-years Gray in children exposed to external photon irradiation in childhood, the lifetime incidence of fatal thyroid cancer would be 7-8 cases per $10^4$ person-years Gray (98,99).

However, it is well recognised that the ratio of total thyroid cancers to fatal thyroid cancers is 10:1 and consequently the lifetime incidence of thyroid cancer would be 70-80 cases per $10^4$ person-years Gray (98,99). Most cases of radiation-induced thyroid cancers are well differentiated tumours which carry a good prognosis with appropriate clinical management (98,99,107,108). The absolute risk of benign thyroid nodules following external radiation therapy in childhood is estimated to be 10.3 cases per $10^4$ person-years Gray (98,99).

Age is the critical factor in determining radiation risk. Using a multiplicative risk-projection model, the International Commission on Radiological Protection (ICRP) estimated 7.3% per Sievert (Sv) lifetime risk of excess fatal cancers for effective dose from medical exposure to ionising radiation when averaged over the whole population (100). Using age-specific coefficients, adults (20-69 years) have an excess fatal cancer risk of 5.5% and children (0-19 years) 11% per Sv.
From ICRP 60 the probability of fatal cancer developing in different organs is shown in Table 3.3.

### Table 3.3: Probability of fatal cancer developing in different organs per 1000 people per Sievert based on ICRP 60

<table>
<thead>
<tr>
<th>Organ</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>0.8</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>3.0</td>
</tr>
<tr>
<td>Breast</td>
<td>2.0</td>
</tr>
<tr>
<td>Lung</td>
<td>8.5</td>
</tr>
<tr>
<td>Stomach</td>
<td>11.0</td>
</tr>
<tr>
<td>Colon</td>
<td>8.5</td>
</tr>
</tbody>
</table>

These values have been used to calculate the risk from a single 20 Gy fraction of SRS as used for the treatment of AVMs (Table 3.4). As thyroid malignancy is considered fatal in only 5-10% of cases, the incidence of radiation-related cancer may therefore be at least tenfold greater using risk estimates of excess fatal cancers.
Table 3.4: Nominal risk of fatal cancer after a 20 Gy fraction using 5 MV photons, four or five arcs and a 20 or 40 mm collimator

<table>
<thead>
<tr>
<th>Organ</th>
<th>Dose range in milliSv.</th>
<th>Risk per 10,000 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>30-400</td>
<td>0.24-3.20</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>20-100</td>
<td>0.60-3.00</td>
</tr>
<tr>
<td>Breast</td>
<td>20-75</td>
<td>0.40-1.50</td>
</tr>
<tr>
<td>Lung</td>
<td>10-100</td>
<td>0.85-8.60</td>
</tr>
<tr>
<td>Stomach</td>
<td>10-60</td>
<td>1.10-6.60</td>
</tr>
<tr>
<td>Colon</td>
<td>3-20</td>
<td>0.26-1.70</td>
</tr>
<tr>
<td>Gonads</td>
<td>2-10</td>
<td>0.20-1.00*</td>
</tr>
</tbody>
</table>

* Risk of severe genetic defect.

The exit dose delivered to an ovary as compared to the testes from a static field traversing the long axis of the body could be significantly higher, due to the different anatomical locations of the gonads in females and males. Consider an off axis fixed field exiting through the long axis of a lung and passing through an ovary. This would result in an absorbed dose 30-40% higher than if the field were exiting down the central axis of a male torso, when the greater central tissue density would have absorbed more dose before the beam reached the scrotum. If the fixed field was part of a five field plan delivering a total dose of 55 Gy at isocentre in 33 daily fractions, in the above treatment scenarios the ovary would be
exposed to a total dose of 0.275 Gy and the testes to a total dose of 0.183 Gy.

The ICRP estimates that the excess risk for serious hereditary defects for all subsequent generations after exposure to be 1% per Sv (100). On the basis of the data presented here, SRS/T can be considered to carry a negligible risk of inducing serious germline defects provided a fixed field exiting down the long axis of the body is avoided.

In summary, attention should be paid to the beam exits when planning SRS/T for treating AVMs or benign tumours, especially in children. The avoidance of a sagittal arc or the use of longer, more numerous arcs reduces exit dose, minimising the amount of transmitted radiation received by the thyroid. When multiple static conformal beams are used, avoiding a beam exiting through the long axis of the torso will help to minimise the radiation dose to the rest of the body. However, extracranial doses should only be considered if relevant to the clinical context of the disease and an optimal isodose distribution over the target volume is still achievable.
CHAPTER 4

COMPARISON OF A MULTILEAF COLLIMATOR WITH DIVERGENT LEAD ALLOY BLOCKS FOR THE DELIVERY OF STEREOTACTICALLY-GUIDED CONFORMAL RADIOTHERAPY

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4.1 Introduction

Stereotactically-guided conformal radiotherapy (SCRT) is a technique for delivering localised irradiation to non-spherical targets in the brain using noncoplanar, conformal fixed fields rather than multiple noncoplanar arcs (36,109). Three, four or six such fields are used to treat primary and secondary tumours at a variety of intracranial sites. Dose volume histogram (DVH) profiles summarise the 3-D dose distribution received by the normal brain and when transformed into graphs of percentages of the brain's volume receiving a certain percentage of the isocentre dose, enable direct comparison of treatment plans generated for different beam arrangements. These can be helpful in the selection of the best treatment plan but the number of beams and their orientation for an individual case are also determined by factors such as tumour position and the proximity of sensitive structures. In addition there are clinical factors to consider which include the total dose and fractionation schedule and whether treatment intent is radical or palliative.

Conventional methods of beam shaping for conformal radiotherapy delivery include the standard multi-leaf collimator (MLC), mini-MLC, micro-MLC and lead alloy conformal blocks (CLB). At the Royal Marsden Hospital (RMH) accurately cast Cerrobend (lead-bismuth-tin-cadmium alloy) CLB have been used to treat planning target volumes (PTVs) with a maximum dimension ranging from 30 to 60 mm. The alternative was a commercially available standard tungsten MLC, a practical and rapid means of shaping fields.
which requires less time for preparation, quality assurance and delivery of treatment (110). Beam shaping is less precise with the standard MLC than with CLB, because the projected width of each leaf at isocentre, known as the leaf pitch, is 10 mm (Figure 4.1). A mini-MLC would conform more precisely to irregular outlines due to its narrower leaves, which typically have a leaf pitch of 3 mm (Figure 4.2). A micro-MLC could improve the conformation further, as its leaf pitch is half that of the mini-MLC (Figure 4.3). At the time this study was undertaken neither of these more sophisticated beam shaping devices were available at our institution for direct comparison with the CLB system.

The aim of high precision localised irradiation techniques, which include stereotactic radiosurgery/therapy (SRS/T) and SCRT, is to minimise irradiation of normal neural structures beyond the treated lesion. Although normal tissue sparing is globally assessed by DVH profiles, the proximity of and dose delivered to critical sensitive structures must also be considered.

The techniques of conformal blocking using CLB and conventional MLC were compared for a range of model targets of increasing size, using DVH to try to define a minimum target size for which standard MLC field shaping is sufficiently accurate to be clinically acceptable. Differences between the two methods were quantified by the DVH data from treatment plans for the model spheroidal and conoidal target volumes. In addition six patient tumour volumes were evaluated. The results and their potential implications for treating small brain lesions are presented and discussed.
Figure 4.1: Beam shaping using a standard MLC with a leaf pitch of 10.0 mm at isocentre. The maximum field size is 40 cm x 40 cm. (Varian, Palo Alto, California, USA)
Figure 4.2: Beam shaping using a mini-MLC whose 14 innermost leaves have a leaf pitch of 3.0 mm at isocentre. The next three leaves have a leaf pitch of 4.5 mm and the outermost three one of 5.5 mm. The maximum field size is 10 cm x 10 cm. (BrainLAB’s m3 mMLC, Munich, Germany)
Figure 4.3: Beam shaping using a micro-MLC with a leaf pitch of 1.7 mm at isocentre. The maximum field size is 7 cm x 7 cm. (MRC Systems’, Heidelberg, Germany)
4.2 Materials and methods

4.2.1 Model volumes

A water-filled human skull phantom (Radionics Inc, Burlington, Mass, USA) containing a sphere, a cone, a cylinder and a rectangle, was imaged in the Gill-Thomas-Cosman (GTC) relocatable frame (Radionics Inc, Burlington, Mass, USA) on a Somatom DR2 CT scanner using a sequential slice thickness of 3 mm. The CT data was transferred to a GE Target 2 planning computer with MLC field shaping software and the sphere and cone were outlined manually. To standardise the maximum dimensions of the sphere (24 mm) and cone (30 mm) a computer generated 3 mm margin was added in the axial plane to the sphere outline set. Manual extrapolation was required in the superior-inferior (z) direction to compensate for the lack of a true 3-D growing facility in this dimension. The resultant volumes were used as PTVs for sphere 1 and cone 1.

To produce a volume for sphere PTV 1 and cone PTV 1 which could be used as a direct beam's eye view (BEV) template for manually drawing CLB portals with the mouse and automatically fitting the MLC field shaping software, a 3 mm margin was added in all dimensions. This accounted for the distance from the 50% field edge to the 90% isodose surface and is dependent on the penumbra of the linear accelerator and beam shaping device. The "template" planning volumes for sphere 2 and cone 2 were produced by adding a further 3 mm margin and this process was repeated twice more to provide the two incremental sets of composite volumes.
Table 4.1: Dimensions of the model PTVs

<table>
<thead>
<tr>
<th></th>
<th>Diameter* mm</th>
<th>Height mm</th>
<th>Volume cm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spheroid 1</td>
<td>30</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td>Spheroid 2</td>
<td>36</td>
<td>-</td>
<td>19</td>
</tr>
<tr>
<td>Spheroid 3</td>
<td>42</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>Spheroid 4</td>
<td>48</td>
<td>-</td>
<td>46</td>
</tr>
<tr>
<td>Conoid 1</td>
<td>27</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>Conoid 2</td>
<td>38</td>
<td>36</td>
<td>16</td>
</tr>
<tr>
<td>Conoid 3</td>
<td>50</td>
<td>42</td>
<td>32</td>
</tr>
<tr>
<td>Conoid 4</td>
<td>60</td>
<td>48</td>
<td>54</td>
</tr>
</tbody>
</table>

* Refers to diameter of base for conoids.

Due to manual extrapolation the spheres and cones generated were not geometrically perfect, which is reasonable for the simulation of clinical situations. As a result the PTVs in Table 4.1 are different from the values that one would obtain using the geometric formula for a sphere or a cone. Consequently the actual PTVs used in this study are spheroidal and conoidal rather than true spheres and cones. Diagram 4.4 shows conoid 1 and the sagittal isodose distributions resulting from treatment using the noncoplanar four field beam arrangement described on page 105. Note the blunt apex of the conoid resulting from manual extrapolation.
Figure 4.4: Conoid 1 demonstrating the blunt apex resulting from manual extrapolation.

Note the effect of the 10 mm MLC leaf pitch on the 90% isodose surface shown in red.
4.2.2 Beam arrangements

The spheroids were planned with three non-opposing, coplanar beams at 120° to each other and the couch at 0°, with a fourth field perpendicular to this plane entering through the skull vertex.

The conoids were planned using a tetrad beam arrangement, comprising three noncoplanar beams arranged at 120° to each other, with the couch at 18° for gantry angles of 1-180° or 342° for gantry angles of 181-360°. The fourth apical beam was aligned with the long axis of the conoid, which was parallel to the z direction.

For each treatment plan CLB portals were drawn using BEVs of the template planning volume and a full dose calculation carried out to generate an isodose distribution which was normalised to 100% at isocentre. Using the template planning volume for constructing the CLB portals ensured that the PTV was enclosed by the 90% isodose line, reflecting our standard practice for treating solitary brain metastases or small recurrent gliomas (111,112).

In each case the same set of BEVs were used to obtain an equivalent treatment plan replacing the CLB portals with best fit MLC fields generated by the MLC shaper software utilising the intrusive or "transecting" leaf fitting technique (113). This convention involves positioning the MLC such that for each individual leaf the area of overlap at the field edge equals the area of underlap (Figure 4.5). A full dose calculation was carried out and the distribution normalised to 100% at isocentre as for CLB.
Intrusive leaf-fitting technique. The leaf edges are ‘chamfered’ at 45° and then brought in to just touch the outline.
4.2.3 Patient volumes

Six patients previously treated with SCRT were used to assess the effect of using the MLC in place of CLB. Their lesions varied in maximum dimension from 35-60 mm, with PTVs of 31-114 cm$^3$ (Table 4.2). Each patient had undergone a CT brain scan in the GTC frame and the data transferred to a GE Target 1 planning computer. The gross tumour volume (GTV) had been outlined manually on the axial CT slices by the clinical oncologist and optimal BEVs selected within constraints imposed by adjacent critical structures. An appropriate margin (including that needed to account for penumbra) was added manually to produce the PTV, the exact size of which depended on the proximity of adjacent critical structures, tumour type, clarity of delineation on the CT scan and treatment intent. Each BEV of the PTV was digitised into a computerised block cutter (Par Scientific ACD4) to produce precise high density styrofoam moulds from which Cerrobend blocks were cast. The treatment plan was generated by digitising each BEV of the PTV back into the planning computer with details of gantry, couch, and collimator rotations, and optimising the beam weighting to achieve homogeneous coverage of the target volume.

Comparison of CLB and MLC was made on original planning CT data transferred onto a GE Target 2 system and planned for four fixed conformal beams. For each plan CLB portals were constructed and best fit MLC fields generated as described above, and used in the calculation of isodose distributions which were each normalised to 100% at isocentre.
Table 4.2: Dimensions of the patient GTVs and PTVs

<table>
<thead>
<tr>
<th>Patient's tumour and dimensions*</th>
<th>GTV**</th>
<th>Margin</th>
<th>PTV**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Meningioma 34 x 35 x 40</td>
<td>11</td>
<td>7 mm</td>
<td>31</td>
</tr>
<tr>
<td>2. Astrocytoma 21 x 27 x 57</td>
<td>6</td>
<td>10 mm</td>
<td>31</td>
</tr>
<tr>
<td>3. Glioblastoma 48 x 44 x 44</td>
<td>28</td>
<td>4 mm</td>
<td>46</td>
</tr>
<tr>
<td>4. Pituitary 31 x 35 x 33</td>
<td>14</td>
<td>7 mm</td>
<td>52</td>
</tr>
<tr>
<td>5. Optic glioma 20 x 40 x 60</td>
<td>17</td>
<td>8 mm</td>
<td>70</td>
</tr>
<tr>
<td>6. Meningioma 58 x 58 x 44</td>
<td>42</td>
<td>10 mm</td>
<td>114</td>
</tr>
</tbody>
</table>

* Measurements in mm taken from cardinal plane printouts of GTV at isocentre, recorded as maximum transverse (xy) x coronal (xz) x sagittal (yz).

** GTV and PTV values in cm$^3$. 
4.2.4 Dose volume histograms

Whole brain differential DVHs which included the PTV, were generated for each plan on the GE Target 2 treatment planning system using a 3 x 3 x 3 mm calculation matrix. The value for each PTV in cm$^3$ was obtained using a 2 x 2 x 3 mm matrix. Isodose bins were calculated in 10% increments up to 80%, above which 2% intervals were used. The maximum rounding error for the volume in each isodose bin was $+/-0.05\%$ of the whole brain volume and constituted the greatest source of inaccuracy in the calculations. Cumulative DVH values were calculated for each model and patient PTV for each technique by adding up the isodose bin values greater than 50% and 80% and converting to actual volumes. To obtain normal brain volumes receiving greater than 50% and 80% of the isocentre dose, the relevant PTVs were subtracted. The excess volume of normal brain irradiated with MLC compared to CLB was expressed as percentage excess over CLB volume:

$$\% \text{ excess volume} = \frac{\text{MLC} - \text{CLB}}{\text{CLB}} \times 100$$

where MLC and CLB are the volumes of normal brain irradiated by each technique to greater than 50% or 80% of the isocentre dose.
4.3 Results

The normal brain volume receiving greater than 50% and 80% of the dose at isocentre using each field shaping technique for the spheroids and conoids is shown in Table 4.3, and for the six patients in Table 4.4. Table 4.5 summarises all these values as the percentage excess volume of normal brain irradiated had MLC been used in place of CLB, and for the six patients this information is displayed graphically in Figure 4.6.

For the spheroids, using the MLC in place of CLB would irradiate 23-35% more normal brain to greater than 50% and 12-48% more to greater than 80% of the isocentre dose. Spheroids 1 and 3 were least well conformed to using the MLC, probably reflecting a worse 'goodness of fit' relationship between the shape and size of the BEV and the finite 1 cm MLC leaf widths. This would account for the jumps seen in the data which, nevertheless, suggest a trend towards a decrease in the volume of excess normal brain irradiated when MLC replaces CLB as the size of the PTV increases (Table 4.5). This trend was confirmed using the Wilcoxon signed-ranks nonparametric test.

For the conoids, MLC field shaping in place of CLB would irradiate 10-17% more normal brain to greater than 50% and 0-20% more to greater than 80% of the isocentre dose. The result for conoid 1 is partly artefactual because of the small size of the PTV resulting in an undulating 90% isodose envelope which just transgressed the target volume at a number of points, whereas the CLB plan produced a consistent 90% isodose envelope and maintained a uniform 2 mm margin.
As a consequence the excess normal brain irradiated using the MLC to treat conoid 1 was underestimated.

**Table 4.3: Normal brain volume (cm³) receiving greater than 50% and 80% of the dose at isocentre, using each field shaping technique for the spheroids and conoids**

<table>
<thead>
<tr>
<th>Target</th>
<th>Technique</th>
<th>Volume&gt;50%</th>
<th>Volume&gt;80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spheroid 1</td>
<td>CLB</td>
<td>28.4</td>
<td>8.7</td>
</tr>
<tr>
<td></td>
<td>MLC</td>
<td>38.2</td>
<td>12.9</td>
</tr>
<tr>
<td>Spheroid 2</td>
<td>CLB</td>
<td>35.8</td>
<td>11.9</td>
</tr>
<tr>
<td></td>
<td>MLC</td>
<td>44.2</td>
<td>13.3</td>
</tr>
<tr>
<td>Spheroid 3</td>
<td>CLB</td>
<td>52.9</td>
<td>16.4</td>
</tr>
<tr>
<td></td>
<td>MLC</td>
<td>67.0</td>
<td>22.0</td>
</tr>
<tr>
<td>Spheroid 4</td>
<td>CLB</td>
<td>98.7</td>
<td>45.3</td>
</tr>
<tr>
<td></td>
<td>MLC</td>
<td>121.2</td>
<td>50.9</td>
</tr>
<tr>
<td>Conoid 1</td>
<td>CLB</td>
<td>42.2</td>
<td>16.5</td>
</tr>
<tr>
<td></td>
<td>MLC</td>
<td>47.8</td>
<td>16.5</td>
</tr>
<tr>
<td>Conoid 2</td>
<td>CLB</td>
<td>74.0</td>
<td>27.6</td>
</tr>
<tr>
<td></td>
<td>MLC</td>
<td>86.6</td>
<td>33.2</td>
</tr>
<tr>
<td>Conoid 3</td>
<td>CLB</td>
<td>118.4</td>
<td>46.7</td>
</tr>
<tr>
<td></td>
<td>MLC</td>
<td>135.2</td>
<td>48.1</td>
</tr>
<tr>
<td>Conoid 4</td>
<td>CLB</td>
<td>177.0</td>
<td>67.0</td>
</tr>
<tr>
<td></td>
<td>MLC</td>
<td>195.0</td>
<td>71.0</td>
</tr>
</tbody>
</table>
Table 4.4: Normal brain volume (cm$^3$) receiving greater than 50% and 80% of the dose at isocentre, using each field shaping technique for the six patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Technique</th>
<th>Volume &gt; 50%</th>
<th>Volume &gt; 80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>CLB</td>
<td>62</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>MLC</td>
<td>81</td>
<td>33</td>
</tr>
<tr>
<td>2.</td>
<td>CLB</td>
<td>47</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>MLC</td>
<td>59</td>
<td>14</td>
</tr>
<tr>
<td>3.</td>
<td>CLB</td>
<td>158</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>MLC</td>
<td>174</td>
<td>26</td>
</tr>
<tr>
<td>4.</td>
<td>CLB</td>
<td>93</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>MLC</td>
<td>101</td>
<td>16</td>
</tr>
<tr>
<td>5.</td>
<td>CLB</td>
<td>108</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>MLC</td>
<td>149</td>
<td>35</td>
</tr>
<tr>
<td>6.</td>
<td>CLB</td>
<td>219</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>MLC</td>
<td>265</td>
<td>77</td>
</tr>
</tbody>
</table>
Table 4.5: Percentage excess volume of normal brain receiving greater than 50% and 80% of the dose at isocentre, if MLC had been used in place of CLB for the spheroids, conoids and six patients

<table>
<thead>
<tr>
<th>Target</th>
<th>% age excess to &gt;50%</th>
<th>% age excess to &gt;80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spheroid 1</td>
<td>35%</td>
<td>48%</td>
</tr>
<tr>
<td>Spheroid 2</td>
<td>23%</td>
<td>12%</td>
</tr>
<tr>
<td>Spheroid 3</td>
<td>27%</td>
<td>34%</td>
</tr>
<tr>
<td>Spheroid 4</td>
<td>23%</td>
<td>12%</td>
</tr>
<tr>
<td>Conoid 1</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>Conoid 2</td>
<td>17%</td>
<td>20%</td>
</tr>
<tr>
<td>Conoid 3</td>
<td>14%</td>
<td>3%</td>
</tr>
<tr>
<td>Conoid 4</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Patient 1</td>
<td>31%</td>
<td>57%</td>
</tr>
<tr>
<td>Patient 2</td>
<td>26%</td>
<td>27%</td>
</tr>
<tr>
<td>Patient 3</td>
<td>10%</td>
<td>13%</td>
</tr>
<tr>
<td>Patient 4</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>Patient 5</td>
<td>38%</td>
<td>119%</td>
</tr>
<tr>
<td>Patient 6</td>
<td>21%</td>
<td>43%</td>
</tr>
</tbody>
</table>
To avoid small parts of the target volume receiving less than 90% of the dose at isocentre would require a small outward adjustment to be made to the position of the MLC leaves causing the impingement.

