

Optimising Radiation Therapy Techniques for Tumours of the Central Nervous System

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Abstract

Introduction: This study aims to assess the early tumour outcome and morbidity associated with radiation therapy (RT) in tumours of the central nervous system (CNS). **Materials and Methods:** Patients receiving RT with radical intent were entered on a prospective database. Tumour types were categorised into glioma, base of skull, pituitary, germ cell or primitive neuroectodermal tumour (PNET) and other malignant CNS tumours. Study endpoints were overall survival and progression free survival. Acute and late toxicity endpoints included Common Terminology Criteria version 3.0 (CTC) grade 3 or 4 events, need for admission during RT and change in performance status at 12 months. **Results:** One hundred and fifty-two patients with CNS tumours were managed with radical intent over the 4-year period. The median age was 49 years and 68.4% were Eastern Co-operative Group (ECOG) 0-1 performance status. The major pathology groups were glioma (59.9%) and base of skull tumours (17.1%). Gross total resection was performed in 28.3% only and RT was delayed after diagnosis until time of progression in 19.7%. For the 91 patients with glioma, the median survival and 2-year survival rate was 19.1 months and 44.1%, respectively. The 2-year survival rates for the subgroups of WHO Grade I or II, III and IV were 100%, 52% and 35%, respectively. For the non-glioma tumour groups, the relapse varied with pathology. Toxicity was minimal with only 3 acute and 3 late CTC grade 3 or 4 events occurring. Overall, 47 or 31% of patients required some inpatient hospitalisation during RT, although this was determined to have some causative relationship to RT in only 12 or 8% of patients. In the 12 months post-RT, performance status was stable or improved in 76.2% of patients, and most deterioration was associated with tumour relapse. **Conclusions:** RT for CNS tumours using modern techniques was well-tolerated with good tumour outcome and minimal morbidity.

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Introduction

Tumours of the central nervous system (CNS) are a diverse group of pathologies with varying natural histories and outcomes. The presence of adjacent sensitive neural structures limits the role of surgery to achieve complete tumour excision; similarly, the blood-brain barrier restricts the penetration and activity of many systemic chemotherapy agents.^{1,2} Radiation therapy (RT) has a major role in the management of CNS tumours, as the ability of fractionated RT to destroy tumour cells but allow normal cell repair results in relative sparing of neural tissues. However, there are concerns regarding the effects of high-dose RT on neurocognitive function, cerebrovascular events and second malignancy.³ This is more relevant for tumours with a long natural history in which delayed morbidity from slow

tumour progression is weighed against the potential early treatment-related toxicity.

This study was undertaken to review the early tumour outcome and morbidity associated with RT of CNS tumours, and to explore the potential improvements from more sophisticated RT techniques that are available in clinical practice.

Materials and Methods

All patients diagnosed with intracranial tumours referred to The Cancer Institute (TCI) Radiation Oncology from May 2002 to June 2006 were entered into a prospective database. Patients receiving RT with radical intent, as defined by a RT dose of more than 50Gy (or more than 35Gy for germ cell tumours) were included in this study

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cohort. Patients were managed at either TCI Radiation Oncology units at the National University Hospital or Tan Tock Seng Hospital. Follow-up varied for each intracranial pathology; however, it was generally performed under a recommended protocol involving 3 to 4 monthly shared care reviews, with initial imaging for assessment of disease at 3 months post-RT.

Decision-making for Radiation Oncology Management

Depending on the institution, patients were referred to either the Neuro-Oncology Multidisciplinary Tumour Clinic or to the radiation oncologist on call. As internal subspecialisation was developed, 1 radiation oncologist ultimately managed the majority of patients referred for treatment. RT was delivered under uniform written TCI Radiation Oncology protocols designed for the majority of intracranial pathologies, and formally updated at a departmental biennial review.

