Stereotactic intracranial radiotherapy/radiosurgery has come of age

P N Plowman

ABSTRACT – The current, highly sophisticated, brain imaging techniques and three dimensional (stereotactic) mapping of intracranial targets, combined with recent developments in concentration of radiation therapy (x- or gamma-ray) onto these targets, have allowed obliterator treatment for many intracranial diseases previously the preserve of the neurosurgeon alone. Vascular malformations, acoustic neuroma, complex meningioma, pituitary adenoma and craniopharyngioma all fall into this category, as well as base of skull tumours. There are occasional indications for single (a few) cerebral metastases and possibly a highly selected role in primary malignant brain tumours. The subject of so-called ‘radiosurgery’ is an important and developing one and is complementary to modern neurosurgery.

Fifty years ago Leksell designed a system of multiple, tightly collimated and cross firing beams to concentrate a dose of ionising radiation on one discrete target inside the brain1,2 – at first for the destruction of neuronal pathways in functional disorders. Since then, not only have the treatment delivery systems become more sophisticated but so too have the imaging and computerised treatment planning systems – essential parts of the current, accurate therapeutic procedure of ‘radiosurgery’.

Ten years ago, in 1989, London’s first radiosurgical facility started practice at St. Bartholomew’s Hospital3 and now has a decade of experience to review.

Vascular malformations

Arteriovenous malformations (AVM) of the brain are the commonest cause of strokes in young people. Radiosurgery is now best standard therapy for deep seated AVM and is equivalent to surgery for more superficially sited lesions. Single large doses of ionising radiation therapy cause obliterator endarteritis of the lesion’s nidus vessels within one to three years (Fig 1) without subsequent recanalisation4. Eighty per cent of small AVM are cured.

The problem of repeat haemorrhage in the interval to obliteration was studied5. We initially concluded, as have others, that the rebleeding rate remains the ‘standard risk’ (say 2% per year) after therapy until obliteration. However, we subsequently obtained evidence of blood flow slowing in the treated vessels in early months after therapy and this may equate with a decrease in risk from that time6.

Epilepsy

Twenty-four per cent of AVM patients referred to our unit complained of epilepsy7. Of 16 evaluable patients, 15 (94%) had better control of fits and 10 (63%) became fit free. Previously, Steiner et al8 had observed improvement in fit control in 70% and Sutcliffe et al9 improvement in 60% of such patients.

Complications

For large AVM (3cm diameter = 14cc or more in volume) we reported an obliteration rate of 40%, or nearer 1/3 if the strictest criteria of absence of any draining vessel are adhered to. We found a complication rate of 1.8% for lesions up to 10cc in volume and 16% (for any complication) in the series of 14cc or over – a larger volume group of lesions than most other workers had studied. Whilst this complication rate may seem high and certainly must be counselled for, nevertheless, it would be rare for an emboliser or neurosurgeon to give a lower rate of some complication when attacking such large lesions. We are currently approaching the treatment of large AVM by utilising a biological response modifier or radioprotector which we hope will act preferentially on normal tissues.

Angiographically occult vascular malformations (AOVM)

AOVM include a variety of pathological entities associated with two imaging hallmarks: well defined areas of abnormal signal with a surrounding low signal haemosiderin deposit – well demonstrated on magnetic resonance (MR) but normal on angiography. Pathological examination of AOVM reveals patent or thrombosed AVM or cavernous angioma; occasionally there may be capillary telangiectasis6,10. Whilst many AOVM remain silent, others are likely to bleed persistently, and because they are frequently sited in deep hemispheric tissue or brain stem, they require therapy. Radiosurgery reduces the haemorrhage risk in cerebral cases11,12. The risk of permanent complications to the surrounding brain is 4%. Unlike AVM, these AOVM do not obliterate completely following therapy (Fig 1) and this is in accord with our observations in ocular cases – where we

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Key Points

Stereotactic radiosurgery is an important new therapeutic tool in neurosciences

It replaces neurosurgery for treating some intracranial conditions and complements neurosurgery and conventional radiotherapy for others

observed a decrease in the leakage but only modest reduction in the volume of the angioma after therapy.

Glomus jugulare tumours

This less than complete response to radiosurgery is also observed after therapy of glomus jugulare tumours (Fig 1) for which there was a previous good body of literature supporting the efficacy of conventional radiotherapy. It has been the view of this centre for the last 20 years that radiation therapy is the treatment of choice for difficult glomus tumours and we believe that stereotactic technology may often be the optimal form of such radiation therapy (Fig 1).

