ADVANTAGE OF PROTONS COMPARED TO CONVENTIONAL X-RAY OR IMRT IN THE TREATMENT OF A PEDIATRIC PATIENT WITH MEDULLOBLASTOMA

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Purpose: To compare treatment plans from standard photon therapy to intensity modulated X-rays (IMRT) and protons for craniospinal axis irradiation and posterior fossa boost in a patient with medulloblastoma.

Methods: Proton planning was accomplished using an in-house 3D planning system. IMRT plans were developed using the KonRad treatment planning system with 6-MV photons.

Results: Substantial normal-tissue dose sparing was realized with IMRT and proton treatment of the posterior fossa and spinal column. For example, the dose to 90% of the cochlea was reduced from 101.2% of the prescribed posterior fossa boost dose from conventional X-rays to 33.4% and 2.4% from IMRT and protons, respectively.

Dose to 50% of the heart volume was reduced from 72.2% for conventional X-rays to 29.5% for IMRT and 0.5% for protons. Long-term toxicity with emphasis on hearing and endocrine and cardiac function should be substantially improved secondary to nontarget tissue sparing achieved with protons.

Conclusion: The present study clearly demonstrates the advantage of conformal radiation methods for the treatment of posterior fossa and spinal column in children with medulloblastoma, when compared to conventional X-rays. Of the two conformal treatment methods evaluated, protons were found to be superior to IMRT.

INTRODUCTION

Medulloblastoma is among the most common pediatric brain tumors. This tumor classically develops in the posterior fossa with frequent metastasis along the craniospinal axis. Up to 30% of patients with medulloblastoma present with radiographic evidence of subarachnoid space seeding, with occult seeding almost certainly higher; thus, a vital component of treatment includes irradiation of the entire craniospinal axis (1). Advances in treatment methods for medulloblastoma, at one time considered incurable, have led to increased survival of children with this disease (2, 3). Current treatment strategies use a combination of surgery, external beam radiation, and chemotherapy to produce a 5-year overall survival in excess of 65% (4, 5). With the increasing long-term survival of this population, there is growing concern regarding treatment-associated side effects. Potential complications resulting from treatment include neurocognitive deficits, hearing loss, pituitary dys-
METHODS AND MATERIALS

This investigation compares the plans for three methods of treating the craniospinal axis of children with medulloblastoma. The isodose distributions and DVHs were compared for the following treatment plans.

1. Standard craniospinal axis irradiation and a posterior fossa boost using conventional 4- and 6-MV X-rays, respectively. The 4-MV cranial fields consisted of parallel-opposed portals with collimation to match the divergence of the spinal field. The junction between the cranial field and spinal field was set to allow a 3-level moving junction of 1 cm each while ensuring that the spinal field would not exit through the mandible. The spinal field consisted of a single posterior-to-anterior portal, sufficiently wide to encompass the bilateral transverse processes. This was followed by a boost to the posterior fossa using opposed-lateral 6-MV X-rays.

2. Whole-brain irradiation with conventional 4-MV X-rays matched using a 3-level moving junction to a spinal field treated by coplanar multifield 6-MV intensity-modulated X-rays. The IMRT spinal plan was developed to include the entire bony spinal column as target volume. The posterior fossa boost was planned using 6-MV multifield IMRT.

3. Whole-brain irradiation using opposed-lateral 160-MeV proton fields matched to a posterior-anterior proton spine field. The posterior fossa was subsequently boosted using 3-field conformal protons consisting of right and left posterior obliques and a posterior field. For all treatment plans, the craniospinal axis was treated in one phase, and the posterior fossa boost was delivered in the second phase. In all cases, 1.8 Gy was planned for daily fractionation. The total craniospinal dose was 23.4 Gy, and the total dose to the posterior fossa was 54 Gy.

As a test case, a 43-month-old boy was sedated and scanned prone with his head in a neutral position using a Duncan headrest. The scan was obtained in 5-mm increments from the top of the head to the lower sacrum. The images were then transferred to the treatment planning systems, where the target and nontarget structures of interest were outlined. The planned craniospinal axis treatment volume consisted of the whole intracranial volume as well as the entire circumference of the spinal column, inclusive of the transverse processes extending from the foramen magnum through the completion and the lateral extent of the thecal sac, as previously described (25). In this particular case, the inferior border of the spinal field was at the S2–S3 interface. The entire posterior fossa, defined superiorly by the tentorium and everywhere else by the bony boundaries, was targeted for the boost fields. The entire spinal column is targeted to prevent the possibility of unbalanced vertebral body growth.

Critical nontarget structures were outlined for evaluation of absorbed dose from the three treatment strategies. Nontarget tissues, including orbits, cochlea, pituitary, hypothalamus, temporomandibular joint (TMJ), parotid gland, pharynx, lungs, heart, esophagus, stomach, transverse colon, and kidneys, were outlined such that isodose distributions and DVHs could be evaluated.

