Intraoperative phosphorus-32 brachytherapy plaque for multiply recurrent high-risk epidural neuroblastoma

Case report

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Achieving local control is a crucial component in the management of neuroblastoma, but this may be complicated in the setting of prior radiation treatment, especially when the therapeutic target is in proximity to critical structures such as the spinal cord. The authors describe a pediatric patient with multiply recurrent neuroblastoma and prior high-dose radiation therapy to the spine who presented with progressive epidural disease. The patient was managed with resection and intraoperative high-dose-rate brachytherapy using a phosphorus-32 (32P) plaque previously developed for the treatment of brain and spine lesions. (http://thejns.org/doi/abs/10.3171/2014.1.PEDS13121)

KEY WORDS • recurrent • re-irradiation • spine • intraoperative • brachytherapy • neuroblastoma • oncology • 32P

NEUROBLASTOMA is the most common extracranial solid tumor in children and the most common malignancy in infants younger than 1 year old.1 The outcome for patients with recurrent high-risk neuroblastoma is very poor,2 and effective curative treatments have not been established in the setting of resistant neuroblastoma. Intraoperative electron beam therapy8,10,16,19,20 or brachytherapy7,13–15,17,21 for pediatric solid tumors has been used in many institutions to increase the likelihood of durable local control. Rich et al.18 recently described the outcomes for 44 patients with recurrent or persistent primary high-risk neuroblastoma treated with resection and intraoperative radiation therapy with iridium-192 (192Ir) high-dose-rate afterloader brachytherapy using the Harrison-Anderson-Mick (HAM) radiation applicator. During a median follow-up of 10.5 months, no operative or postoperative deaths were observed, and local control was approximately 50% with a median overall survival of 19 months.

Intraoperative brachytherapy has the advantage of direct placement of the radioactive source at a tumor site and rapid dose falloff with distance to permit localization of conformal dose to the site with relative sparing of nearby normal tissues. However, with 192Ir, a 50% reduction in dose requires a separation of approximately 8 mm from the source.3 At sites close to previously treated areas, this distance may be inadequate for sufficient sparing of normal tissue. Recently, an intraoperative brachytherapy applicator incorporating phosphorus-32 (32P) in a flexible film was developed.4 The benefit of this applicator is a sharp dose falloff, with a decrease to < 5% of the prescription dose within 3–4 mm (Fig. 1).

Case Report

History. A 6-year-old girl with multiply recurrent high-risk neuroblastoma was referred to our radiation oncology and neurosurgical services because of progressive disease in her thoracic spine resulting in spinal cord compression. She had been in her usual state of good health (41 months earlier, February 2009) when she experienced symptoms of constipation, abdominal pain, and low-grade fever. Her workup included an abdominal CT scan, which revealed a retroperitoneal mass and prominent lymph nodes. A biopsy revealed neuroblastoma—poorly differentiated, stroma poor, mitosis-karyorrhexis index > 100 (unfavorable histology), and N-myc nonamplified. Bone marrow studies were positive for neuroblastoma. Bone scan was negative for disease. Metaiodobenzylguanidine (MIBG) was positive in the abdomen only. A chronologi-
Intraoperative $^{32}$P brachytherapy for recurrent neuroblastoma

Fig. 1. Percent depth dose (PDD) curve for an intraoperative $^{32}$P brachytherapy plaque, with measurements for radiation dose at a depth relative to prescription dose (10 Gy to 1-mm depth).

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Discussion

The standard of care for high-risk neuroblastoma is maximal safe resection after neoadjuvant chemotherapy,
followed by postoperative radiation therapy. For patients with recurrent or refractory neuroblastoma, a number of therapies exist including salvage surgery, chemotherapy, and/or radiation therapy, as well as targeted radionuclide delivery via MIBG, newer retinoid compounds, and immunotherapy; however, the cure rate is low in patients whose aggressive up-front therapy has failed.

Intraoperative radiation therapy offers an option for patients who have had prior radiation and in whom there is concern for toxicity from additional radiation treatment. As the radiation is delivered locally and does not encompass the same degree of healthy tissue as in external beam radiation therapy, there is a significant reduction in the incidence and degree of toxicity to normal tis-

Fig. 2. Timeline of diagnostic and therapeutic interventions prior to thoracic epidural recurrence and evaluation by a multidisciplinary pediatric oncology tumor board.