Haemangioblastoma

Haemangioblastoma form another interesting group of vascular abnormalities, particularly difficult to deal with in the setting of multiple tumours in the von Hippel Lindau syndrome (VHL). Sung et al. reported a series of patients treated with conventionally fractionated radiotherapy and reported good responses, particularly in the subgroup which had received more than 4000cGy. Smalley et al. found higher control rates at doses of conventionally fractionated radiation above 5000cGy. We described the control of 5/5 haemangioblastomas in four patients following radiosurgery, with shrinkage or obliteration in 4/5 cases. We have subsequently outlined our current preferred management plan for multifocal (particularly posterior fossa VHL patients) haemangioblastomas.

Acoustic neuroma

Vestibular schwannoma accounts for 8% of primary tumours presenting to a neurosurgical service and is likely to be bilateral in neurofibromatosis 2 (NF-2). Surgical resection has long been the mainstay of therapy but even with ‘hearing preservation’ (microsurgical resection, with coincidental neuropathological nerve monitoring) the operation is not without morbidity and the preservation of hearing is less than excellent. There is now a large experience with the use of stereotactic radiosurgery for therapy of acoustic neuroma. The Pittsburgh group has recently reported five year follow-up on 162 patients so treated. The rate of tumour control was 98%, with one hundred tumours becoming smaller (62%), fifty-three (33%) remaining the same and nine (6%) becoming larger. A slight enlargement at three to six months may be a radiation related swelling — a subacute reaction to the radiation and one that precedes shrinkage; however, such enlargement may be clinically critical as these patients may develop obstructive hydrocephalus at this time. A tumour tombstone of similar size to the original one is not uncommon but frequently with a low signal centre and high signal rim on MR — again features of radiation damage. In the Pittsburgh experience, the hearing remained unchanged in 51%, a percentage that compares favourably with neurosurgical series. Facial nerve function was preserved in 79%. Radiosurgery for tumours up to 3cm diameter is now a first line therapy. We have recently drawn attention to the potential risks of late oncogenesis in this condition, particularly in NF-2 cases.

Our current protocols are examining fractionated therapy on the lower internal dose gradient x-knife system in the attempt to preserve/improve hearing (Fig 2).

Meningioma

Simpson described a 9% recurrence rate when meningiomas were removed with involved dura and bone, but 40% if the resection was subtotal; these results have been confirmed. Considerable data strongly support the use of radiotherapy after subtotal resection. Salazar reviewed pooled data demonstrating a fall in the five year recurrence rate from 40 to 18% when radiotherapy followed subtotal surgery. In a UK study, 82 base of skull meningiomas had been treated by subtotal resection and radiotherapy, and the ten year disease-free progression rate was 83% (92% at five years). There was a disproportionately large number of meningiomas in the cavernous sinus region. Our treatment guidelines reflect the safety of single shot radiotherapy (radiosurgery) when treating targets of varying sizes that abut the critical nervous system, and allow the increasing exploitation of ‘CNS friendly’

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Fig 1. The response of vascular malformations to brain radiosurgery.

(a) carotid arteriography demonstrating an AVM (i) before and (ii) after obliteration by radiosurgery.

(b) axial MR images of an angiographically occult vascular malformation with the imaging characteristics associated with a cavernous angioma, (i) before and (ii) two years after radiosurgery, demonstrating good shrinkage.

(c) axial MR scans of the posterior cranial fossa of a patient with von Hippel Lindau syndrome and multiple cerebellar haemangioblastomas, (i) before radiosurgery and (ii) two years later, demonstrating the good efficacy of the procedure on one lesion whilst another line of three lesions grows.

(d) axial CT scans of a patient with an intracranially extending glomus jugulare tumour after several previous skull base operations (i) before and (ii) three years after radiosurgery, demonstrating a good response to therapy.
fractionated radiation therapy utilising the stereotactic mapping and dosimetric advantages of radiosurgery\textsuperscript{30}.

In summary, we advocate stereotactic single shot radiotherapy for tumours less than 3cm in diameter and conventionally fractionated radiotherapy for larger ones, with increasing use of fractionated stereotactic technology where smaller tumours abut critical nervous system.

