REVIEW ARTICLE

High Precision Radiotherapy Techniques in the Management of Brain Tumours: Evolution and Clinical Experience

Rakesh Jalali

Introduction

Brain tumours are relatively rare and account for 2-5% of all neoplasms. Advances in imaging and refinement in treatment modalities including surgery, radiotherapy and integration of chemotherapeutic schedules in the management paradigm of these tumours have generally led to improvement in survival. From a prognostic view, these tumours seem to broadly divide themselves rather distinctly as seen in the adult and paediatric age groups. Malignant gliomas and metastases are commonly seen in adults and universally associated with dismal outcomes. On the other hand, paediatric brain tumours, the commonest solid tumours in this patient population, are potentially curable but can result in moderate to severe late disease and treatment related sequelae. Radiotherapy is an important treatment modality in the management of several brain tumours, resulting in good to excellent long-term survival rates in a majority of childhood tumours and in adults with benign tumours. However, while the local control in these tumours has been reasonably effective, there have been concerns about treatment related morbidity, which includes neuropsychological impairment, endocrine dysfunction, growth retardation, risk of second malignancy and cerebrovascular events (1,2). Although the exact role of radiotherapy in the causation of these sequelae is not yet completely understood, it is fair to assume that radiotherapy is at least partly responsible. There have been attempts to modify the management in terms of avoiding, delaying radiotherapy or reducing the total radiation dose to the tumour with a view to reduce its impact on long term toxicity. However, reduction of radiotherapy doses to the tumour has shown to result in poor local control rates. Also, a majority of the patients in whom the radiation is delayed eventually do require radiation therapy at later stage. New techniques of radiotherapy are hence being explored since last few decades, to minimise the irradiation to the normal brain with critical structures without compromising radiotherapy doses essential for tumour control.

Conventional Radiation Therapy

Conventional radiation therapy to a majority of brain tumours involves 2-3 static open beams with simple coplanar field arrangement. The field dimensions are chosen to cover the tumour adequately as deemed appropriate on planning X-ray images (as on a simulator) with respect to the surface and bony anatomy. Typically, a generous margin of 2-3 cms (sometimes more) is given in order to overcome the possible errors in judging the coverage of the tumour, its microscopic extension and uncertainties in daily set up and treatment delivery. This may lead to irradiation of significant volumes of normal brain and adjacent critical structures. The three-dimensional picture of the tumour is difficult to appreciate in the conventional two-dimensional (2D) planning. Similarly organs at risk are also not visualised properly and it is very difficult to compute the dose received by various tissues. 2D planning also leads to restriction of the treatment using coplanar beams only. Three-dimensional (3D) planning evolved in an attempt to overcome these problems of 2D planning.

Last few years have seen a tremendous refinement in the techniques of radiation planning and delivery. This

From Postgraduate Department of Radiation and Neuro-Oncology Tata Memorial Hospital Parel, Mumbai 400012
Correspondece to: Dr. Rakesh Jalali , Astt. Prof. & Consultant Radiation and Neuro-Oncologist Tata Memorial Hospital Parel Mumbai.

has been largely possible with major advances in integrating imaging such as computerised tomography (CT) and magnetic resonance imaging (MRI) for better delineation of tumour volumes in treatment planning. There has been also a simultaneous technological revolution in radiotherapy planning with the emergence of dedicated computerised treatment planning workstations, which have helped in the evolution of newer high precision treatment techniques. Three dimensional conformal radiation therapy (CRT), stereotactic radiosurgery (SRS), and fractionated stereotactic radiotherapy (SRT) or stereotactic conformal radiotherapy (SCRT) are such techniques that have the potential to minimise doses to the normal brain and critical structures as compared to conventional radiotherapy.

CRT

CRT is a technique in which radiation beams are conformed to the shape of the tumour with the help of multileaf collimators (MLC) or customised shielding blocks in multiple static beams.

