Fractionated Stereotactic Conformal Radiotherapy following conservative surgery in the control of Craniopharyngiomas

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Key words: fractionated stereotactic radiotherapy, craniopharyngioma, hypopituitarism, complications.

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Abstract

Purpose: To describe the technique and results of stereotactically guided conformal radiotherapy (SCRT) in patients with craniopharyngioma after conservative surgery.

Methods and Materials: 39 patients with craniopharyngioma aged 3-68 years (median age 18 years) were treated with SCRT between June 1994 and January 2003. All patients were referred for radiotherapy after undergoing one or more surgical procedure. Treatment was delivered in 30-33 daily fractions over 6-6.5 weeks to a total dose of 50 Gy using 6MV photons. Outcome was assessed prospectively.

Results: At a median follow-up of 40 months (range 3-88 months) the 3 and 5 year progression free survival (PFS) were 97% and 92%, and 3 and 5 year survival 100 %. Two patients required further debulking surgery for progressive disease 8 and 41 months after radiotherapy. Twelve patients (30%) had acute clinical deterioration due to cystic enlargement of craniopharyngioma following SCRT and required cyst aspiration. One patient with severe visual impairment prior to radiotherapy had visual deterioration following SCRT. Seven out of ten patients with a normal pituitary function before SCRT had no endocrine deficits following treatment.

Conclusion: SCRT as a high-precision technique of localized RT is suitable for the treatment of incompletely excised craniopharyngioma. The local control, toxicity and survival outcome are comparable to results reported following conventional external beam RT. Longer follow-up is required to assess long term efficacy and toxicity, particularly in terms of potential reduction in treatment related late toxicity.
Introduction

The optimal management of craniopharyngiomas continues to be debated. Complete excision has been reported in 45-90% of patients at a cost of treatment related mortality and morbidity, particularly hypothalamic damage, visual deterioration and endocrine complications, which occur in 30-70% of patients (5, 11,20,25,47,49, 50,55,62).

Partial excision followed by fractionated external beam radiotherapy achieves a 10 years progression free survival of 75-85% with low risk of toxicity in the form of radiation optic neuropathy (1-2%), second intracranial neoplasms, and neurocognitive impairment when the treatment is delivered within the radiation tolerance limits of central nervous system (9,12,18,19,21,31,41,43,49,56-58,61).

Pituitary endocrine deficiency is common following primary surgery and incidence increases following radiation (12,41,56).

Fractionated stereotactic conformal radiotherapy (SCRT) as high precision focal irradiation technique has been employed to deliver more localised irradiation than achieved with conventional radiotherapy, with a steeper dose gradient between tumour and the surrounding normal tissue (15,28). Patients are immobilized in a relocatable stereotactic frame and irradiation can be appropriately delivered using multiple fixed non-coplanar individually shaped conformal fields (16). We have developed and optimized the technique of SCRT (27,38) to make it relatively suitable for an appropriately equipped radiotherapy department and previously reported an excellent early control for skull base tumours including pituitary adenomas (33) and meningiomas (2,22). We report the experience of SCRT in a cohort of patients with craniopharyngioma treated at the Royal Marsden Hospital.

Patients and Methods

Patient Characteristics
Between June 1994 and January 2003, 39 consecutive patients with craniopharyngioma were treated with SCRT at the Royal Marsden Hospital as the standard method of delivering external beam radiotherapy. The clinical characteristics of patients are shown in Table 1. Twenty-two were males, 17 females. The median age was 18 years (range 3-68 years). Nineteen were children (<16 years old). All patients were initially treated surgically. Thirty patients had one surgical resection and 9 had two or more surgical interventions. Twenty-five patients were treated following first conservative surgery and all had residual disease on postsurgical imaging. Nine patients received treatment after second or subsequent surgery for known progressive disease. Five patients were irradiated at the time of known disease progression after a period of surveillance following surgery. At the time of irradiation seven patients had a VP or similar shunt in situ and 5 patients had cyst catheter with an Ommaya reservoir available for cyst aspiration. None of the patients had received previous radiotherapy. A complete or partial hypopituitarism was present in 29 patients at the time of SCRT as a consequence of the tumour itself (n = 24) and/or surgical intervention (n = 5). Twenty patients had diabetes insipidus and 4 patients had severe obesity as consequence of hyperphagia. Thirty-seven patients had a tumour in the suprasellar region and 20 patients had involvement of the pituitary fossa.