The variation in 'goodness of fit' between the dimensions and shape of the BEV and the MLC leaves required to treat the conoids, like the spheroids, probably explains why a clear cut relationship between increase in volume and decrease in percentage excess volume of normal brain irradiated using MLC in place of CLB is not seen (Table 4.5).

Had the MLC been used instead of CLB for the six patients studied, 9-38% more normal brain would have received greater than 50% and 0-119% more greater than 80% of the isocentre dose (Figure 4.6). The wider ranges of values reflects the diversity of shape of the different tumour volumes. As one would anticipate the target volumes that were relatively straight sided and approximated a rectangular or cuboidal shape were best dealt with by the MLC. On the information obtained from this small sample of patients, shape appears to be a more important determinant of equivalence between MLC and CLB than size.
Figure 4.6: Percentage excess volume of normal brain receiving greater than 50% and 80% of the dose at isocentre, if MLC had been used in place of CLB for the six patients.

Note that for patient 4 with a PTV of 52 cm$^3$ there was no measurable percentage excess volume of normal brain receiving greater than 80% of the dose at isocentre had MLC been used in place of CLB.
4.4 Discussion

Conforming radiation fields to multiple noncoplanar BEVs of a three dimensional target minimises the volume of normal tissue receiving a clinically significant radiotherapy dose. Potential benefits include a reduced side effect profile for conventional treatment schedules or the possibility of dose escalation, aiming at higher local control or cure rates for a similar risk of both early and late treatment related morbidity.

This principle of conformal radiotherapy has been tested in patients with prostate cancer. A reduction in treatment related morbidity using conventional radiotherapy schedules has been reported (114,115,116) and dose escalation achieved, apparently without excess morbidity (117). Longer follow up is necessary to assess potential benefit in local control, particularly in view of uncertainties regarding optimal patient immobilisation (118) and changes in the position of the target volume with bowel movement and bladder filling (119).

The problems of immobilisation and target volume movement in the evaluation of conformal radiotherapy in the pelvis are considerably less of an issue in the brain. However, intracranial structures and tumours do move to some degree with changes in position, particularly when moving from prone to supine, as well as with respiration and vascular pulsation. This is well recognised in patients treated with intracranial brachytherapy. In addition, cerebral oedema causes mass effect which can result in significant displacement of tumour and normal structures during treatment and the use of steroids can also be influential. Cystic collections would also displace
structures and their drainage can cause significant positional shifts.

Nevertheless, the GTC relocatable frame accurately immobilises the patient with millimetre precision (120,121) and the position of the brain within the skull is not changed by visceral movement. The brain is, therefore, a suitable site for assessing the potential benefit of conformal radiotherapy and comparing alternative methods of beam shaping.

The conformal blocks used for SCRT at the RMH are produced by a computerised block cutting facility to maximise the precision of converting the BEV templates into blocks. The process of making the blocks is labour-intensive and should preferably be networked to the planning system to eliminate digitisation inaccuracy.

A standard tungsten MLC provides a more practical means of field shaping as less time is needed to prepare for and deliver treatment (110). Additional advantages include on line acquisition of conformal field settings by the treatment unit and potential modification of a MLC portal during a course of treatment if required. Treatment of consecutive fields is possible from outside the treatment room and is the first step towards dynamic conformal therapy and intensity beam modulation. Consequently the MLC is a more desirable beam shaping modality provided it does not result in the irradiation of a clinically significant excess volume of normal tissue.

CLB precisely match the contour of any BEV. A standard MLC with a 10 mm leaf pitch at isocentre best conforms the radiation beam using the intrusive leaf fitting approach (Figure 4.5), thus minimising the volume of
additional normal brain treated. In general, the effect of the finite leaf size on the equivalence of the MLC to CLB becomes more pronounced the smaller the PTV, and this difference is further exacerbated the more irregular the 3-D volume.

The use of multiple noncoplanar circular arcing beams to optimally treat spherical target volumes is well established (36,64). The sphere was used in this study as it was the most challenging model volume available for MLC leaf fitting, not because SCRT should be considered an alternative to multiple arcs in this treatment setting. The cone was chosen as the next most difficult geometric target volume. As one might expect it was noted that the equivalence of the MLC fit was generally better for flat rather than convex surfaces as seen through the BEVs.

The incremental range of spheroidal and conoidal volumes (11-46 cm$^3$ for the spheroids; 6-54 cm$^3$ for the conoids) was selected to overlap with the smaller of the patient PTVs (31-114 cm$^3$), all of which had been suitable for treatment with SCRT using the CLB system developed at RMH. This part of the study attempted to ascertain the importance of the effect of size, rather than shape, on how well the MLC compared with CLB.

The greatest percentage excess volume of normal brain was irradiated when the MLC was used to treat the smallest spheroidal PTV, resulting in a poor approximation of the high dose envelope to the spheroid. The relatively good conformation achieved with the MLC for spheroids 2 and 4 partly reflects the better 'goodness of fit' of the MLC leaves to the template BEVs for the three coplanar fields, which was
subsequently shown to be a function of fractional leaf widths. This effect occurs because the presence of a partial leaf-width at the volume edge is equivalent to having a smaller leaf in this region (Figure 4.7), allowing a better fit and improved normal tissue sparing as a consequence. This phenomenon is particularly important for shapes such as circles, where the MLC incidence is far from normal at the edges. Although less pronounced it was also seen when the series of conoids was analysed.

In addition, scrutiny of the isodose line plots revealed that the invasive leaf fitting technique results in undulating high dose isosurfaces which were tighter to the PTV at some points compared with those produced using the CLB. These two factors explain the apparently anomalous result obtained for spheroid 3. The maximum $z$ dimensions of the template BEVs were slightly less than the diameter of each spheroid because of the difficulties inherent in manually extrapolating the model target volumes.

A similar pattern of values was obtained for the conoids, except that it was the better 'goodness of fit' of the MLC to the BEVs of the three fields at the base of the tetrad for conoids 1 and 3 that more closely approximated CLB. The near equivalence of the MLC to CLB for treating conoids 1 and 3, particularly in terms of the normal brain volume receiving $>80\%$ of the isocentre dose, also reflects the fact that the invasive leaf fitting technique results in undulating high dose isosurfaces which were tighter to the PTV at many points (Figure 4.4) compared with those produced using the CLB.
Figure 4.7: The fractional leaf width effect: a partial leaf width at the volume edge is equivalent to having a smaller leaf in this region.

Schematic diagram of MLC fitting to a circle. The white area between the PTV + penumbral margin and the MLC leaves is the area of underlap. (a) With a partial leaf at the edge of the volume; (b) with a whole leaf at the edge of the volume.
If the possibility of slight underdosing at these points was clinically important either a bigger margin or a non-invasive leaf-fitting MLC technique would be required, both of which would inevitably increase the radiation dose to normal brain.

The six patient tumour volumes used in this study span the range treated using CLB and the SCRT system in routine use at RMH. The differences in normal tissue volumes that would have been irradiated had the MLC been used in place of CLB varied from 8-46 cm$^3$ to greater than 50% and 0-23 cm$^3$ to greater than 80% of the target dose. Expressed as the percentage excess normal brain volume irradiated, values ranged from 9-38% to greater than 50% and 0-119% to greater than 80% of the target dose. Inferences regarding the size of the lesion and the appropriateness of using MLC in place of CLB are difficult to draw from the patient data (Tables 4.4 & 4.5), as variability in 3-D outline is an important factor. BEV shape was a major determinant of how closely the MLC matched the ideal contour, the closer the BEV approximated a rectangular shape the better the equivalence between MLC and CLB.

The process of conforming radiation fields with either technique will reduce the volume of normal brain that will receive greater than 50% of the target dose, compared with conventional technique. This will usually outweigh small differences in DVH profiles determined by which method is used for beam shaping when the target is relatively uniform and approximates simple geometric shapes such as rectangular or cuboidal volumes. However, the data presented here suggest CLB beam shaping is preferable when the PTV is a complex
shape, to minimise the volume of normal brain receiving greater than 50% of the isocentre dose.

In practical terms treating an additional 20 or 30 cm$^3$ of non-eloquent normal brain to 50-100% of 55-60 Gy at 1.5-1.8 Gy per fraction using the MLC would be unlikely to cause a clinically detectable increase in morbidity. However, reducing the dose to normal brain using CLB in place of MLC would be expected to have a significant clinical benefit in children and when critical structures abut or are involved in the high dose volume. Elderly patients are also likely to benefit from minimising the volume of normal brain receiving a significant radiation dose and tolerate a radical course of treatment more easily.

Patients with recurrent gliomas are of particular relevance as they are being reirradiated and the propensity for causing radiation-related side effects is considerable (112,122). Consequently use should be made of arcing circular radiation beams to optimally treat spherical lesions and CLB to maximally conform the high dose envelope to non-spherical targets.

Since the original work on this subject was carried out mini/micro-MLCs with leaf pitches of 1.7-3.0 mm at isocentre have become commercially available (Figures 4.2 & 4.3), which compare favourably with other methods of field shaping for SRS/T (123,124) and clearly have the capability to overcome the limitations of the conventional MLC summarised in this thesis (125). Such devices provide conformation which is very similar to that achieved with CLB and have the additional benefits of being a practical and rapid means of
shaping fields which requires less time for preparation, quality assurance and delivery of treatment.

How well the method of beam shaping conforms the prescription isodose surface to the clinical target volume is summarised by the conformity index. This parameter is obtained by dividing the volume of tissue encompassed by the prescription isodose surface by the clinical target volume and is known as the 'PITV ratio'. The closer this value is to unity, the better the conformation and a ratio within the range of 1.0-2.0 is usually considered acceptable.

In conclusion the use of CLB in SCRT achieves better sparing of normal brain compared to conventional MLC, the degree of benefit relating mainly to the shape and to a lesser extent the size of the lesion. Although potentially of clinical benefit the manufacture and use of CLB is labour and cost intensive and this should be weighed against the relative ease and accuracy of repeated MLC application. In deciding which technique to use for individual cases, the proximity of critical structures and adequacy of shielding need to be taken into account, as well as benefits predicted by normal tissue DVH data.
CHAPTER 5

HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY IN THE MANAGEMENT OF RECURRENT GLIOMA

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5.1 Introduction

Hypofractionated stereotactic radiotherapy (HSRT) is a non-invasive method of delivering focal irradiation in a small number of fractions, typically of 5 Gy each, and potentially of lower toxicity than single fraction stereotactic radiosurgery (SRS). The impetus for using HSRT in recurrent gliomas comes from Phase II studies of interstitial radiotherapy (IRT) reporting favourable survival (126). HSRT may be considered a non-invasive alternative to IRT and on theoretical grounds should carry a similar risk of normal tissue toxicity. It is important to remember, however, that there are crucial differences between IRT and HSRT. The use of IRT is limited to superficial cortical sites and can be traumatic. Unlike HSRT it is a low dose rate technique, has larger dose gradients and very different dose distributions. The expectation of a true isoeffect can only be obtained at one isodose surface for IRT, where the biological effects are matched, as at all other surfaces the effects should be different.

Initial experience with HSRT in a small group of selected patients with recurrent high grade glioma treated at RMH (127), was sufficiently encouraging to justify continuing the use of the technique and undertaking a Phase II study. This paper reports the clinical outcome of the patients treated in this study, which includes mature data on the initial cohort, and attempts to define the efficacy and toxicity of HSRT for the treatment of patients with recurrent high grade glioma.
5.2 Materials and methods

From January 1989 to July 1994, thirty three patients with high grade glioma at the time of recurrence were treated at the Royal Marsden Hospital (RMH) with HSRT. Written informed consent was obtained prior to entry into the study, which had local ethics committee approval. The patients and disease characteristics are shown in Table 5.1. All patients recurred after receiving radical conventionally fractionated radiotherapy to doses ranging from 45 Gy in 20 fractions to 60 Gy in 30 fractions (median dose 55 Gy) as part of their initial treatment. Median time interval between initial radiotherapy and HSRT was 29 months (range 5-174 months). All tumours recurred at the original site within the previous high dose region.

The recurrent tumour dimension ranged from 1.4 to 7.0 cm (median 4.8 cm), as measured by the maximum diameter of enhancement on CT or MRI scans. Recurrent tumour volume ranged from 3 to 93 cm$^3$ (median 24 cm$^3$), as calculated by summation of the outlined region of interest on adjacent CT slices on the planning computer. Since 1991 only recurrent tumours with a maximum dimension of up to 5.0 cm have been treated.
Table 5.1: Characteristics of patients with recurrent high grade glioma treated with hypofractionated SRT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (and sex) of patients</td>
<td>33 (18 males; 15 females)</td>
</tr>
<tr>
<td>Median age in years (range)</td>
<td>37 (19-55)</td>
</tr>
<tr>
<td>Median KPS at SRT (range)</td>
<td>80 (60-100)</td>
</tr>
<tr>
<td>Initial histologic diagnosis:</td>
<td></td>
</tr>
<tr>
<td>High grade astrocytoma</td>
<td>21</td>
</tr>
<tr>
<td>Low grade astrocytoma</td>
<td>8</td>
</tr>
<tr>
<td>High grade oligodendroglioma</td>
<td>3</td>
</tr>
<tr>
<td>High grade ependymoma</td>
<td>1</td>
</tr>
<tr>
<td>Tumour site:</td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>7</td>
</tr>
<tr>
<td>Temporal</td>
<td>7</td>
</tr>
<tr>
<td>Parietal</td>
<td>11</td>
</tr>
<tr>
<td>Occipital</td>
<td>2</td>
</tr>
<tr>
<td>Thalamic</td>
<td>3</td>
</tr>
<tr>
<td>Posterior fossa</td>
<td>3</td>
</tr>
<tr>
<td>Median time from initial RT in months (range)</td>
<td>29 (5-174)</td>
</tr>
<tr>
<td>Median initial RT dose in Gy (range)</td>
<td>55 (45-60)</td>
</tr>
<tr>
<td>Median tumour dimension in cm (range)</td>
<td>4.8 (1.4-7.0)</td>
</tr>
<tr>
<td>Median tumour volume in cm$^3$ (range)</td>
<td>24 (3-93)</td>
</tr>
</tbody>
</table>

KPS = Karnofsky performance status
RT = radiotherapy
SRT = stereotactic radiotherapy
Eleven patients had Grade 3 and ten Grade 4 astrocytoma on initial histology using the Kernohan classification (128). Only two patients had tumour recurrence biopsied. Eight patients with an initial histological diagnosis of Grade 2 astrocytoma were classified as high grade at relapse, of whom six underwent surgery prior to HSRT. Three had transformed to Grade 3 and three to Grade 4 astrocytoma. Two patients had rapid disease progression and high grade features on imaging. Three patients with initial high grade oligodendroglioma had biopsies at relapse. Two showed no change and the third a mixed oligoastrocytoma. One patient had recurrent high grade ependymoma.

In addition to the patients treated for recurrent high grade glioma, three children with recurrent pilocytic astrocytoma were treated with HSRT. Recurrent tumour volumes were 1, 1 and 5 cm$^3$. One boy was initially treated with surgery alone but recurred 11 months later at the age of five. Two girls were treated with surgery and radiotherapy to a dose of 50 Gy in 25 fractions and 54 Gy in 30 fractions. The former recurred 7 years later at the age of fourteen, the latter 2 years later at the age of sixteen. Both underwent further surgery which allowed confirmation of the original diagnosis prior to HSRT.

### 5.2.1 Stereotactic technique

The technique of fractionated SRT has been described in detail elsewhere (59,60,64,127). Patients were immobilised in a Gill-Thomas-Cosman (GTC) relocatable frame (Radionics Inc, Burlington, Mass, USA). Localising CT scans were
transferred to a GE Target 1 planning computer and three
dimensional isodose distributions were obtained using 3-6
(median 3) noncoplanar arcs or 4-6 noncoplanar static beams.
The planning target volume was defined as the enhancing
tumour with a 2 mm margin. The treatment plans were
normalised to 100% at the isocentre and prescribed to the 90%
isodose surface in thirty one patients and 80% isodose surface
in five patients.

All patients received 5 Gy fractions daily five days a
week, initially on a dose escalation program (127), with doses
ranging from 20 to 50 Gy. Of the high grade patients, two
received 20 Gy, eight 30 Gy, eight 35 Gy, nine 40 Gy, five 45
Gy and one 50 Gy. Two of the three children with recurrent
pilocytic astrocytoma received 35 Gy and the third 40 Gy.

5.2.2 Patient evaluation

Patients were evaluated by clinical examination and
functional status assessment, measured as activities of daily
living on a verbally administered Barthel index (BI) (129)
before HSRT, 2-4 weeks after and then every 2-3 months. A
change of three or more points on the BI was considered to be
significant. A CT or MRI scan was performed at six weeks
after HSRT and subsequently every other month. More
recently imaging has been performed 3-4 months after HSRT
and at the time of clinical deterioration.

Diagnosis of radiation-induced damage was made
clinically and defined as neurological deterioration in physical
performance, cognitive function, or speech without evidence of
progressive tumour, with improvement on corticosteroids that
was maintained for at least two months. A Cox proportional hazards model analysis was used to determine factors predictive of radiation damage. Total HSRT dose, recurrent tumour volume, previous radiotherapy, age at HSRT, and initial tumour grade were investigated. Survival was measured from the time of HSRT and calculated by the Kaplan-Meier method (130). Comparison of prognostic factors was assessed by the log-rank test (131).

5.2.3 Comparison with chemotherapy

The survival of the twenty nine patients with high grade astrocytoma was compared with that of a matched control group treated with nitrosourea-based chemotherapy at recurrence (132). Eight of the twenty nine patients had received chemotherapy at first recurrence, prior to HSRT, and were excluded from this comparison. The remaining twenty one patients were each matched to a chemotherapy control for the known prognostic factors of grade at initial diagnosis, disease-free interval of less versus (vs) more than 2 years, age and performance status at recurrence. Eighteen of the matched controls were treated prior to the introduction of HSRT and three were ineligible for HSRT because of the size of the recurrent glioma.
5.3 Results

5.3.1 Survival

The median survival of the thirty two patients with recurrent high grade glioma was 11 months from the time of HSRT. Median survival of the twenty nine patients with high grade astrocytoma at the time of recurrence was 10.7 months. After exclusion of eight patients who transformed from low to high grade astrocytoma, the median survival of the remaining twenty one patients was 9.6 months (Figure 5.1).

At the time of analysis twenty four patients had died. Twenty one from recurrent disease in direct continuity with the irradiated site and two who progressed more than 3 cm away from the treated volume, one of whom had disease in the spinal cord. One patient died from pulmonary embolism.

Three patients with oligodendroglioma remain alive 11, 23 and 34 months after HSRT, and three patients with recurrent pilocytic astrocytoma are alive without disease progression at 14, 41 and 55 months.

The results reported here for selected patients with small volume locally recurrent high grade astrocytoma treated with HSRT, reflect the uniformly poor prognosis of this tumour due to its intrinsic biology and infiltrative nature. However, the results so far for the small number of patients with the better prognosis recurrent oligodendrogliomas and pilocytic astrocytomas are encouraging. These two patient subgroups may have local control rates closer to those seen when treating persistent or locally recurrent nasopharyngeal carcinoma with focal irradiation techniques (133,134,135,136,137,138,139).
Figure 5.1: Actuarial survival of patients with recurrent high grade glioma treated with hypofractionated SRT.
5.3.2 Toxicity

All patients completed HSRT treatment as outpatients without acute adverse effects. Dexamethasone was not used routinely and only introduced in the presence of raised intracranial pressure or progressive focal neurological deficit. Alopecia was limited to a small region for lesions close to the skull.

Late, presumed radiation-induced, damage was seen in thirteen of the patients (36%). The degree of deterioration varied from mild to life threatening. In twelve of the thirteen patients, assessment using physical examination, the BI, and Karnofsky performance status (KPS) quantified the extent of functional deficit. One patient required hospitalisation and urgent therapy with intravenous mannitol and dexamethasone for raised intracranial pressure.

In four patients presumed radiation necrosis was verified by positron emission tomography (PET) using 18-fluoro-deoxyglucose. In two others it was confirmed histologically, following reoperation for progressive deficit and features of raised intracranial pressure requiring prolonged high dose corticosteroids. The actuarial risk of developing presumed delayed radiation complications was 34% (95% CI 17-51%) at 12 months and 45% (95% CI 21-70%) at 24 months from the time of HSRT (Figure 5.2).
Figure 5.2: Actuarial cumulative toxicity for all patients from the time of SRT.
The relationship between recurrent tumour volume, HSRT dose in Gy and complications is shown in Figure 5.3. A HSRT dose greater than 40 Gy was a significant predictor of radiation damage ($p < 0.005$). Patients who received either 45 or 50 Gy had 6.4 times the risk of damage (95% CI 1.8-22.8), compared with those who received 40 Gy or less. No other factor was found to be of independent prognostic significance.