Radiation Therapy Delivery

Both radiation oncology centres had 3-dimensional (3D) computed tomographic (CT) planning capabilities and megavoltage linear accelerator delivery from the commencement of the study period. Thermoplastic cranial immobilisation devices and CT-MRI (magnetic resonance imaging) fusion were available. Sophisticated therapy procedures for CNS tumours were implemented gradually over the time period of the study. Stereotactic radiotherapy (SRT) was commissioned in October 2003, intensity modulated radiation therapy (IMRT) in December 2004 and micromultileaf collimator (mMLC) SRT in January 2006. Selection of the appropriate treatment technique was based on many factors including tumour target dimensions, intracranial site of the tumour, patient funding capability and a comparison of radiation dosimetry for standard or sophisticated treatment plans.

Intercurrent Therapies

Decision-making for therapies usually incorporated a multidisciplinary approach, especially at 1 campus where there was joint referral to a formal neuro-oncology multidisciplinary clinic. The role of surgical therapy or systemic chemotherapy was based on the intracranial pathology and individual patient or tumour factors.

Data Collection

Patient-related data collected included basic demographic data and Eastern Co-operative Group (ECOG) performance status.

Tumour-related data included pathology, intracranial site and tumour size. The pathological groups were categorised into 5 groups for analysis: glioma (WHO I to IV), base of skull tumours (meningioma, haeman-

giopericytoma, lymphoma, clival chordoma), pituitary tumours (macroadenoma), germ cell or primitive neuro-ectodermal tumours (germinoma, non-germinatous germ cell tumours, medulloblastoma) and non-glioma high-grade malignant tumours (malignant meningioma, primary CNS lymphoma, CNS sarcoma). RT data included RT technique, use of CT-MRI Fusion Planning and RT dose.

Other associated treatment data regarding surgical and systemic therapies were included, specifically the extent of surgical resection and the use of chemotherapy

Tumour Outcome Endpoints

The major study endpoint was overall survival, which was defined to be from the time of surgical diagnosis immediately prior to RT to the date of censor. For tumours treated with RT only at the time of progression, the start of RT was used as the commencement point to assess survival duration. Progression-free survival was also measured for all non-glioma pathology, with relapse reported at the time of symptomatic or radiological progression.

RT Toxicity Endpoints

For late toxicity (defined as occurring after 3 months post-RT), the major endpoint was a Common Terminology Criteria (CTC) grade 3 or 4 event, principally a symptomatic cerebrovascular event in RT field, symptomatic cerebral necrosis interfering with activities of daily living (ADL) or severe cognitive disability with impairment of life or work performance. Another late toxicity endpoint was the change in ECOG performance status, defined as the change from initial baseline score to the score at 12 months or at last follow-up. Patients with death at 12 months were recorded as deteriorated ECOG status.

For acute toxicity (defined as occurring during or before 3 months post-RT), the major endpoint was a CTC grade 3 or 4 event, principally interpreted as arising from raised intracranial pressure causing severe cognitive impairment or ADL impairment as above. Another acute toxicity endpoint was inpatient admission during RT.

Statistical Considerations

All patients had their data entered on an Access database at TCI Radiation Oncology and updated for outcome events. The major study endpoint chosen for glioma was overall survival, while for the other tumours it was progression-free survival. Date of death was obtained from medical records or family contact at the time of bereavement. If the date of death was unavailable, these patients were censored as deceased at last review if they had evidence of radiological progression. The median survival was calculated using the Kaplan-Meier method. Analysis for the relationship of potential prognostic factors with survival

was done using the log rank tests.

Chi-square tests were used for the association of toxicity events (inpatient admission during RT and reduction in ECOG performance status at 12 months) with clinical factors.

Results

A total of 175 patients with primary intracranial tumours were managed at TCI Radiation Oncology during the study period from May 2002 to May 2006. Of this group, 152 patients were managed with radical intent and form the basis of the study cohort. The median follow-up of the total group was 11.9 months (range, 2 to 45.7), while for surviving patients it was 12.2 months (range, 2 to 45.7).

