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# Fractionated stereotactic radiotherapy for pediatric brain tumors: the Chicago children's experience

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**Abstract** Thirty-three children with a total of 35 benign/malignant brain and eye neoplasms were treated with fractionated stereotactic radiotherapy. In the first 11 children immobilization for treatment was achieved with plaster of Paris casts or aquaplast masks. In the remaining 22 children the Laitinen stereoadapter was used. Radiation was delivered with noncoplanar static or rotational beams. The dose fractionation used was 50.4–60 Gy in 28–30 fractions in patients receiving treatment with curative intent, and 10–32 Gy at 2–4 Gy/fraction for reirradiation. The accuracy of daily treatment was <2 mm. After a median follow-up of 27 months, 22 of the 25 children treated with curative intent achieved local control. One child had progressive brain necrosis following 54 Gy in 30 fractions for a pontine astrocytoma. The exact etiology of this complication is unknown. This series demonstrates that in children fractionated stereotactic radiotherapy using the Laitinen stereoadapter is well tolerated and accurate and results in good local control.

**Keywords** Children · Brain tumor · Linear accelerator · Radiation · Stereotactic radiotherapy

## Introduction

Brain tumors are the second most common cancer among children and the second leading cause of childhood cancer deaths [14]. Surgery, radiation and chemotherapy are the mainstays of treatment of childhood brain tumors. An important goal in brain tumor therapy in children, in addition to tumor control, is to limit long-term damage to the developing brain. Stereotactic radiosurgery has been used in the treatment of brain tumors in children [1, 2, 8, 15, 16, 20]. The advantages of stereotactic radiosurgery include greater precision in radiation treatment delivery and increased sparing of normal structures. However, a significant disadvantage, particularly in children, is the potential for long-term central nervous system sequelae from the use of large single doses. Fractionated stereotactic radiation has the combined advantages of the precision of a stereotactic system and the superior protection of the developing brain afforded by the use of fractionated radiation. This paper describes our experience with the use of fractionated stereotactic radiotherapy in children with brain and eye tumors.

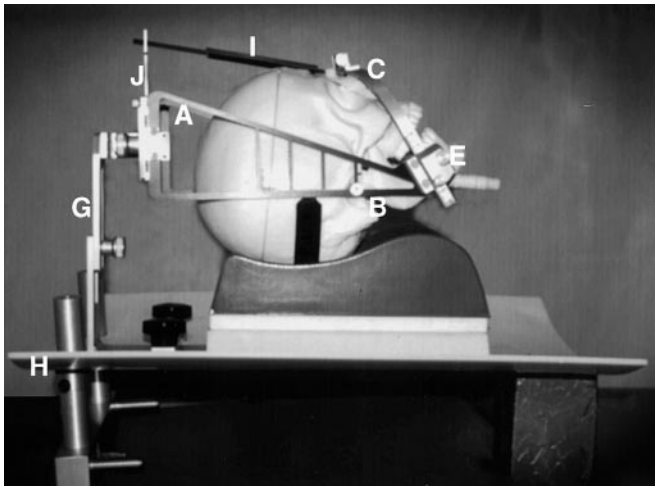


**Fig. 1** The Laitinen frame mounted on a plastic model of a human skull in the GE 9800 Quick CT adapter system. The frame consists of two triangular sidebars (*A*), which serve as fiducial markers. The frame is secured to the patient via earplugs (*B*) placed in the auditory canals and a nasion support assembly (*C*). Reproducibility is achieved by noting the lateral separation of the sidebars on a scale (D in Fig. 2), the reading on the nasion support assembly at the cog wheel (*E*) and number of turns the thumbscrew is turned to make the plugs fit snugly in the ear canals (F in Fig. 2). The frame also serves as an immobilization device via its attachment (*G*) to the CT adapter plate (*H*). If patient geometry allows, a midline marker (*I*) can be placed between the nasion support assembly and an adjustable fork (*J*)

## Patients and methods

This report is a retrospective analysis of 33 children with brain and eye tumors, who received fractionated stereotactic radiotherapy at the Northwestern Memorial Hospital and the Children's Memorial Hospital. The clinical and treatment data presented in this paper were obtained from review of patient charts, radiation treatment records and diagnostic imaging studies.