For a HSRT dose of i) 35 Gy and ii) 40 Gy in 5 Gy fractions after initial treatment with a) 55 Gy or b) 60 Gy in 1.8 and 2.0 Gy fractions respectively, total BEDs in Gy using an alpha/beta ratio of 2 ($\text{BED}_2$) are: ia) 228, ib) 243, iia) 245 and iib) 260. With an alpha/beta ratio of 3 ($\text{BED}_3$) these values work out as follows: ia) 182, ib) 193, iia) 195 and iib) 207.
5.3.3 Palliative efficacy

Functional assessment using the BI was recorded in twenty five patients with high grade glioma at the time of HSRT and at 3 and 6 months after treatment. The maximum achievable score was 20. At the time of HSRT, twenty two of twenty five (88%) patients had no or mild disability with BI scores of 18-20. At 3 and 6 months after HSRT, BI scores of 18-20 were recorded in twenty of twenty four (83%) and fourteen of twenty two (64%) patients respectively. Six patients deteriorated between the 3 and 6 months post treatment assessments.

5.3.4 Prognostic factors

Initial histological grade, sex, age up to vs over 35 years, KPS up to vs more than 70, HSRT dose up to vs more than 35 Gy, HSRT dose up to vs more than 40 Gy and recurrent tumour volume up to vs more than 35 cm$^3$ were all assessed by univariate analysis in the patients with high grade glioma, to test for any prognostic significance in predicting survival.

Only initial histological grade was of prognostic significance ($p < 0.05$). Patients who initially presented with low grade tumours had a median survival of 21 months compared to 10 months for patients presenting with high grade tumours.
5.3.5 Comparison with chemotherapy

Survival results for the twenty one patients treated with HSRT who had not received chemotherapy, were compared to the twenty one matched control patients with recurrent astrocytoma who had been treated with nitrosourea-based chemotherapy at RMH (132). The most commonly used regime was the combination of procarbazine, lomustine and vincristine given every six weeks, typically for 4-6 cycles. Although a well established and widely used chemotherapy schedule for the treatment of patients with high grade glioma, the six week cycle time is not ideal when treating a tumour that usually behaves aggressively and grows quickly. This is in direct contrast to the HSRT protocol which is completed in less than two weeks.

The median survival of the patients treated by HSRT was 11 months compared to 7 months ($p < 0.05$) for the matched control patients (Figure 5.4). However, patients were not matched for volume of recurrent tumour which could have been an influential factor on outcome and case selection in the HSRT group may account for the survival difference. In view of this, if HSRT availability was limited or there was no access to a suitable facility, palliative chemotherapy as described above should be offered to suitable patients. Similarly if the waiting time until the start of HSRT were long, it would be appropriate to offer chemotherapy to patients in the interim period.
Figure 5.4: Comparison of survival for two groups of patients with high grade astrocytoma at recurrence matched for age, KPS, initial histological grade and disease-free interval, treated with SRT or nitrosourea-containing chemotherapy.
5.4 Discussion

Stereotactic radiotherapy as a non-invasive means of accurate delivery of localised irradiation to small target volumes (140) is being explored in the treatment of brain tumours on the assumption that such focussed radiation may improve tumour control without increased toxicity. In small localised tumours, high dose can be largely confined to the tumour with little dose reaching the surrounding normal brain (64). The conventional linear accelerator technique of multiple noncoplanar arc therapy is suitable for small spherical tumours. Larger and non-spherical lesions may best be treated with noncoplanar conformal fixed fields using the technique of SCRT (109). Both fractionated SRT and SCRT are used in the treatment of recurrent tumours.

There is a clear need to improve local tumour control in high grade gliomas, as most patients die from progressive disease at or in close proximity to the primary site (141). However, high grade gliomas in the recurrent setting are seldom small enough to be suitable for SRT and retreatment with CT planned external beam radiotherapy and cytotoxic chemotherapy (142) or chemotherapy alone (132) is well established. Neutron therapy was shown to be too toxic (143).

The impetus for using SRT in recurrent gliomas comes from Phase II studies of IRT reporting favorable survival (126). Stereotactic radiotherapy may be considered a noninvasive alternative to IRT and, on theoretical grounds, fractionated SRT may carry similar normal tissue toxicity to IRT and potentially less than SRS.
The selected patients with recurrent high grade glioma reported in this study, which represents only a small proportion of those with recurrent high grade tumours, had a median survival of 11 months. This is equivalent to the median survival achieved in patients with recurrent high grade glioma treated with IRT. The selection criteria in terms of patient characteristics and tumour size are likely to be similar.

As this was not a randomised study the results were compared to a cohort of patients treated at the same institution with nitrosourea containing chemotherapy at the time of recurrence (132), matched for the known prognostic factors of age, initial histological grade, and performance status, as well as disease-free interval. Although the patients treated with HSRT appear to have better survival, other factors may have introduced bias in their favour, as in the case of IRT (144). The HSRT patients were selected by tumour size and this may predict for favourable survival not corrected for in this analysis. Retrospective studies of primary treatment for high grade gliomas suggest that patients with smaller tumours after surgery have better survival (145) and tumours up to 4 cm diameter suitable for SRS also carry a better prognosis (146). Smaller tumours are also subject to lead time and length bias.

This study represents a continuation of a previous dose escalation Phase I/II study (127) trying to define the appropriate dose of HSRT given at 5 Gy per fraction, in terms of toxicity and survival. Because of the poor prognosis of patients with recurrent high grade glioma and the overall palliative and non-invasive nature of fractionated SRT, it is not justifiable to mount a toxicity study based on the histological
verification of radiation necrosis. We identified a clinically appropriate surrogate endpoint of presumed radiation damage defined as neurological deterioration without evidence of progressive tumour which improved and was maintained for at least two months on corticosteroids. This endpoint is similar to that used in studies of SRS toxicity (14) and is therefore likely to represent true radiation damage.

The frequency of presumed radiation damage was 36%. When expressed in cumulative actuarial terms it reached 45% at two years. It is difficult to compare the toxicity results with other studies as actuarial risk has not previously been reported. However, the overall risk is high which would be expected for high dose retreatment following previous radiotherapy to tolerance doses.

The analysis suggests that the major predictor of clinically significant radiation damage is HSRT dose. A HSRT dose greater than 40 Gy was a significant predictor of radiation damage \((p < 0.005)\). Patients who received either 45 or 50 Gy had 6.4 times the risk of damage (95% CI 1.8-22.8), compared with those who received 40 Gy or less.

It is generally accepted that a \(\text{BED}_2\) of more than 200 Gy is very toxic in conventional radiotherapy treatment. By selecting patients with small recurrent gliomas and restricting the volume of reirradiated brain using stereotactic treatment delivery, we had hoped to avoid significant radiation-related toxicity even though the total \(\text{BED}_2\) after HSRT was more than 200 Gy for most of the patients. To minimise the risk of significant morbidity a total \(\text{BED}_2\) of 250 Gy should not be exceeded when retreating appropriately selected patients with
this HSRT regime. The probability of radiation damage could be reduced further by using a smaller fraction size and treating on alternate days, as radiation repair in the brain is known to have slow kinetics (28,29). Although irradiated volume is likely to be relevant, this parameter did not reach statistical significance because of the small numbers of patients treated.

Radiation damage is usually not an acceptable consequence of radiotherapy. Certainly as a cause of neurological deficit it adversely affects function and quality of life, although in the majority of patients it was reversible with corticosteroids. Patients who experienced radiation damage, already selected by surviving long enough for it to develop, had no worse survival than those without such damage. It would therefore appear that radiation damage did not adversely affect survival, and as with IRT series, is considered an acceptable consequence of treatment with high dose radiation.

Patients with recurrent glioma are treated with palliative intent and in the majority a non-invasive approach to therapy could be maintained, as only two patients (6%) required reoperation for problems requiring prolonged use of high dose corticosteroids. The rate of reoperation was considerably lower than that reported for patients treated with IRT (147) or SRS (122,148). This may be due to a less aggressive reoperation policy as well as lower toxicity of HSRT, particularly at doses of 30-35 Gy.

As with other forms of localised high dose irradiation, HSRT is not a curative treatment for patients with recurrent high grade glioma. Nevertheless, the overall results are favourable and on the basis of survival and acceptable toxicity,
it is a reasonable treatment option for patients with small tumours at the time of recurrence. However, the results are based on relatively small numbers of patients and the conclusions cannot be considered fully proven.

The efficacy of HSRT in patients with recurrent low grade tumours is difficult to assess. Treatment appears to be effective as all previously progressive tumours remained static, but the results must be considered in the context of the known natural history of low grade tumours. Patients with recurrent oligodendroglioma retain their more favourable prognosis at the time of recurrence (132). The indolent natural history of pilocytic astrocytomas also precludes definite conclusions about the long-term control following HSRT, although the results so far are encouraging.

Is HSRT useful in the primary therapy of high grade gliomas? So far no definite survival advantage has been demonstrated for SRS boost as part of the initial treatment (149,150). However, it would be appropriate to test in a randomised study a HSRT boost as a less toxic, non-invasive alternative to SRS or IRT. Future studies of HSRT either in the primary or recurrent setting will need to concentrate not only on survival, but also on quality of life. Any survival benefit will have to be carefully weighed against the potential of increased toxicity.

In the meantime it is reasonable to argue that the equivalent dose distribution, non-invasive nature, similar efficacy and lower toxicity of HSRT compared to IRT make it the favoured localised high dose treatment in suitable patients.
CHAPTER 6

SUMMARY OF CONCLUSIONS

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6.1 Introduction

The three interrelated areas of research contained within this thesis were conducted within the context of a rolling programme of SRT treatment development at RMH, established in 1988 under the auspices of Dr Michael Brada, Head of the Neuro-oncology Unit, and Mr Alan Warrington, Senior Physicist. Joint collaboration with Mr Stephen Gill and Professor David Thomas, neurosurgeons at the Institute of Neurology, Queen Square, resulted in a prototype relocatable stereotactic head frame, based on an impression of the upper dentition, suitable for multiple sequential imaging and fractionated radiotherapy treatments. Mr Eric Cosman of Radionics Inc, an American company specialising in medical technology, has made the frame commercially available as the GTC localiser which provides a non-invasive, accurate method of immobilisation for giving SRT using a linear accelerator.

The Neuro-oncology Unit at RMH has an international reputation for both technical development and defining the clinical situations in which SRT should be considered as a treatment modality. At the time of my appointment as the third clinical research fellow on the programme, much of the basic work had been completed and the technique was established in clinical practice worldwide. The main thrust of the developmental work during my fellowship was to examine possible ways of optimising treatment planning and delivery for linac-based SRS/T and SCRT. The main results and conclusions are summarised in this chapter and their implications for clinical practice and further work discussed.
6.2 Whole body doses from linac-based SRS/T

The results of the whole body dose measurements show significantly higher values throughout the length of the torso when a sagittal arc is used as part of an arcing beam configuration. This was most striking in the thyroid gland dose, which was three to four times higher with the five rather than four arc beam arrangement. The 355°-5° apical sector of a sagittal arc effectively equates to a fixed field, delivering more than 95% of the body dose. The larger the collimator size the higher the central axis exit dose and the greater the effect of lung scatter. Increasing from a 20 mm to a 40 mm collimator resulted in twice the mediastinal dose and a 30-40% greater lung dose. The four arc technique with beams exiting through the shoulder girdle avoids irradiating the thyroid and other centrally placed organs.

The fixed beam exiting through the long axis of the phantom gave a tenfold greater dose than the 90° sagittal arc at all levels, including the gonads. An additional 30-40% dose increase to organs below the level of the diaphragm was recorded due to pulmonary transmission, when the fixed beam or sagittal arc traversed the long axis of the lung.

The issue of arc or fixed beam exit through extracranial structures is of no clinical importance when therapeutic intent is palliative such as in the treatment of cerebral metastases or recurrent high grade glioma, but should be considered when treating benign lesions and low grade malignant tumours in children and younger adults with a normal or near normal life expectancy after SRS/T. Exposure before the age of five years
may result in three times the risk of thyroid cancer than following exposure in adulthood (98,99,100). Females are two to three times more likely than males to develop both naturally occurring and radiation-induced thyroid cancers (98,99). Thyroid malignancy is well established as a late complication of thyroid irradiation and the principle of ALARA should be applied (97).

The avoidance of a sagittal arc or a fixed field exiting through the long axis of the torso will help to minimise the radiation dose to the rest of the body. When it is of clear benefit to include a sagittal or near sagittal arc in a treatment plan, an alternative to increasing the number of arcs is to interrupt the sagittal arc over the 355°-5° apical sector. Such considerations should minimise the risk of extracranial radiation-induced malignancy, notably in the thyroid gland of younger patients.

6.3 Comparison of MLC with CLB for the delivery of SCRT

The process of conforming radiation fields with either MLC or CLB will reduce the volume of normal brain irradiated compared with conventional technique. This will usually outweigh small differences in DVH profiles determined by which method is used for beam shaping when the target is relatively uniform and approximates simple geometric shapes such as rectangular or cuboidal volumes.

When the PTV is a more complex shape with convexities and concavities the preferred method of beam conformation is
CLB, to minimise the volume of normal brain receiving greater than 50% of the isocentre dose. Optimal shaping of the high dose treatment isoenvlope to the PTV would be expected to confer particular clinical benefit in the treatment of children, when critical structures abut or are involved in the high dose volume or when large fraction sizes are used in the treatment of solitary brain metastases or recurrent gliomas.

Subsequent to the completion of my research fellowship, the facility to genuinely grow 3-D margins became available and this was used to generate a new series of spheres and conoids by Elizabeth Adams, research physicist, who had joined the department just before I left. She repeated the calculations on the new series of geometric as well as the patient volumes following some methodological refinements. These included adding the penumbral margin in the BEV (it was now appreciated that a 4mm penumbral margin was required for MLC fields to achieve the same 90% coverage obtained with a 3mm margin for CLB), outlining the actual brain instead of using the external contour of the skull, extending the lower limit of the field data available in Target, optimising the creation and placement of conformal blocks and asymmetric jaws and collecting DVH data for both the normal brain and the PTV.

The repeat analyses confirmed the original findings that CLB are superior to conventional MLC for the optimal delivery of SCRT and that the accuracy of the MLC fit is strongly dependent on the shape of the lesion. Further work defined a 'goodness of fit' parameter for the intrusive leaf fitting method which could be calculated for each individual
BEV. When this parameter was calculated for each of the true 3-D model spheres and plotted against radius a graph with cyclical characteristics was obtained, confirming the pattern of variation seen with the original spheroid data. Spheres with radii equal to a whole number of leaf-widths were least well accommodated by the MLC, whilst those with radii which required half a leaf-width at the field edge spared the maximal amount of normal brain achievable with the MLC. This effect occurs because the presence of a partial leaf-width at the volume edge is equivalent to having a smaller leaf in this region (Figure 4.7), allowing a better fit and improved normal tissue sparing as a consequence. This phenomenon is particularly important for shapes such as circles, where the MLC incidence is far from normal at the edges. Although less pronounced it was also seen when the series of conoids was analysed.

This fractional leaf-width effect explained why it was not possible to demonstrate a clear relationship between the size of the spheres, spheroids or conoids. To do so it was necessary to assess a series of spheres with radii corresponding to the same fractional leaf-widths. When this was undertaken some improvement in the performance of the MLC compared with CLB could be demonstrated with increasing sphere PTV. As a result of these findings it can be seen that a 'goodness of fit' parameter needs to be incorporated into the MLC fitting programme to assess how appropriate it is to consider using MLC for a particular tumour shape and size. This additional work is included in the final published paper (151).
Since the original work on this subject was carried out mini/micro-MLCs with leaf pitches of 1.7-3.0 mm at isocentre have become commercially available, which compare favourably with other methods of field shaping for SRS/T (123,124) and clearly have the capability to overcome the limitations of the conventional MLC summarised in this thesis (125). Such devices provide conformation which is very similar to that achieved with CLB and have the additional benefits of being a practical and rapid means of shaping fields which requires less time for preparation, quality assurance and delivery of treatment.

In conclusion the use of CLB or a mini/micro-MLC in SCRT achieves better sparing of normal brain compared to conventional MLC, the degree of benefit depending mainly on the shape of the lesion. Increasing volume does not correlate with improved agreement between conventional MLC and CLB field shaping, the large variations in the differences relating to the PTV shape and leaf-width effects. The ability of the MLC to fit to a lesion is strongly dependent on its shape in BEV and on the orientation of the leaves relative to the shape, requiring the optimal collimator angle to be chosen during planning. (Some linacs do not allow unlimited freedom of collimator position as their wedge orientation is also dependent on the collimator angle, a factor that needs to be borne in mind at the time of linac purchase). A further factor which contributes to the 'goodness of fit' of the conventional MLC is the presence of partial leaf-widths at the edges of the volume. A conventional MLC would not be considered a suitable method for beam shaping when it would be approaching the PTV outline at
shallow incidence and/or there were undulations smaller than the 1 cm leaf pitch.

Although potentially of clinical benefit, the manufacture and use of CLB is labour and cost intensive and this should be weighed against the relative ease and accuracy of repeated conventional MLC application. In deciding which technique to use for individual cases the proximity of critical structures and adequacy of shielding need to be taken into account, as well as benefits predicted by normal tissue DVH data. For centres providing SCRT where the choice of beam shaping technique lies between CLB and conventional MLC, the incorporation of a 'goodness of fit' parameter into the MLC fitting programme will enable appropriate case selection for each modality. This is a measure of how closely conformation with the conventional MLC equates to that using CLB. The 'PITV ratio' (page 124) is used to compare the plans generated by different beam shaping techniques. The mini/micro-MLC achieves normal tissue sparing closely matching that of CLB in most clinical situations whilst retaining the practical benefits already stated (123,124,125).

6.4 HSRT in the management of recurrent glioma

There is a clear need to improve local tumour control in high grade gliomas, as most patients die from progressive disease at or in close proximity to the primary site (141,152). Stereotactic radiotherapy may be considered a noninvasive alternative to IRT and, on theoretical grounds, fractionated
SRT may carry similar normal tissue toxicity to IRT and potentially less than SRS.

The work presented in this thesis has defined a practical HSRT regime, delivering 5 Gy per fraction, with acceptable toxicity and survival equal or superior to the other treatment options. The selected patients with recurrent high grade glioma reported in this study, which represents only a small proportion of those with recurrent high grade tumours, had a median survival of 11 months. This is equivalent to the median survival achieved in patients with recurrent high grade glioma treated with IRT. The selection criteria in terms of patient characteristics and tumour size are likely to be similar (144) and a recent paper has again demonstrated the predictive value of recurrent tumour volume on the length and quality of survival following reirradiation with brachytherapy (153).

Retrospective studies of primary treatment for high grade gliomas suggest that patients with smaller tumours after surgery have better survival (145) and tumours up to 4 cm diameter suitable for SRS also carry a better prognosis (146). Patients with smaller tumours are also subject to lead time and length bias, whereby it is commonly the case that they will remain relatively well and survive for longer than patients whose tumours are larger at diagnosis, regardless of any beneficial effect of treatment. Consequently patient selection clearly played an important part in the favourable outcome seen in the cohort treated in this study when compared with the median survival of an unselected group with recurrent high grade glioma suitable for palliative chemotherapy.

Nevertheless it is appropriate to have reliable criteria to
select the subgroup of patients who are most likely to benefit from HSRT, considering the complex process of treatment planning and delivery and the rising risk of radiation toxicity as the volume of reirradiated brain increases.

The frequency of presumed radiation damage was 36%, which expressed in cumulative actuarial terms reaches 45% at two years. It is difficult to compare the toxicity results with other studies as actuarial risk has not previously been reported. However, the overall risk is high which would be expected for high dose retreatment following previous radiotherapy to tolerance doses. The major predictor of clinically significant radiation damage using this protocol is HSRT dose and eight of the thirteen patients who developed toxicity received 40 Gy or higher in 5 Gy fractions. Based on this data we would recommend that a total $\text{BED}_2$ of 250 Gy should not be exceeded. By limiting the HSRT dose to 30-35 Gy in fractions of less than 5 Gy and treating on alternate days, the risk of causing serious radiation toxicity should be lower (28,29,154).

Those patients who experienced radiation damage, already selected by surviving long enough for it to develop, had no worse survival than those without such toxicity. Radiation damage did not appear to adversely affect survival and in IRT series has been considered an acceptable consequence of high dose radiation treatment.

Patients with recurrent glioma are treated with palliative intent and in the majority a non-invasive approach to therapy could be maintained. Two patients needed reoperation for necrosis causing mass effect and impairment of neurological function, which did not improve with prolonged use of high
dose corticosteroids. The rate of reoperation was considerably lower than that reported for patients treated with IRT or SRS, probably reflecting a less aggressive reoperation policy as well as the lower toxicity of HSRT at doses of 30-35 Gy.

