

Proton Beam Radiation Therapy in the Treatment of Pediatric Central Nervous System Malignancies: A Review of the Literature

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One of 5 pediatric cancers occurs within the central nervous system. Although outcomes have improved, the greatest challenge with these patients remains the balance between cure and long-term morbidity. Patients who have undergone radiation therapy remain at high risk for developing a multitude of severe long-term sequelae. As radiation therapy remains a mainstay of treatment much attention has gone into improving its quality and precision. Multiple options exist for these patients, including conventional photon radiotherapy, conformal radiation, and now, proton beam radiotherapy. Proton beams are able to provide utmost precision for targeting the site of the tumor while decreasing radiation doses to surrounding tissues. Studies are showing that the benefits of proton therapy surpass both conventional radiation as well as conformal radiation therapy, and as a result medical centers around the United States are working to open more facilities and improve patient access. As research becomes more readily available and new centers open, pediatric patients will have the option to be treated with this technology in order to preserve cognitive function and decrease long-term effects.

Key words: *proton beam radiation, pediatric, brain tumors*

Each year in the United States approximately 10,000 children younger than 14 years of age are

diagnosed with cancer. Due to the advances of modern medicine, the overall survival rates have improved dramatically to a rate of nearly 80% (National Cancer Institute, 2007). Of these, malignancies of the central nervous system (CNS) comprise approximately 21% of all cases (Gurney, 1999). Unfortunately, scientific knowledge has not affected these malignancies as it has other areas of cancer such as leukemia and lymphoma. Despite the fact that nearly half of all patients with CNS tumors are cured from their disease, they continue to suffer from both the acute toxicity side effects related to treatment as well as the devastating long-term effects. In treating patients with cancers of the CNS, one of the greatest complexities is achieving the balance between morbidity and cure. Because brain tumors lead to significantly worse long-term effects than both hematologic malignancies and other solid tumors much of the current research is focused on improving the outcomes for the patients who survive their disease.

Currently, the 3 options for the treatment of CNS malignancies include surgery, radiation, and chemotherapy. Often, to achieve a cure a combination of the 3 treatment types is required. Radiation therapy is one of the mainstays of treatment; however, it is responsible for the greatest amount of deleterious effects. The combination of radiation and certain

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chemotherapeutic drugs results in an even greater amount of long-term damage due to their synergistic properties (Brière, Scott, McNall-Knapp, & Adams, 2007). Because of severe neurocognitive damage associated with cranial radiation, physicians attempt to spare patients younger than the age of 3 years from this therapy. In doing so they prevent some of the long-term toxicities yet limit the treatment options and possibly chance for cure. While attempting to reduce adverse effects, many studies have been performed on the effects of conformal radiation therapy (CRT), a technique in which the dose of radiation conforms to the target site of the tumor and limits the radiation dose delivered to healthy tissue (Kirsch & Tarbell, 2004). Proton beam therapy is a new and more advanced treatment variant of conformal radiation that is able to spare healthy tissue and can be used on younger patients. One of its main advantages is precise accuracy, which delivers exact doses of treatment to specific tumor target sites. In doing so, proton therapy is able to spare vital organs and their surrounding tissues from radiation exposure and subsequent acute and long-term effects. Increasingly, more centers are starting to implement this therapy into their practice. As research continues to show that protons provide improved treatment options, superior outcomes, and significantly less toxicity than standard external beam radiation therapy, pediatric oncology nurses will begin to care for an increasing number of these patients.

Current Treatment for Brain Tumors

A multimodal treatment approach is required for most patients with CNS malignancies to achieve the highest probability of cure. Frequently, because of the size and location of these malignancies, many surgeons are unable to achieve gross total resection. Radiation therapy is often required to eradicate residual tumor burden, while the addition of chemotherapy plays an important role in eliminating microscopic disease.