### Dose fractionation

The children treated with curative intent received 50.4–60 Gy in 28–30 fractions. The doses used for reirradiation ranged from 10–32 Gy at 2–4 Gy per fraction. In 5 children irradiation was given as part of high-dose chemotherapy with autologous bone marrow transplantation. Six children received chemotherapy prior to radiation. Three children with choroidal hemangiomas received 12 Gy in 6 fractions. One child with retinoblastoma was treated at 1 Gy b.i.d. to a total dose of 50 Gy. Prescribed isodose lines encompassing the target volume ranged from 90% to 100%.

### Immobilization and target localization

When the fractionated small-field, noncoplanar radiotherapy program was first initiated, immobilization was achieved by means of a plaster of Paris cast or aquaplast cast. Each child was casted in a prone position with plaster, and when an aquaplast mask was used the child was in a supine position. Simulation was done using a three-point set-up, and these points were tattooed. Computerized axial tomography (CT) scanning with 2- to 3-mm-thick slices was then performed in the treatment position with metal markers on the tattoos. Since September 1995 we have been using the Laitinen stereoadapter (Figs. 1, 2) for immobilization and stereotactic localization (Sandstrom Trade & Technology, Ontario, Canada). This is a noninvasive frame made of reinforced plastic and aluminum alloy. It is mounted to the patient's head by means of two earplugs and a nasion support. Two cogwheel cases serve to press the nasion support against the bridge of the nose. A threaded screw at the nasion support serves to press the ear plugs into the external auditory meati. The lateral triangular components of reinforced plastic are pressed tightly against the scalp by a connector plate over the vertex. A flexible band strapped against the occiput can be used for additional immobilization if necessary. The lateral triangular component has four transverse bars 25 mm apart from each other. The bars have a dorsoventral thickness of 2 mm. The nasion support arms and the connector plate are supplied with millimeter scales to facilitate exact repositioning of the adapter. A frontal pin joins the two halves of the nasion support assembly. The reference structures of the stereoadapter are the frontal pin for the lateral coordinate *x*; a line on the anterior edge of the posterior bars of the lateral triangular components, for the anterioposterior coordinate, *y*; and the center of the most inferior transverse bars, for the longitudinal coordinate, *z*. This frame has shown a high degree of reproducibility with less than 2 mm error in all coordinates [9].

All patients underwent a "fitting session" in the department prior to the CT scan in order to ascertain the appropriate size of headrest and earplugs and the best settings on the frame for each. This session also made the patient aware of what to expect on the day of the CT scan. Only 1 child was found not to be able to tolerate the frame, because of sensitive ears, and in her case the aquaplast system was used for immobilization. On the day of the CT scan, the CT adapter was attached to the scanner couch. After the administration of contrast, the patient was laid on the preselected headrest and the frame repositioned on the patient using the settings determined in the fitting session. Adjustments were made to head tilt by using styrofoam slabs of varying thickness under the headrest so as to make the posterior ear bars as near to horizontal as possible and thus minimize the CT gantry tilt angle. The frame

