

Evolution and Techniques of 3Dimensional Conformal/Stereotactic Radiation/Stereotactic Surgery for Brain Tumours : their impact on management of intracranial lesions

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Abstract: 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. Conventional radiation therapy to a majority of brain tumours involves 2-3 static open beams with simple coplanar field arrangement, which may however lead to irradiation of significant volumes of normal brain and adjacent critical structures. Last few years have seen a tremendous refinement in the techniques of radiation planning and delivery. Three dimensional radiotherapy (CRT) is a technique in which radiation beams are conformed to the shape of the tumour with the help of multileaf collimators (MLC) or shielding blocks in multiple static beams while stereotactic radiosurgery (SRS) is a high precision technique 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. Stereotactic conformal radiation (SCRT) is a further advancement of CRT and SRS in which highly precise radiation can be delivered with firm immobilisation with relocatable frames, accurate target localisation, highly conformal shielding with micromultileaf collimators (mMLC) and focused radiation delivery in a fractionated manner. SRT/SCRT is particularly indicated in young patients with benign/low grade neoplasm where long-term survivals are expected and at risk to develop radiation induced morbidity.

Key words : *Stereotactic radiotherapy, radiosurgery, 3D conformal radiotherapy.*

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 some 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, 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 poorer 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 has been largely possible with major advances in integrating imaging such as CT and 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 CRT, SRS, and fractionated SRT or SCRT are such techniques that have the potential to minimise doses to the normal brain and critical structures as compared to conventional radiotherapy.

Conformal Radiation Therapy (CRT) : Conformal radio therapy is a technique in which radiation beams are conformed to the shape of the tumour with the help of MLC or customised shielding blocks in multiple static beams (Fig.1). The aim of CRT is to achieve a high dose differential between the tumour and the surrounding normal tissues, which may allow for either an increase in the tumour dose to improve local control or for a potential decrease in radiation damage to the normal brain. 3D conformal radio therapy is used in the treatment of various brain tumours like meningioma low-grade gliomas, pituitary adenoma, and craniopharyngioma.

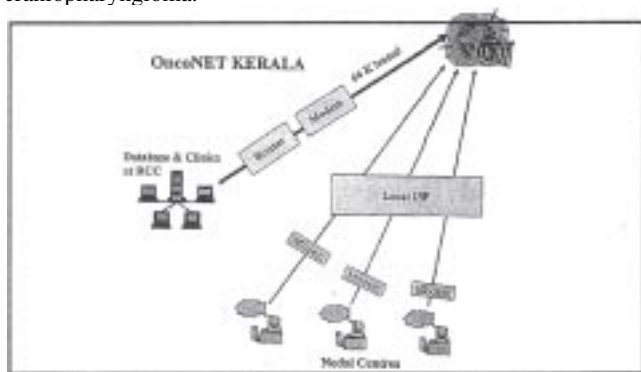


Fig.1: Schematic diagram of onconet kerala

Stereotactic Radio Surgery (SRS) : Stereotactic radiosurgery 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 Curieci. 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 produce spherical dose distribution. Tumours being irregular are conformed only using multiple isocentres, which may lead to considerable dose inhomogeneity. The optimum manner to treat irregular shaped targets (frequently the case in clinical practice) is with multiple conformal static fields³. There is a large experience of stereotactic radio surgery in the treatment of artero venous malformations,

brain metastases and small tumours such as meningiomas and acoustic neuromas. Single fraction stereotactic radio surgery 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 stereotactic radio surgery may provide highly conformal doses around the tumours, 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.

Stereotactic Radio Therapy/Stereotactic Conformal radiotherapy (SRT/ SCRT) : stereotactic conformal radiotherapy 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 with 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 3conformal techniques 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 for radio surgery 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 conformal radio therapy, 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 conformal radio therapy. 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 stereotactic conformal radiation 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 around 1-2 mm (6) (Fig 2).

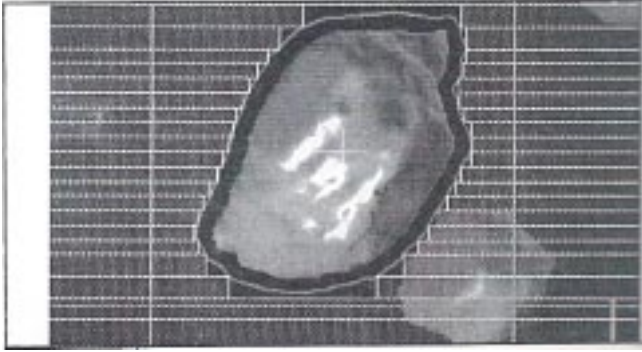


Fig. 2: Beam's Eye View of a conformal radiotherapy portal showing conformation achieved with the help of multileaf collimators.

Radiotherapy planning scans : Patients immobilised in their moulds or stereotactic frame undergo a contrast enhanced planning computerized tomography scans with 2-5 mm slice thickness at 2-5 mm separation. The computerized tomography data of patients is networked to the dedicated treatment planning system. Radio surgery/stereotactic radio therapy patients also undergo a planning magnetic resonance imaging scan which is also networked to the planning computer, where these images are fused with the planning CT scans images by an image fusion software. Integration of magnetic resonance imaging 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, positron emission tomography etc. are being currently explored to help in more accurate tumour visualisation.

Planning target volume (PTV) : A margin has to be defined around gross tumour 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 conformal radiation typically a margin of 10-20 mm is grown around the gross tumour to give the final planning target volume. SRS/SCRT involves firmer immobilisation, frequent use of MRI in tumour volume delineation and accurate treatment delivery. Hence the margin for stereotactic conformal radiation is 5 to 10mm while for stereotactic radio surgery, no margin is usually given (6).