Craniopharyngioma

In a pooled series of 111 subtotally resected craniopharyngiomas, Amacher\textsuperscript{31} found that 75\% regrew and the difficulty for the neurosurgeon to achieve complete resection is highlighted by the data of Baskin and Wilson\textsuperscript{32} who claimed that they had obtained this objective in only

\begin{itemize}
  \item [\textbf{Fig 2.} (a) and (b) Coronal and T1 weighted MRI scans of two patients with acoustic neuroma: The lesions are shown (i) before and (ii) some time after radiosurgery. The good responses are well seen, although it should be noted that in many tumours good responses may be only attended by stabilisation of size. (c) Audiograms in a third patient with acoustic neuroma: (i) before and (ii) after radiosurgery, demonstrating an unusually good hearing response after therapy.]
\end{itemize}
10% of 74 operated patients. Post-operative radiotherapy reduces the risk of recurrences. Heideman et al. pooled the published data from several series to produce the following results with regard to actuarial 5 and 10 year survival results:

- 'total resection' cases: 58–100% and 24–100%
- subtotal resection cases: 37–71% and 31–52%
- subtotal and conventionally fractionated radiotherapy cases: 69–95% and 62–84% respectively.

Many stereotactic radiosurgical units have tended to avoid craniopharyngioma therapy because of the frequent envelopment of the disease around the optic chiasm – a notoriously radiosensitive structure. Lunsford et al. observed complete regression of post-operative remnants of a previously resected solid craniopharyngioma following radiosurgery, and disease stabilisation in another two patients – but two patients suffered deterioration in their vision and in at least one of them it was radiation related.

We have recently reported our own experience – radical radiosurgery in two patients and salvage radiosurgery (i.e. after conventionally fractionated therapy) in four patients. We observed complete responses in two patients (Fig 3) and stabilisation in others. We advocate radical stereotactic radiosurgery for small volume and discrete disease well away (more than 5mm) from the chiasm – intrasellar disease or cavernous sinus extensions would seem the most appropriate indication. For disease enveloping the chiasm, fractionated radiosurgery using the relocatable stereotactic frame may well have a competitive role to that of standard planning, conventionally fractionated radiotherapy.

It is important to mention the use of beta emitting colloidal solutions instilled into the cystic components of craniopharyngiomas – a recurring symptomatic problem requiring repeated interventions in some patients. This technique differs from the 'radiosurgical' external beam technology to which the rest of this manuscript refers. We recently collated the published literature in this field: a total

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Fig 3. (a) Axial CT scans of a patient with recurrent craniopharyngioma following conventional surgery and radiotherapy. (i) shows the tumour before and (ii) after radiosurgery, demonstrating the complete response.
(b) Sagittal, T1 weighted MR scans of a patient with an intrasellar relapse of craniopharyngioma: (i) before and (ii) after radiosurgery, demonstrating complete imaging response.
of 149 cysts had been treated in 127 patients: 121 (81%) had either shrunk in size or become obliterated\textsuperscript{37}. More than half that number had been treated as a primary radical therapeutic procedure. Our own experience has been with seven cysts in six patients – previously treated by surgery and radiotherapy. Five cysts previously requiring repeated aspirations at intervals of 2–20 weeks, required no further aspirations after 90–Y instillations\textsuperscript{37}. Intracystic beta emitting isotope instillation is now to be considered best standard therapy for cystic craniopharyngioma recurrences and may be used side by side with optimal radiation therapy to solid disease.

**Pituitary adenoma**

Radiotherapy unquestionably reduces the recurrence rate of pituitary adenoma after neurosurgical resection\textsuperscript{38,39}. The results of modern postoperative radiotherapy have been reported in terms of tumour-free survival and marker/hormone response: Brada \textit{et al}\textsuperscript{40} found an actuarial disease-free survival rate of 88% at ten years (94% at five years) with routine postoperative radiotherapy. Other data unequivocally demonstrate the progressive decline in hormone marker levels in acromegaly\textsuperscript{41}. Cushing's disease/Nelson's syndrome\textsuperscript{42,43} and prolactinomas\textsuperscript{44} with low risk to the optic chiasm but with a finite new endocrine replacement need with the passage of time (e.g. 25% of acromegals require a new endocrine replacement by five years after radiotherapy in the Barts' series\textsuperscript{45}). Whether late carcinogenesis is as high as 1% remains controversial\textsuperscript{46–48}.