The patient characteristics are detailed in Table 1. The median age was 49 years (range, 3 to 79), 53.3% were male gender, and 68.4% had ECOG performance status of 0 or 1 at initial presentation for RT. The majority of the 152 patients had gliomas (59.9%), with the remaining non-glial tumours comprising base of skull (17.1%), germ cell tumour (GCT) or primitive neuroectodermal tumour (PNET) (11.8%), pituitary (6.6%) and other malignant tumours (5.3%).

Treatment details are shown in Table 2. Surgical resection was determined to be gross total resection in 28.3%, whilst

32.9% had biopsy or no tissue diagnosis. The base of skull tumours (38%) and GCT or PNET (66%) contributed the majority of cases managed without attempted resection. 19.7% of patients were managed with RT at time of progression, rather than at initial diagnosis. This was higher in the 35 patients with base of skull and pituitary tumours, as 37% were managed at progression. 3D conformal RT was the most common RT technique (82.9%), although SRT/mMLC and IMRT were used in 11.2% and 5.9% of patients, respectively. CT-MRI fusion planning was used in 75% of plans. Adjuvant systemic chemotherapy was administered in 32.2% of patients.

Tumour Outcome

The tumours were grouped as glioma and non-glioma tumours. For the 91 patients with glioma, the median survival and 2-year survival was 19.1 months and 44.1%. The 2-year survival rates for the subgroups of WHO Grade I or II, III and IV were 100%, 52% and 35%, respectively (Fig. 1).

For the non-glial tumours, the progression-free survival for the tumour subgroups is shown in Figure 2. For the pituitary (n = 9) and base of skull tumours (n = 26) there was only 1 tumour progression post-RT; this was a 15-year-old with clival chordoma who had radiological and symptomatic progression at 29 months. Another patient died from an unrelated cardiac event at 9 months.

Treatment-related Acute Toxicity

Endpoints for acute treatment toxicity are detailed in Table 3. A CTC grade 3 or 4 toxicity during RT occurred

Table 1. Patient and Tumour Characteristics

	Subgroups	Total (%) (n = 152)
Age	Median age	49 years (range, 3 to 79)
	<15 years	7.9%
	<16-55 years	61.8%
	>55 years	31.3%
Gender	Male	53.3%
	Female	46.7%
ECOG performance status pre-RT	0	29.6%
	1	38.8%
	2	19.1%
	3	9.2%
	4	3.3%
Timing of RT	Initial diagnosis	80.3%
	At progression	19.7%
Pathology	Glioma WHO 1,2	6.6%
	Glioma WHO 3,4	53.3%
	Base of skull tumours	17.1%
	Pituitary tumours	5.9%
	Germ cell/PNET	11.8%
	Non-glial malignant tumours	5.3%
Tumour size	<2 cm	3.9%
	2-5 cm	53.3%
	>5cm	42.8%

ECOG: Eastern Co-operative Group; PNET: primitive neuroectodermal tumour; RT: radiation therapy; WHO: World Health Organization

Table 2. Treatment Characteristics

		Subgroups	Total (%) (n = 152)
Surgery	Extent of surgery	Biopsy or nil	32.9%
		Subtotal resection	38.8%
		Gross total resection	28.3%
Radiation	RT technique	3D conformal RT	82.9%
		SRT/mMLC	11.2%
		IMRT	5.9%
	CT-MRI fusion	Yes	75%
		No	25%
	RT dose	<45 Gy	6.6%
		45-53 Gy	9.9%
		54-59 Gy	30.9%
		>59 Gy	52.6%
Systemic chemotherapy	Use of chemotherapy at initial treatment	Yes	32.2%
		No	67.8%

3D: 3-dimensional; CT-MRI: computed tomography-magnetic resonance imaging; IMRT: intensity modulated radiation therapy; mMLC: micromultileaf collimator; RT: radiation therapy; SRT: stereotactic radiotherapy