**Stereotactic Conformal Radiotherapy**

Technical characteristics of apparatus and procedure have been described in details previously (1,14,28,34). Patients were treated supine and immobilized in a Gill-Thomas-Cosman frame or a specially designed paediatric version of the frame. Children unable to tolerate the frame or requiring a general anaesthetic were immobilised in a customised thermoplastic shell and individually shaped vacuum-moulded bags of polystyrene beads (VacFix®, QADOS, Berkshire, UK) extending under the head, neck and upper body. High-resolution planning CT scan (2 or 3-mm slice thickness and separation through the target area and 5-mm outside) was fused with magnetic resonance imaging (MRI) scan. The GTV was manually contoured on the fused MRI images. The visible residual lesion
including both solid and cystic components was outlined as the gross tumour volume (GTV) on the MRI. The 3D volume growing algorithm was utilized to expand the GTV by a 5 mm for frame-based immobilization and 8 mm for the shell-based treatments to generate the PTV. CTV was considered the same as GTV as the known microscopic extension of craniopharyngioma is not considered a predictor of recurrence (32,60). The margins to cover uncertainties in patient positioning were based on previous studies (59), with higher precision achieved on more recent assessment which led to a subsequent margin reduction (27).

Critical structures including the eyes, optic nerves, optic chiasm and in children the hypothalamus were also outlined. Treatment planning was carried out using a Varian Cadplan®, Philips Pinnacle® or GE Target® planning software. The technical details of treatment are summarized in Table 2. The median GTV was 10 cm$^3$ (range 2 – 36 cm$^3$) and the median PTV was 36 cm$^3$ (range 15 – 90 cm$^3$). Early in the study 3 patients were treated with 3 and one patient with 5 fields, subsequently 35 patients were treated with 4 non-coplanar conformal fixed fields based on a class solution reported previously (Perks 1999). Conformation of each field was achieved initially with customized lead alloy blocks (n =32) and more recently a 120 multileaf collimator (n = 7). The accuracy of relocation was assessed by isocentre position with a second CT scan in the frame taken just prior to the start of treatment. The required relocation tolerance was < 1.5 mm in any direction. Dose was prescribed at the isocentre according to ICRU 50 criteria with PTV covered by the 95% isodose in 3-D. Treatment was delivered in 30-33 daily fractions over 6-6.5 weeks to a dose of 50 Gy using 6 MV photons on an Elekta SL15, Varian 600C or 2100CD linear accelerator. Routine QA of SCRT is as described previously (59) and the accuracy of the system is detailed in a previous publication (27).

**Clinical Assessment and Follow-up**

Patients were seen weekly during the course of radiotherapy and 1, 3 and 12 months after the completion of treatment with a clinical assessment of
neurological status and visual fields on confrontation. MRI and/or CT scans were performed 3 months after completion of SCRT as a baseline and thereafter annually or as warranted by symptoms. The detection of acute deterioration relied on self reporting and detection of clinical features as described previously (42) confirmed on imaging looking specifically for cystic enlargement and its complications, particularly hydrocephalus.

Acute and late effects of radiotherapy were assessed according to the National Cancer Institute Common Toxicity Criteria (Version 2.0 December 1994). Pituitary function was assessed in an endocrine clinic by complete basal hormonal assessment and dynamic testing, as appropriate,. Vision was assessed by serial ophthalmological examinations.

Results

Tumour Control and Response
Thirty-nine patients with craniopharyngioma were treated with SCRT between 1994 and 2002. At a median follow-up of 40 months (range 3-88 months) the 3 and 5 year progression free survival (PFS) were 97% and 92%, and survival (S) was 100 % (Figure 1). Sixteen patients had a reduction in the size of craniopharyngioma and in 21 patients there was no change in size. Two patients progressed and required further debulking surgery 8 and 41 months after SCRT. No difference in PFS and S was observed in paediatric and adult patients.