Treatment plan

An in-house 3D (RX) treatment planning system was used for the development of the standard photon and proton treatment plans (26). The photon plan consisted of opposed-lateral 4-MV fields designed to treat the whole brain. The dose distribution was optimized using a partial-transmission block to reduce the hot spots along the skin surface. A single 4-MV posterior field calculated to a depth of 2.5 cm was
used to treat the spinal axis. This was the average depth to the posterior aspect of the vertebral body as determined from an MRI scan. The posterior fossa was boosted with conformal parallel-opposed 6-MV lateral fields optimized with wedge filters.

The IMRT plans in this study were generated using the KonRad (MRC GmbH, Heidelberg, Germany) treatment planning software (27, 28). Whole brain was planned as described for conventional X-rays. No significant improvement was achieved with IMRT or protons when considering the whole-brain treatment fields. Two separate IMRT plans were generated for the spinal column and the posterior fossa boost. The entire spinal column was planned for treatment with 7 isocentric, coplanar equally spaced beams that started at a straight posterior field at gantry angle 0 and that were chosen to avoid entrance through the arms. The bixel size (Bixel is the subdivision of the fluence modulation pattern into individual beam elements) was chosen to be 0.5 × 1.0 cm with the smaller dimension in the direction perpendicular to the spinal axis, to allow for a greater number of degrees of freedom in the optimization process. This in turn leads to greater conformality. The posterior fossa was boosted with 7 isocentric beams chosen to best avoid critical structures such as the eyes and minimize the dose to the cochlea, at angles of 0°, 43.7°, 94.1°, 128.6°, 231.4°, 265.9°, and 320.3°, respectively. A bixel size of 0.5 × 0.5 was chosen to achieve better conformality than obtainable with a larger bixel size (29).

The proton plan was developed for a 160-MeV proton beam available at the Harvard Cyclotron Laboratory. Conformal right and left lateral beams were designed to treat the whole brain. Compensators were designed to conform the dose to the brain tissue profile for the lateral beams. A single posterior field that conformed the dose to the anterior surface of the vertebral body was used to treat the spinal axis. The posterior fossa was boosted using 3 fields, right and left posterior obliques and a posterior field. Margining for each plan included a 3-mm setup error and an appropriate penumbra.

RESULTS

Figure 1 depicts in an axial view radiation dose distributions generated by conventional X-rays or IMRT photons or protons for a posterior fossa boost. The transaxial plane shown in Fig. 1 is at the cochlear level and demonstrates the substantial dose sparing of the hearing apparatus and pituitary achieved by conformal radiation methods. This illustration demonstrates also the rapid dose falloff outside the posterior fossa. Dose–volume histograms for cochlea and pituitary are shown in Fig. 2. These results demonstrate that the greatest dose sparing of the hearing apparatus and pituitary was achieved with conformal protons. Ninety percent of the cochlea volume was projected to receive 101.2% of the prescribed posterior fossa boost dose from standard X-rays, whereas IMRT or protons were projected to deliver 33.4% and 2.4% of the prescribed dose to 90% of the cochlea volume. The dose to 90% of the pituitary gland was reduced from 62.7% from X-rays to 19.3% and 0.1% for IMRT and protons, respectively. Table 1 lists the percentages of the prescribed posterior fossa dose received by 5%, 50%, and 90% of organ volumes for the cochlea, pituitary, hypothalamus, TMJ, parotid, and pharynx. Proton beam therapy yielded the greatest dose reduction for all nontarget sites evaluated. IMRT also produced substantial radiation dose reduction regarding the cochlea, pituitary and hypothalamus, and TMJ compared to conventional X-rays. In addition, IMRT spared the parotid from the higher doses incurred with conventional X-rays, but resulted in greater low-dose delivery to 90% of the organ volumes, consistent with the high-dose/low-dose trade-off previously described for IMRT treatment plans (30). Of the three treatment plans, the IMRT plan gave the highest dose to the pharynx. This was a result of beam arrangement.