Traditionally, external beam radiation has been the standard of care for radiation therapy. In this type of treatment the linear accelerator creates high-energy photon beam X-rays using two-dimensional (2D) plain radiographs to design the radiation field. Extensive nontarget tissue damage frequently occurs

because of the large margin requirements surrounding the target site (Gibbs, Tuamokumo, & Yock, 2006). Photons enter the patient at a specific site and the amount of energy distributed initially increases over the first several centimeters and then decreases exponentially until it exits the patient. Therefore, the entire path of the photon—from the point of entry through the target site and out the exit site—is irradiated (Kirsch & Tarbell, 2003). Many pediatric brain tumors, such as tumors of the optic pathway, are positioned in such a way as to make it difficult to be removed completely via surgery. The location of these tumors makes radiation a necessity for cure, yet in radiating the field required to target the tumor the contralateral optic nerve, chiasm, and pituitary gland are often radiated as well, leading to significant adverse effects (Wilson, McDonough, & Tochner, 2005). The dose to these nontarget areas is referred to as the integral dose and is one of the leading causes of neurocognitive deficits experienced by patients who have undergone cranial irradiation. Locations of CNS tumors vary greatly by the type of tumor and patient. Some of the tumors may be situated in close proximity to the surface of the skull; however, many tumors are located deep within the brain parenchyma. These tumors require higher doses of radiation to reach the target site and the integral dose becomes quite substantial. Because external beam radiation does not target the dose specifically to the tumor bed, structures distal and proximal to the tumor inevitably become irradiated. With repeat exposure these structures suffer irreversible damage.

Long-term effects of radiation can be predicted by looking at the daily fractional dose of radiation, the total dose of radiation received, the combination of radiation with other treatment modalities, and patient's age (Kirsch & Tarbell, 2004). Although patients of all ages experience adverse effects from treatment with craniospinal radiation, children younger than the age of 36 months experience the most severe cognitive delays. Radiation has been proven to cause severe changes in white matter with the damage increasing significantly as the dose is escalated (Corn et al., 1994). In children less than 36 months of age, white matter has not yet completely myelinated and therefore the effects are significantly more pronounced. For these children, radiation is withheld and chemotherapy is administered in an effort to delay tumor recurrence or growth until the patient reaches an

appropriate age and the effects are less detrimental. In patients with progressive tumor burden prior to 36 months that cannot be well controlled with radiation and chemotherapy alone, the treatment options to date have been minimal. In a large multicenter study, which looked at delaying radiation for young patients, the response rates to surgery and chemotherapy were promising for patients with medulloblastoma, malignant glioma, and ependyomas but dismal in patients suffering from brainstem gliomas or embryonal tumors. Overall the study found that children younger than 24 months of age at diagnosis had 2-year progression-free survival of 39% (Duffner et al., 1993).

Patients older than 36 months have less serious effects but can be significantly affected as well. Long-term side effects of cranial radiation have been thoroughly studied and are well documented. Although these effects vary based on the location of the tumor and radiation field some of the most common include organ dysfunction, hypothyroidism, hearing loss, decreased IQ, learning difficulties, decreased growth, impaired hypothalamic–pituitary axis, structural abnormalities, and secondary malignancies (Ward, 2000). Growth retardation may be due to the direct affect on the spine or secondary decreased growth hormone. Declining IQ affects nonverbal cognitive ability, visual perceptual skills, as well as the speed of information processing. One study demonstrated that attention and freedom from distractibility are 2 IQ indices that continue to decline up to 5 years post-diagnosis and treatment, providing evidence that the necrosis of white matter greatly affects a wide array of neurologic systems (Brière, 2008). The learning difficulties commonly found include visual–motor integration, problem solving, and impaired memory (Ward, 2000). Secondary malignancies pose one of the greater risks to radiation therapy. A study looking at 10-year actuarial incidence of treatment-related secondary malignancies found the risk to be approximately 14%, with 90% of the tumors occurring within radiation fields (Li et al., 1975). Recent studies have shown that the effects of cranial irradiation may be monitored with magnetic resonance imaging. Three months following a radiation dose of 20 cGy, white matter that was previously healthy shows significant changes (Kirsch & Tarbell, 2004).

Effectiveness of radiation therapy is dependent not only on the tumors' responsiveness but also on the dose of therapy delivered directly to the tumor bed.