Vision
Eighteen patients had impaired vision presumed to be the result of tumour growth (n = 16) or/and surgery (n = 2) prior to starting radiotherapy. At a median follow-up of 40 months vision improved in 3 and remained stable in 32 patients. Four patients had worsening vision after radiotherapy. This was due to cystic enlargement in 2 patients with immediate improvement after cyst aspiration and due to benign intracranial hypertension in one patient requiring a shunt placement with recovery of vision. One child with severe visual impairment
before SCRT (6/36 in one eye) had further deterioration 6 months following SCRT to 6/60. The optic chiasm was included in the PTV of the majority of patients (n = 36) and received the prescribed dose of 50 Gy.

\textit{Pituitary and hypothalamic function}

At the time of SCRT 10 patients had normal pituitary function and 29 patients had hypopituitarism affecting one or more hormones (Table 3). A development of new or worsening of pre-existing hypopituitarism occurred in 8/19 (42\%) patients after a median follow-up of 40 months, requiring hormone replacement therapy with gonadal steroids and growth hormone in 6 patients (32\%), and thyroxine and hydrocortisone in 5 (26\%). The pituitary fossa contained residual tumour in 20 patients, and was included in the PTV. Twenty patients had diabetes insipidus (DI) before treatment, which remained unchanged during the subsequent follow-up. No further patients developed DI after SCRT. Development of new hypothalamic disorder such as sleep disorders, apathy and appetite changes was not recorded following irradiation.

\textit{Toxicity}

Acute toxicity in the form of transient skin erythema and/or small patches of hair loss (grade 1-2) occurred in 13 patients. Post-radiotherapy somnolence occurred in 5 patients, lasting for 2-4 weeks after treatment. Four patients had nausea and vomiting which resolved with medical therapy. Twelve patients developed acute deterioration defined as progressive visual disturbance, hydrocephalus, and/or global neurological disturbances affecting consciousness during (n = 7) or 2, 3 and 8 months following SCRT (2, 2 and 1 patients respectively). All had cystic enlargement confirmed by MRI scan. Five patients underwent cyst aspiration of a previously inserted Ommaya reservoir and 7 patients had a new reservoir inserted. All patients who deteriorated during SCRT completed the full course of RT to the prescribed dose without treatment modification. No formal neurocognitive testing was carried out in this cohort of patients before or after treatment. Nevertheless one adult and 4 children were
noted to have neurocognitive problems (memory deficits and/or reduced performance at school) before radiotherapy. New clinically apparent neurocognitive dysfunction (memory) was reported in one patient. No cerebrovascular accidents or second tumours have so far been noted.

**Discussion**

39 adults and children with craniopharyngioma were treated with SCRT after limited surgery. The progression free survival was 97% at 3 and 92% at 5 years and respective survival was 100%. The results are similar to other reports of SCRT (22,45,46) and conventional external beam radiotherapy (8,12,18,19,21,31,37,41,43,49,56-58,61).

The reported 5-year tumour control following complete removal is 80-90% and after incomplete removal is 50%-60%, and the respective survival is 85-90% and 95-100% (11,55,62), with the majority of recurrences occurring within the first 3 years after surgery. The outcome in terms of tumour control and survival following limited surgery and RT are better than following incomplete surgery alone as reported previously (41) The rate of complications after “conservative” surgery was acceptable, consisting mainly in worsening vision (5%) and pituitary function (13%)

The external beam radiation dose for craniopharyngioma that represents the best balance of tumour control and a low complication rate has not been defined. Most published series report a similar tumour control with doses between 50 and 60 Gy (9,12,21,31,41,43,49,56-58,61). However doses over 55 Gy are associated with an increased incidence of late toxicity without a significant improvement in tumour control (12,56). The present results, with >90% tumour control at 5 years, suggest that a dose of 50 Gy in 30 fractions may achieve a good local tumour control with acceptable toxicity and this conforms to a recent National Audit in the UK (24).
Stereotactic radiosurgery (SRS) has been advocated as an alternative to fractionated radiotherapy in patients with craniopharyngioma (3,7,26,39,53). In a study of 98 patients treated with radiosurgery, the reported actuarial PFS was 61% at 5 and 54% at 10 years (26). Because of close proximity of craniopharyngiomas to the optic chiasm, it is likely that only small residual lesions were treated with SRS to avoid optic neuropathy which occurs in 1-2% of patients following doses to optic chiasm below 10 Gy (29,48,52) The reported results of SRS for such tumours suggest that tumour control following SRS is inferior to that achieved with SCRT.