Since the publication of this patient cohort (112) a very similar study has been reported from Philadelphia (154). Nineteen patients with glioblastoma multiforme and one with anaplastic astrocytoma had previously received conventionally fractionated postoperative radiotherapy to a mean and median dose of 60 Gy (range 44-72 Gy). A median of 3.1 months later (range 0.7-45.5 months), sixteen patients had one site, three patients two sites and one patient three sites reirradiated with HSRT using daily fractions of 3.0-3.5 Gy. Three different total dose levels were sequentially evaluated: 24 Gy in 8 fractions (five lesions), 30 Gy in 10 fractions (ten lesions) and 35 Gy in 10 fractions (nine lesions). Median treated tumour volume was 12.66 cm$^3$ (range 0.89-47.5 cm$^3$). None of the patients required hospitalisation or surgery for early or delayed radiation-related toxicity. Response was determined by clinical neurological improvement, a decrease in steroid dose requirement without clinical deterioration and/or radiological imaging.

The median survival from completion of HSRT was 10.5 months, virtually identical to our group of patients. Neurological improvement was found in 45%, steroid dose could be decreased in 60% and minor imaging response was seen in 22% of their patients. None of the lesions treated with 24 Gy appeared to respond compared with a 79% response rate for the nineteen lesions treated with 30-35 Gy.
Such remarkable correlation between these two independently conducted studies provides good grounds for using HSRT to treat small volume recurrent gliomas. The overall results are favourable and on the basis of survival and acceptable toxicity, it is a reasonable treatment option for patients with small tumours at the time of recurrence. However, the results are based on relatively small numbers of patients and the conclusions cannot be considered fully proven.

On the basis of the clinical data discussed above the question arises of whether HSRT should be used to deliver a boost as part of the primary treatment for patients with high grade gliomas of an appropriate size. Brachytherapy (155) and SRS (156,157) have both become established techniques for localised dose escalation in the primary management of high grade gliomas to try to improve local control. A number of retrospective studies have suggested an improvement in the median survival of patients boosted with intracranial brachytherapy in this context (155,158,159,160,161). However it is well recognised that patients in these studies are highly selected (162) and the importance of pretreatment variables in predetermining and influencing outcome is unquestionably established (161,163). Conflicting results from two randomised studies of brachytherapy boost in the initial management of patients with malignant glioma, one indicating benefit (164) and the other no difference (165) over and above conventional management, have not helped to resolve the issue. However, differences in technique and time scheduling are the most likely explanation and a confirmatory trial using the
protocol which gave the positive outcome would be one way of answering this question.

Interestingly, a randomised trial of surgery, external beam radiotherapy and radioactive iodine brachytherapy with or without the addition of hyperthermia for adults with newly diagnosed, focal, supratentorial glioblastoma up to 5 cm in diameter, demonstrated a statistically significant survival benefit in the arm which received the hyperthermia (166).

By using the criteria of the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis to define prognostically distinct patient subgroups, a recent retrospective analysis found that case selection alone did not account for the benefit seen when stereotactic implantation of radioactive iodine was used in the primary management of high grade glioma and supported the use of a focal boost (167).

Nevertheless, it is clear that patient selection plays a major part in determining outcome and one cannot exclude the possibility that this alone accounts for the majority, if not all, the apparent benefit seen in the two patient cohorts treated for persistent/recurrent disease. This issue can only be adequately resolved by conducting prospective randomised controlled trials.

It is to this end that the RTOG and the European Organisation for Research on Treatment of Cancer (EORTC) are each running a trial to test whether local control can be improved by using a stereotactic boost after a course of conventionally fractionated radiotherapy for the primary treatment of patients with high grade gliomas that fit the size and other selection criteria, with stratification for the
established pretreatment prognostic variables. The RTOG trial is examining the potential benefit of adding a SRS boost at the end of conventional treatment vs no boost. The EORTC trial is using a HSRT boost in the same context. Provided both trials recruit successfully and run to their conclusion, they should also provide an answer to the question of how much patient selection accounts for the apparent improved survival reported in single arm studies and how much is attributable to the focal treatment techniques under evaluation.

6.5 Future applications and developments

What improvements in radiation treatment morbidity within the cranium could reasonably be anticipated from the use of SCRT in place of conventional treatment technique? Intracranial factors which need to be taken into account when deciding upon the optimal beam arrangement include tight conformation and homogeneity of target dose, as well as minimising dose to the eyes, eloquent intracranial structures and the rest of the brain.

The risk of second brain tumour after conventionally delivered and fractionated radiotherapy to the pituitary fossa is well established (104,105). One might expect to see a similar incidence when using SCRT for optimal conformation and maximal sparing of normal brain at this and other intracranial sites, as the risk arises primarily from the use of radiotherapy. However the modality of delivery may also be important, as if the volume of brain tissue receiving a certain radiation dose is a significant factor in determining the incidence of iatrogenic
tumours, the use of SCRT in place of conventional treatment technique may reduce this risk. Long term follow up of large numbers of patients will be needed to clarify this issue.

By using SCRT to treat tumours in and close to the pituitary fossa the potential exists to reduce the incidence of subsequent hypothalamic-pituitary dysfunction if the radiation dose to the hypothalamus can be restricted (168) or the pituitary gland excluded from the target volume (169). Though less likely it is possible that the risk of cerebrovascular accidents might also be lessened (170).

6.5.1 Optimising SCRT

Work with which I was involved that followed on from the MLC vs CLB study but not directly constituting part of this thesis, examined the optimization of SCRT for treating the sellar and parasellar region using normal brain DVH analyses (excluding the PTV), to evaluate treatment plans using a conventional 3-coplanar and 3-, 4-, 6- and 30-noncoplanar fixed beam arrangements (41). Conformal field shaping was achieved by generating CLB in all cases using the BEV facility. Using a 4-noncoplanar, conformal fixed field arrangement (Figure 6.1) in place of the conventional 3-coplanar, conformal fixed field technique to produce treatment plans for six pituitary adenomas and two parasellar meningiomas, decreased the mean volume of normal brain receiving 80% or more of the prescribed dose by 22% and that receiving 60% or more by 48%.
Figure 6.1: Class solution four noncoplanar conformal fixed field arrangement for treating sellar and parasellar tumours.
An optimised 6-noncoplanar, conformal fixed field arrangement could only improve these mean volumes by a further 4% and 3% respectively, neither of which were statistically significant. However, each clinical case needs individual consideration as a wide range is seen in the volume spared when increasing the number of fields from four to six. Comparing the 4- and 6-noncoplanar, conformal fixed field techniques to a 30-noncoplanar, conformal fixed field approach (simulating a dynamic arc plan) revealed near equivalence of normal brain sparing.

The conclusions drawn from this study were that four to six widely spaced, noncoplanar, conformal fixed fields provide the optimum class solution for the treatment of sellar and parasellar lesions, both in terms of normal brain tissue sparing and providing a relatively straightforward patient setup. Increasing the number of fields did not result in further significant sparing of normal brain and consequently no clear benefit was demonstrable for techniques approaching dynamic conformal radiotherapy in the cases examined. The absence of any significant demonstrable clinical benefit for dynamic collimation systems over an optimal number of noncoplanar, conformal fixed fields based on physical dose distributions was also the conclusion reached by Solberg and colleagues (171).

There is considerable commercial pressure from medical technology companies to adopt their products into routine clinical use before even the most rudimentary clinical evidence is available to justify such a change in practice. Dynamic arc conformal therapy is a clear example of this process (172). The combination of an arcing gantry and constantly changing
micromultileaf collimator may increase the frequency of mechanical failure as well as the potential for geographic miss when compared with SCRT, even with the most stringent of quality assurance programmes. In the absence of reliable, persuasive clinical data which clearly demonstrate an advantage for a new technology, it should only be used in the context of well conducted, scientifically sound, clinical trials, ideally randomised against current established best practice.

6.5.2 Intensity-modulated radiotherapy

The other potential advance in optimising radiotherapy treatment delivery which is currently undergoing extensive assessment is intensity modulated radiotherapy (IMRT). This uses the technique of inverse planning in which one begins by defining the desired dose distribution for the treatment of the target lesion. A treatment plan is subsequently derived, commonly using a computerised iterative planning process, which determines the modulation required for the radiation beam during treatment to optimally conform the treatment isodose to the target, whilst keeping the dose to critical structures within preset limits. The main commercial system currently available comprises an integrated 3-D conformal planning facility and a multivane intensity-modulating compensator (Peacock system, Nomos Corporation). The compensator consists of two banks of twenty independent divergent tungsten vanes, each 8 cm thick and each of which projects a 1 x 1 cm block at isocentre (Figure 6.2).
Figure 6.2: The NOMOS Peacock multivane intensity-modulating compensator.
Plate 11: The NOMOS IMRT and IMRS MIMiC system.
It functionally narrows the beam coming from the accelerator down into two thin "slices", further dividing these "slices" into 40 small "beams", 20 for each slice. As the gantry rotates around the patient, each of these 40 small beams can be turned on or off by movement of its vane for a variable period of time, thus creating the intensity modulation required by the inverse solution. Attached to a linac it modulates the intensity of a slit-collimated radiation beam as the gantry rotates around the patient (Plate 11), conforming the radiation dose to the shape of the target volume within a cross-section equivalent to the thickness of a CT slice. In a system analogous to CT the treatment table is indexed and each slice is treated in turn for each couch angle in the plan. How does IMRT compare with SRS/T and SCRT?

Two studies comparing the SRS treatment modalities of gamma knife, linac and protons, based on physical dose distributions in the first paper and normal tissue complication and tumour control probabilities in the second, concluded that differences between treatment plans were dependent on size, shape and location of the target, treatment technique, the amount of time and effort expended on the treatment plan, its complexity and the time available for its execution (173,174). In essence, the more conformal the treatment plan and the better the accuracy and precision of its delivery, the greater the likelihood of success and the smaller the risk of treatment-related complications from SRS.

A study using similar parameters to compare the potential clinical efficacy of IMRT with multiple noncoplanar arcs to treat small intracranial lesions with SRS, showed little
difference in the conformation of the high isodose lines with the target volume but IMRT was inferior to stereotactic treatment planning in terms of normal tissue toxicity index (175). This was acknowledged by the authors to be a function of the inherent limitations of the IMRT system used, namely the 1 cm resolution of the collimator leaf size and background leakage dose. The physical constraint of the 1 cm leaf width is a clear example of how a more sophisticated technology for treatment planning and delivery does not automatically confer improved treatment conformality. It underlines the importance of conducting scientifically rigorous, comparative studies to fully evaluate any new system or modification of an existing technique before its implementation into clinical practice.

However, this paper also compared IMRT with conformal radiotherapy treatment plans for larger, irregular targets adjacent to critical structures in the head and neck region and at other extracranial sites. In particular tumour volumes which wrap around the brainstem, spinal cord or other critical structures in a horseshoe shape are usually better conformed to by IMRT with superior vital normal tissue sparing. Improvements in homogeneous dose delivery to skull base chordomas and chondrosarcomas by reducing underdosage within the target volume would be expected to result in improved local control rates (176).

A comparative study of SCRT and IMRT (Peacock system) treatment plans for five patients who had convex-shaped brain tumours with PTVs ranging from 62-119 cm$^3$, was unable to demonstrate a significant improvement in either PTV conformation or dose to adjacent critical structures (177).
It was considered likely that further improvements could be expected using alternative methods of IMRT planning and treatment delivery that were not limited to the transaxial arc technique.

This premise would seem likely based on a study that evaluated a different treatment system, which used six noncoplanar static beams dynamically shaped by a mini-MLC for IMRT delivery (178). Three intracranial test targets were utilised, consisting of an ellipsoid with major axis dimensions of 4.0, 2.0 and 2.0 cm, a hemisphere with a diameter of 4.0 cm and an irregular volume with a maximum dimension of 5.3 cm. Treatment plans using the IMRT technique were generated for each target volume, assessed using DVH data and compared with those for a five noncoplanar arc and a six noncoplanar fixed conformal field arrangement respectively. The ellipsoid volume was best treated using the multiple noncoplanar arcs. For the hemisphere and irregular volume the IMRT technique achieved the best isodose to PTV conformation and the lowest dose to normal brain outside of the PTV in both high and low isodose regions. The authors cite both the improved accuracy of beam shaping by the mini-MLC due to its leaf pitch of 3 mm at isocentre and the ability to use noncoplanar beams in place of transaxial arcs as key factors to explain their favourable IMRT results. On this evidence it would appear that the method outlined above is superior to the Peacock system for treating brain tumours with IMRT, in the situations in which it is likely to be of significant clinical benefit in place of SCRT.

The importance of careful evaluation and follow up of patient cohorts treated with a new technology is underlined by
Uy and colleagues who report on their experience of IMRT using the Peacock system (Nomos Corporation) to treat forty patients with intracranial meningioma between 1994 and 1999 (179). Although they concluded that "IMRT is a promising new technology that is safe and efficacious in the primary and adjuvant treatment of intracranial meningiomas" no evidence was presented to indicate that the technique is superior to SCRT. In addition, a 51 year old female patient was thought to have experienced a treatment-related death from brainstem necrosis, which is of particular concern when the details of the case are examined. Even after the treatment plan had been reviewed by the authors it was still considered to have been optimal, despite almost 5 cm$^3$ of brainstem exceeding the assigned maximum dose limit of 54 Gy and receiving between 54-55.6 Gy (BED = 106-111 Gy). Radionecrosis developed within this portion of brainstem and was proven on biopsy. These values seem particularly surprising when the prescribed tumour dose was 50.4 Gy in 28 fractions (BED = 96 Gy).

Most clinicians would ascribe a lower maximum safe dose to the brainstem and the implication would seem to be that there was a belief that IMRT could deliver radiotherapy more accurately and safely than previous methods used to treat this group of patients. It is clearly very important to continue to apply established normal tissue tolerances and radiobiological principles when introducing new techniques to deliver therapeutic radiation.
6.5.3 Proton therapy

An alternative approach to potentially improve upon the conformation achievable using SCRT has been reported (180). This paper compared the dose distributions of photons delivered by SCRT and a micro-MLC with those achieved by proton beams from an isocentrically mounted gantry using the spot-scanning technique and energy modulation. Seven cases were planned on 3-D treatment planning systems using each technique and dose distributions for PTV and critical structures calculated and assessed by DVH data, conformity index and visual inspection. For simple geometries and superficial lesions there was no advantage to the use of protons, but when the PTV was complex or critical structures were in close proximity to it the proton plans were potentially better, principally because of the absence of an exit dose. As previously mentioned, access to proton treatment has been very limited due to the small number of clinical facilities available. The USA has the two best known facilities and has many more planned. However, this international lack of clinical facilities is changing rapidly with centres already operational in France, Japan, Sweden and Switzerland. Germany will soon join this group of countries and planned developments are well advanced in Australia, Taiwan and China. Specific clinical situations are already being defined where proton therapy is the treatment of choice. It is rumoured that there may soon be consensus that paediatric solid tumours such as medulloblastoma should only be treated with protons.
6.5.4 Image fusion

Radiotherapy treatment planning systems use CT scan data as the standard imaging modality for target volume definition and subsequent dose calculations. It is at this stage of the SCRT treatment planning process that uncertainty about tumour extent often arises and the potential for error in defining the true target volume is at its greatest. The integration of MRI data onto the CT planning scan is desirable in many clinical situations to improve the definition of the target and critical structures (181,182). Software packages are available that enable MRI images to be merged onto the planning CT scan data set with millimetre accuracy and precision provided tissue-air interfaces are avoided, using an image fusion process to overcome the potential problem of MRI distortion (183). This enhanced image is then used for outlining in the usual way, greatly reducing the risk of a geographical miss when the tumour is poorly defined on the plain CT images.

It is possible to use MRI scans directly for planning larger target volumes in the brain with an appropriate software package, provided the scanning conditions have been optimised to minimise distortion (184). Furthermore, digitally reconstructed radiographs generated from MRI can be used for treatment planning, virtual simulation and visual comparison avoiding the need for CT verification (185). The development of PET scanning provides a further way to enhance the definition of the true tumour volume (186). This makes bioconformal treatment possible with the option of delivering a higher dose to a portion of the target containing higher signal.
6.5.5 **Paediatric neuro-oncology**

In paediatric neuro-oncology, SCRT enables the precise and accurate delivery of radiation treatment to central nervous system tumours, minimising the amount of normal brain irradiated \((187,188)\). Children have the most to gain from avoiding unnecessary exposure of neural tissue to radiotherapy and it is also important to keep the risk of extracranial radiation-induced malignancy as low as possible, particularly in the thyroid gland \((189)\).

Clinical data is already emerging in support of conformal radiotherapy techniques to treat children with localised brain tumours to minimise adverse effects on cognitive function \((190)\) and reduce the risk of endocrine disorders \((169)\). A lightweight paediatric version of the adult GTC frame for routine use and a shell-based alternative for children requiring general anaesthesia for treatment have been developed at RMH to cover all eventualities \((191)\).

6.5.6 **Adult neuro-oncology**

On the basis of the established and emerging clinical evidence SCRT provides accurate and precise treatment for adult patients with brain tumours, particularly those in the younger age group. The ideal case scenario is a benign or malignant tumour without microscopic disease outside the high dose treatment volume, the extent of which is accurately and clearly defined by appropriate imaging, usually MRI. This group typically includes patients with pituitary adenomas, craniopharyngiomas, localised pilocytic astrocytomas, meningiomas and other rarer tumours such as chordoma and
chondrosarcoma in the parasellar and skull base region. Utilising 4-6 fixed fields SCRT delivers treatment with maximum normal tissue sparing (41,151). It is a proven optimal beam arrangement for irradiating tumours at this site with the potential to reduce treatment-induced endocrine dysfunction and other late effects, including vascular complications and stochastic induction of both intra- and extra-cranial second tumours.

Where the target volume is horseshoe-shaped and wrapping around a vital structure, the developing technology of IMRT or the use of protons appear to be the most promising treatment techniques to achieve homogeneous dose delivery whilst keeping the radiation dose to the critical normal tissue within tolerance (178,180).

Extensive work published by Flickinger's group at the University of Pittsburgh on their treatment of patients with acoustic neuroma using SRS has established this technique as clearly efficacious but associated with a significant risk of damaging the fifth, seventh and eighth cranial nerves (16,22). Plowman and colleagues at St. Bartholomew's Hospital have also made important contributions to the literature on the treatment of acoustic neuroma using stereotactic technology (192,193,194). The relationship between SRS dose, the length and diameter of the nerve and the risk of neuropathy have been examined (23,26,195,196) and this knowledge applied to try to reduce the risk of cranial nerve damage (197). The results of prospective studies comparing SRS with SRT are now becoming available which should provide the evidence required
to prove which is the superior treatment modality, based on long term tumour control and neurological morbidity (27,198).

The rationale for using stereotactic treatment delivery in the management of patients with high grade gliomas has already been discussed in detail. It is based on the premise that dose escalation to the region of the tumour with greatest cell density may improve the duration of local control and maintain a better quality of life for longer, even though cure will not be achievable with the therapeutic modalities presently available. The relative risks and benefits of dose escalation in the primary management of these patients is currently the subject of RTOG and EORTC trials.

Two single arm studies have shown HSRT to be safe and efficacious for treating small volume recurrent high grade gliomas, concluding that it should be the favoured localised high dose treatment for suitable patients (112,154). However it remains unclear how much patient selection played in determining the favourable survival figures.

Patients with solitary or a very limited number of brain metastases are usually treated with SRS in place of neurosurgical resection, as the results are equivalent in terms of tumour control and survival (199). Suitable case selection is important, particularly for patients with more than one metastasis, to ensure that this more aggressive, complex and expensive approach to treatment is appropriate and justified (200). The use of SRS or SRT in place of whole brain radiotherapy alone for patients with two or more metastases remains controversial, some believing that the case is not yet proven (201). Nevertheless, although the addition of whole
brain radiotherapy at the time of initial SRS/SRT treatment has not resulted in a survival benefit over SRS/SRT alone (201), it does improve the duration of local control which in turn is likely to maintain a better quality of life for longer (202,203). Further clinical evidence is awaited from RTOG 9508 regarding the optimal management of patients with a few brain metastases. This phase III trial is comparing whole brain irradiation alone with whole brain irradiation plus SRS for patients with two or three brain metastases.

The use of HSRT in place of SRS is being examined for the treatment of patients with a limited number of brain metastases (204), particularly as modelling studies demonstrate a potential biological advantage for HSRT over SRS for the treatment of malignant brain tumours (29).

**6.5.7 SRS for AVMs**

The principle of using SRS to treat an AVM is that by delivering a sufficiently large single dose of radiation with great accuracy and precision, obliteration will result due to highly localised, permanent late damage developing within it but without collateral neurological damage. This results in high obliteration rates with few complications for small AVMs, but when the diameter of the AVM exceeds 3 cm the much lower obliteration rate and higher risk of significant neurological sequelae argues against the use of SRS (7,8,9,10). Intriguingly, despite the extensive use of SRS for the treatment of AVMs, a reduction in the frequency of bleeding and an improvement in survival has not yet been unequivocally demonstrated (205,206,207). The gold standard treatment for
AVMs remains neurosurgery but SRS is used for inoperable situations or when the patient refuses surgical intervention.

6.5.8 Extracranial SRS/T

Areas of development utilising stereotactic principles and technology outside of the brain include SRS boost following conventional external beam radiotherapy in the primary management of nasopharyngeal carcinoma (208), treating limited, locally persistent or recurrent nasopharyngeal carcinoma with SRS (137,139) or SRT (138), as well as other head and neck tumour sites (209). A modification of the GTC frame facilitates the treatment of an extended range of skull base, nasopharyngeal, accessory sinus and other superior tumours of the head and neck region (210).

