Efficacy of high precision radiotherapy in the management of primary brain tumours

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Abstract

High precision radiotherapy (RT) is exiting and has shown promise in dose escalation to target while reducing dose to adjacent critical structures and thus reducing complications while maintaining or improving survival functions. High precision RT techniques used in brain tumours are usually three dimensional conformal RT (3D-CRT), intensity modulated RT (IMRT), stereotactic conformal radiotherapy (SCRT) and radiosurgery (SRS). These high precision techniques needs expertise, time, resources and are expensive. Recent results from prospective studies have suggested favorable clinical outcome in the form of improved local control, survival and importantly minimizing later morbidity, after conformal techniques and justify their use in clinical practice.

Keywords: High precision radiotherapy, brain tumour, clinical outcome

Introduction

Brain tumours are relatively rare and consists only 1-2% of all tumours. Brain tumour consists of various types of benign, low grade and malignant tumours with different clinical presentation and management principles. In present era with advent of refined imaging techniques and refinement in treatment modalities including surgery, radiotherapy (RT) and integration of chemotherapeutic schedules in the management paradigm of these tumours there is improvement in survival and decrease in treatment related complications. 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.

RT is an important treatment modality in the management of several brain tumours, resulting in 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).

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 computerised tomography (CT) and magnetic resonance imaging (MRI) for better delineation of tumour volumes in treatment planning.

Radiation therapy techniques

There has been technological revolution in RT planning with 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), fractionated stereotactic radiotherapy (SRT) or stereotactic conformal radiotherapy (SCRT) and intensity modulated radiotherapy (IMRT) are such techniques that have the potential to minimize doses to the normal brain and critical structures as compared to conventional radiotherapy (3).

Conventional radiation therapy

Conventional RT usually involves 2-3 static open beams with simple coplanar field arrangement. Field dimensions are chosen to

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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 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.

Last few years with advent of better imaging techniques (computerized tomography and magnetic resonance imaging) better delineation of tumour volumes are possible. There has been also a simultaneous technological revolution in RT planning with the emergence of dedicated computerized treatment planning workstations, which have helped in the evolution of newer high precision treatment techniques. Three dimensional conformal radiation therapy (3D CRT), stereotactic radiosurgery (SRS), and fractionated stereotactic radiotherapy (SRT) or stereotactic conformal radiotherapy (SCRT) are such techniques that have the potential to minimize doses to the normal brain and critical structures as compared to conventional RT (3).

Conformal RT

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

Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) is a high precision technique of RT 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. SRS requires accurate immobilisation, precise definition of the volume to be irradiated, localization of critical organs and ability to produce multiple plans (4). On a modified linear accelerator, SRS conventionally is delivered as an arc therapy. However, in modern LA based SRS multiple fixed non-coplanar fields with micro-MLCs are usually used.

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).

Stereotactic conformal radiotherapy (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 localization, highly conformal shielding with micro-multileaf collimators (mMLC) and focused radiation delivery in a fractionated manner (5). 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 3DCRT/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.

Immobilization

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 around 1-2 mm (Fig 1).

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 localization 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 immobilization, 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.

Field arrangement and plan evaluation (CRT)

Treatment planning is based on planning optimization utilizing beam energy, appropriate weighting, and wedges with different field arrangements. The plans are finalized 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 multi-leaf 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. 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 arrangements 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 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 (5). 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 (3,4). 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. Our initial experience with SCRT in craniopharyngioma had shown to preserve neurocognitive function at 2 year median follow up (6).

In recent update of prospective study suggests that after RT, reading appears more vulnerable than other academic skills and may decline over time despite stable intellectual functioning. In a phase II study comprising of 78 low grade gliomas with median follow-up of 89 months and treated with conservative margin CRT had 5- and 10-year event-free survival in 87.4% and 74.3% respectively (7). This large, prospective series in pediatric LGGs demonstrates that CRT with conservative margin does not compromise disease control.

In recently published prospective study with conformal RT in pediatric patients and 5 year follow up had showed that long term cognitive effects correlated with patient age, neurofibromatosis type 1 status, tumor location and volume, extent of resection, and radiation dose (8). Patients younger than 5 years experienced greatest decline in cognitive function. At 10-year cumulative incidence of GH, thyroid hormone, cortisol replacement was 48.9%, 64.0% and 19.2% respectively. Math and spelling performance remained stable. Supratentorial tumor location and multiple surgeries were predictive of worse reading performance (9). Carpentari et al had shown that in pediatric ependymoma patients focal conformal RT preserves neurocognitive function at reasonable follow up evaluation (10).

In medulloblastoma randomized trial in craniospinal radiation dose (36 Gy versus 23.6 Gy) had shown that with lower dose of CSI (23.6 Gy) there is significantly less reduction of both neuropsychological and neuroendocrine function compared with higher dose CSI (36 Gy) (11). Randomized study had shown that lower age (<7 years) and higher radiation dose (>23.6 Gy) deleterious effect of cognitive function. However, patients with recurrent disease also had significantly worse quality of life and cognitive function (12). In PNET 3 study, health status was significantly poorer in the group treated with CSI plus chemotherapy than in the CSI alone arm, and there were also trends to poorer outcomes for behavior and quality of life scores (13).

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 54 Gy in 30 fractions over 6 weeks. Stereotactic techniques allow smaller margin of the PTV and hence better sparing of the normal tissues. SRS/SCRT had been explored in patients with cavernous sinus and parasellar meningiomas (14,15). 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 . IMRT has also been evaluated as a promising new technology that is safe and efficacious in the primary and adjuvant treatment of intracranial meningiomas.