Many tumors are responsive to radiation therapy; however, the amount of radiation that can safely be delivered is significantly limited by the radiation dose tolerated by surrounding healthy tissue. Much research has gone into decreasing the side effect profile of radiation therapy while maintaining effective patient outcomes. To decrease the adverse effects, the dose to nontarget tissues must be significantly decreased or eliminated. CRT is any radiation in which the treatment dose is shaped to surround the target site of the tumor. There are several types of radiation that are able to use high-energy photons while decreasing the integral dose. One type of conformal radiation is the 3D therapy, in which computer simulation creates an illustration of the tumor as well as surrounding structures, enabling multiple beams of radiation to enter from various sites and target the specific area of the tumor. The beams converge on the target creating a dose that conforms to the shape of the tumor (Gibbs et al., 2006). In focusing the beams as well as dividing the areas from which they enter, more normal tissue is able to be spared. The radiation beams overlap at the tumor site, thereby allowing the tumor bed to receive a concise and relatively high dose of radiation while lowering the dose delivered to surrounding structures (Kirsch & Tarbell, 2004). Another common type of conformal radiation is intensity-modulated radiation therapy or IMRT. Much like 3D therapy, this computer-controlled treatment allows for radiation beams to be deposited at the tumor site while decreasing the radiation to healthy tissue. The therapy is able to create multiple targets as well as avoidance sites. Unlike standard radiation, various structures can be organized in order of importance. "IMRT has been shown to minimize acute treatment-related morbidity, making dose escalation feasible which may ultimately improve local tumor" (Teh, Woo, & Butler, 1999, p. 433).

Although these therapy options provide a vast improvement from standard radiation therapy, they continue to have many limitations as well as adverse effects. Healthy tissue is spared with 3D therapy and IMRT by spreading the dose out over several sites. Sparing one area is thereby accomplished by irradiating other areas of the brain and spine. One example is in the treatment of medulloblastoma, where, to limit the dose to the cochlea with posterior fossa boost radiation, the dose to other normal structures such as the temporal lobes must be increased. Another

disadvantage to these types of therapies is that the radiation dose is still largest at the entry site, which is not necessarily the target site. For the radiation to then exit the patient, the healthy tissues distal to the tumor continue to be irradiated as well (Kirsch & Tarbell, 2004). Although improving the integral dose as compared with standard radiation when studying the actual doses nontarget tissues receive with 3D and IMRT, the numbers continue to be significant. One retrospective study found that 5 Gy of treatment in patients with retinoblastoma using 3D-CRT as compared with IMRT resulted in an integral dose to the orbital bone of 25% and 69%, respectively, both sufficient to cause long-term effects. The same study found that 10 Gy of posterior fossa boost radiation in medulloblastoma patients irradiated 91% of the hypothalamic–pituitary axis with 3D-CRT as compared to 81% with IMRT (Lee et al., 2005). Although this particular study did not compare these treatments to standard radiation, the integral doses were rather significant and sufficient to cause long-term toxicity.

Proton Beam Therapy

In a continuous effort to improve the outcomes of treatment as well as long-term quality of life, current research has spent a great deal of resources in developing proton beam therapy centers and studying the effects of treatment. Proton therapy was first suggested for the use of cancer treatment in 1946 by Robert R. Wilson. Two years later at the Lawrence Berkeley Laboratory the first studies on protons were conducted. Initial human treatment was done on patients with hormone sensitive metastatic breast cancer and consisted of irradiation to destroy the pituitary gland. Results were positive. In addition to this study and much research, the development of the computed tomography (CT) scanner, which allowed for improved tumor definition, was a major innovation. Four decades following Robert Wilson's proposal, the first proton center in the United States was built at Loma Linda University Medical Center in 1990 (Metz, 2006). Since then, 4 other major centers have been built at MD Anderson, Massachusetts General, Indiana University, and the University of Florida. Three other centers are currently underway, including what is slated to become the largest proton beam therapy institution in the world at the University

of Pennsylvania Perelman Center for Advanced Medicine. Proton beam therapy differs greatly from both standard radiation therapy as well as conformal radiation in that it is able to provide precise treatment along with outstanding dose distribution to the site of the tumor (Wilson et al., 2005). One of the greatest challenges with photon therapy is decreasing the radiation to the entry site in order to spare healthy tissue while maintaining sufficient doses to properly target the malignancy. Similarly to conformal radiation, proton beams enter the patient from several sites conforming to the exact shape of the target. Unlike photon therapy, however, with protons the radiation dose is smallest at the site of entry and provides the maximal radiation dose known as the Bragg peak exactly at the site of the target (Kirsch & Tarbell, 2004). The greatest dose of radiation is therefore neither lost at the entry site nor distributed amongst healthy tissue. The remaining energy is absorbed by the tumor leaving no exit site or distal tissue damage (Merchant et al., 2008). Using advanced technology and computer graphics, radiation oncologists are able to place the target site at a specific tissue depth to correlate the Bragg peak with the exact location of the malignancy (Wilson et al., 2005). When used in cranial radiation, healthy brain matter is greatly spared both proximal and distal to the tumor, preserving healthy neurons and cognitive function. With spinal radiation, the lack of an exit site is able to spare distal organs such as the lungs and heart as well as surrounding CNS tissue. In addition, proton beams have more precise borders allowing for minimal lateral scatter.