Dose distributions for spinal axis irradiation from conventional X-rays, IMRT, and proton beam therapy are shown in Fig. 3. This is a midline sagittal view through the spinal column, illustrating the isodose distributions for the various treatment plans; it demonstrates the dose distribution achieved with IMRT photons or protons compared to standard X-rays. DVHs for heart, lung, stomach, and transverse colon from the three spinal axis treatment strategies are shown in Fig. 4. The percentages of the prescribed spinal column dose received by 5%, 50%, and 90% of the
heart, lungs, esophagus, stomach, kidneys, and transverse colon are shown in Table 2. Dose to 50% of the heart volume from treatment of the spinal column was reduced from 72% from X-rays to 29.5% for IMRT and 0.5% for protons. The projected dose received by 50% of the stomach volume was reduced from 61% for standard X-rays to 32% for IMRT and 0.5% for protons, whereas dose to the transverse colon dropped from 63.2% to 26.5% and 0.5% for X-rays, IMRT, and protons respectively. Table 2 demonstrates that the 90% organ volumes for all organs evaluated, except heart, received a higher dose from the IMRT plan compared to conventional X-rays or protons. Fifty percent of the right lung volume and right kidney volume received higher dose from the IMRT plan compared to X-rays or protons. In comparing the IMRT plan to conventional X-rays, a trade-off is often seen between the low-dose and high-dose involvement of critical structures. The DVH for the heart, lung, stomach, or transverse colon may serve as an example. The conventional photon plan shows greater dose delivery to smaller volumes, but lower dose delivery to larger volumes of the organ compared to the IMRT plan (Fig. 4). This is attributed to the larger number of beam portals used with the IMRT treatment plan.

The proton treatment plan produces marked dose reduction for all nontarget organ volumes evaluated, except the posterior esophagus (Table 2). The proton plan was designed to encompass the entire bony spinal column to preclude growth differential between the anterior and posterior bony elements. Because the esophagus resides immediately anterior to the vertebral column, its posterior wall receives nearly 100% of the prescribed spinal column doses. As a result of the rapid dose falloff beyond the spread-out Bragg with protons, a lower dose is delivered to the anterior esophagus.

Multifield IMRT generated a slightly lower posterior esophageal dose compared to either conventional X-rays or proton therapy. IMRT-directed photons also provide substantial normal-tissue sparing compared to conventional photons for heart, stomach, transverse colon, and esophagus. However, at the 50% organ volume, less normal-tissue sparing was realized for lung and kidney with IMRT compared to conventional photons.

This comparative analysis demonstrates that protons and IMRT are superior to conventional photons for delivering dose to the posterior fossa, with protons superior to IMRT. Regarding spinal axis irradiation, the multifield IMRT plan produced substantial sparing for some nontarget organs but not others, whereas the proton plan with its rapid dose

<table>
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<tr>
<th>Site</th>
<th>X-ray</th>
<th>IMRT</th>
<th>Proton</th>
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<tr>
<td></td>
<td>5%</td>
<td>50%</td>
<td>90%</td>
</tr>
<tr>
<td>Cochlea</td>
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<td>102.2</td>
<td>101.2</td>
</tr>
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<td>96.4</td>
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</tr>
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</tr>
<tr>
<td>Pharynx</td>
<td>9.4</td>
<td>7.9</td>
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**Abbreviation:** TMJ = temporomandibular joint.
falloff beyond the spread-out Bragg peak greatly limits dose to all nontarget organs evaluated.

**DISCUSSION**

Over the past 30–40 years, the 5-year survival for medulloblastoma has increased from 25% to greater than 65% (4, 5). With improved survival, more attention has been directed to treatment-related effects. In the future, all treatment modifications should be scrutinized for efficacy as well as side effects. Local posterior fossa recurrence remains the most common site of failure, followed by thecal sac seeding. Thus, conformal radiation treatment of the spinal axis and posterior fossa is ideally suited for treating the anatomic sites at greatest risk while limiting radiation dose to adjacent nontarget tissue.

Limiting toxicity associated with the posterior fossa boost for pediatric medulloblastoma patients is currently an area of great interest. The improvements in radiographic imaging have eliminated the dependence of field placement based on bony landmarks. The development of ototoxicity and neuroendocrine and neurocognitive late effects provides the impetus to seek alternate methods to deliver radiation to the posterior fossa while limiting dose to nontarget structures. This investigation demonstrates that the greatest dose sparing of nontarget tissues was achieved with protons. We found that the proton posterior fossa boost delivered less dose to all nontarget structures, including cochlea, pituitary, hypothalamus, TMJ, parotid, and pharynx. The advantage realized by proton therapy may be particularly important for the treatment of childhood malignancies, because of the rapid anatomic and neurocognitive development occurring in this population. The current national protocol for low-stage medulloblastoma treats with 23.4 Gy CSI and a subsequent posterior fossa boost of 30.6 Gy, along with three-drug chemotherapy. As more radiation dose is delivered to the posterior fossa via boost fields, sparing of non–posterior fossa structures is increased. The results of this study demonstrate that protons deliver the most conformal treatment to the posterior fossa.