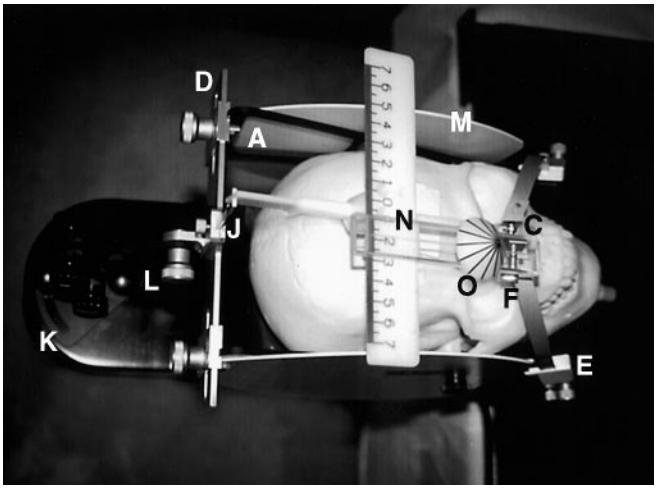


**Fig. 2** The Laitinen frame mounted on a plastic model of a human skull on the treatment couch adapter device (*K*). The device is secured to the table with Velcro and the frame is secured to the adapter plate via the screw (*L*). The *y*-*z* coordinates of isocenter are marked on the target plates (*M*) mounted to the side bars (*A*). If patient geometry allows, the device (*N*) mounted between the nasion support assembly and the adjustable fork (*J*) can be used to set the *x* coordinate. The pyramid (*O*) can be used to confirm the isocentricity of table rotation

and patient together were then squared up with the line lasers of the CT scanner and rigidly attached to the couch via a multijoint system on the CT adapter insert. This procedure took about 5 min. A lateral scout view was acquired, from which the gantry tilt angle (<3°) was determined such that the CT slices would be parallel to the transverse bars. The scanning was done with 3-mm-thick slices. Large hardcopies (one on one) of the lateral and AP scout views were obtained.

### Treatment planning

Anatomical information was acquired from the CT scans, and the target volume was outlined. Noncoplanar static or rotational beams were used, and the prescribed isodose lines ranged from 90% to 100%. All patients were treated with one isocenter for a given lesion. The isocenter was localized on the lateral and AP scout films and localization field was drawn on each. The *y,z* coordinates were drawn on the target plates, and the *x* coordinate was referenced to the patient's midline. The field size varied from 2.5 cm to 6 cm. The number of radiation fields varied from 3 to 8, with a mean of 5. All treatments were delivered using 6-MV or 10-MV X-rays (Philips SL 15 linear accelerator).

### Patient treatment

For each treatment, a couch adapter was attached to the treatment table. The Laitinen stereoadapter was mounted on the patient in a fashion similar to the set-up in the CT scanner. Adjustments were made to level the posterior ear bars relative to the side localizing lasers before rigidly affixing the frame to the couch adapter via a multijoint mechanism. The projection of isocenter drawn on each target plate was then made to line up with the side localization lasers by adjusting the treatment couch. Couch rotation about its midpoint (not about isocenter) facilitated squaring up the frame (and patient) relative to the axis of gantry rotation. The mismatch between the target points on the lateral plates and the crosses defined by the side lasers was corrected using tabletop rotation to correct for half the error and table in–out motion to correct for the other half of the error. Within two iterations the patient was on target in the *y-z* plane. The lateral coordinate, *x,* was set relative to the midline of the patient. Orthogonal localization films were taken before the first treatment and then twice weekly. Accuracy of the set-up was assessed by comparing the portal films with the set-up fields drawn on the CT scout films. During treatment the patient is continuously monitored on a TV screen, and no patient required a break in treatment because of head motion.

### Follow-up

All children were followed up in the multidisciplinary clinic at the Children's Memorial Hospital. Complete neurological evaluation and MRI/CT scans were obtained at approximately 3-month intervals to assess patients' response to the treatment.

## Results

Between 1994 and 1998, 33 children (20 boys and 13 girls) with 35 benign/malignant brain and eye tumors were treated with fractionated stereotactic radiotherapy at the Northwestern Memorial Hospital and the Children's Memorial Hospital (Table 1). Their median age was 11 years (range 3–19 years). The tumor types are shown in Table 1. Gliomas, recurrent medulloblastomas and craniopharyngiomas accounted for 20 of the neoplasms. Early in our experience, immobilization for stereotactic radiation was accomplished using aquaplast masks in 2 and plaster of Paris casts in 9 children. Subsequently, 22 children with 24 lesions were studied for design of their treatment schedules and also treated using the Laitinen stereoadapter. The median age of children immobilized using plaster of Paris casts was 10 years. (7–13 years). The median age of children immobilized with a Laitinen stereoadapter was 12 years (3–19 years).