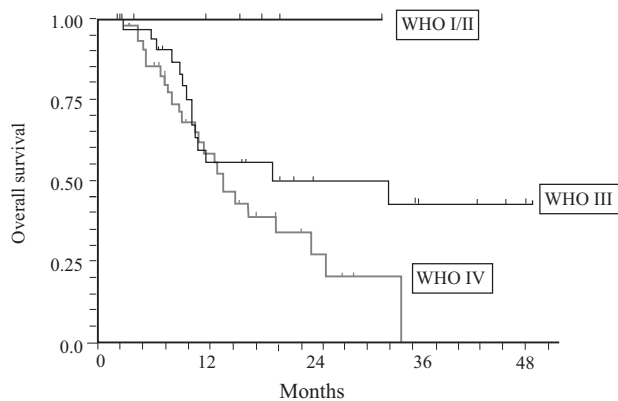


Fig. 1. Overall survival in patients with glioma (n = 91).

in only 3 patients. These events were specifically raised intracranial pressure during the early weeks of RT that required hospital admission to stabilise neurological function. Overall, 47 or 31% of patients required some inpatient hospitalisation during RT, although this was determined to have some causal relationship to RT in only 12 or 8% of patients. The majority of admissions were related to effects from the underlying neurological dysfunction resulting from tumour or postoperative sequelae. The factor associated with any hospital admission was initial ECOG performance status ($P < 0.001$), and there was no relationship with the extent of surgery, pathology, or use of chemotherapy.

Treatment-related Late Toxicity

Three patients (2.0%) experienced CTC grade 3 toxicity events at 6, 9 and 14 months post-RT respectively. An 11-year-old male with brainstem glioblastoma had tumour necrosis causing major neurological deficit. He remains alive at 28 months. The second patient, aged 48 years with

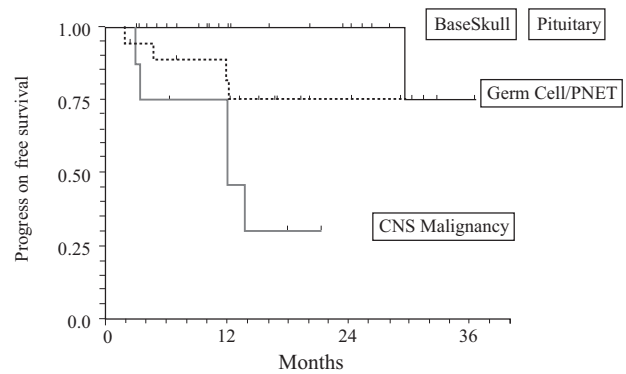


Fig. 2. Progression-free survival in patients with non-glioma tumours (n = 61).

no pre-existing vascular disease, had a bulky unresectable oligodendroglioma causing brainstem compression. The vascular event was a major cerebrovascular accident involving the right middle cerebral artery, which was within the RT field (54Gy). The third patient, aged 43 years, had pre-existing vascular disease and was managed with SRT for a clival chordoma. A brainstem infarct occurred within the high-dose region (59.4Gy). No other CTC grade 3 or 4 toxicities occurred.

Deterioration in ECOG performance status at 9 months post-RT was used as a correlate for late treatment-related toxicity. 30.9% of patients were recorded as ECOG 2 or 3 at 9 months post-RT compared to 31.6% patients at baseline pre-RT. ECOG performance status deteriorated in 23.8%, while improvement occurred in 27.2% of patients. However, the major factors associated with a reduction of performance status in the 9 months post-RT were tumour-related events such as relapse ($P < 0.001$), tumour size ($P < 0.001$) and high-grade glioma pathology ($P = 0.015$); although admission during RT ($P = 0.046$) and the presence of late RT toxicity ($P = 0.013$) were also associated factors. Age ($P = 0.93$), extent of surgical resection ($P = 0.54$), RT dose ($P = 0.24$) and chemotherapy use ($P = 0.84$) were not associated with a deterioration in ECOG at 9 months.