On casual analysis, it would seem that a highly tailored radiation field could be designed to treat only the thecal sac with vertebral body sparing. However, the complexity of the growing vertebra precludes such a simple treatment approach. At birth, the developing vertebra contains three ossification centers that fuse during childhood (5–8 years of age). Five secondary ossification centers develop during puberty. The primary and secondary stages of ossification include both the vertebral body and vertebral arch (31). Probert and Parker found two phases of increased sensitivity; the first occurred at less than 6 years of age and the second at the time of puberty (32). Delivery of radiation to the spinal cord and thecal sac with uniform sparing of all growth plates is not possible with the conformal therapy methods currently available. This is a special concern regarding the posterior arch of the spinal column. The arachnoid membrane terminates at or just short of the spinal ganglion that resides within the intervertebral foramen (33). Therefore, the posterior elements of the spinal column must be included in the planned radiation field to adequately encompass the subarachnoid space enveloped by the thecal sac.

Whereas the implications of selective posterior arch irradiation in children are unknown, information is available regarding surgical manipulation of the posterior components of the spinal column. Surgical disruption of cervical spine facet joints in young patients is associated with a substantial increase in kyphosis and swan neck deformity, and cases of c-spine dislocation have been reported (34, 35). Cadaver studies demonstrate the importance of the articular facet joint for spinal stability (36, 37). Thus, for children with substantial growth potential, it is prudent to intentionally treat the entire vertebral column, to preclude growth imbalance between the anterior and posterior components of the spinal column, at least until further information is available regarding the effects of radiation on spinal growth.

This study, comparing three methods for treatment of the spinal axis in children, demonstrates the superiority of protons over standard photon methods or intensity-modulated...
photons. The data from this study demonstrate that both IMRT and protons are capable of treating the spinal axis target with substantial sparing of nontarget tissues compared to standard X-rays. With the exception of the posterior esophagus, protons consistently deliver less dose to nontarget tissues compared to IMRT.

This study used IMRT fields composed of $0.5 \times 1.0$-cm bixels for the spinal irradiation and $0.5 \times 0.5$-cm bixels for the posterior fossa treatments. This should be compared to the $1.0 \times 1.0$-cm bixel size of conventional multileaf collimator technology. Our study used smaller bixel size to achieve a higher degree of control over the dose distribution in terms of target volume conformation and normal structure avoidance. Although it was not demonstrated, we expect that the use of $1.0 \times 1.0$-cm bixel size will degrade the results for IMRT. It is important to note that delivery

<table>
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<th>Site</th>
<th>X-ray 5%</th>
<th>X-ray 50%</th>
<th>X-ray 90%</th>
<th>IMRT 5%</th>
<th>IMRT 50%</th>
<th>IMRT 90%</th>
<th>Proton 5%</th>
<th>Proton 50%</th>
<th>Proton 90%</th>
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<tbody>
<tr>
<td>Heart</td>
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<td>72.2</td>
<td>18.2</td>
<td>44.9</td>
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</tr>
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<td>3.5</td>
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<td>21.9</td>
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<td>85.4</td>
<td>11.9</td>
<td>66.6</td>
<td>44.4</td>
<td>32.1</td>
<td>99.0</td>
<td>74.7</td>
<td>10.2</td>
</tr>
<tr>
<td>Stomach</td>
<td>80.3</td>
<td>61.3</td>
<td>3.7</td>
<td>50.4</td>
<td>31.9</td>
<td>20.6</td>
<td>1.0</td>
<td>0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Right kidney</td>
<td>85.6</td>
<td>6.7</td>
<td>3.3</td>
<td>50.3</td>
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<td>Transverse colon</td>
<td>73.7</td>
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<td>18.0</td>
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Fig. 4. Dose–volume histograms for the heart, right lung, stomach, or transverse colon from spinal irradiation by X-rays or IMRT or protons.
technologies with smaller bixel sizes are available with multileaf collimators that have smaller leaf width or that use dynamic and continuous leaf motion during the delivery of the fluence-modulated field. The results for IMRT delivery are thus relevant and can be delivered. We do not explicitly report our dose constraints used in the IMRT optimizations, because these are specific to the Konrad system. This is done intentionally, because the various IMRT optimization engines vary greatly in their handling of various dose constraints and penalty factors. Rather than explicitly give the constraints and penalties, which are not transferable from one IMRT treatment planning system to another, we refer the reader to the results achieved by these choices in the form of the DVHs given.

In an attempt to further diminish the dose to adjacent nontarget structures, we developed a second IMRT plan for spinal axis irradiation. In the second plan, the thecal sac was treated as the primary target with the constraint of delivering a minimum of 20 Gy to the bony spinal column. This was done to provide at least the minimum dose, for spinal bone growth retardation (14). However, the complex subject of pediatric bone growth and development may preclude such a treatment approach in a clinical setting at present.

The present study clearly demonstrates the advantage of conformal radiation methods, compared to conventional X-ray treatment, for the treatment of posterior fossa and spinal column in children with medulloblastoma. Of the two conformal treatment methods, protons were found to be superior to IMRT. This approach of using focal radiation, especially in combination with concurrent chemotherapy, is very attractive for treating young children with substantial growth potential.

REFERENCES