SRS

Stereotactic radiosurgery (SRS) is a high precision technique of radiotherapy in which multiple collimated beams of radiation are stereotactically aimed to a well defined target volume so as to deliver a single, high dose of radiation to a small volume of tissue. The concept and initial implementation of radiosurgery was introduced by Lars Leksell in 1950s using initially orthovoltage and later multiheaded cobalt unit (described as gamma knife). Gamma knife consists of 201 cobalt sources focused towards one isocentre, with the activity of the total cobalt ranging from 5500 to 6000 Ci. SRS requires accurate immobilisation, precise definition of the volume to be irradiated, localisation of critical organs and ability to produce multiple plans. On a modified linear accelerator, SRS conventionally is delivered as an arc therapy. However, both gamma knife and arc therapy typically produces spherical dose distribution. Tumours being irregular are conformed only using multiple isocentres, which may lead to considerable dose inhomogenity. The optimum manner to treat irregular shaped targets (frequent the case in clinical practice) is with multiple conformal static fields (3). There is a large experience of SRS in the treatment of AVMs, brain metastases and small tumours such as meningiomas and acoustic neuromas. Single fraction SRS has however been sometimes shown to be associated with considerable neurological toxicity to the optic apparatus, the cranial nerves and normal brain (4,5). While SRS may provide highly conformal doses around the tumour, its lack of superior local control in brain tumours to conventional management strategies and considerable risk of neurotoxicity has prompted to explore other means of irradiation to achieve less toxicity and maintain or improve local control rates. One of the ways is to deliver stereotactic radiotherapy in a fractionated manner, known as stereotactic radiotherapy (SRT).

SRT/SCRT

SCRT is a further advancement of CRT and SRS in which highly precise radiation can be delivered with very firm immobilisation with relocatable frames, accurate target localisation, highly conformal shielding with micromultileaf collimators (mMLC) and focused radiation delivery in a fractionated manner. It also ensures homogeneous dose distribution within the irradiated volume, further reducing the risk of damage. Larger volumes therefore can be treated with multiple daily fractions like conventional radiation, to benefit from normal tissue sparing properties of fractionated radiation therapy. This has become possible with the utilisation of high precision relocatable non-invasive means of immobilisation. Initial experience with fractionated stereotactic radiotherapy involved varying dose schedules with relatively large dose per fraction. However, any part of the normal brain encompassed in high dose volume could result in significant radiation injury. On the other hand, fractionated stereotactic treatment with standard dose per fraction of less than 2 Gy has been shown to be safe without any increased toxicity.

Technical Aspects

The treatment with CRT/SRS/SRT involves few basic steps like accurate immobilisation, radiotherapy planning scans, target delineation, planning using multiple conformal beams, quality assurance and plan implementation. Few important steps in each are described below.

Immobilisation

Immobilisation for SRS is done using the fixed frame. The frame is fixed to the patient's skull using four pins till they hit the periosteum. It affords excellent immobilisation and no margin is generally given for set up errors. For CRT and SCRT, the treatment lasts for 6-7 weeks and therefore the immobilisation device should be reproducible so as to maintain the accuracy of desired treatment delivery. An individual customised thermoplastic mould is used for patients planned for CRT. The possible patient motion with this mould over a fractionated course of radiotherapy has been estimated to be between 5mm to 10mm. Patients considered for SCRT are immobilised using the specialised relocatable mask based stereotactic frame. This provides even firmer immobilisation than the thermoplastic mould with possible patient movement estimated to be around 1-2 mm (6).

Radiotherapy Planning Scans

Patients immobilised in their moulds or stereotactic frame undergo a contrast enhanced planning CT scans with 2-5 mm slice thickness at 2-5 mm separation. The CT data of patients is networked to the dedicated treatment planning system. SRS/SCRT patients also undergo a planning MRI scan which is also networked to the planning computer, where these images are fused with the planning CT scans images by image fusion software. Integration of MRI in planning has demonstrated to provide significant improvement in delineation of the tumours and normal structures facilitating the accuracy of localisation of the tumour and critical structures.

Contouring

Gross tumour volume (GTV) defined as the area of visible tumour or areas deemed to contain tumour is manually contoured by the clinician on each CT or CT-MRI fused slices. All pre-treatment imaging is generally reviewed to help in defining this volume. Critical structures such as the optic chiasm, pituitary hypothalamic axis, brain stem and the normal brain are also contoured. Target delineation remains one of the very important areas and recent advances in functional imaging such as magnetic resonance spectroscopy (MRS), positron emission tomography (PET) etc. are being currently explored to help in more accurate tumour visualisation.

Planning Target Volume (PTV)

A margin has to be defined around GTV to take into account the possible microscopic extension of the tumour not seen on the planning images and the spatial uncertainties in day to day set up. This margin depends upon the type of tumour, confidence in tumour volume definition, immobilisation device used and the set up uncertainty in daily treatment delivery. For patients treated with CRT typically a margin of 10-20 mm is grown around the GTV to give the final planning target volume (PTV). SRS/SCRT involves firmer immobilisation, frequent use of MRI in tumour volume delineation and accurate treatment delivery. Hence the margin for SCRT is 5 to 10 mm while for SRS; no margin is usually given (6).