Discussion

This study demonstrates that the delivery of high-dose RT for CNS tumours is well-tolerated with a minimal risk of significant acute or late toxicity. Although a heterogeneous group of patients with various pathologies, all patients were managed with radical intent using high doses of radiation therapy. Thus, the outcomes of the total group in relation to morbidity and effect on performance status are relevant despite the different tumour pathology. Most acute morbidity experienced by patients is related to pre-existing tumour or postoperative-related neurological deficits. Late toxicity, such as a cerebrovascular event, is potentially a risk to patients managed with high-dose RT,

Table 3. Acute and Late Toxicity Endpoints

		Subgroups	Total (%) (n = 152)
Acute toxicity	CTC Grade 3 or 4 event	Yes	2.0%
		No	98.0%
	Inpatient admission during RT	Nil	69.1%
		RT-related	2.0%
		Disease-related	23.2%
		Mixed causation	6.0%
Late toxicity	CTC Grade 3 or 4 event	Yes	2.0%
		No	98.0%
	ECOG performance status at 12 months	0,1	69.1%
		2,3,4	30.9%
	Change in ECOG performance status at 12 months	Improved	27.0%
		Stable	49.3%
		Deterioration	23.7%

CTC: Common Terminology Criteria; ECOG: Eastern Co-operative Group; RT: radiation therapy

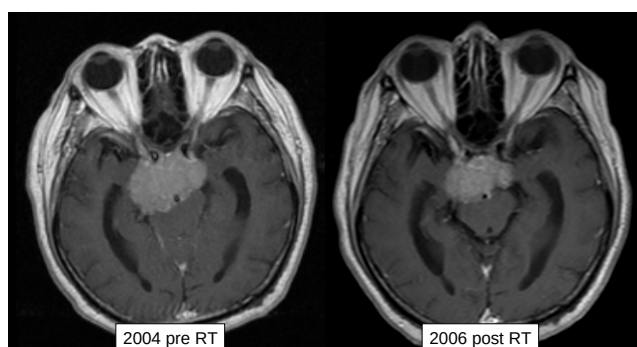


Fig. 3. Example of expected partial radiological response in base of skull meningioma at 18 months post-RT.

but pleasingly this occurred in only 2 patients, consistent with estimate from prior series.³⁻⁶ Importantly, in the 12 months post-RT, performance status was stable or improved in 76.2% of patients and most deterioration was associated with tumour relapse.

The tumour outcome was dependent upon the initial tumour pathology, but favourable initial results are evident in most subgroups including the high-grade glioma (WHO III and IV).^{7,8} In patients with tumours that demonstrate a long natural history, such as base of skull meningiomas, the absence of progression without RT-related toxicity is an important endpoint.⁹⁻¹¹ In this series, 38.5% of patients with base of skull tumours initially had RT deferred and only received RT at progression. The reasons for initial avoidance of RT may include a presumed low risk of progression or perhaps potential concerns regarding the morbidity of RT. This series, demonstrating good tumour control without significant RT-related toxicity, provides confidence for patients to accept RT earlier in their disease presentation. The major endpoint after RT for these types of tumours is reduction in radiological and symptomatic CNS progression. Radiological responses after RT for tumours such as meningioma are often delayed or partial, with a residual mass still being present.¹¹ Successful therapy will be a treatment that stops neurological progression without causing new morbidity. Figure 3 illustrates an example of this type of endpoint in a patient with an unresectable bulky base of skull meningioma with the sequential MRI images reflecting a partial radiological response at 18 months post-RT. However, the preservation of neurological function through the delay of tumour progression is the significant patient-related endpoint.

The development of more sophisticated RT techniques, such as SRT or IMRT that can deliver a more accurate dose to the target and reduce the dose to surrounding normal tissues, has allowed RT in being utilised more frequently and earlier in the clinical history. Optimising RT technique involves selecting which patients would be appropriate for these more sophisticated (and resource intensive)

techniques. The decision is usually based on particular clinical, pathological and radiological factors that reflect both the natural history of the tumour, as well as the physical geometry of the tumour target to be treated.