Hypopituitarism represents the most commonly reported late complication of radiotherapy, occurring in more than 30-50% of irradiated patients after 5-10 years (18,41,58). At a median follow-up of 40 months a new hormone deficit occurred in more than 1/3 of patients. However, most patients with normal pituitary function before SCRT had no deficits following treatment. The incidence of hypopituitarism is likely to remain the major late effect of SCRT, as the present technique does not result in the reduction of dose to the hypothalamus and the residual pituitary gland. No cases of hypothalamic damage in the form of hyperphagia, diabetes insipidus and sleepiness, which are frequent complications of aggressive surgery (20, 25, 62), have occurred following SCRT.

Vision remained stable in 32 and improved in 3 patients with visual deterioration, possibly related to radiation in one patient with severely compromised vision prior to SCRT. The late effects of radiotherapy in terms of normal tissue damage expressed as radiation optic neuropathy and radiation necrosis occur usually within 1-5 years of treatment. The low incidence of radiation optic neuropathy and absence of radiation necrosis at a median follow-up of 40 months provide some reassurance about the safety of the present dose and technique.

During (n = 7) or within 8 months (n = 5) after SCRT, 28% of patients had enlargement of the cystic portion of the craniopharyngioma causing visual deterioration and/or hydrocephalus and all required cyst aspiration. Although the
mechanism of cyst enlargement is not clear, continuous formation of microcysts has been reported as part of the natural history of craniopharyngioma and as a result of radiation or surgical trauma (4,13,54). Accumulation of fluid in cystic portion of craniopharyngioma does not represent tumour progression and with appropriate surgical intervention and completion of treatment the prognosis should remain similar to patients without cystic degeneration (42). We have therefore adopted a policy of close follow-up which includes regular assessment of visual status and surveillance to detect early features of chiasmatic compression or global deterioration due to hydrocephalus. This is implemented from the first visit and continued 6 months after completion of SCRT.

Neurocognitive dysfunction is a recognized consequence of large volume radiotherapy for brain tumours in children (8,10,30,35,44,51). Surgery for large sellar/extrasellar lesions and the craniopharyngioma itself are also associated with neurocognitive deficit (6,8,17,36,40). In our cohort prospective neuropsychological testing was not performed and the frequency of treatment induced deficit cannot be assessed, although mild neurocognitive dysfunction was recorded in one patient after SCRT. No cases of radionecrosis, CVA, and second tumour have been noted so far. Minimizing the radiation dose to normal brain through SCRT has the potential of reducing the risk of developing late complications, although this requires longer follow-up. Currently it is not possible to conclude that SCRT is safer than conventional radiotherapy.

In conclusion, limited surgery followed by radiotherapy continues to be a safe and effective option for patients with craniopharyngioma and avoids the morbidity and mortality of radical surgery. The use of 4-5 mm margin from GTV to generate PTV possible with high precision stereotactic technique reduces the volume of normal brain irradiated to high radiation doses and the present technique achieved good tumour control and low toxicity similar to that seen following conventional radiotherapy using a dose of 50 Gy. The potential benefit in reducing long term side effects of treatment will require longer follow-up of a
large cohort of patients.

Acknowledgements
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References


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Table 1. Clinical characteristics of 39 patients with craniopharyngioma treated with fractionated stereotactic radiotherapy.

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<tr>
<td>Median age (range)</td>
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<tr>
<td></td>
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<td></td>
<td>children (&lt; 16 yrs) 19</td>
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<td></td>
<td>Median</td>
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<tr>
<td><strong>Gross tumour volume (GTV)</strong></td>
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<td><strong>Planning target volume (PTV)</strong></td>
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<td>Conformation of PTV</td>
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<td>Customized blocks</td>
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<td><strong>Dose prescription</strong></td>
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Figure 1. Progression free survival in 39 patients with craniopharyngioma after SCRT.
Table 3. Prevalence of hypopituitarism amongst 39 patients with craniopharyngioma before and after SCRT.

<table>
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<th>Pituitary function</th>
<th>Pre-SCRT</th>
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