Benefits of proton therapy lie in sparing healthy tissue, as well as delivering precise and high doses of radiation directly to the tumor. In creating such an exact treatment modality physicians are able to achieve equal or even improved tumor control with significantly less adverse effects. In a study cited above comparing IMRT with 3D-CRT in patients with retinoblastoma target doses resulted in 96% and 95% respective tumor coverage, whereas proton beam therapy was able to cover 100% of the target site. In the same study, when looking at radiation doses to nontarget tissues, 5-Gy treatment resulted in integral doses to the orbit bone of 69% using IMRT and 25% using 3D-CRT. However, when comparing the same dose using proton beam therapy the integral dose to the orbit bone was found to be only 10% (Lee

et al., 2005). By sparing healthy tissue, proton therapy is also estimated to significantly decrease the risk for second malignancies, which currently pose a great threat for patients treated with radiation therapy (Miralbell, Lomax, Cella, & Schneider, 2002). Using a comparative risk assessment, a study by Schneider, Lomax, and Lombriser (2000) estimated the risk of second malignancy following proton radiation therapy at 50% of conventional proton radiation.

Common Malignancies That Benefit From Proton Beam Radiation

Medulloblastoma

One of the more common CNS malignancies, standard risk medulloblastoma, carries long-term control rates more than 50% (Yuh et al., 2004). Regrettably, at diagnosis approximately 20% to 30% of tumors are disseminated throughout the brain and spinal canal. Because of their high risk for spread, these tumors require radiation to the entire neuroaxis, making the greatest challenge in the treatment of these patients a balance between effective treatment and long-term effects (Gibbs et al., 2006). Radiation doses vary between the brain and posterior fossa boost. Although often curative, the combination of high-dose radiation, surgery, and chemotherapy frequently results in significant long-term impairment. Patients commonly experience endocrine dysfunction due to the damage of the hypothalamic–pituitary axis, ototoxicity due to cochlear damage, and cognitive impairment following whole brain irradiation. Additionally, the exit dose with photon therapy results in damage to the heart, lungs, kidneys, and ovaries, thereby creating a high risk for second malignancies (Yuh et al., 2004). Proton therapy is able to decrease the integral dose thereby decreasing the damage to surrounding structures. At the University of Texas, proton therapy was compared with 3D-CRT electrons and 3D-CRT photons. Although this retrospective study calculated similar dose delivery to the target site using all 3 methods, the integral doses were significantly varied. In looking at craniospinal irradiation major structures affected by the treatment of medulloblastoma were studied. When using 35-Gy radiation, with both 3D therapies 100% of the cochlea was irradiated as compared to 16% with proton therapy. In the hypothalamic–pituitary axis 40 Gy resulted in 54%

irradiation with 3D-CRT electrons, 64% with 3D-CRT photons, and only 3% with the use of proton beams (Lee et al. 2005). Similar results were found with other nontarget structures. Because proton therapy does not have an exit dose, structures within the thorax and abdomen, including the heart and liver, may be spared (Miralbell, Lomax, & Russo, 1997). Another study in Loma Linda University demonstrated excellent radiation dose elimination to organs anterior of the spinal cord as well as sparing of the thyroid gland, heart, esophagus, and bowel. Acute short-term effects such as odynophagia, hoarseness, cough, dysphagia, as well as nausea and vomiting, were decreased. Studying the effects of proton therapy on 3 children with medulloblastoma, the study found that in addition to the known benefits of decreased long-term toxicity and decreased acute effects, when using inhomogeneous radiation doses to the vertebrae none of the patients experienced a decrease in their white blood cell count. This indicates a potential sparing effect of the bone marrow (Yuh et al., 2004). For patients receiving high-dose radiation to their entire brain and spinal cord, even mild sparing of critical structures may result in decreased long-term effects. When compared with photon therapy, protons are able to provide a significant difference in the amount of intermediate dose radiation, and a small difference in the amount of low-dose and high-dose radiation delivered to the brain. These differences proved to be sufficient in decreasing the loss of IQ points in patients (Merchant et al., 2008).