Stereotactic radiosurgery might initially seem appealing as an alternative to conventionally planned and fractionated radiotherapy, as the disease is frequently relatively small bulk (postoperatively anyway) and without the perceived need for wide margins of safety radiation therapy required by many malignant tumours. However, potential disadvantages to the use of this technique include the proximity of the optic nerves and chiasm (notoriously sensitive to high single shot radiation therapy) and the fact that 'partial fossa' radiation technology may lead to the same recurrence rates as partial hypophysectomy surgery alone, probably more so for the more aggressive and larger tumours\textsuperscript{49}. Indeed, apart from promising early proton (charged particle) radiosurgery data\textsuperscript{50} the data on this technique for pituitary adenomas have so far been unimpressive. Landolt \textit{et al}\textsuperscript{51} compared a non-randomised series of 50 acromegals, presenting with a mean pre-treatment growth hormone (GH) of 28 mIU/l after treatment with conventional radiotherapy (follow-up 7.5 years), with 16 patients with a presenting mean GH of 18 MIU/l and 1.4 years follow-up after radiosurgery. These workers reported a faster normalisation of GH levels after radiosurgery (70% of patients had achieved this by 18 months) whereas after conventional radiotherapy the same percentage took 7 years to do so. The radiosurgical follow-up is short and this needs to be studied. This is critical for acceptance of radio-
surgery as primary radiation therapy for pituitary adenoma as there are:

- more perceived risks
- the technique must be considered to be 'partial fossa' radiation therapy
- conventionally fractionated therapy is safe and highly effective.

Of 21 pituitary adenoma patients accepted for stereotactic radiosurgery at St Bartholomew's Hospital in the decade 1989–1998, 20 had previously been treated by conventionally fractionated radiotherapy – the majority from other centres. Persistent disease in the cavernous sinus was the commonest site for the persistent tumour. One patient was accepted for radical radiosurgical treatment – this patient having a discrete, low lying and small pituitary adenoma (in other circumstances ideal for transphenoidal resection).

Whilst our indications may broaden in the future, the place of stereotactic radiosurgery as first line therapy for pituitary adenoma remains controversial\textsuperscript{49}.

**Glioma**

The previous literature concerning radiosurgery in the treatment of gliomas has been based, to a large extent, on the therapy of high grade tumours\textsuperscript{52–55}. Arguing that high grade gliomas grow from the edges, we have reasoned, both in our implant brachytherapy and radiosurgery programmes, that low grade gliomas are the more likely ones to benefit from more 'focussed' radiation therapy\textsuperscript{56,57}.

Of twelve low grade gliomas treated by a radiosurgery boost after conventional radiotherapy, there was complete disappearance of disease in eight\textsuperscript{56}.

**Metastases**

The standard approach to managing brain metastases is whole brain radiotherapy, but surgical resection prior to radiotherapy is best for apparently single and superficially located metastases in good performance patients. The swing towards radiosurgery for such patients with one or 'a few' metastases has been excessive in some centres, because further metastases (which would have been obliterated in the whole brain series) appear and progress. However, for the patient with multiple brain metastases, who does well for a time after whole brain therapy and then relapses in one problem-causing site, focal radiosurgical technology may well be appropriate if the patient is otherwise in reasonable health. Occasional, single, late, deep metastases may also be an indication for this technique.

**Other conditions**

Skull base tumours such as chordoma of clivus lend themselves well to radiosurgical attack and most centres now combine radiosurgery in the treatment algorithm\textsuperscript{59,60}. Other diagnoses accepted for therapy by radiosurgery at Bart's in
the last decade have been: (mastoid) Langerhans cell histiocytosis, (infratemporal fossa) rhabdomyosarcoma in local relapse, plasmacytoma of skull base, angiofibroma and recurrent nasopharyngeal carcinoma. Orbital conditions include local relapse of orbital rhabdomyosarcoma (after conventional radiotherapy) and adenoid cystic carcinoma of the orbital apex (3 cases). We have been using the PET scanning facility to help in the mapping of viable tumours (Fig 4). It is clear to us that there is a selected place for this technology in the treatment of head and neck cancer that lies within stereotactic space.

Beta emitting colloidal solution. This refers to a solution of fluid containing atoms of a radioactive isotope which emit beta rays or electron particles during radioactive decay. Due to the physical properties of charged particles, the path length of the particle in biological tissue is determined by the energy of the particle emission and is limited (brachytherapy); unlike x-rays, the beam has a finite penetration. Therefore the amount of biological tissue treated can be selected by choosing an isotope emitting beta rays of desired energy/path length.

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