Fig. 3. Presurgical planning sagittal (left) and axial (right) T2-weighted MR images showing an epidural mass extending from T-3 to T-7, compressing and displacing the spinal cord.

Fig. 4. Axial T2-weighted MRI sequences, proximal (left) and distal (right) to the site of compression, showing the measurement of CSF thickness from the interior surface of the dura mater to the surface of the cord.
Intraoperative $^{32}$P brachytherapy for recurrent neuroblastoma

The dose of brachytherapy radiation decreases with the square of the distance from the applicator, leading to rapid dose falloff. High doses can be delivered in a single fraction, potentially resulting in a significantly increased radiobiological treatment effect.2,6

Specifically in the setting of neuroblastoma, most institutions have used intraoperative electron beam radiation therapy;8,10,16,19,20 the use of intraoperative brachytherapy has been reported at a smaller number of institutions.7,18 While intraoperative brachytherapy with flexible applicators is highly versatile, allowing ease of access to and conformal placement in anatomical locations that a bulky electron cone applicator may not be able to reach, the dose falloff with $^{192}$Ir, while rapid, may not allow sparing of sensitive structures such as the spinal cord when the dura (only 3–4 mm away) must be effectively treated. In this setting, a brachytherapy applicator with significant falloff in only a few millimeters is required.

The use of an intraoperative $^{32}$P brachytherapy plaque has been described.4 $^{32}$P is a pure $\beta$-emitter ($E_{\text{max}} = 1.71$ MeV, $T_{1/2} = 14.28$ days) with a maximum electron range of approximately 7 mm in water). The RIC-100 conformal $^{32}$P source (RI Consultants) consists of $^{32}$P bound chemically to a flexible and transparent polymer layer and coated with silicone. Given a depth of approximately 3 mm from the dural surface to the surface of the cord, a standard prescription of 10 Gy at 1 mm will result in a maximum cord dose of approximately 1.6 Gy (Fig. 1). The dose at the dural surface would be approximately 25.5 Gy; the dose delivered at a depth of 4 mm from the surface is approximately 5% of the prescribed dose at 1 mm and < 1% of the prescribed dose at 5 mm (4 mm from the prescribed treatment depth).

The use of a $^{32}$P plaque in the intraoperative setting dramatically simplifies treatment; the size and shape of the plaque are determined preoperatively, but the film can be folded (or partially shielded) to account for smaller target volumes. It is very flexible, allowing for easy fit into tight spaces and is easily conformed to the target surface. No additional planning time is needed, and treatment duration is very short (generally on the order of 10–15 minutes), minimizing the prolongation of anesthesia and/or the immobilization generally needed for intraoperative treatment.

The primary limitation of the plaque relates to the same property that gives it such a dosimetric advantage for its use near critical structures; the rapid dose falloff means that the plaque is ineffective in the treatment of gross residual disease or microscopic disease extending more than a few millimeters. As such, the decision to use the $^{32}$P plaque should be based in part on the surgeon’s confidence that GTR can be achieved. For adequate dose falloff, the dura should not be violated to prevent loss of CSF; dural compromise is considered a contraindication to proceeding with intraoperative $^{32}$P brachytherapy.

Conclusions

This is the first reported case in which intraoperative $^{32}$P brachytherapy has been used in the pediatric population. We demonstrated that brachytherapy was safely delivered with no immediate toxicity and effective local control to date. The dosimetric advantages and relative ease of use of $^{32}$P brachytherapy allow it to be an effective modality for delivering intraoperative radiation, and this therapy warrants consideration for further use in selected cases.

Disclosure

Dr. Yamada is a consultant for Varian Medical Systems and is a member of the Speakers Bureau for the Institute for Medical
References


This work was presented in part as a poster discussion at the 2013 American Brachytherapy Society Annual Meeting held in New Orleans, Louisiana, on April 18–20, 2013.

Please include this information when citing this paper: published online January 31, 2014; DOI: 10.3171/2014.1.PEDS13121

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