The development of a noninvasive immobilisation system that combines a circumferential body cast and a head mask system in a rigid stereotactic body frame, has enabled the delivery of extra-cranial SRT with millimetre accuracy to treat primary or secondary paraspinal tumours (211). More recently a targeting system that integrates a CT-on-rails scanner with a linear accelerator has been described for the stereotactic treatment of spinal or paraspinal tumours (212).

In the thorax and abdomen sufficiently accurate patient positioning for SRS/T has been achieved using the combination of an individually shaped vacuum pillow and an abdominal pressure device to reduce abdominal wall movement (213). This has been used to safely and accurately deliver SRS to a small cohort of 10 patients with stage I non-small cell lung
cancer (214) and a larger group of 37 patients with liver
tumours, the great majority of which were metastases (215).

Hypofractionated SRT utilising fiducial marker
localisation has been used to treat 47 patients with prostate
cancer who have a low risk of extracapsular extension (216).
An average intrafractional prostate movement of 2 mm or less
has been demonstrated using the methodology described in this
phase I study and the authors plan to report acute and late
toxicity data in 2005.
6.6 Final conclusions

The three constituent parts of this thesis have contributed to the optimisation of stereotactic radiotherapy treatment delivery and have been published as original papers. Chapters two and four appeared in the International Journal of Radiation Oncology Biology and Physics (189,112) and chapter three in Radiotherapy and Oncology (151). Research published in these two journals has the potential to influence clinical practice worldwide.

Apart from the obliteration of AVMs and for the creation of a lesion for functional neurosurgical purposes, there is no evidence that SRS is either safer or more effective than HSRT or conventionally fractionated SCRT for treating benign or malignant brain tumours.

Most brain tumours present an irregular target volume and SCRT provides the optimum technique for the accurate delivery of a homogeneous dose of radiation. Usually four to six noncoplanar, conformal, fixed fields maximally spare normal tissue, using lead alloy blocks or a micro-MLC to shape the beams. A spherical or elliptical target volume is best conformed to by three to five noncoplanar arcs using circular collimators of an appropriate diameter. Avoidance of a sagittal arc or fixed field exiting down the long axis of the body, minimises the risk of inducing a radiation-related malignancy in other organs, particularly the thyroid gland.

The use of IMRT should be restricted to specific clinical indications where it is likely to be superior to SCRT, typically where the tumour is wrapped around a critical structure such
as the brainstem. On current evidence the delivery system should involve a micro-MLC for maximal sparing of the critical structure and established safe tolerance doses for the normal tissues should not be exceeded.

The routine clinical use of a new technology for the delivery of highly localised radiotherapy must be based on robust clinical evidence of benefit from well conducted, scientifically sound, prospective studies, ideally randomised, with appropriate endpoints of survival, quality of life and disease control. If the study was not a randomised controlled trial, these endpoints need to be assessed against those obtained with well established, proven treatment techniques and only if benefit and superior outcome without increased morbidity can be demonstrated, should the new technology be adopted as best standard practice. This is of particular relevance when there is increased potential for geographic miss or underdosing due to reducing conventional margins around the target volume or increased toxicity from unconventional fractionation schedules.
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PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS THESIS

Papers


Abstracts


**Poster Presentations**


12. "Whole body doses from linear accelerator-based stereotactic radiotherapy". British Oncological Association Meeting, Cardiff University, Cardiff, Wales. 7-9 July 1996.


15. "Whole body doses from linear accelerator-based stereotactic radiotherapy". European Association for Neuro-Oncology 2nd Congress, Wurzburg, Germany. 6-9 Oct 1996.

**Invited Lectures**


18. "Delivery of External Beam Conformal Therapy - Stereotactically-Guided Conformal Radiotherapy ". Shaping Treatments to Tumours, 9th Annual Oncology Symposium, Rusacks Hotel, St Andrews, Scotland. 16-17 Feb 1996.


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APPENDIX I

Clinical Investigation

HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY IN THE MANAGEMENT OF RECURRENT GLIOMA

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Purpose: This study aimed to assess the efficacy and toxicity of hypofractionated stereotactic radiotherapy (SRT) in the management of patients with recurrent glioma.

Methods and Materials: From January 1989 to July 1994, 36 patients with glioma were treated at the time of recurrence. Twenty-nine had recurrent high-grade astrocytoma, 3 high-grade oligodendroglioma, 1 high-grade ependymoma, and 3 pilocytic astrocytoma. Hypofractionated stereotactic radiotherapy was given using either three noncoplanar arcs or four to six noncoplanar fixed beams at 5 Gy/fraction, to doses ranging from 20 to 50 Gy initially on a dose escalation program. Two patients received 20 Gy, 8 received 30 Gy, 10 received 35 Gy, 10 received 40 Gy, 5 received 45 Gy, and 1 received 50 Gy, treating 5 days/week.

Results: The median survival of 29 patients with recurrent high-grade astrocytoma was 11 months from the time of SRT. This compared to a median survival of 7 months for a cohort matched for age, performance status, and initial histologic grade who received nitrosourea-based chemotherapy at recurrence (p < 0.05). Initial low-grade astrocytoma histology was the only favorable prognostic factor for survival on univariate analysis. Three patients with recurrent oligodendroglioma remain alive 11, 23, and 34 months after SRT. Three children treated for recurrent pilocytic astrocytoma remain alive 14, 41, and 55 months following SRT. Presumed radiation damage, defined as reversible steroid-dependent toxicity, was observed in 13 patients (36%) and required reoperation in 2 (6%). A total dose of >40 Gy was a major predictor of radiation damage (p < 0.005).

Conclusion: Hypofractionated SRT is a noninvasive, well-tolerated, outpatient-based method of delivering palliative, high-dose, focal irradiation. © 1997 Elsevier Science Inc.

INTRODUCTION

Hypofractionated stereotactic radiotherapy (SRT) is a noninvasive method of delivering focal irradiation, potentially of lower toxicity than single-fraction radiosurgery (RS). We previously published initial results in selected patients with recurrent high-grade astrocytoma (9). This study has continued and we report an update of a larger number of patients with recurrent glioma to further define the efficacy and toxicity of hypofractionated SRT.

METHODS AND MATERIALS

From January 1989 to July 1994, 33 patients with high-grade glioma at the time of recurrence were treated at the Royal Marsden Hospital with hypofractionated SRT. The patients and disease characteristics are shown in Table 1. All patients recurred after receiving radical radiotherapy to doses ranging from 45 Gy in 20 fractions to 60 Gy in 30 fractions (median dose 55 Gy) as part of their initial treatment. Median time interval between initial radiotherapy and SRT was 29 months (range 5–174). All tumors recurred at the original site within the previous high-dose region.

The recurrent tumor dimension ranged from 1.4 to 7.0 cm (median 4.8), as measured by the maximum diameter of enhancement on computed tomographic (CT) or magnetic resonance imaging (MRI) scans (Table 1). Recurrent tumor volume ranged from 3 to 93 cm³ (median 24), as calculated by summation of the outlined region of interest on adjacent CT slices on the planning computer (Table 1). Since 1991 only recurrent tumors with a maximum dimension ≤5 cm have been treated.

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Eleven patients had Grade 3 and 10 Grade 4 astrocytoma on initial histology using the Kernohan classification (8). Only 2 patients had tumor recurrence biopsied. Eight patients with an initial histologic diagnosis of Grade 2 astrocytoma were classified as high grade at relapse, of whom six underwent surgery prior to SRT. Three had transformed to Grade 3, and three to Grade 4 astrocytoma. Two patients had rapid disease progression and high-grade features on imaging. Three patients with initial high-grade oligodendroglioma had biopsies at relapse: two showed no change, and one a mixed oligoastrocytoma. One patient had recurrent high-grade ependymoma.

Three children with recurrent pilocytic astrocytoma were treated with SRT. One boy initially treated with surgery alone recurred 11 months later at the age of 5. Two girls were treated with surgery and radiotherapy to a dose of 50 Gy in 25 fractions and 54 Gy in 30 fractions. The former recurred 7 years later at the age of 14, the latter 2 years later at the age of 16. Both underwent further surgery which allowed confirmation of the original diagnosis prior to SRT. Recurrent tumor volumes were 1, 1, and 5 cm³.

**Stereotactic technique**

The technique of fractionated SRT has been described in detail elsewhere (5, 6, 9). Patients were immobilized in a relocatable Gill–Thomas–Cosman frame.¹ Localizing CT scans were transferred to the planning system² and three-dimensional isodose distributions were obtained using three to six (median of three) noncoplanar arcs or four to six noncoplanar static beams. The planning target volume was defined as the enhancing tumor with a 2-mm margin. The treatment plans were normalized to 100% at the isocenter and prescribed to the 90% isodose surface in 31 patients and 80% isodose surface in 5 patients.

All patients received 5 Gy fractions daily 5 days/week, initially on a dose escalation program (9), with doses ranging from 20 to 50 Gy. Of the high-grade patients, two received 20 Gy, eight received 30 Gy, eight received 35 Gy, nine received 40 Gy, five received 45 Gy, and one received 50 Gy. Two children with recurrent pilocytic astrocytoma received 35 Gy, and 1 received 40 Gy.

**Patient evaluation**

Patients were evaluated by clinical examination and functional status assessment, measured as activities of daily living on a verbally administered Barthel index (BI) (13) before SRT, 2–4 weeks after, and then every 2–3 months. A change of ≥3 points on the BI was considered to be significant. A CT or MRI scan was performed at 6 weeks after SRT and subsequently every other month. More recently imaging has been performed 3–4 months after SRT and at the time of clinical deterioration.

Diagnosis of radiation-induced damage was made clinically and defined as neurologic deterioration in physical performance, cognitive function, or speech without evidence of progressive tumor, with improvement on corticosteroids that was maintained for at least 2 months. A Cox proportional hazards model analysis was used to determine factors predictive of radiation damage. Total SRT dose, recurrent tumor volume, previous radiotherapy, age at SRT, and initial tumor grade were investigated. Survival was measured from the time of SRT and calculated by the Kaplan–Meier method (7). Comparison of prognostic factors was assessed by the log rank test (16).

**Comparison with chemotherapy**

The survival of the 29 SRT patients with high-grade astrocytoma was compared with that of a matched control group treated with nitrosourea-based chemotherapy at recurrence (17). Eight of the 29 patients had chemotherapy at first recurrence, prior to SRT, and were excluded from this comparison. The remaining 21 patients were each matched to a chemotherapy control for the known prognostic factors of grade at initial diagnosis, disease-free interval (=2 or >2 years), age (=10 years), and performance status at recurrence. Eighteen of the matched controls were treated prior to the introduction of SRT, and three were ineligible for SRT because of the size of the recurrent glioma.

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¹Radionics, Inc., Burlington, MA.
²GE Target 1, Buc, France.
Hyypofractionated stereotactic radiotherapy § S. F. SHEPHERD et al.

Survival
The median survival of 32 patients with recurrent high-grade glioma was 11 months from the time of SRT (Fig. 1). Median survival of 29 patients with high-grade astrocytoma at the time of recurrence was 10.7 months. After exclusion of 8 patients who transformed from low- to high-grade astrocytoma, the median survival of the remaining 21 patients was 9.6 months (Fig. 1). At the time of analysis, 24 patients had died: 21 from recurrent disease in direct continuity with the irradiated site, 2 who progressed >3 cm away from the treated volume, and 1 with disease in the spinal cord. One patient died from pulmonary embolism.

Three patients with oligodendroglioma remain alive 11, 23, and 34 months after SRT, and three patients with recurrent pilocytic astrocytoma are alive without disease progression at 14, 41, and 55 months.

Toxicity
All patients completed SRT treatment as outpatients without acute adverse effects. Dexamethasone was not used routinely and was introduced only in the presence of raised intracranial pressure or progressive focal neurologic deficit. Alopecia was limited to a small region for lesions close to the skull.

Late presumed radiation-induced damage was seen in 13 of the patients (36%). The degree of deterioration varied from mild to life threatening. In 12 of the 13 patients, assessment using physical examination, the BI, and Karnofsky performance status (KPS) quantified the extent of functional deficit. One patient required hospitalization and urgent therapy with intravenous mannitol and dexamethasone for raised intracranial pressure. In four patients, presumed radiation necrosis was verified by positron emission tomography (PET) using 18-fluoro-deoxyglucose, and in two others, it was confirmed on histology available following reoperation for progressive deficit and features of raised intracranial pressure requiring prolonged high-dose corticosteroids. The actuarial risk of developing presumed delayed radiation complications was 34% [95% confidence interval (CI) 17–51%] at 12 months and 45% (95% CI 21–70%) at 24 months from the time of SRT (Fig. 2).

The relationship between recurrent tumor volume, SRT dose, and complications is shown in Fig. 3. A stereotactic radiotherapy dose of >40 Gy was a significant predictor of radiation damage ($p < 0.005$). Patients who received >40 Gy had 6.4 (95% CI 1.8–22.8) times the risk of damage, compared with those who received ≤40 Gy. No other factor was found to be of independent prognostic significance. However, there was a trend toward a higher risk of complications for larger tumor volumes >35 cm³.

Palliative efficacy
Functional assessment using the BI was recorded in 25 patients with high-grade glioma at the time of SRT, and at 3 and 6 months after treatment. The maximum achievable score was 20. At the time of SRT, 22 of 25 patients (88%) had no or mild disability with BI scores of 18–20. At 3 and 6 months after SRT, BI scores of 18–20 were recorded in 20 of 24 (83%) and 14 of 22 (64%) patients, respectively. Six patients deteriorated between the 3 and 6 months of assessments.

Prognostic factors
Initial histologic grade, age (<35 vs. >35 years), performance status (<70 vs. >70), SRT dose (<35 Gy vs. >35 Gy and ≤40 Gy vs. >40 Gy), sex, and recurrent tumor volume (<35 cm³ vs. >35 cm³) were assessed for prognostic significance for survival on univariate analysis in patients with high-grade glioma. Only initial histologic grade was of prognostic significance ($p < 0.05$); patients with initial low-grade tumors had a median survival of 21 months compared to 10 months in patients with initial high-grade tumors.

Comparison with chemotherapy
Survival results for the 21 patients treated with SRT who had not received chemotherapy were compared to the
21 matched control patients with recurrent astrocytoma who had been treated with nitrosourea-based chemotherapy at the same institution (17). The median survival of the patients treated with SRT was 11 months, compared to a median survival of 7 months in the matched control patients ($p < 0.05$) (Fig. 4).

**DISCUSSION**

Stereotactic radiotherapy as a noninvasive means of accurate delivery of localized irradiation to small target volumes (1) is being explored in the treatment of brain tumors on the assumption that such focused radiation may improve tumor control without increased toxicity. In small localized tumors, high dose can be largely confined to the tumor with little dose reaching the surrounding normal brain (6). The conventional linear accelerator technique of multiple noncoplanar arc therapy is suitable for small spherical tumors. Larger and nonspherical lesions may best be treated with noncoplanar conformal fixed fields using a technique of stereotactically guided conformal radiotherapy (SCRT) (2). Both fractionated SRT and SCRT were used in the treatment of recurrent tumors.

There is a clear need to improve local tumor control in high-grade gliomas, as most patients die from progressive disease at or in close proximity to the primary site (20). However, high-grade gliomas in the recurrent setting are seldom small enough to be suitable for SRT. The impetus for using SRT in recurrent gliomas comes from Phase II studies of interstitial radiotherapy (IRT) reporting favorable survival (19). Stereotactic radiotherapy may be considered a noninvasive alternative to IRT, and on theoretical grounds fractionated SRT may carry similar normal tissue toxicity to IRT and potentially less than single-fraction radiosurgery (RS).

The selected patients with recurrent high-grade glioma reported in this study, which represents only a small proportion of those with recurrent high-grade tumors, had a median survival of 11 months. This is equivalent to the median survival achieved in patients with recurrent high-grade glioma treated with IRT. The selection criteria in terms of patient characteristics and tumor size are likely to be similar.

As this was not a randomized study, the results were compared to a cohort of patients treated at the same institution with nitrosourea containing chemotherapy at the time of recurrence, matched for the known prognostic factors of age, initial histologic grade, and performance status (17), as well as disease-free interval. Although SRT patients appear to have better survival, other factors may have introduced bias in their favor, as in the case of IRT (4). The SRT patients were selected by tumor size, and this may predict for favorable survival not corrected for in this analysis. Retrospective studies of primary treatment for high-grade gliomas suggest that patients with smaller tumors after surgery have better survival (21), and tumors ≤4 cm diameter suitable for RS also carry a better prognosis (3). Smaller tumors are also subject to lead time and length bias.

This study represents a continuation of a previous dose-escalation Phase I/II study (9) trying to define the appropriate dose of hypofractionated SRT (given at 5 Gy/fraction) in terms of toxicity and survival. Because of the poor prognosis of patients with recurrent high-grade glioma and the overall palliative and noninvasive nature of fractionated SRT, it is not justifiable to mount a toxicity study based on the histologic verification of radiation necrosis. We identified a clinically appropriate surrogate endpoint of presumed radiation damage defined as neurologic deterioration without evidence of progressive tumor which improved and was maintained for at least 2 months on corticosteroids. This endpoint is similar to that used in studies of RS toxicity (15), and is therefore likely to represent true radiation damage.

![Fig. 4. Comparison of survival for two groups of 21 patients with high-grade astrocytoma at recurrence matched for age, Karnofsky performance status, initial histologic grade, and disease-free interval. Treated with SRT or with nitrosourea-containing chemotherapy.](image-url)
The frequency of presumed radiation damage was 36%. When expressed in cumulative actuarial terms it reached 45% at 2 years. It is difficult to compare the toxicity results with other studies, as actuarial risk has not previously been reported. However, the overall risk is high, which would be expected for high-dose retreatment following previous radiotherapy to tolerance doses. The analysis suggests that the major predictor of clinically significant radiation damage is SRT dose. Although irradiated volume is also likely to be relevant, this parameter did not reach statistical significance because of the small numbers of patients treated.

Radiation damage is usually not an acceptable consequence of radiotherapy. Certainly as a cause of neurologic deficit it adversely affects function and quality of life, although in the majority of patients it was reversible with corticosteroids. Patients who experienced radiation damage, already selected by surviving long enough for it to develop, had no worse survival than those without such damage. It would therefore appear that radiation damage did not adversely affect survival and, as with IRT series, is considered an acceptable consequence of treatment with high-dose radiation. Patients with recurrent glioma are treated with palliative intent, and in the majority a non-invasive approach to therapy could be maintained, as only two patients (6%) required reoperation for problems requiring prolonged use of high-dose corticosteroids. The rate of reoperation was considerably lower than that reported for patients treated with IRT (10) or single-fraction RS (12–18). This may be due to a less aggressive reoperation policy, as well as lower toxicity of fractionated SRT, particularly at doses of 30–35 Gy.

Hypofractionated SRT, as with other forms of localized high-dose irradiation, is not a curative treatment for patients with recurrent high-grade glioma. Nevertheless, the overall results are favorable, and on the basis of survival and acceptable toxicity it is a reasonable treatment option for patients with small tumors at the time of recurrence. However, the results are based on relatively small numbers of patients and the conclusions cannot be considered fully proven.

It is difficult to assess the efficacy of hypofractionated SRT in patients with recurrent low-grade tumors. The suggestion is that the treatment is effective as all previously progressive tumors remained static. The results must, however, be considered in the context of the known natural history of low-grade tumors. Patients with recurrent oligodendroglioma retain the more favorable prognosis of low-grade tumors at the time of recurrence (17). The indolent natural history of pilocytic astrocytomas also precludes definite conclusions about the long-term control following fractionated SRT, although the results so far are encouraging.

Is SRT useful in the primary therapy of high-grade gliomas? So far, no definite survival advantage has been demonstrated for RS boost as part of the initial treatment (11, 14). However, it would be appropriate to test in a randomized study a fractionated SRT boost as a less-toxic noninvasive alternative to RS or IRT. Future studies of SRT either in the primary or recurrent setting will need to concentrate not only on survival, but also on quality of life, and any survival benefit will have to be carefully weighed against the potential of increased toxicity. In the meantime it is reasonable to argue that the equivalent dose distribution, noninvasive nature, similar efficacy, and lower toxicity of SRT compared to IRT make it the favored localized high-dose treatment in suitable patients.

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APPENDIX II

WHOLE BODY DOSES FROM LINEAR ACCELERATOR-BASED STEREOTACTIC RADIOTHERAPY


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INTRODUCTION

Stereotactic radiosurgery/therapy (SRS/T) using a linear accelerator has become a widely used technique for the treatment of intracranial arteriovenous malformations (AVM) and malignancy. Focal irradiation is delivered with isocentric multiple noncoplanar arcing beams or fixed fields. The optimal arc arrangement has not been clearly defined and a wide variety of techniques have been reported ranging from a single transverse to a combination of 11 noncoplanar beams (1, 6). There is little reduction in the volume of normal brain receiving >50% of the isocenter dose using more than four arcs to treat spherical targets from 10 to 55 mm in diameter (5). However, dose to critical structures and along beam exit paths can be reduced by increasing the number of arcs further. One possibility involves five evenly spaced 90° arcs comprising a sagittal, two transverse, and an intermediate arc placed at 45° to the plane of each transverse and sagittal arc (9). Concern over whole body doses from different beam arrangements, especially in children with a nonmalignant condition, led us to compare techniques particularly with and without a sagittal arc.