Field Arrangement and Plan Evaluation (CRT)

Treatment planning is based on planning optimisation utilising beam energy, appropriate weighting, and wedges with different field arrangements. The plans are finalised using ICRU 50/62 recommendations ensuring PTV coverage by 95% isodose line and maintaining uniform dose homogeneity. CRT plans typically involve 3-4 conformal field arrangements. With the help of beam's eye view facility, conformation is achieved for all fields with either standard multileaf collimators having 1 cm leaf width at the isocentre or using conformal blocks. Analysis of rival plans is done by visual assessment and with the help of dose volume histograms (DVH) of the PTV and critical structures. Plan, which delivers uniform dose distribution in the PTV with adequate coverage and minimal possible doses to the normal brain and adjacent critical structures, is chosen as the final plan. Treatment parameters are then networked to the treatment machine where the treatment is delivered by 6 MV photons.

SRS/SCRT

Planning of SRS/SCRT is more complex than CRT. Every effort has to be made to achieve the best possible plan with respect to desired dose delivery to the target and minimal dose to the critical structures. The field arrangement typically used is 4-10 widely spaced non-

coplanar beams using 6 MV photons (7). Uniform dose homogeneity as per standard ICRU criteria is necessary for all approved plans, particularly for SCRT. All radiation portals are individually conformed to the shape of the PTV with micromultileaf collimators.

Quality Assurance and Plan Implementation

It is very important to have a good quality assurance program while implementing these relatively conformal techniques. The portal films for the isocentre check should be taken on the first day of treatment and compared with the digitally reconstructed radiograph (DRR), generated from the treatment planning system. Portal films should be repeated at least once weekly. For SRS/SCRT the isocentre of the linear accelerator is checked with Lutz test before the actual treatment is delivered. Care is taken to ensure isocentre accuracy and all fields checked before treatment, using the target positioner box.

Clinical Experience

Paediatric Brain Tumours

Radiation therapy is the mainstay of treatment for optic chiasmal gliomas, a common paediatric brain tumour, as surgical excision is not possible due to risk of damage to optic nerves. Craniopharyngiomas are benign tumours in the suprasellar region arising from the Rathke's pouch, mainly seen in children and conservative surgery followed by radiation therapy gives 5-year survival rates of 70-80%. Radiation therapy for both is generally delivered with anterior and two lateral wedge pair portals encompassing the tumour with 1-2 cm margin. The recommended dose is 50-55Gy in conventional fractionation to the tumour as seen on CT or MRI with 1-2 cm margin all around. The use of CRT and SCRT with 4-6 fields may particularly be useful in children where it is important to spare the surrounding normal critical structures like pituitary and hypothalamus in the vicinity (7,8). SRS is associated with high morbidity and damage to optic nerve and is not advocated. Considerable activity is currently going on to evaluate the role of CRT and SCRT in irradiation of the tumour bed as boost in medulloblastomas to minimise the treatment related toxicity (9).

Meningioma

Radiation therapy for meningiomas is generally considered when the excision is partial or in cases of recurrence. The long-term tumour control rate using modern imaging and treatment delivery systems has been reported to be 80-90%. The recommended technique is to treat the residual tumour with 1 cm margin to a dose of 54Gy in 30 fractions over 6 weeks. Stereotactic techniques allow smaller margin of the PTV and hence better sparing of the normal tissues. SRS/SCRT have been explored in patients with cavernous sinus and parasellar meningiomas (10,11). Early results suggest good initial tumour control with less toxicity to the trigeminal and optic nerves. Both small and large tumours can be treated with SCRT with potentially reduced complication rates (11).

Pituitary Adenomas

The initial management of these tumours is surgical excision, which is generally done by transphenoidal approach. The timing of radiotherapy is a matter of debate and this issue is being addressed in an ongoing randomised trial at our centre. Radiotherapy achieves excellent long-term control to the order of >90% at 10-20 years (12). The risk of optic nerve damage and second malignancies with conventional radiation is 1-2% at 10-20 years. SCRT is the appropriate treatment for these tumours and should be preferred over SRS, which has more risk of optic nerve and neurological damage (5,13,14).