Field arrangement and plan evaluation : Treatment planning is based on planning optimisation utilising beam energy, appropriate weighting, and wedges with different field arrangements. The

plans are finalised using International Commission on Radiological Units 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 planning target volume and critical structures. Plan, which delivers uniform dose distribution in the planning target volume 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 6MV photons.

Stereotactic Radio Surgery/Radio Therapy : Planning of Stereotactic Radio Surgery/Radio Therapy is more complex than conformal radiation. 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 are 4-10 widely spaced non-coplanar beams using 6 MV photons. Uniform dose homogeneity as per standard ICRU criteria is necessary for all approved plans, particularly for stereotactic radiation. 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, generated from the treatment planning system. Portal films should be repeated at least once weekly. For stereotactic treatments 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

Low grade glioma (in adults) : The management options for low-grade gliomas are observation, surgery alone and surgery followed by radiation therapy. Surgery is indicated in symptomatic patients where surgical debulking is likely to reduce the symptoms. The European Organisation for Research and Treatment of Cancer prospective randomised trial has not shown any improvement in survival in early Vs delayed radiation therapy (7). In patients with progressive disease radiotherapy to a conventionally given dose of 50-54 Gy* stabilises or improves the neurological symptoms. The use of conformal radiation may be helpful to reduce the long-term toxicity due to the large volumes of brain irradiated.

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, conformal radiation 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 stereotactic treatment with reasonable efficacy comparable to chemotherapy but may carry a relatively high risk of radiation necrosis necessitating re-operation⁸. Stereotactic Radiosurgery boost has been attempted in small malignant gliomas as a part of dose escalation but has failed to demonstrate any advantage. In fact, the recent randomised radiation therapy oncology group trial of Stereotactic Radiosurgery boost Vs no boost showed worse survival in the boost arm (unpublished data).

Optic chiasmal gliomas : Radiation therapy is the mainstay of treatment for optic chiasmal gliomas as surgical excision is not possible due to risk of damage to optic nerves. The recommended dose is 50-55 Gy in conventional fractionation to the tumour as seen on CT or MRI with 1-2 cm margin all around. conformal techniques may be helpful particularly as most of the patients are children and there are critical structures like pituitary and hypothalamus in the vicinity⁹.

Medulloblastoma : The standard treatment for medulloblastoma is surgery followed by radiation therapy with or without chemotherapy. Radiation therapy involves treatment of the whole craniospinal axis using a bilateral shaped cranial portals and single posterior spinal portal to the dose of 35 Gy/21 fractions over 4 weeks. This is then followed by tumour bed boost of around 20 Gy, delivered to the entire posterior fossa with bilateral portals. But as most of the recurrences are seen in the tumour bed itself, the need to irradiate the entire posterior fossa is questioned. Considerable activity is currently going on to evaluate the role of conformality in irradiation of the tumour bed as boost in order to minimise the treatment related toxicity¹⁰.

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 1cm margin to a dose of 54Gy in 30 fractions over 6 weeks. Stereotactic techniques allow smaller margin of the Planning target volume and hence better sparing of the normal tissues. radio surgery and conformal treatment have been explored in patients with cavernous sinus and parasellar meningiomas^{11,12}. 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 Stereotaxy based treatments with potentially reduced complication rates¹².

Craniopharyngioma : Craniopharyngiomas are benign tumours in the suprasellar region arising from the Rathke's pouch, mainly seen in children. Conservative surgery followed by radiation therapy gives 5-year survival rates of 70-80%¹³. Radiation therapy is generally delivered with anterior and two lateral wedge pair portals encompassing the tumour with 1-2 cm margin. The use of Radiation Therapy Oncology Group with 4-6 fields may particularly be useful in children where it is important to spare the surrounding normal critical structures¹⁴. The recommended dose is 50-55Gy in conventional fractionation over 5-6 weeks. Radio surgery is associated with high morbidity and damage to optic nerve and is not advocated.

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 years¹⁵. The risks of optic nerve damage and second malignancies with conventional radiation is 1-2% at 10-20 years. Stereotactic conformal is the appropriate treatment for these tumours and should be preferred over Radio surgery, which has more risk of optic nerve and neurological damage^{5,16,17}.

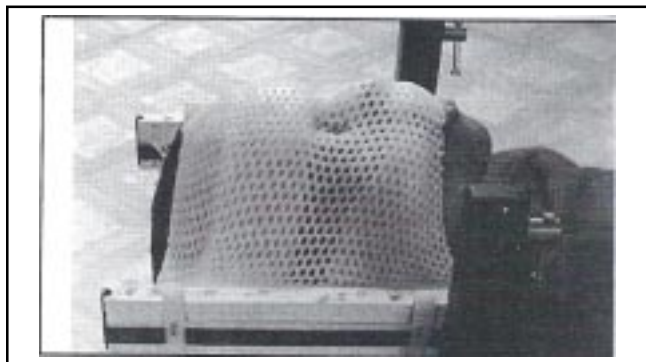


Fig.3: Patient immobilised in stereotactic relocatable mask for SCRT

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 radio surgery may be associated with a relatively high risk of damage to VII and VIII nerve. Stereotactic conformal radiation is potentially a better option in which similar tumour control can be achieved with decreased neurotoxicity¹⁸.

Brain Metastasis : Conventional management of brain metastasis involves whole brain radiotherapy. However, surgical excision in solitary metastasis improves survival marginally. Radio surgery 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 status¹⁹.

There is increasing experience of utilisation of high precision techniques which have indeed become integrated in routine clinical practice in several centres of the world, including ours. 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 existing 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 stereotactic conformal radiation 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

*1GRAY = 100 Centi GRAY = 100 rads (unit of radiation prescription)

importantly, it will evaluate the efficacy of stereotactic conformal radiation 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.

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