**Table 1** Patient/tumor characteristics

| | |
|---|---|
| Histology | |
| Low-grade glioma | 7 |
| Mixed glioma | 1 |
| High-grade glioma | 2 |
| Medulloblastoma | 4 |
| Craniopharyngioma | 6 |
| Mixed germ cell tumor | 3 |
| Germinoma | 3 |
| Hemangioma | 3 |
| Rhabdomyosarcoma | 1 |
| PNET | 1 |
| Retinoblastoma | 1 |
| Pinealoblastoma | 1 |
| Location | |
| Hemisphere | 3 |
| Parasellar | 11 |
| Cerebellum | 5 |
| Brain stem | 3 |
| Pineal | 4 |
| Hypothalamus | 2 |
| Orbit/ocular | 5 |
| Indications | |
| Primary | 14 |
| Recurrent | 19 |

The median follow-up is 27 months (range 3–44 months). The Laitinen stereoadapter was well tolerated, and no child required anesthesia or sedation. A common complaint was a pressure sensation in the ear canals and at the site of the nasal bridge. Even the youngest child, at 3 years of age, did not require sedation or anxiolytics. The total treatment time was 30–60 min. There were no frame set-up-related complications, and all children completed therapy without interruption. Relocation accuracy was within 3 mm with plaster casts and within 2 mm with the Laitinen frame. This was assessed by comparing the portal film with CT scout films. The status of disease at the last follow-up is detailed in Table 2. Local control was achieved initially in 20 of 25 children treated with curative doses (≥50 Gy) of radiation. In 2 of 5 children with local failure, subsequent surgical resection achieved local control. Thus, a total of 22 of 25 children treated with curative doses of radiation achieved local control. In addition, 1 of 5 children who underwent reirradiation for recurrent medulloblastoma achieved local control. This child had three lesions, which were con-

**Table 2** Treatment results [*LC* local control, *LF* local failure, *NED* no evidence of disease, *DOC* died of complication (brain necrosis), *BMT* bone marrow transplant]

| No. | Age (years) | Diagnosis | XRT dose | Status at last follow-up |
|---|---|---|---|---|
| 1 | 7 | Recurrent low-grade glioma | 54 Gy/30 fr | LF at 2 years LC after surgery |
| 2 | 10 | Recurrent low-grade glioma | 54 Gy/30 fr | LC |
| 3 | 14 | Recurrent low-grade glioma | 54 Gy/30 fr | LC |
| 4 | 7 | Recurrent low-grade glioma | 54 Gy/30 fr | LC |
| 5 | 15 | Recurrent low-grade glioma | 54 Gy/30 fr | LF |
| 6 | 14 | Recurrent low-grade glioma | 54 Gy/30 fr | LC but DOC |
| 7 | 9 | Recurrent low-grade glioma | 54 Gy/30 fr | LC |
| 8 | 15 | Recurrent mixed glioma | 32 Gy/8 fr BMT | LF |
| 9 | 15 | Anaplastic astrocytoma | 60 Gy/30 fr | LF |
| 10 | 11 | Glioblastoma multiforme | 60 Gy/30 fr BMT | LF |
| 11 | 16 | Recurrent medulloblastoma | 10 Gy/5 fr | LF |
| 12 | 11 | Recurrent medulloblastoma | 12 Gy/4 fr BMT | LF |
| 13 | 16 | Recurrent medulloblastoma | 30 Gy/3 fr (3 sites) BMT | LC but PD |
| 14 | 15 | Recurrent medulloblastoma | 15 Gy/5 fr BMT | LF |
| 15 | 19 | Recurrent craniopharyngioma | 55.8 Gy/31 fr | LC |
| 16 | 8 | Recurrent craniopharyngioma | 54 Gy/30 fr | LC |
| 17 | 11 | Recurrent craniopharyngioma | 55.8 Gy/31 fr | LC |
| 18 | 11 | Recurrent craniopharyngioma | 54 Gy/30 fr | LC |
| 19 | 16 | Recurrent craniopharyngioma | 55.8 Gy/31 fr | LC |
| 20 | 13 | Recurrent craniopharyngioma | 55.8 Gy/31 fr | LC |
| 21 | 14 | Mixed germ cell tumor | 54 Gy/30 fr plus chemo | LC |
| 22 | 15 | Mixed germ cell tumor | 54 Gy/30 fr plus chemo | LC but PD |
| 23 | 11 | Mixed germ cell tumor | 54 Gy/30 fr plus chemo | LC |
| 24 | 8 | Germinoma | 50.4 Gy/28 fr plus chemo | LC |
| 25 | 12 | Germinoma | 50.4 Gy/28 fr | LC |
| 26 | 15 | Germinoma | 50.4 Gy/28 fr | LC |
| 27 | 8 | Orbital rhabdomyosarcoma | 50.4 Gy/28 fr plus chemo | LC |
| 28 | 7 | Recurrent pinealoblastoma | 54 Gy/30 fr | LF at 2.5 years; NED after surgery |
| 29 | 3 | PNET | 55.8 Gy/31 fr | LC but PD |
| 30 | 3 | Retinoblastoma | 50 Gy/50fr 1 Gy b.i.d. plus chemo | LC |
| 31 | 10 | Choroidal hemangioma | 12 Gy/6 fr | Stable |
| 32 | 12 | Choroidal hemangioma | 12 Gy/6 fr | Stable |
| 33 | 11 | Choroidal hemangioma | 12 Gy/6 fr | Stable |