Acoustic Neuroma

Various treatment options for acoustic neuroma include observation, surgery alone and radiation therapy. Radiosurgery is being done for acoustic neuromas with a 90-95% progression free survival at 5 years. But SRS may be associated with a relatively high risk of damage to VII and VIII nerve. SRT/SCRT is potentially a better option in which similar tumour control can be achieved with decreased neurotoxicity (15).

High Grade Glioma

Surgery followed by radiation therapy is the standard treatment for high-grade gliomas. Radiation therapy involves radiation to the tumour as visualised on the

contrast enhanced CT or MRI with a margin of 2-3 cm all around. The dose recommended is 60 Gy in conventional fractionation over a period of 6 weeks. As this may encompass large volume of normal brain, CRT can be used in dose escalation protocols, hyperfractionation and accelerated fractionation to decrease normal tissue toxicity. In recurrent gliomas radiation therapy can be delivered as SRS or SCRT with reasonable efficacy comparable to chemotherapy but may carry a relatively high risk of radiation necrosis necessitating re-operation (16). SRS boot has been attempted in small malignant gliomas as a part of dose escalation but has failed to demonstrate any advantage.

Brain Metastasis

Conventional management of brain metastasis involves whole brain radiotherapy. However, surgical excision in solitary metastasis improves survival marginally. SRS with or without whole brain radiation therapy have also shown encouraging results in solitary metastasis or upto 3 lesions. The maximum advantage is seen in patients with absent/ controlled extracranial disease and with good performance status (17).

Scientific Rigour of High Precision RT Techniques (TMH study)

There is increasing experience of utilisation of high precision techniques of CRT and SCRT which have indeed become integrated in routine clinical practice in several centres of the world, including ours (18). Clinical experience in a range of tumours employing these techniques has shown comparable results to that of conventional radiotherapy. Because of their ability to conform radiation doses tightly around the target volume resulting in significantly less volumes of adjacent brain receiving high doses, they have the potential to minimise some of the radiation induced morbidity. However, most of the data addressing these issues is premature. Also, there has been some concern that these techniques typically employ tight margin and some concern, justifiably so, have been also raised to assess long term local control because of the real potential of geographical misses. These technologies, while exciting are also expensive and their benefit needs to be validated in appropriately conducted clinical trials. In this regard, we are at present conducting a randomised trial comparing SCRT and conventional radiotherapy in minimising late sequelae in children and young adults. The trial aiming to study 200 patients would provide very important longitudinal and reliable data regarding long-term sequelae in patients receiving focal brain radiation. More importantly, it will evaluate the efficacy of SCRT with respect to conventional radiotherapy in terms of long-term local control and the incidence and magnitude of treatment related complications in the two arms. Preliminary analysis of 35 patients done recently revealed mean baseline global-IQ (normal 90-109) of patients in SCRT and ConvRT arms to be 84 and 91 respectively with 10/16 patients assessed in SCRT and 6/13 in ConvRT having below normal IQ's even before starting radiotherapy, the corresponding values at 6-months evaluation being 95 and 91 (19). VITHOBA battery (normal-100) for blind patients revealed pre-RT values of 97 in SCRT and 56 in ConvRT arms. Memory remained maintained in SCRT (mean 101 baseline and 114 at follow-up) but worsened in ConvRT (107 pre-RT and 57 post-RT). LOTCA neurocognitive battery used for patients aged>6 revealed respective average baseline and 6-month follow up values of 95&100 for SCRT and 98&90 for ConvRT. Anxiety assessments with C1, C2 (no anxiety<35) & Hamilton scale (normal<17) showed mean baseline values of 48, 40 & 20 in SCRT reducing to 31, 25 and 20 respectively at follow-up but worsened in ConvRT (mean respective baseline of 42, 32, 18 Vs 37, 30 and 24 at follow-up). Mean depression values using Hamilton scale (normal<17) was 19 before and 10 after SCRT, which was better than seen in ConvRT (13 and 19 respectively). SCRT at a short follow-up seems to show non-significant improvement in levels of anxiety, depression and memory compared to conventional radiotherapy, which however clearly needs mature data in larger number of patients for firm conclusions.

Conclusion

High precision conformal radiotherapy techniques have the potential to minimise the doses of radiation to adjacent normal tissues and should be considered in brain tumours,

especially in benign/low grade tumours. The techniques need considerable expertise and meticulous QA but have become a part of routine in daily practice in many centres of the world including ours. Although the preliminary experience is encouraging, long term data is required to confirm the efficacy in term of sustained local control and reduced toxicity.