For the treatment of nonspherical lesions, four or more static, noncoplanar, conformal fields result in better sparing of normal brain compared with multiple arcs (2, 8). Although the best practical beam arrangement is not defined, tetrahedral or hexagonal spacing of beams may be optimal on theoretical grounds (14). A possible practical field arrangement may include a beam exiting through the length of the body and the dose received by organs outside...
The brain may be an additional factor in deciding the most appropriate beam configuration.

**METHODS AND MATERIALS**

A comparison of the two multiple arc arrangements (Table 1) was performed on a 5-MV Philips SL75/5 linear accelerator (linac) which was used for SRS/T until March 1994, after which it was replaced by a 6-MV Varian 600C. The measurements for the five-arc arrangement were repeated on the 6-MV Varian to assess a potential difference in whole body doses, and provide a midthoracic axial dose distribution. Using lithium fluoride (LiF) thermoluminescent dosimetry (TLD), whole body measurements were carried out on a supine Alderson–Rando anthropomorphic phantom. For each experimental treatment exposure, dosimeters were placed in the coronal and sagittal planes on an axial grid of 3-cm separation, and four were taped in a position equivalent to the testes and covered with a sheet of wax to simulate the scrotum. Measurements were made on consecutive axial slices at a 2.5-cm separation to the midthoracic level and at a 7.5-cm slice separation for the remainder of the torso. The midthoracic axial dose distribution was recorded using a 3 × 3 cm grid of LiF dosimeters covering the area of slice 16. Readings were made on a Teledyne 7300 reader (Teledyne Isotopes, Westwood, NJ).

Fixed field and solitary 90° sagittal arc measurements were taken on the 6-MV Varian with the phantom upright. A Farmer graphite-walled 0.6-cm³ ionization chamber and an electrometer (Farmer Dosemeter 2570, Nuclear Enterprises, Reading, UK) were used to record central and off-axis exit doses at slice levels 13, 16, 18, 21, 23, 25, 28, and 33. The chamber was securely fixed within a specially machined, 2.5-cm-thick, body-contoured Perspex sheet which replaced the relevant slice to maintain a constant exit path length.
Table 1. Details of beam arrangements

<table>
<thead>
<tr>
<th>Technique</th>
<th>Table angle*</th>
<th>Gantry angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four-arc rotation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arc 1</td>
<td>20°</td>
<td>20° to 110°</td>
</tr>
<tr>
<td>Arc 2</td>
<td>65°</td>
<td>20° to 110°</td>
</tr>
<tr>
<td>Arc 3</td>
<td>-20°</td>
<td>-20° to -110°</td>
</tr>
<tr>
<td>Arc 4</td>
<td>-65°</td>
<td>-20° to -110°</td>
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<tr>
<td>Five-arc rotation</td>
<td></td>
<td></td>
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<tr>
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<td>20°</td>
<td>20° to 110°</td>
</tr>
<tr>
<td>Arc 2</td>
<td>50°</td>
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<tr>
<td>Arc 3</td>
<td>90°</td>
<td>20° to 110°</td>
</tr>
<tr>
<td>Arc 4</td>
<td>-20°</td>
<td>-20° to -110°</td>
</tr>
<tr>
<td>Arc 5</td>
<td>-50°</td>
<td>-20° to -110°</td>
</tr>
</tbody>
</table>

* Clockwise table rotation is positive, anticlockwise is negative.
° Gantry vertical: 90° = left lateral; -90° = right lateral.
+ Long sagittal arc: 20° to 160°.

With the phantom in the supine position, the isocenter of a spherical target volume situated in the midline in the middle of slice 2 (equivalent to a lesion in the corpus callosum) was positioned at the radiation isocenter using isocentric localizing lasers. A 20- and a 40-mm collimator (Radionics Inc. Burlington, MA) were used with the linac secondary collimating jaws set to a 5 × 5 cm field, to provide two sets of measurements for each arc arrangement. The collimator sizes were chosen to represent the range commonly used in clinical practice. All arcs were 90° except for one set of measurements where the sagittal arc was lengthened to 140° to assess the potential effect on the thyroid dose. Each degree of arc was equally weighted and an isocenter dose of 20 Gy was delivered during each experimental exposure, one for each different treatment scenario.

The leakage radiation dose was determined by TLD in the humanoid phantom using the four-arc arrangement (Table 1) to deliver 20 Gy at the isocenter with secondary collimators fully closed and a lead block placed centrally on the lead tray.

Fixed-field measurements were taken with the phantom upright, gantry and couch at 0°, secondary jaws set to 5 × 5 cm, with the 40 mm circular collimator. To determine the highest density fixed-field exit path through the head, neck, and thorax, the minimum dose position in the central sagittal plane just below the diaphragm (phantom slice 21) was located with the ionization chamber. The treatment isocenter was situated in the middle of slice 2 along this vertical axis. The linac light field was used to position the ionization chamber in the center of the radiation field and isocentric localizing lasers aligned with marks on the phantom ensured its correct relocation before each measurement. A second set of measurements was recorded using the same setup but with a more anterior isocenter such that the beam exit passed through the pharynx, trachea, thyroid, and main upper airways. A final set of readings was taken using a central beam axis 4.5 cm to the right of the first. This was sufficiently lateral to include the long axis of the right lung in the beam exit while minimizing the effect of neck curvature on transmission. At each fixed-field exposure, 500 monitor units were given as an applied dose and the ionization chamber measurements converted to Gray using the relevant calibration factors. To provide a comparative dataset, 1000 monitor units (to ensure adequate chamber readings) were given using a single 90° sagittal arc and the 40-mm circular collimator to treat the first (maximum density path) and third (lateral) isocenters. A sagittal section isodose plot was generated at each isocenter from CT data of the phantom entered onto a GE Target 1 planning computer and, from these, the percentage depth dose at each isocenter determined. For direct comparison with the solitary arc values the fixed-field values were doubled. Both sets of results were divided by five to represent body dose values from treatment plans using five fixed fields or arcs, as negligible.

Fig. 2. Midline sagittal isodose lines for a 20-mm collimator comparing the four- and five-arc techniques on the 5-MV Philips.
Fig. 3. Coronal isodose lines for a 40-mm collimator comparing four- and five-arc techniques on the 5-MV Philips SL75/5. Isodose line values expressed as percent of isocenter dose.

Table 2. Mean organ doses as a percentage of the dose at target isocenter

<table>
<thead>
<tr>
<th>Organ</th>
<th>Collimator</th>
<th>Photon energy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 MV*</td>
</tr>
<tr>
<td>Thyroid</td>
<td>20 mm</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>40 mm</td>
<td>0.45</td>
</tr>
<tr>
<td>Ovary</td>
<td>20 mm</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>40 mm</td>
<td>0.015</td>
</tr>
<tr>
<td>Testis</td>
<td>20 mm</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>40 mm</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* Philips SL75/5.
' Varian 600C.
Table 3. Probability of fatal cancer developing in different organs per 1000 people per Sievert based on ICRP 60

<table>
<thead>
<tr>
<th>Organ</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>0.8</td>
</tr>
<tr>
<td>Esophagus</td>
<td>3.0</td>
</tr>
<tr>
<td>Breast</td>
<td>2.0</td>
</tr>
<tr>
<td>Lung</td>
<td>8.5</td>
</tr>
<tr>
<td>Stomach</td>
<td>11.0</td>
</tr>
<tr>
<td>Colon</td>
<td>8.5</td>
</tr>
</tbody>
</table>

contribution to body dose from the four beams other than the sagittal beam had been noted in the planned five multiple-arc experiments.

RESULTS

Multiple arcs

Figures 1–4 display isodose plots in the sagittal and coronal planes for each arc arrangement and collimator on the 5-MV Philips linear accelerator. The contribution of the sagittal arc was most noticeable in the coronal plane, causing the isodose lines to penetrate much further along the central axis (Figs. 1 and 3). By increasing the sagittal arc length from 90° to 140° the midline isodoses were less penetrant, thus reducing the thyroid dose (Fig. 5). A greater reduction in thyroid dose was achieved by using a four-arc arrangement without a sagittal arc (Figs. 2 and 4), where two arcs exit through the shoulders avoiding the long axis of the body. There was a three- to fourfold greater exit dose to the neck and superior mediastinum when comparing the five-arc with the four-arc arrangement. The abdomen received <0.2% of the isocenter dose with the five-arc and <0.1% with the four-arc technique. The pelvis received <0.05% of the isocenter dose with either technique.

Repeating the measurements using the five-arc technique on the 6-MV Varian 600C gave similar isodose plots with the absolute dose 10–15% higher at thyroid level. The midthoracic axial isodose distributions are shown in Fig. 6. A higher central axis exit dose and a greater effect of lung scatter were demonstrated for the 40-mm collimator, resulting in twice the mediastinal dose and a 30–40% greater lung dose than that measured for the 20-mm collimator.

The effect of a sagittal arc on dose to critical organs is summarized in Table 2 with doses expressed as a percentage of the isocenter dose. Each of the mean thyroid dose values was the average of two dosimeter readings, whereas each gonad dose value was derived from four readings. The errors associated with the TLD powder measurements were 3% for the thyroid and 10% for the gonads. Lengthening the sagittal arc by 50° reduced the thyroid dose by 25%, but it remained considerably higher than with the four-arc technique. Although the gonad dose was different between the two arc techniques, this was largely due to leakage radiation on the 5-MV Philips SL75/5, with relatively small contributions from primary and internally scattered radiation. Nevertheless, a dose increase due to the sagittal arc was
detectable when the five-arc technique was used. Leakage from the 6MV Varian 600C contributed only one quarter of the dose at the gonad level, the majority being from the sagittal arc. Leakage radiation on the 5-MV Philips SL75/5 and the 6-MV Varian 600C was 0.02–0.03% and 0.005–0.008% of the dose at the isocenter, respectively.

Fixed fields
The fixed beam exiting through the long axis of the phantom gave a tenfold greater dose at all levels, including the gonads, than the 90° sagittal arc (Fig. 7). An additional 30–40% dose increase to organs below the level of the diaphragm was recorded when the fixed beam or sagittal arc traversed the long axis of the right lung (Fig. 7), or the pharynx and main upper airways of the phantom (data not shown).

DISCUSSION
When the linear accelerator was first adapted to deliver SRS/T, a variety of techniques were developed involving up to 11 noncoplanar arcs of rotation. Currently, four to six arcs are most widely used. Dose-volume histogram analysis of the volume of brain receiving >50% of the isocenter dose when treating a range of spherical targets has shown no advantage to support the routine use of more than four arcs (5). However, the use of five or more arcs will lower the exit dose from each and can help reduce the dose to critical structures adjacent to the target volume.

Important considerations when deciding upon the optimal beam arrangement include tight conformation and homogeneity of target dose, as well as minimizing dose to eloquent intracranial structures and to the rest of the brain. The issue of arc or fixed beam exit through extra-
cranial structures is of less importance but should be considered when treating benign lesions in young patients with a normal or near-normal life expectancy after SRS/T.

The Alderson–Rando anthropomorphic phantom and LiF TLD provides an in vitro method for the measurement of radiation dose received by different parts of the body. Potential errors need to be quantified for the particular system used as these are variable. For this study the error in the measured doses was 10% for those <5 cGy and 3% for those >5 cGy.

The results of the whole body dose measurements show significantly higher values throughout the length of the torso when a sagittal arc is used. This was most striking in the thyroid gland dose, which was three to four times higher with five rather than four arcs. The four-arc technique with beams exiting through the shoulder girdle, avoids irradiating the thyroid and other centrally placed organs. An alternative means of reducing central dose is by using a higher number of longer arcs (4). When it is of clear benefit to include a sagittal or near-sagittal arc in a treatment plan, an alternative to increasing the number...
Fig. 7. Coronal isodose lines for central and off-axis (i) single 90° arc and (ii) fixed-field measurements using a 40-mm collimator. Isodose line values expressed as percent of isocenter dose when the arc or fixed field is one of five equally weighted fields.

of arcs would be to interrupt the sagittal arc over the higher risk exit region. The 355°-5° apical sector was noted to deliver >95% of the body dose and could be excluded in clinically appropriate situations. Lengthening the sagittal arc also reduced the central dose, but this required the gantry to rotate into the undercouch position, which may not be possible with stereotactic techniques in which the head is supported on a floor stand separate from the treatment couch (10).

Four to six fixed conformal fields may provide the optimum way of minimizing the volume of normal brain irradiated to >50% of the isocenter dose for larger, nonspherical targets (2, 8). The static beam measurements recorded show the importance of considering the path of a beam which exits down or near to the long axis of the body and the radiation dose delivered along it. The dose to the thyroid and the rest of the body should be taken into account in appropriate cases when deciding upon the optimal treatment plan.

The primary reason for considering dosimetry outside the brain is the risk of radiation-induced second malignancy. The most likely site for such tumors following SRS/T would be intracranial, although so far no cases have been reported. This absence probably reflects the relatively short follow-up of the majority of this patient group and over the next 10-20 years the risk may become apparent. The combination of smaller target volumes and steep dose fall-off may result in a lower incidence than described following fractionated radiotherapy for pituitary adenomas (3).

Thyroid malignancy is well established as a late complication of thyroid irradiation and the principle of
ALARA (as low as reasonably achievable) should be applied where practical (13). Exposure before the age of 5 years may result in three times the risk of thyroid cancer than following exposure in adulthood. Females are two to three times more likely to develop both naturally occurring and radiation-induced thyroid cancers. Applying these risk coefficients to a general population comprising equal numbers of both genders of adults and children, and using an absolute risk estimate of 2.5 cases per 10^4 person-years Gray in children exposed to external photon irradiation in childhood, the lifetime incidence of fatal thyroid cancer would be 7-8 cases per 10^4 person-years Gray (11, 12). The absolute risk of benign thyroid nodules following external radiation therapy in childhood is estimated to be 10.3 cases per 10^4 person-years Gray (11, 12).

Age is the critical factor in determining radiation risk. Using a multiplicative risk-projection model, the International Commission on Radiological Protection (ICRP) estimated a 7.3% per Sievert (Sv) lifetime risk of excess fatal cancers from medical exposure to ionizing radiation when averaged over the whole population (7). Using age-specific coefficients, adults (20-69 years) have an excess fatal cancer risk of 5.5% and children (0-19 years) have an excess fatal cancer risk of 11% per Sv. From ICRP 60, the probability of fatal cancer developing in different organs is shown in Table 3. These values have been used to calculate the risk from a single 20-Gy fraction of SRS as used for the treatment of AVMs (Table 4). As thyroid malignancy is considered fatal in only 5-10% of cases, the incidence of radiation-related cancer may therefore be at least tenfold greater using risk estimates of excess fatal cancers.

The ICRP estimates the excess risk for serious hereditary defects for all subsequent generations following exposure to be 1%/Sv (7). On the basis of the data presented, SRS/T can be considered to carry a negligible risk of inducing serious germline defects provided static beams exiting down the long axis of the body are avoided.

In summary, attention should be paid to the beam exits when planning SRS/T for treating AVMs or benign tumors, especially in children. The avoidance of a sagittal arc or the use of longer, more numerous arcs reduces exit dose, minimizing the amount of transmitted radiation received by the thyroid. When multiple static conformal beams are used, avoiding a beam exiting through the long axis of the torso will help to minimize the radiation dose to the rest of the body. However, extracranial doses should only be considered if relevant to the clinical context of the disease and an optimal isodose distribution over the target volume is still achievable.

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APPENDIX III

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Comparison of a multi-leaf collimator with conformal blocks for the delivery of stereotactically-guided conformal radiotherapy.

Comparison of a multi-leaf collimator with conformal blocks for the delivery of stereotactically guided conformal radiotherapy

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Abstract

Stereotactically-guided conformal radiotherapy is a practical technique for irradiating irregular lesions in the brain. The shaping of the conformal fields may be achieved using lead alloy blocks, a conventional multi-leaf collimator (MLC) or a mini/micro-MLC. Although the former gives more precise shaping, it is labour intensive. The latter methods are more practical as both mould room and treatment room times are reduced, but the shaping is limited by the finite leaf-width. This study compares treatment plans, in terms of normal tissue doses and tumour coverage, for fields shaped using conformal blocks and a conventional MLC in two series of geometrical shapes and nine patient tumours. For the range of tumour sizes considered (volumes 14–264 cm³, minimum dimension 30 mm, maximum 102 mm), the MLC treats, on average, 14% (range 3–34%) and 17% (range 0–36%) more normal brain tissue than conformal blocks to >50% and >80% of the prescription dose, respectively. The large variability is due to strong dependence on tumour shape and the presence of partial leaf-widths in the MLC fit. It is therefore important to consider both of these effects when deciding whether the MLC is appropriate for a particular target volume. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Stereotactic radiotherapy; Conformal; Multi-leaf collimator

1. Introduction

Stereotactically-guided conformal radiotherapy (SCRT) is a technique which delivers radiation using fixed, non-coplanar, conformal fields. It has been shown [8,9,11] that for irregular lesions, using three to six such fields gives improved normal tissue sparing when compared to single-isocentre multiple-arcing techniques. Although multiple isocentres may be used with arcing techniques to achieve better normal tissue sparing, this results in increased dose inhomogeneity within the target and extended treatment times. For this reason, SCRT can be considered the most appropriate treatment for irregular lesions.

Shaping of the fields can be achieved using lead alloy conformal blocks, a standard multi-leaf collimator (MLC) or a mini/micro-MLC [2,3,11,13–15]. We compared the two techniques that are commonly available in modern radiotherapy departments, i.e. divergent blocks and standard MLC. At our hospital, a specially designed conformal block holder allows Cerrobend (MCP 70: lead-bismuth-tin cadmium alloy) blocks to be accurately attached to the treatment head. This blocking system can be used for planning target volumes (PTVs) of dimensions between 20 and 110 mm. Although blocks can accurately conform radiation fields to the PTV, their production is labour intensive [7]. Commercially available tungsten MLCs offer a practical and rapid means of producing conformal fields, but beam shaping is less precise due to the 10 mm stepping of the leaves at isocentre [4,14].

The aim of this study was to compare the normal tissue doses resulting from these two shaping methods. Cumulative dose–volume histogram (DVH) analyses were therefore performed for two series of model volumes within a phantom, and for nine patient tumours.
2. Materials and methods

2.1. Geometrical shapes

A water-filled human skull containing a sphere and a circular cone (Radionics Inc.) was used. The phantom was scanned in a Siemens Somatom DR2 computed tomography (CT) scanner using 3 mm contiguous slices. The scan data were transferred to a GE Target II planning system where all of the planning and DVH calculations were carried out. The two volumes were outlined manually and then grown 3-dimensionally to create a range of sizes using in-house software [1]. Fifteen spheres were used, with diameters ranging from 30 to 66 mm (volumes 14-204 cm³). Five cones, which had their long axes lying in the superior-inferior direction, were used with dimensions ranging from 34 × 40 mm (base diameter × height) to 64 × 70 mm (volumes 15-131 cm³). This range of volumes was chosen to encompass the typical range for patient tumours.

2.2. Patient volumes

Nine patients who had been previously treated with SCRT using conformal blocks were chosen to assess the differences between blocks and MLC for realistic, clinical situations. All patients were CT-scanned in a Gill-Thomas-Cosman (GTC) stereotactic frame [5,6], with 3 mm contiguous slices being taken over the tumour region and 6 mm contiguous slices elsewhere. The CT data were transferred to the Target planning system where the gross tumour volume (GTV) was outlined manually by the clinical oncologist. A margin was then added to create the PTV. This margin included both that required to produce the clinical target volume (CTV) and that allowed for patient set-up variations (i.e. CTV to PTV margin).

The exact size of the GTV to CTV margin depended on the tumour type, clarity of tumour delineation on the images and treatment intent. Details of the patient tumours are given in Table 1. The brain was also outlined to allow DVH calculations for this organ.

2.3. Treatment planning

For each of the model volumes, a tetrad beam arrangement, which gives maximal beam separation for four non-coplanar beams, was maximal. For both shapes, a vertex field, parallel to the long axis of the cone, was used in conjunction with an inferior anterior oblique and two inferior posterior lateral oblique fields. For the patient volumes, four field arrangements were designed taking into account the proximity of critical structures, as would be done clinically. Planning was carried out for an Elekta SL25 at 6MV, with an Elekta MLC that has a 1 cm leaf pitch at isocentre.

In-house software was used to create block and MLC shapes based on the beam’s eye view (BEV) of the tumour in each field. This process involved a margin being added to the PTV in beam’s eye view to account for the 50-90% penumbra of the block/MLC, thus ensuring 90% coverage of the PTV. The required margins were determined from isodose plots for a variety of field sizes and were set as 3 mm and 4 mm for the blocks and MLC, respectively.

The blocks or MLC were fitted to the PTV plus this penumbral margin. The conformal blocks, which had 3% transmission, had a central open ‘island’, which exactly followed the shape defined by this added margin. For the MLC, an intrusive leaf fitting technique was used. In this technique, the edges of the leaves are ‘chamfered’ and then brought in until they just touch the outline, thus allowing the leaf to intrude into the field by up to half of its width, as shown in Fig. 1. The MLC leaf banks were modelled within Target by two blocks, each with 5% transmission. In some cases, the optimum MLC fit required asymmetric jaws to be used. As these were not available on the Target planning system, they were simulated by adding a divergent lead block to one side of a symmetric field, with the block edge defined to the nearest millimetre.