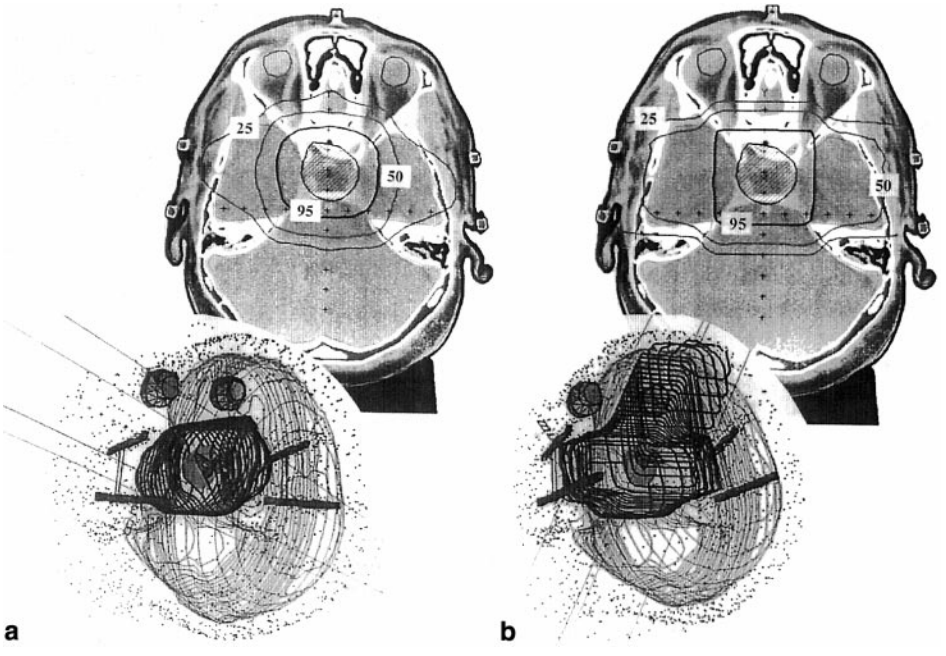


**Fig. 3a, b** Axial CT images of a child with recurrent craniopharyngioma **a** treated with noncoplanar arc technique and **b** as if treated with a three-field technique (two opposed lateral fields and a vertex field). The 95%, 50% and 25% isodose lines are shown at the level of the isocenter. The *insets* at *lower left* in **a** and **b** show the 50% isodose surface (*heavy lines*) surrounding the target volume and adjacent brain. Lower dose to the temporal lobe and lower volume of normal brain irradiated (*inset*) with the noncoplanar arc technique is demonstrated