References

1. Jannoun L, Bloom HGJ. Long term psychological effects in children treated for intracranial tumours. *Int J Radiat Oncol Biol Phys* 1990; 18: 747-54.
2. Jenkin D, Greenberg M, Hoffman H, Hendrick B, Humphreys R,Vatter A. Brain tumours in children: long term survival after radiation treatment. *Int J Radiat Oncol Biol Phys* 1995; 31 (3): 445-51.
3. Laing RW, Bentley RE, Nahum AE *et al.* Stereotactic radiotherapy for irregular targets: A comparison between static conformal beams and non-coplanar arcs. *Radiother Oncol* 1993; 28: 241-46.
4. Leber KA, Bergloff J, Pendl G. Dose-response tolerance of the visual pathways and cranial nerves of the cavernous sinus to stereotactic radiosurgery. *J Neurosurg* 1998; 88 (1): 43-50.
5. Mitsumori M, Shreive D, Alexander E *et al.* Initial results of LINAC based stereotactic radiosurgery and stereotactic radiotherapy for pituitary adenomas. *Int J Radiat Oncol Biol Phys* 1998; 42: 573-80.
6. Alheit H, Dornfeld S, Dawel M *et al.* Patient position reproducibility in fractionated stereotactically guided conformal radiotherapy using the BrainLab mask system. *Strahlenther Onkol* 2001; 177 (5): 264-68.
7. Perks J, Jalali R, Cosgrove V *et al.* Optimisation of stereotactically guided conformal treatment planning of sellar and parasellar tumors based on normal brain dose volume histograms. *Int J Radiat Oncol Biol Phys* 1999; 45: 415-25.
8. Debus J, Kocagoncu KO, Hoss A, Wenz F, Wannenmacher M. Fractionated stereotactic radiotherapy (FSRT) for optic glioma. *Int J Radiat Oncol Biol Phys* 1999; 44 (2): 243-48.
9. V Murthy, Jalali R, Sarin R *et al.* Stereotactic conformal radiotherapy for posterior fossa tumours: a modelling study for potential improvement in therapeutic ratio. *Radiother Oncol* 2003; 67 (2): 191-98.
10. Shafron DH, Freidman WA, Buatti JM *et al.* Linac radiosurgery for benign meningiomas. *Int J Radiat Oncol Biol Phys* 1999; 43: 421-27.
11. Jalali R, Loughrey C, Baumert B *et al.* High Precision Focused Irradiation in the form of fractionated stereotactic conformal radiotherapy for benign meningiomas predominantly for base skull location. *Clin Oncol* 2002; 14: 103-09.
12. Brada M, Rajan B, Traish D *et al.* The long term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. *Clin Endocrinol (Oxford)* 1993; 38: 571-81.
13. Jalali R, Brada M, Perks JR *et al.* Stereotactic conformal radiotherapy for pituitary adenomas: technique and preliminary experience. *Clin Endocrinol* 2000; 52: 695-702.
14. Jalali R, Brada M. Radiosurgery for pituitary adenomas. *Critical Rev Neurosurg* 1999: 9 (3): 167-73.
15. Meijer OW, Vandertop WP, Baayen JC *et al.* Single-fraction vs. fractionated linac-based stereotactic radiosurgery for vestibular schwannoma: a single-institution study. *Int J Radiat Oncol Biol Phys* 2003; 56 (5): 1390-96.
16. Shephard SF, Laing RW, Cosgrove VP *et al.* Hypofractionated stereotactic radiotherapy in the management of recurrent glioma. *Int J Radiat Oncol Biol Phys* 1997; 37: 393-98.
17. Jyothirmayi R, Saran FH, Jalali R *et al.* Stereotactic radiotherapy for solitary brain metastases. *Clin Oncol* 2001; 13 (3): 228-34.
18. Deshpande DD, Sharma D, Jalali R *et al.* Stereotacic radiotherapy for intracranial lesions with micromultileaf collimator mounted on a LA. *J Med Phys* 2002; 27 (1): 1-8.
19. Jalali R, Sarin R, More N *et al.* Prospective neuropsychological and endocrine evaluation in children with benign/low-grade brain tumours treated with SCRT and conventional RT: early results of a randomised trial. Proc. 11th Int Symposium on Peditriac Neuro-Oncology, Boston. 2004; pp. 106.