Pituitary adenomas

The initial management of these tumours is surgical excision, which is generally done by trans-sphenoidal 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 (16-18). 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.

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 (19).

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 (20). SRS boot 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 RTOG trial of SRS boost Vs no boost showed worse survival in the boost arm. The initial results of a dose escalation study for GBM with IMRT have revealed that IMRT was delivered successfully in 21 patients. There were three dose levels of 70Gy, 75Gy and 80Gy. No dose limiting toxicities were observed and median overall survival time was 68 weeks.

Our experience with high precision RT techniques

High precision RT techniques have potential of increasing doses to target volumes and reducing doses to normal critical structures but are labour intensive and expensive (21-25). We initiated SCRT for childhood brain tumors in a prospective protocol and recorded neurological, endocrine and neuropsychological data before starting SCRT and thereafter at regular intervals. Between April 2001 and March 2009, sixty seven pediatric and young adults with low grade and benign residual/progressive brain tumours have been treated with SCRT. Patients have to qualify for our institutional SCRT protocol, which includes patients aged between 4 to 25 years with brain tumours of low malignant potential and meriting radiotherapy in view of residual or progressive disease (21). Patients had to undergo a detailed baseline neurological, opthalomological, endocrine and neuropsychological assessments as a part of designed protocol and these tests were repeated at regular intervals after the completion of radiotherapy.

Neuropsychological assessments

Baseline neuropsychological evaluations were done before starting SCRT and at 6 and 24

months follow up after the completion of treatment (21). Patients undergo yearly assessments thereafter as per the required protocol. An age-appropriate neuropsychological battery was administered for each patient. Intelligence quotient (IQ) was measured by an age-adjusted and validated Wechsler Intelligence Score Chart (WISC) to give verbal quotient (VQ), performance quotient (PQ) and full-scale quotient (FSIQ). For patients more than 16 years, memory quotient (MQ) measured by Wechsler memory scale (WMS) was done instead of verbal quotient. In blind patients, specialized Vithoba Paknikar performance test battery for assessments were used. Cognition was also measured by the Lowenstein Occupational Therapy Cognitive Assessment (LOTCA) battery (max value:119), which assesses seven major areas including orientation, visual perception, spatial perception, motor praxis, visuomotor organization, thinking operations and attention concentration (22). We also measured anxiety levels in children by the State-Trait Anxiety Inventory for Children (STAIC). In patients aged more than 16 years, anxiety and depression were measured by Hamilton anxiety rating scale (HARS; for adults) and Hamilton depression rating scale (HDRS) respectively.

There is a relative paucity of data employing conformal techniques in childhood brain tumours to demonstrate their safety in terms of acceptable local control and minimization of treatment related morbidity. We recently evaluated our preliminary experience in one twenty eight children with low grade/benign brain tumours treated with focal conformal radiotherapy and neuropsychological evaluation was done using neuropsychological battery (23). As many as 69 (64.3%) of the 128 evaluable patients had FSIQ values below normal expected levels before starting RT, although overall mean VQ (85.7), PQ (85.6), and FSIQ (83.4) were only slightly less than expected values. Patients with moderate/severe hydrocephalus (p=0.087) and with impaired hormone axis (p=0.014) had significantly lower IQ score. However, performance status (KPS), type of surgery, economic and educational status of the patient had not shown to effects pre-RT IQ score. Among 28 patients treated with SCRT and had at least 2 year follow up, a third of patients did show a >10% decline in FSIQ as compared to pre-SCRT assessment. Logistic regression analysis demonstrated patients <15 years of age had a significantly higher chance of developing >10% drop in FSIQ than older patients [53% vs. 10%, p=0.03]. Dosimetric comparison showed that patients receiving >43.2 Gy to >13% of volume of left temporal lobe were the ones to show significant drop in FSIQ (p=0.048). RT doses to other normal structures including supra-tentorial brain and right temporal lobe did not reveal any significant correlation.

A significantly high proportion of patients had showed severe anxiety (score more than 30) in the state C1 form (19/41 evaluable patients, 46%) than in the trait C2 form (14 patients, 34%)(p=0.008). In the LOTCA battery, proportion of patients with less than expected scores was seen significantly more in the visual (p=0.007), orientation (p<0.001) and spatial perception (p<0.001) than visuomotor, motor praxia, thinking and attention domains (22).

In 38 low grade glioma patients treated with SCRT mean total modified Barthel's ADL score (Barthel' Index, BI) before staring SCRT was 94.5; at 2 and 3 year follow up mean BI was maintained to 97.1 and 99 respectively (24). At pre-SCRT assessment, patients with impaired visual function and with low performance status (KPS<70) had significantly lower BI than those with normal vision (p=<0.001) and with good performance status (p=0.001). On follow up, maximum improvement in individual BI was seen in the ambulation related domain in patients with impaired visual function (p=0.027), low KPS (p=0.015) and age <13 years (p=0.103).

Before starting SCRT, baseline endocrinologic evaluation revealed that 41 out of 67 patients (61%) had hormone deficiency in at least one axis (25). Hormone dysfunction was significantly more in sellar/suprasellar tumors (p=0.005) and tumors close to hypothalamic pituitary axis (HPA) (p=0.019) than tumors located in other sites. Hormonal dysfunction was seen more in growth hormone axis (48%) and thyroid axis (46%) than corticosteroid (28%) and sex hormone axis (2%). At 2 and 3 year follow up, 8/34 (24%) and 4/27 (15%) patients developed additional hormone axis deficit.

Conclusions

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.

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