The created blocks (conformal blocks or MLC) were added to the appropriate fields and the dose distribution was calculated, normalising to 100% at the isocentre. The

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Table 1

<table>
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<th>Max./min. PTV dimensions (mm)</th>
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<th>PTV volume (cm³)</th>
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<tr>
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<td>52</td>
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<td>62/31</td>
<td>14</td>
<td>57</td>
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<td>5. Optic glioma</td>
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<td>9. Meningioma</td>
<td>102/80</td>
<td>137</td>
<td>264</td>
</tr>
</tbody>
</table>

*These are the maximum and minimum dimensions for the PTV in the beam’s eye views used in the plan. They do not include the penumbral margin.

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Fig. 1. Intrusive leaf-fitting technique. The leaf edges are ‘chamfered’ at 45° and then brought in to just touch the outline.
calculation was based on the Bentley-Milan model [12]. This employs 47 fanplanes, each with 47 fanlines, for the calculation of the dose distribution from each beam, making corrections to the output and depth dose based on the equivalent square of the blocked field. For the patient data, an equivalent pathlength correction was made along each of the fanlines, based on the CT data; for the model volumes, the phantom was assumed to be entirely water-filled. The model applies a correction factor to model the penumbra of the blocks.

The accuracy of the penumbral modelling was tested by comparison with film measurements. Three circular fields, of diameters 36, 48 and 60 mm, were created using both blocks and MLC, and the measured and predicted isodoses were compared. The agreement between predicted and measured 50%, 80% and 90% isodoses for blocks was generally better than 1 mm with occasional maximum discrepancies of 1.5 mm. For the MLC, the planning system tended to over-emphasise the stepping of the isodoses; agreement was within 1 mm at leaf edges and ends, but discrepancies of up to 2.5 mm were seen at leaf corners. To investigate the effect this would have on the calculated dose-volume histograms, blocks were created within the planning system with rounded leaves to give agreement of 1 mm between predicted and measured isodoses. Data were calculated with both the normal MLC blocks and these modified blocks for four circular fields arranged in a tetrad. Volume differences of <1.5% on the 50% volume and <2.5% on the 80% volume were found, indicating that the modelling by the planning system is adequate for these comparisons.

2.4. Dose-volume histograms

Differential dose-volume histograms (dDVHs) were calculated on a 2 mm × 2 mm × 2 mm grid. For the patients, calculations were carried out for whole brain and for PTV. For the model volumes, calculations were carried out for the volume of the skull and for the PTV. The PTV dDVH was subtracted from that for the brain/skull volume to give the dDVH for normal tissue. Cumulative dose–volume histograms (DVHs) were then calculated for both PTV and normal brain tissue. These were checked to ensure that 90% coverage of the PTV was achieved in all cases.

The DVHs for blocks and MLC shaping were compared in terms of the normal tissue volume treated to >50% and >80% of the isocentric dose. The percentage increase in these volumes when using MLC rather than conformal blocks was calculated to remove the effect of PTV size on the absolute volumes.

3. Results and discussion

Fig. 2 shows the percentage increase in normal tissue treated to >50% and >80% of the prescription dose when using MLC rather than blocks for all of the volumes used in the study. The change in volume that this represents for the patients is shown in Table 2. It had been expected that there would be a convergence of the MLC and block volumes as the volume of the PTV increased, as the effect of the 10-mm leaf width should be less important when fitting to a large area. However, no such trend is apparent. Instead, there are large variations which follow no obvious pattern, although both the >50% and >80% values tend to fluctuate in the same way. Some variations can be explained in terms of tumour shape such as for patient 2 who has a regular tumour that is almost rectangular in beam’s eye view. The MLC is able to fit well to such a shape and this is reflected by a small increase in normal tissue volumes when moving from blocks to MLC. The ability of the MLC to fit to a shape depends on the orientation of the leaves relative to the shape, i.e. on the collimator angle. It is therefore desirable to choose the collimator angle such that the best fit can be obtained. However, for the accelerator used in this study, this is not always possible since the wedge orientation is also dependent on the collimator angle.

Another factor affecting the MLC fit is the presence of partial leaves at the edge of the volume, created by the secondary collimation system. This is most easily seen by considering the series of spheres, since variation in shape is
not a factor and the beam's eye view of the PTV is the same for all four fields. The results plotted against the PTV volume show fluctuations that follow an almost sinusoidal pattern (Fig. 3a). Plotted against the radius of the sphere to which the MLC has been fitted (Fig. 3b), it can be seen that the peaks occur around radii which are a whole number of leaf-widths. The MLC fit is therefore worst for these cases while more closely approaching the conformal blocks for cases with partial leaf-widths. This effect occurs because the presence of a partial leaf at the volume edge is equivalent to having a smaller leaf width in this region, allowing a better fit and thus giving better normal tissue sparing (see Fig. 4). This effect is particularly important for shapes, such as circles, where the MLC incidence is far from normal at the edges.

If the fit of the MLC leaves to the beam's eye view projection of the PTV is considered, it is possible to define an area of underlap, i.e. the extra area enclosed by the MLC leaves (Fig. 4). This quantity should correlate to the increase in irradiated volume when using the MLC rather than blocks, although it will not account for scatter, which reduces the 'step' effect of the leaves. The 'area of underlap' was calculated for each of the spheres, assuming a circular projection in beam's eye view, and the volume increases at the 50% and 80% isodose levels were plotted against this quantity (Fig. 5). Significant relationships were found (>50%: gradient = 19.5 ± 4.3, >80%: gradient = 13.1 ± 1.6 (mean ± standard deviation)), with a large 'area of underlap' corresponding to a large increase in normal tissue volume, as expected. The points are quite widely scattered about the trend lines. This is to be expected since the calculation of 'area of underlap' is purely geometrical and neglects some factors that will affect the dose distribution, such as radiation scatter and the interaction of multiple fields.

Although 90% coverage of the PTV was chosen as the criterion for accepting the plans, ideally, the majority of the PTV will lie within the 95% isodose. Fig. 3 shows the percentage increase in the 95% coverage of the PTV which varies in the same way as the normal tissue pattern, i.e. increases in normal tissue volumes are associated with improved PTV coverage, as would be expected. The mean increase in PTV treated to ≥95% is -0.8 ± 1.5 cm³, corre-
sponding to $-1.2 \pm 2\%$, indicating that the conformal block and MLC treatments are well matched in terms of both PTV coverage and homogeneity.

Taking the mean of all of the patient and geometrical volumes, the MLC treats $14.1 \pm 6.1\%$ (range 3–34%) more normal tissue to >50% of the prescription dose and $17.4 \pm 10.2\%$ (range 0–36%) to >80%. For the patient volumes alone, the mean increases are $13.3 \pm 5.6\%$ (range 3–21%) and $22.6 \pm 10.7\%$ (range 0–36%). Some of the normal tissue increases will be due simply to the larger penumbra margin required for the MLC used in this study.

This analysis has assumed that the conformal block and MLC shapes can be transferred exactly to the treatment unit and does not consider the effect of patient movement and set-up errors. Such errors will tend to reduce differences between the two methods of treating these lesions [4,10].

4. Conclusions

Using a conventional MLC instead of conformal blocks for SCRT results in an increased volume of normal tissue being treated to >50% of the prescription dose; on average, 14% more normal tissue is treated to this dose level, with a range from 3–34%. Similar effects are seen at >80% of the prescription dose, where a mean increase of 17% (range 0–36%) in the volume of normal tissue enclosed by this isodose level is seen for MLC treatments. Increasing volume does not correlate with improved agreement between MLC and conformal block field shaping. The large variations in the differences between MLC and block shaping are related to shape and leaf-width effects. The ability of the MLC to fit to the lesion is strongly dependent on the shape of the PTV in beams eye view. Another contributing factor to the MLC fit is the presence of partial leaf-widths at the edges of the volume. The BEVs for a lesion should therefore be studied carefully when considering whether to use MLC shaping. In particular, regions where the MLC approaches the outline at shallow incidence should be avoided, as should shapes with undulations smaller than the pitch of the MLC. It may be helpful to introduce a 'goodness-of-fit' parameter into the MLC fitting program to assess how appropriate MLC fitting is for a particular shape.

The MLC used in this study was a 'conventional' MLC with a 1 cm leaf pitch. Use of a mini/micro-MLC would be expected to show smaller discrepancies compared to conformal blocks due to the smaller leaf pitch [8,13,15]. The large variations seen here due to shape and leaf-width effects would also be reduced. Introducing the effects of patient movement and set-up errors would also reduce the differences between using conformal blocks and MLC.

Acknowledgements

The authors would like to thank Phil Evans for helpful discussion. This work was supported by the Children’s Cancer Unit Fund, the Neuro-Oncology Research Fund, the Julian Bloom Research Fund, the Royal Marsden NHS Trust and the Cancer Research Campaign.

References

APPENDIX IV

OPTIMIZATION OF STEREOTACTICALLY-GUIDED CONFORMAL TREATMENT PLANNING OF SELLAR AND PARASELLAR TUMORS, BASED ON NORMAL BRAIN DOSE VOLUME HISTOGRAMS

JULIAN R. PERKS, PH.D.,* RAKESH JALALI, M.D.,† VIVIAN P. COSGROVE, PH.D.,* ELIZABETH J. ADAMS, M.SC.,* STEPHEN F. SHEPHERD, F.R.C.R.,† ALAN P. WARRINGTON, M.SC.,* AND MICHAEL BRADA, F.R.C.R.†

*Physics Department and †Neuro-oncology Unit and Academic Unit of Radiotherapy and Oncology, The Royal Marsden NHS Trust and Institute of Cancer Research, London and Sutton, United Kingdom

Purpose: To investigate the optimal treatment plan for stereotactically-guided conformal radiotherapy (SCRT) of sellar and parasellar lesions, with respect to sparing normal brain tissue, in the context of routine treatment delivery, based on dose volume histogram analysis.

Methods and Materials: Computed tomography (CT) data sets for 8 patients with sellar- and parasellar-based tumors (6 pituitary adenomas and 2 meningiomas) have been used in this study. Treatment plans were prepared for 3-coplanar and 3-, 4-, 6-, and 30-noncoplanar-field arrangements to achieve 95% isodose coverage of the planning target volume (PTV) for each plan. Conformal shaping was achieved by customized blocks generated with the beams eye view (BEV) facility. Dose volume histograms (DVH) were calculated for the normal brain (excluding the PTV), and comparisons made for normal tissue sparing for all treatment plans at 280%, 260%, and 240% of the prescribed dose.

Results: The mean volume of normal brain receiving ≥80% and ≥60% of the prescribed dose decreased by 22.3% (range 14.8-35.1%, standard deviation σ = 7.5%) and 47.6% (range 25.8-69.1%, σ = 13.2%), respectively, with a 4-field noncoplanar technique when compared with a conventional 3-field conformal technique. Adding 2 further fields, from 4-noncoplanar to 6-noncoplanar fields reduced the mean normal brain volume receiving ≥80% of the prescribed dose by a further 4.1% (range -6.5-11.8%, σ = 6.4%), and the volume receiving ≥60% by 3.3% (range -5.5-12.2%, σ = 5.4%), neither of which were statistically significant. Each case must be considered individually however, as a wide range is seen in the volume spared when increasing the number of fields from 4 to 6. Comparing the 4- and 6-field noncoplanar techniques to a 30-field conformal field approach (simulating a dynamic arc plan) revealed near-equivalent normal tissue sparing.

Conclusion: Four to six widely spaced, fixed-conformal fields provide the optimum class solution for the treatment of sellar and parasellar lesions, both in terms of normal brain tissue sparing and providing a relatively straightforward patient setup. Increasing the number of fields did not result in further significant sparing, with no clear benefit from techniques approaching dynamic conformal radiotherapy in the cases examined. © 1999 Elsevier Science Inc.

INTRODUCTION

Stereotactic conformal radiotherapy (SCRT) is a high-precision, multiple, fixed-field technique utilizing customized shielding. We have previously demonstrated that for nonspherical lesions, multiple, noncoplanar, conformal fixed fields achieve better normal tissue sparing than multiple noncoplanar arcs (1, 2).

The technique of SCRT has been implemented at the Royal Marsden Hospital for the treatment of benign sellar and parasellar tumors since 1993. Patients are immobilized in a relocatable stereotactic Gill-Thomas-Cosman (GTC) frame (3, 4) and tumor localization is achieved through CT scanning using a Cosman-Robert-Wells (CRW) fiducial system (Radiacions Inc., Burlington, MA). Conformal field shaping is carried out using low-melting-point lead alloy blocks. Block shapes are defined based on the beams eye view (BEV) projection for each field. Construction of the alloy blocks is carried out using a Par Scientific MKII computer-controlled block cutter (Par Scientific, Odense, SV, Denmark). The completed blocks are positioned on the linear accelerator using a custom built block holder.

Sellar lesions are treated conventionally with three-copla-

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Reprint requests to: Dr. Michael Brada, Royal Marsden NHS Trust, Downs Road, Sutton, SM2 5PT, UK. Accepted for publication 14 April 1999.
Table 1. Details of tumors evaluated

<table>
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<th>Patient no.</th>
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Table 2. Beam arrangements evaluated

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METHODS AND MATERIALS

The eight sets of patient CT data used were selected from a database of patients previously treated with SCRT at the Royal Marsden Hospital. The tumor type and volume is given in Table 1. For this study, optimization is defined as the minimization of normal brain tissue irradiation to moderate and high percentages of the dose prescription, while maintaining homogeneous coverage of the planning target volume (PTV).

We compared a conventionally accepted treatment plan of 3 coplanar beams (2 opposing lateral fields and 1 anterior) with 3-, 4-, and 6-field noncoplanar techniques. In all noncoplanar cases, the beams were maximally separated in space to minimize beam overlap (6), allowing for restrictions due to critical structures and mechanical collision avoidance. The dynamic conformal technique was achieved using 30 fields arranged in three 120-degree arc planes, each separated by 60 degrees, with 10 conformally-shaped fields in each arc. The field arrangements are shown in Table 2.

All treatment planning and DVH calculations were carried out on a Varian/Dosetek Cadplan v2.7.9 planning system with the beam data adjusted to fit small, conformal field sizes (Varian Corp, Palo Alto, CA). Planning CT scans for each of the patients were transferred to the planning system by DICOM 3 transfer. The CT data set consisted of 3-mm slices through the target area and 5-mm slices outside. The gross tumor volume (GTV) was manually contoured on the appropriate CT slices by the clinician. The 3D volume growing algorithm was utilized to expand the GTV by a 5-mm margin to give the PTV.

All conformal fields were shaped using a BEV graphics facility and an automatic field-shaping tool. In practice, a dynamic conformal treatment would have to be carried out using an MLC or mMLC, leading to the precision of any field shaping being compromised by the resolution of the leaves. In this study, all fixed fields were considered with precise conformal blocking of the PTV.

Each plan was calculated using the beam data of a Varian Clinac 600C, in clinical use at the Royal Marsden Hospital, London. All dose distributions were produced with a minimum 95% isodose covering the PTV in 3D with the distribution normalized to 100% at the isocenter. Beam weightings and dynamic wedges were altered to ensure dose homogeneity across the PTV of ±5% in accordance with ICRU 50 guidelines (7). The conformal block edge had a fixed margin of 3.5 mm around the PTV in BEV to account for the beam penumbra in the noncoplanar plans. For coplanar plans, a larger margin was required in the lateral direction, where a manually adjusted margin was used to ensure that coverage of the PTV was achieved.

The dose distributions for all plans were calculated with the minimum available matrix resolution of 2.5 mm. Normal brain was contoured within the external volume to exclude the PTV. Cumulative dose volume histograms for the PTV and the normal brain were computed, and comparisons of rival plans made with respect to the percentage of normal brain spared. The "conventional" 3-field coplanar technique was chosen as the technique to which the other plans were compared. The percentage volumetric sparing, relative to the volume of normal brain treated by the 3-field coplanar plan was calculated at dose levels of ≥80%, ≥60%, and ≥40% of the prescribed dose.
RESULTS

The cumulative DVH of the target volume for each of the treatment plans for a representative case is shown in Fig. 1. The planning target volume was covered by the 95% isodose in 3D for all of the plans in each patient, with dose distributions normalized to 100% at the isocenter.

The normal brain DVH for one patient with 3-field coplanar and 4-, 6-, and 30-field noncoplanar plans is shown in Fig. 2. The percentage of normal brain volume spared at ≥60% and ≥80% of the prescribed dose for the rival plans in comparison to the conventional 3-field coplanar plan is shown in Figs. 3a and 3b, respectively. The mean percentage volume sparing is summarized in Table 3. The 4-field noncoplanar plan consistently spared greater volume of normal brain tissue receiving ≥80% of the prescribed dose as compared to the 3-field coplanar plan in all patients (mean 22.3%, range 14.8–35.1%, standard deviation σ = 7.5%).

Comparing a 6-field noncoplanar plan with the 4-field noncoplanar plan in all patients revealed only a 4.1% (range −6.5–11.8%, σ = 6.4%) mean, further sparing of normal brain tissue receiving ≥80% of the prescribed dose.

The cumulative DVH of normal brain tissue for the 30-field arrangement (simulating a dynamic arc plan) was assessed in 5 patients. The 30-field plan was superior in terms of normal brain sparing at ≥80% prescribed dose compared to the 3-field coplanar technique (range 11.8–50.5%), (Fig 2). However, on average, the 30-field plan spared less normal brain than either the 4- or 6-field arrangements, at both the 60% and 80% dose levels. At 60% of the isocenter dose, the 30-field plan spares 1.8% (σ = 8.3%) and 4.7% (σ = 4.8%) less normal brain than the 4-field and 6-field arrangements, respectively. At the 80% dose level, the 30-field plan spares 17.2% (σ = 25.3%) and 18.9% (σ = 25.5%) less normal brain than the 4- and 6-field arrangements, respectively.

The sparing of normal brain irradiated to ≥60% and ≥40% of the prescribed dose revealed the same trends as seen at ≥80%. The 4- and 6-field noncoplanar plans spared more normal brain tissue than the 3-field coplanar arrangement (Table 3). The mean normal brain sparing at ≥60% and ≥40% of the prescribed dose was greater with the 6-field plan by only 8.0% (range −38.1–28.3%, σ = 19.9%) and 3.3% (range −5.5–12.2%, σ = 5.4%), respectively, on comparison to the 4-field noncoplanar plan, neither of which were statistically significant.

DISCUSSION

Sellar and parasellar lesions, including pituitary adenoma, craniopharyngioma, meningioma, and optic chiasm glioma, are effectively treated with conventional fractionated radiotherapy with standard dose fractionation schedules (45–55 Gy in 25–33 fractions). The doses employed are well within tolerance limits of the brain (8–10), with <1% risk of structural damage (necrosis). Nevertheless, functional damage in terms of cognitive function (particularly in
children) and hypothalamic-pituitary endocrine function are dose and volume dependent (11, 12). It is therefore reasonable to reduce the volume of normal brain irradiated, particularly to higher doses, which can be achieved with the technique of SCRT. The present study examined the reduction in the volume of the whole normal brain irradiated, and not individual critical structures, such as the hypothalamus.

The comparison of techniques is based on the parameter of volume sparing of normal brain tissue receiving ≥80%, ≥60%, and ≥40% of the prescribed dose. With the dose and fractionation schedules used, which are within tolerance limits, no single brain site, such as the brain stem or optic apparatus was singled out. Specific avoidance of such critical regions of the brain is, however, of relevance in the context of dose escalation or retreatment. While the comparison concentrates on higher doses, it is also not possible to exclude the potential risk of low-dose irradiation to larger volumes, which results from increasing the number of spatially distributed fields. Similar studies have assessed fixed field (13-16) and intensity-modulated radiotherapy plans (17) in the context of single fraction radiosurgery, where sparing of normal brain with doses beyond conventional tolerance is critical.

In this study, dose homogeneity within the PTV was maintained to within ±5% of the isocenter dose by the use of dynamic wedges and adjustment of the relative beam weights, and all plans were designed to give equal PTV-DVH plots. This ensured that comparisons of the average volumetric sparing between patients were valid. However, the differences between the various DVH curves becomes smaller with higher dose prescription levels. Rival techniques were compared with 3-field noncoplanar plan to visualize the differences in comparison to conventional treatment.

Conventional radiotherapy of sellar and parasellar lesions is delivered with 3 nonoblique fields, 2 opposed lateral fields, and 1 anterior oblique field inclined to avoid the eyes. To reduce the crossover effect of the opposing lateral fields, extra weight may be given to the anterior field; however, this is at the expense of a higher frontal lobe dose. By breaking the conventional opposition of the lateral fields, equally weighted nonopposing, noncoplanar fields can be used with the aim of reducing the dose to both the temporal and frontal lobes. A moderate sparing of the normal brain, mean 3.1% (range 20.6-15.4%) at the ≥80% dose level, was achieved by the 3-field noncoplanar plan over the 3-field plan.