trolled with reirradiation. Tumor control was not achieved in any of the children treated with radiation for previously irradiated recurrent malignant gliomas. There were no treatment-related complications in 32 of the 33 children treated. One child who had a low-grade pontine glioma had evidence of radiation necrosis inside the treated field. He initially underwent subtotal resection of his tumor, and this was followed by fractionated stereotactic radiation to a dose of 54 Gy over 30 fractions. The dose was prescribed to the 95% isodose line and was delivered using 10-MV X-rays with six 7×7 cm arcs. The dose inhomogeneity across the target volume was 6%. He was well until 1 year later, when he developed symptoms of headache and progressive neurological deficits. MRI at that time revealed cystic necrosis in the irradiated field. Steroid treatment was started, but the boy's symptoms and neurological deficits progressively worsened. Repeat MRI showed evidence of progression of necrotic lesions and he died 1 year after completion of radiation. An autopsy was done and pathological evaluation of the brain revealed extensive gliosis and necrosis without any evidence of tumor in the irradiated field.

## Discussion

Stereotactic radiosurgery and fractionated stereotactic radiotherapy represent two major advances in the field of neuro-oncology. While application of these techniques in adult brain tumors is rapidly expanding, their role in the treatment of pediatric brain tumors is still being defined. The advantages of fractionated stereotactic radiation are many. Long-term effects of radiation of particular concern in children include optic neuropathy, pituitary-hypothalamic dysfunction, memory and intellectual deficits, psychological disturbances, vasculopathy and induction of second malignant neoplasms [19]. The factors that influence the incidence of such complications include patient age, sex, extent of surgical resection, tumor volume, total radiation dose, total dose inhomogeneity, dose per fraction and use of concurrent chemotherapy [4, 10, 11, 19]. Fractionated stereotactic radiation uses low doses per fraction and hence allows for repair of sublethal damage in the normal brain during a course of treatment, so that it may lower the incidence of late neurological sequelae. Further, this technique may permit dose escalation in certain tumors, such as astrocytomas, medulloblastomas, and craniopharyngiomas, because of superior targeting and the ability to limit the dose delivered to such critical structures as retina, optic chiasm, brain stem and temporal lobe (Fig. 3a, b). Another advantage of fractionated stereotactic radiation is the ability to treat large tumors with doses up to therapeutic levels, whereas with radiosurgery greater target volumes necessitate lowering of the dose because of a significant increase in the incidence of complications [4, 11]. A number of relocatable frames have been used for fractionated stereotactic radiotherapy, including the Gill-Thomas-Cosman frame (GTC), the Boston Children's frame [6, 12], and the Laitinen frame [7, 13]. The Boston Children's and Laitinen frames have an advantage over the GTC frame in that no mouthpiece is required for immobilization, as a mouthpiece cannot be reliably used in children. Both these frames are well tolerated and accurate for multiple treatment immobilization in children treated with stereotactic radiotherapy. Another significant advantage of the Laitinen frame is the ability to treat low-lying targets such as tumors below the base of the skull, as they are not easily accessible by the Leksell or GTC frames. An important but less documented disadvantage of radiosurgery and fractionated stereotactic radiotherapy is the increase in the volume of adjacent brain and other viscera, such as thyroid gland, which are treated by lower isodose lines and exit radiation dose from noncoplanar beams [18]. Likewise, in gamma knife radiosurgery long treatment times and proximity of the entire body of the child to Co-60 sources mean delivery of doses of radiation with a potential for late sequelae. In a report from UCSF on use of the gamma knife in children the estimated mean radiation doses to lens and thyroid were 0.21 Gy and 0.19 Gy [2]. As more children are treated and with longer follow-up we will learn more about the incidence of these complications.