An example of this alteration to clinical practice is in the management of pituitary macroadenoma.¹¹ Often, decompression of the suprasellar mass from neural structures by a transfrontal or transsphenoidal approach was initial management, with RT delayed until significant radiological or symptomatic progression. There has now been a paradigm shift to using RT in the initial phase after surgical decompression, at a point in time when the tumour bulk is minimised and the neurological deficits have been reversed. The outcome in series utilising this approach has been favourably reported with minimal morbidity.^{11,12} This approach is being paralleled in other pathologies, including paediatric tumours, where there is an awareness of the morbidity of progressive tumour and the minimal impact of sophisticated RT techniques.^{13,14}

The RT technique is generally considered to have 3 components: planning, delivery and verification. All these components of therapy have developed significantly with the introduction of digital imaging, with both improved target localisation and incorporation of images into RT planning systems and linear accelerators.¹⁵ Patient immobilisation using individualised thermoplastic devices and radiological image fusion (CT-MRI fusion in RT planning system) allows for greater accuracy in defining the tumour target while reducing the margin for error.¹⁶ The diagnostic neuro-radiologist can assist oncologists with the delineation of tumour and selection of best imaging techniques to be used for RT planning.¹⁷

Once the target is defined, the subsequent choice of RT delivery technique will depend on the tumour characteristics, specifically the target size, shape and proximity to sensitive normal structures. 3D conformal RT, now the standard therapy for external beam RT, utilises large beam field sizes that are generally in a limited number of beam planes or angles. Sophisticated therapies such as SRT, mMLC or IMRT are more resource-intensive, but can utilise smaller field sizes, a greater number of beam angles and varying shapes of fields. All RT techniques can deposit high doses of radiation within a target, but the sophisticated therapies minimise the “splash” dose to surrounding tissues. SRT is principally used for small tumours less than 40 mm in size that are uniform in shape and spherical, whilst IMRT or mMLC is useful for larger or more irregularly shaped targets. The planning techniques are varied, with a major feature of IMRT involving “inverse-planning” algorithms, which utilise computer software rather than a “forward” (trial and error) method to calculate the optimal RT field arrangement.

Once the optimal therapy has been designed, the delivery is programmed into the linear accelerator for the daily treatment delivery. Verification of the treatment accuracy is a vital component of the quality assurance, with reproduction of the beam delivery traditionally based upon patient surface reference points, but now becoming more “image-guided” with digital images of the field delivery being taken. Linear accelerators are equipped with X-ray cameras to image the beam as it is delivered, thus demonstrating accuracy. The improvements in digital technology are now allowing more detailed CT scanners to be attached to the linear accelerator or to be inherent within the treatment machine.¹⁸

Whilst it is uncertain that dose escalation for CNS tumours plays any major role, these sophisticated therapies allow potentially lower doses to be delivered to the adjacent brain tissues.^{5,19} For tumours such as high-grade gliomas, the potential benefit is limited because the aggressive natural history of the lesions is more significant than the natural history of late radiation effects.¹⁹ However for base of skull tumours and low-grade glioma with a longer natural history measured in 10 to 20 years, the reduction in dosage to the surrounding brain structures does become clinically significant. Although it is too early to quantitatively assess outcome data from the reduction of normal brain dose using these sophisticated therapies, the improvement from two-dimensional methods to 3D conformal methods has significantly reduced late neurocognitive morbidity.^{20,21} In recent multicentre studies in patients with low-grade glioma, significant neurocognitive deficits are uncommon, although there is still a risk of vascular events. By avoidance of large volumes of sensitive neural tissues such as brainstem, there may be a further reduction in risk of long-term cerebrovascular events.²²

Conclusion

The study demonstrates that RT for CNS tumours can result in good tumour outcomes with minimal acute or late morbidity. Tumour progression is dependent upon pathology; however, careful RT delivery can optimise outcomes even for high-grade glioma. Sophisticated RT techniques such as SRT and IMRT allow more accurate targeted therapy avoiding normal tissues, so as to minimize the risk of late toxicity especially in patients whose tumours have a long natural history.

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