The basis for the beam arrangements used in the 4-field plan is a tetrahedron, a 4-cornered shape whose vertices are maximally spaced. The exact beam orientations to match the tetrahedron are not practically possible. The 2 lateral fields are restricted by couch/gantry collision prevention, and the 2 superior fields have to be oriented to avoid eyes, and to exit through the thyroid. Considerable sparing was achieved in the ≥80% and ≥60% dose regions (mean 22% and 48%, respectively) by the 4-field plan when compared to the 3-field conventional technique. The reduction in the high-dose volume was a result of both increasing the num-

Table 3. Mean percentage extra volume of normal brain tissue spared by rival plans with respect to the 3-field coplanar plan

<table>
<thead>
<tr>
<th></th>
<th>3-field noncoplanar (%)</th>
<th>4-field noncoplanar (%)</th>
<th>6-field noncoplanar (%)</th>
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<tbody>
<tr>
<td>≥40%</td>
<td>1.4</td>
<td>22.8</td>
<td>31.9</td>
</tr>
<tr>
<td>≥60%</td>
<td>13.3</td>
<td>47.6</td>
<td>50.9</td>
</tr>
<tr>
<td>≥80%</td>
<td>3.1</td>
<td>22.3</td>
<td>26.5</td>
</tr>
</tbody>
</table>

Fig. 3. Volume of normal brain tissue spared at ≥60% (a) and ≥80% (b) of the prescribed dose for the 8 tumors (expressed as percentage of the volume of normal brain treated by a 3-field conventional plan).
Optimization of stereotactic conformal radiotherapy

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Fig. 4. 3D representations of the treatment techniques (a) 3-field coplanar arrangement, (b) 3-field noncoplanar arrangement, (c) 4-field noncoplanar arrangement, and (d) 6-field noncoplanar arrangement.

ber of fields and ensuring their orientations were maximally spaced.

One method of orientating 6 field plans is with equidistant couch positions (0 degree and ±60 degree) as with a conventional arcing plan (1). The 6-field plan used in this study was devised as a progression from the 4-field tetrahedron arrangement. The 2 lateral fields were kept and the 2 superior fields were split equally about midline. However, increasing the number of fixed, conformally-blocked fields from 4 to 6 did not, on average, spare significant additional brain volume irradiated to high doses. 3D representations of the coplanar and noncoplanar 3-field, the 4-field, and the 6-field arrangement are shown in Fig. 4.

The 30-field plan was used to assess the potential advantage of a dynamic conformal treatment approach. However, this plan did not simulate a varying intensity across the field, as would be the situation for intensity-modulated radiotherapy (IMRT). The 30-field arrangement consists of separate fields, each conformally shaped in the BEV, differentially weighted and wedged to give adequate PTV coverage (i.e., 95% of the isocenter dose), as in the other field arrangements. Five cases were chosen to be planned with 30 fields as representative of the sellar cases seen. There was only a marginal improvement in the volume of normal brain spared compared to the 4-field plan.

While it is possible to conclude that the four-field, conformal noncoplanar arrangement is appropriate for sellar and parasellar lesions, this has to be accepted and applied with caution. The range seen across the results is considerable, and the interpretation is based on the mean of all the results. In the majority of cases the six-field noncoplanar plan spared more normal brain, even though the actual sparing in volume terms was small and not considered clinically relevant. Additionally, in individual patients, organs at risk may also need to be avoided (18). It is therefore appropriate to consider not only a class solution, but also individual requirements, such as tumor size and shape, and occasionally, the proximity of critical structures.

The results suggest a relationship between normal brain sparing and PTV size, with maximum sparing at the ≥80% and ≥60% dose levels seen with the smallest lesions (Fig. 3). The trend is more pronounced for the near spherical pituitary adenomas rather than the irregular meningiomas, where shape also plays a role (19). However, only two meningiomas were studied, which is not sufficient for es-
mMLCs are increasingly used as an alternative to individual cast conformal blocks. An mMLC with a 3–4-mm central leaf pitch at isocenter (21) provides acceptable, although not ideal, conformation. However, an mMLC is less labor-intensive in the treatment process and eliminates the need for block manufacture. The class solution for SCRT of sellar and parasellar lesions described here is equally applicable to mMLC, where increasing the number of fields is of little benefit in terms of normal brain sparing, regardless of the method of conformation. The use of a larger number of fields with an mMLC than with blocks should not be guided by the technical ability to deliver such complex treatments, but by objective evidence of benefit in terms of worthwhile sparing of normal structures.

The aim of stereotactically-guided conformal radiotherapy is to deliver a uniform, therapeutic dose to the target region with maximum sparing of normal tissues. This was determined by comparing normal tissue DVH for a number of different techniques. In view of the practical time constraints and resource requirements, a limited number of fields is preferable. This analysis shows that four conformal-fixed fields achieve near optimum normal tissue sparing in terms of the volume receiving ≥60% of the prescribed dose, provided that they are maximally separated in 3D, with little extra benefit achieved by increasing the number of fields above four. There is also no apparent advantage to be gained by using a plan simulating a dynamic conformal treatment for such lesions. We conclude that four static, conformal, noncoplanar beams provide an acceptable, practical, and adaptable class solution for SCRT of sellar and parasellar tumors, both in terms of normal tissue sparing and feasibility within the routine clinical practice of a radiotherapy department.

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**Table 4. Estimated time required for stages of patient preparation and treatment**

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<tr>
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<th>3-field coplanar</th>
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<tr>
<td>Conformal block</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>manufacture</td>
<td>3 h</td>
<td>4 h</td>
<td>6 h</td>
</tr>
<tr>
<td>manufacture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient setup</td>
<td>5 min</td>
<td>10 min</td>
<td>15 min</td>
</tr>
<tr>
<td>Treatment delivery</td>
<td>10 min</td>
<td>10 min</td>
<td>15 min</td>
</tr>
</tbody>
</table>


APPENDIX V

Stereotactically guided conformal radiotherapy for meningiomas

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Abstract

Purpose: Stereotactically guided conformal radiotherapy, (SCRT) is a high precision technique of conformal radiotherapy (RT) which reduces the volume of normal tissue irradiated compared to conventional RT and may lead to a reduction in long-term toxicity. We describe the technique and the preliminary results in patients with inoperable, residual or recurrent meningiomas.

Material and methods: From July 1993 to November 1997, 24 patients (median age: 56 years, range: 28-72) with base of skull (\(n = 21\)), falx or upper skull (\(n = 3\)) meningiomas were treated with SCRT. The technique employed immobilization in a Gill-Thomas-Cosman (GTC) frame and CT localization with a Brown-Roberts-Wells (BRW) fiducial system for stereotactic space definition. The planning target volume (PTV) was defined as gross tumour volume (GTV) and a 0.5-1 cm margin. Treatment was delivered with three (12 patients) or four non-coplanar conformal fixed fields (12 patients). Conformal blocking was achieved either with lead alloy blocks (\(n = 11\)) or with a multi-leaf collimator (MLC) (\(n = 13\)). Patients were treated on a 6 MV linear accelerator to doses of 50-55 Gy, in 30-33 daily fractions. The treatments were carried out as part of a routine work of a busy radiotherapy department.

Results: Median GTV for 24 meningiomas was 21.7 cm\(^3\) (range: 4.4-183 cm\(^3\)). SCRT was well tolerated with minimal toxicity. Three months after the end of radiotherapy, seven of 15 patients with neurological deficit had an improvement and eight remained unchanged. Two patients experienced early side effects (one VII nerve palsy, one Addisonian state). At a median follow-up of 13-months (range: 3-43) the 1 year progression free survival and overall survival are 100%, which is within the range expected for conventional fractionated radiotherapy for meningiomas.

Conclusions: SCRT is a feasible technique of high precision conformal RT for patients with meningiomas. Potential advantages in tumour control, survival and toxicity over conventional RT, require evaluation in long-term prospective studies. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Meningioma; Stereotactic conformal radiotherapy; 3-D planning

1. Introduction

The treatment of choice for benign meningioma is radical surgical resection [20,26]. The probability of complete surgical excision depends on tumour and patient related factors, including tumour size, location and the general condition of the patient [17]. Following complete tumour excision recurrence rate is low.

The progression rate in patients with residual tumours after surgery is up to 40% at 5 years and up to 80% in 10 years [2,22,26]. Tumours around the skull base may encase cranial nerves, centre: cerebral arteries or venous sinuses [18] and complete resection without morbidity may be difficult. The recurrence rate at 15 years has been reported in up to 32% of patients with skull base meningiomas following surgery alone. The risk of recurrence remains considerable despite improvements in skull base surgical technique [10,25].

It has been suggested that in patients with inoperable and incompletely resected tumours, postoperative radiotherapy may improve local tumour control [2,6,19]. Using modern radiotherapeutic techniques with CT and MRI guided treatment planning, the reported 10-year progression free survival in patients with sub-totally resected benign meningiomas, is over 90% [7].

However in the absence of randomized studies testing the efficacy of radiation, the benefit of postoperative radiotherapy continues to be debated and remains unproven.
Table 1
Patient, disease and treatment characteristics

<table>
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<th>Variables</th>
<th>Years</th>
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</tr>
</thead>
<tbody>
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<td>Median: 56</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>28-72</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male: 5</td>
<td>Female: 19</td>
</tr>
<tr>
<td>Timing of SCRT</td>
<td>After primary surgery for residual tumors: 11</td>
<td>Following first recurrence (after second surgery): 10</td>
</tr>
<tr>
<td>Location</td>
<td>cavernous sinus: 6</td>
<td>sphenoid: 10</td>
</tr>
<tr>
<td>Histology</td>
<td>benign: 19</td>
<td>benign aggressive (high mitotic rate): 1</td>
</tr>
<tr>
<td>Surgery</td>
<td>SCRT after primary tumor surgery: 11</td>
<td>incomplete resection: 6</td>
</tr>
</tbody>
</table>

The usual external beam radiotherapy technique employed in the treatment of meningiomas consists of two or three dimensional planning (3-D) and delivery with two to four coplanar beams. With the advent of high precision focal irradiation techniques, stereotactic radiosurgery (SRS) has been used to treat small inoperable meningiomas. However, because of the toxicity of single fraction SRS [1,3,27], this technique is currently restricted to small tumours away from critical structures, such as the cranial nerves and the brain stem, and the long-term efficacy of this approach is not clear [1,12].

The principles of precise patient immobilization, tumour localization and stereotactic focal delivery have been combined with fractionation in stereotactic radiotherapy (SRT). The recognition that non-spherical lesions are better treated by fixed non-coplanar conformal fields, than multiple arcs with better sparing of normal brain [14], has led to the development of stereotactically guided conformal radiotherapy (SCRT) [21,23,24]. SCRT combines the high precision of stereotactic irradiation with the advantages of fractionation, which allow higher doses to the tumour with more effective sparing of normal tissue. SCRT is particularly applicable to meningiomas, which are localized non-spherical tumours enclosing or in close proximity to critical structures. We report the technique of stereotactically guided conformal radiotherapy using readily available radiotherapy equipment, its clinical application and preliminary results in patients with meningioma.

2. Patients and method

2.1. Patients

Between July 1993 and November 1997, 24 patients with meningiomas were treated with fractionated stereotactically guided conformal radiotherapy (SCRT) at the Royal Marsden NHS Trust (Table 1). Patients were aged 28-72 years (median: 56 years), five were men and 19 women. Eleven received SCRT as part of the primary treatment, six following incomplete surgical resection and three after biopsy alone, and in two patients, medically unfit to undergo surgery, diagnosis was based on imaging alone. Ten patients were treated at first recurrence and three patients at second recurrence following surgery. Twenty-one patients had tumours at the base of skull (six cavernous sinus, ten sphenoid wing, one petrous wing, two occipital at the foramen magnum, one suprasellar and one base of skull invading the brain stem). Three patients had tumours at the falk or upper skull. Nineteen patients had histologically benign meningiomas, one benign aggressive, two malignant meningiomas and two were not histologically verified.

2.2. SCRT technique

Patients were immobilized in a relocatable Gill-Thomas-Cosman (GTC) frame as described previously and the Brown-Roberts-Wells (BRW) fiducial system was used for stereotactic space definition [5,8,13]. All patients underwent a post-contrast CT scan in the GTC-frame, with a 2 mm slice thickness and 2 mm slice separation in the tumour bearing area, and 4 mm slice thickness and 4 mm slice separation outside. The data were transferred to a planning computer (Cadplan® or GE Target 2®). The gross tumour volume (GTV) was defined as enhancing mass and abnormal bone presumed to contain active tumour. The planning target volume (PTV) was defined as GTV plus a 1 cm margin in three dimensions (3-D). In the later part of the study the margin was reduced to 0.5 cm. Critical structures, such as the brain stem, eyes, optic nerves and optic chiasma were outlined. The PTV adjacent to critical structures was adjusted to reduce the risk of normal tissue toxicity. Computer 3-D reconstruction, beam's eye view (BEV) facilities and dose volume histograms (DVH) were used to optimize the treatment plan according to ICRU50 criteria, with respect to dose
Fig. 1. Standard four field treatment plan with conformal lead blocking for a patient with a benign meningioma of the left spheroid wing.

homogeneity, to minimize the dose to normal brain outside the PTV and dose received by critical structures.

2.3. Beam arrangements

Optimal dose distribution with dose homogeneity within the PTV and minimal dose to normal brain and critical structures was achieved with three to four fixed, non-coplanar beams [21]. Twelve patients were treated with three, and 12 patients with four non-coplanar fixed fields. A typical three-field treatment plan consisted of two lateral fields, made non-coplanar by a couch rotation of ± 10–15° and one coronal field. The standard four beam approach for centrally located lesion (Fig. 1) consisted of two lateral posterior inferior oblique beams and two coronal beams. Non-opposing gantry angles were used to minimize the overlap of the beams entering and exiting the treated volume. Beam angles were separated as far as possible from each other to avoid high dose regions outside the PTV. Coronal fields were set up with a 90° couch angle and a 70–90° hinge angle around the straight vertex to avoid the eyes. Dose homogeneity within the PTV was achieved by optimizing the beam weights, wedge angles and beam directions. In each case, the geometry was individually customized according to size and location of the tumour and critical structures, particularly the eyes.

2.4. Conformal blocking

All patients had conformal blocking of all fields either with individual lead alloy (Cerrobend®) blocks (11 patients) or with multileaf collimator (MLC) (13 patients). The shape of the blocks was created from BEV for each field, by encompassing the PTV with a margin of 0.25 cm to account for penumbra. To obtain individual conformal blocks, each BEV shape was digitized into a computerized block cutter (Par Scientific ACD4) to produce high density styrofoam moulds from which Cerrobend® blocks were cast. Conformal blocking for field sizes greater than 6–3 cm in any direction was achieved using a multi-leaf collimator (MLC), with a 1 cm leaf separation at the isocentre. The portals were fitted, using a computer program utilizing the ‘transsecting’ leaf fitting technique [16]. The leaf position data for MLC were transferred directly to the treatment machine.

2.5. Verification and quality assurance

The isocentre position was verified with CT scans in the plane of the isocentre as well as 2 and 4 mm superior and inferior. The accuracy of relocation was assessed by comparison of anatomical landmarks from the localizing isocentre slice and the verification slice. The tolerance of the relocation was set at 1.5 mm in any direction.

The procedure of quality assurance was described in detail elsewhere [29]. A check of the position of the customized blocks was performed by comparing the light field given by the block at the treatment machine, in a source-plane-distance of 2 m with the printout of the BEV at the same distance for each block. To avoid set up errors, all blocks were cut from the same direction and were located using two unique localizing studs. All blocks were labelled to indicate positioning direction, beam number and patient identification.

2.6. Treatment

Treatment was delivered with a 6 MV linear accelerator (Varian 2100C/600C). Frame relocation prior to each treatment was checked, as reported previously [29]. The frame was positioned in a fixation bracket on the couch with the patient supine. The isocentre was set up by aligning calibrated lasers [28] to markers on the templates of the localizer box.

2.7. Dose and fractionation

Twenty-three patients were treated to a dose of 55 Gy at isocentre in 33 fractions at 1.67 Gy per fraction over 6 and a half weeks. Standard ICRU50 criteria were applied. One patient with an optic nerve meningioma received 50 Gy in 30 fractions.

3. Results

The mean GTV of 24 patients with meningioma was 36.6 cm³ with a median of 21.7 cm³ (range 4.4–183 cm³). The median GTV in patients treated with conformal
blocks was 17.9 cm$^3$ and with a multi-leaf collimator 24.7 cm$^3$.

The treatment was associated with little acute toxicity. Six patients had temporary alopecia at the entrance of the treatment fields. Five patients developed transient headache during treatment controlled with a short course of corticosteroids. One patient with a small tumour (GTV = 4.4 cm$^3$) deteriorated with transient confusion, headaches and tiredness which resolved with corticosteroids. One patient with a spheroid wing meningioma had a single seizure within 3 months of completion of radiotherapy and developed a VII nerve palsy 6 months later. A further patient where PTV included the sella, developed an Addisonian state 5 months after SCRT treated with hydrocortisone replacement therapy. No further acute or early delayed side-effects were seen.

The median follow-up of 24 patients with meningioma is 13 months (range 3–43 months). Three months after radiotherapy, seven of 15 evaluable patients with neurological deficit, had improvement and eight had no change. Twenty-one patients had follow-up imaging 3–29 months after the completion of treatment. There was a slight reduction in the size of the tumour in three patients and no change in others. Progression free survival and overall survival at 1 year are 100%.

4. Discussion

Radiotherapy is frequently used for the treatment of residual or recurrent meningiomas, where complete surgical resection is not considered an option. With the advent of high precision radiotherapy derived from the practice of stereotactic radiosurgery, we developed and implemented a technique of irradiation which combines the high precision of stereotaxy, with principles of three dimensional conformal radiotherapy. This is similar to techniques described previously [4,23,24]. The aim of stereotactic, or for that matter, other high precision radiotherapy techniques, is to achieve the highest dose differential between tumour and normal tissue. The sparing of normal brain beyond that achieved with conventional radiation technique, allows for potential reduction in radiation induced side effects and/or an increase in tumour dose and tumour control without increasing normal tissue damage. This can be combined with fractionation which is less damaging to normal brain when compared with single fraction treatment [11]. This approach may be of particular relevance to skull base tumours where critical normal structures, such as the brain stem and cranial nerves lie either in close proximity to the tumour or are intimately involved with the tumour, such as cavernous sinus and sphenoid wing meningiomas.

Linac based multiple arc radiotherapy or treatment with a multiheaded Cobalt unit (Gamma Knife®) produce spherical high dose volumes. The advantage over conventional fixed field radiotherapy in terms of sparing normal tissue is only seen for tumours less than 4–4.5 cm in diameter [7].

The majority of meningiomas considered for irradiation are not spherical and are generally larger. We have previously demonstrated that optimal sparing of normal brain tissue around non-spherical lesions is achieved with fixed non-coplanar conformal beams [14]. Further optimization studies suggested that little additional sparing of normal tissue is achieved with more than three or four non-coplanar conformal fixed beams [21]. The method described is the practical implementation of these findings.

The technique of SCRT with conventional linear accelerator combines the use of stereotactic fixation and localization devices with commonly available methods of collimation, using lead-alloy blocks or MLC. The arrangement of three to four fixed fields makes this a practical technique for everyday use in a radiotherapy department with a high workload and allows for conventional fractionation which carries little long-term morbidity. Compared with conventional coplanar fractionated radiotherapy, the treatment procedure takes marginally longer, and this relates to the number of treatment fields and the setting-up and quality assurance of conformal blocks. The use of a relocatable frame for immobilization and a localizer box for setting up fields does not prolong the treatment time on the machine [15]. SCRT is now routinely applied for the radiotherapy of pituitary adenomas, cranio-pharyngiomas and localized paediatric brain tumours. We describe the application of this technique in patients with meningioma.

One of the critical issues of all forms of conformal therapy is the definition of PTV. While GTV adjacent to the brain parenchyma for meningioma is reasonably well-defined, there is uncertainty about possible microscopic involvement of overlying bone and adjacent meninges. The margin for clinical target volume (CTV) and PTV was initially set at a conservative 1 cm in three dimensions. This was adjusted in the vicinity of critical structures. While the ideal safety margin is not known, the benign nature of the tumour and the accuracy of the SCRT technique has lead to a gradual reduction of the margin to 0.5 cm. With greater experience and with routine use of both CT and MRI for treatment planning, it may be possible to reduce it further, although the safety of this approach in terms of potential marginal miss will not be known for many years.

The cohort of selected patients referred for SCRT to the Royal Marsden Hospital includes a range of tumour sizes and locations, the majority of which would not be amenable for safe SRS. Currently the results are comparable to those reported with conventional fractionated radiotherapy [7] and stereotatic conformal radiotherapy [4], and are without treatment-related severe acute morbidity or mortality. However, the short follow-up precludes any assessment of long-term tumour control and late toxicity.

While it is possible to demonstrate a technical benefit
over conventional radiotherapy in terms of sparing of normal tissue, the clinical benefit of such technology which increases the demand on staff and resources needs to be demonstrated. In the first instance, it will be necessary to perform phase II studies with clear clinically and statistically achievable objectives of tumour control and toxicity. These will need to be compared with cohorts of conventionally irradiated patients. The excellent long-term control rate (70–85% at 10 years) and survival (60–80% at 10 years) following conventional fractionated radiotherapy will, however, make it difficult to prove a benefit for SCRT, particularly as selected patients tend to have favourable prognostic factors. It may also prove difficult to demonstrate reduction in early and late radiation-induced side effects, as the incidence of late radiation damage following conventional radiotherapy is low. It will, therefore, become necessary to score other parameters of CNS function, such as cognitive impairment and hypothalamic-pituitary function.

High precision conformal radiotherapy is a reasonable technical aim of external beam radiotherapy. The technique of SCRT, as described, is feasible within the daily routine of a radiotherapy department with a high workload and can be applied to the irradiation of residual or recurrent meningiomas, where radiotherapy is considered appropriate. The technique is also applicable for the treatment of other localized tumours where involved field irradiation is an important component of local therapy such as pituitary adenoma, craniopharyngioma and a variety of localized paediatric tumours. However, the clinical benefits over conventional radiotherapy techniques remains to be demonstrated.

Acknowledgements

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