There are a number of published reports on the efficacy of stereotactic radiosurgery in children with CNS neoplasms. In the University of Pittsburgh experience 13 children with predominantly malignant gliomas received 11–20 Gy using gamma knife radiosurgery. The majority of children had had prior radiation; 3 children had local control at the time of writing, and 2 of these had surgery after treatment for local progression. Three children had a transient increase in peritumoral edema, which responded to steroids [8]. In the University of California San Francisco experience, 29 children were treated with 12–21 Gy gamma knife radiosurgery. After a median follow-up of 43 weeks, 5 of 7 children with low-grade gliomas, 5 of 14 with high-grade gliomas, and 4 of 5 with craniopharyngiomas achieved local control. Three children who were heavily pretreated with radiation developed necrosis after radiosurgery [2]. In the Mayo Clinic experience with linear accelerator-based radiosurgery, 12 children received doses of 7–30 Gy for recurrent brain tumors. In children with low-grade tumors the local control rate was 75%, while 3 of 4 children with malignant tumors died [20]. In a series of 14 children with residual and recurrent medulloblastoma from Boston Children's Hospital treated with linear accelerator-based radiosurgery to a median dose of 12 Gy, 12 of the children achieved local tumor control. However, more than half the children with recurrent medulloblastoma died of progressive leptomeningeal disease [15]. In another report from the St. Jude Cancer Research Hospital, stereotactic

radiosurgery boost was used after external beam radiation in the primary management of 5 children with ependymoma. There was good local control with no excessive neurotoxicity [1]. Craniopharyngiomas have also been treated with radiosurgery: in a series of 9 children treated with gamma knife radiosurgery at the University of Virginia with peripheral doses of 9–17 Gy, 7 of the children achieved local control. The dose to the optic apparatus was <9 Gy in all patients, and none developed any visual complications [16].

Fractionated stereotactic radiotherapy has also been used in children [3, 7]. In the Harvard Joint Center for Radiation Therapy series, 33 children with a variety of intracranial neoplasms were treated with fractionated stereotactic radiotherapy. The doses ranged from 45 to 54 Gy at conventional fractionation of 1.8–2 Gy. The modified Gill-Thomas-Cosman relocatable frame or Boston Children's frame was used for treatment immobilization. The treatments were well tolerated, and excellent accuracy in daily set-up was achieved. At a median follow-up of 16 months there was no major acute or long-term toxicity [3]. The present report represents the largest series of children treated with fractionated stereotactic radiotherapy using the Laitinen stereoadapter. The local control rates obtained in the different tumor types are similar to those reported with conventional external beam radiation and radiosurgery. The treatments were well tolerated in all age groups (3–19 years), and there was no toxicity except in a 14-year-old child who developed necrosis after a standard dose of 54 Gy in 30 fractions for a recurrent pontine astrocytoma. This complication is extremely rare (0.04–0.4%) with this dose fractionation, which is commonly used for treatment of most tumors [17]. A thorough review of the treatment plan did not reveal any significant hot spots. His prior surgical resection may have been a contributing factor [10]. Further, he did not receive any chemotherapy or radiosensitizer, which could have potentiated the effects of radiation.

Recurrent astrocytomas, craniopharyngiomas and medulloblastomas were the major tumor types in this series. Emerging data show that in primary medulloblastomas a boost target volume less than the entire posterior cranial fossa may be treated with good local control and less ototoxicity and deafness [5]. This is an area of immense interest in applications of fractionated stereotactic radiotherapy for the future.

## Conclusion

This series demonstrates that in children with benign and malignant CNS and ocular tumors, fractionated stereotactic radiotherapy using the Laitinen stereoadapter is accurate and well tolerated and results in good local control. Longer follow-up is required to check whether there is a difference in tumor control and the incidence of complications according as whether conventional external beam radiation, radiosurgery or fractionated stereotactic radiotherapy is used. As our understanding of acute and long-term sequelae of radiation, surgery, and chemotherapy improves, the application of stereotactic techniques for irradiating pediatric brain tumors will undoubtedly increase. Clinical trials have already adopted stereotactic techniques for treatment, and hence it is very important to define the application of different relocatable frames for such therapy. We believe that this series lends support to further investigation of this technique for the management of primary and recurrent pediatric brain tumors.

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