Tumors of the Optic Pathway

Tumors of the optic pathway, commonly gliomas, comprise between 1% and 5% of all pediatric gliomas. Although rare, they have a good prognosis for long-term survival with the use of appropriate therapy. Gross total resection is not always possible and when used may cause blindness of the affected eye (Wilson et al., 2005). Radiation therapy combined with chemotherapy is therefore frequently a mainstay of treatment for children older than 5 years of age (Merchant et al., 2008). Although the overall 5-year survival for these patients is 70% to 100% (Massimi, Tufo, & Di Rocco, 2007), a wide variety of adverse effects, including damage to the pituitary gland, endocrine dysfunction, and cognitive delays persist. One study found that by using proton therapy, the integral doses to the contralateral optic nerve chiasm

and pituitary gland were significantly decreased. Additionally, researchers concluded that with larger sized tumors proton therapy was able to achieve more confined tumor markers as well as improved target dosing (Fuss et al., 1999). Another research hospital found that although proton therapy may decrease the dose delivered to the hypothalamic–pituitary axis, it is still sufficiently high to result in growth hormone deficiency. On the other hand, the same study showed that with regard to high-frequency hearing loss associated with radiation therapy, protons provided dose distributions below the necessary 35-Gy threshold (Merchant et al., 2008).

Retinoblastoma

Retinoblastomas comprise the largest and most common group of malignant intraocular tumors in pediatrics. Many of the tumors may be completely removed with enucleation of the affected eye. However, some patients with familial retinoblastoma and a positive RB1 gene experience bilateral disease in which case sparing of the less affected eye is preferred. In these patients, radiation therapy provides an effective treatment alternative. Long-term adverse effects of radiation in these patients have been well documented and include severe facial bone growth abnormalities and lacrimal gland dysfunction (Kirsch & Tarbell, 2004). In addition, patients with familial retinoblastoma have approximately a 25% 50-year risk of second malignancy without the use of radiation. With the use of photon radiation therapy, the risk of secondary malignancies increases to 50% over a period of 50 years (Wong et al., 1997). As discussed earlier, retinoblastomas can have significant improvement in adverse effects with the use of proton beam therapy with increased target coverage as well as decreased integral dosing to the orbit bone and the ipsilateral optic nerve (Lee et al., 2005). Currently, additional studies are underway exploring the full potential of proton beam therapy and the decrease in both long-term effects as well as secondary malignancies (Wilson et al., 2005).

Other CNS Malignancies

Current research supports the idea that many additional pediatric CNS malignancies as well as other forms of cancer may benefit from proton beam therapy. Some examples of tumors in which early studies

suggest a benefit from proton beam include neuroblastoma, ocular melanoma, craniopharyngioma, base of the skull tumors, and low-grade astrocytomas.

Limitations to Proton Beam Therapy

Despite all of the benefits and positive aspects to proton therapy, limitations as well as adverse effects continue to exist. Unfortunately, it is inevitable for some amount of healthy tissue to receive an integral dose even when using the most precise dose distribution criteria. Because many tumors are encased in healthy tissue, in the process of eradicating malignant cells, healthy cells are irradiated as well. Long-term effects are theorized to be significantly decreased with proton therapy; however, they may still be sufficient to affect overall cognition and quality of life. Short-term effects have been proven to be similar with proton therapy as other forms of radiation and skin reactions as well as fatigue have been reported (Brière et al., 2008). Additionally, proton therapy runs a minor risk of neutron contamination during the production process. Unlike protons, neutrons deposit the radiation dose over the entire path of the beam and do not stop at the tumor target site. If contamination occurs, a large area of the brain may be exposed to significant amounts of radiation, unbeknown to the provider. Neutron contamination may therefore lead to a potential risk for radiation-induced tumors as well as other significant adverse effects (Kirsch, 2004). Perhaps the greatest challenge in using proton beam therapy continues to lie in its cost and accessibility. Thousands of adult and pediatric patients may possibly benefit from the use of proton therapy; however, to date only 5 centers exist. The cost of building a proton therapy facility is tremendous and sufficient funding is required to simply begin the process of proposing a new center. Additionally, running a proton beam center costs significantly more than conventional as well as conformal radiation and the cost would be passed on to the patient and their insurance providers.

Implications for Nursing Care

As research continues and an increasing number of centers offer proton beam therapy, many more patients will be able to benefit from this cutting edge technology. With multiple centers conducting simultaneous

studies, many more opportunities for patients to participate in these studies and benefit from proton beams will become available. It is imperative for bedside nurses, clinical nurse specialists, as well as nurse practitioners, to be aware of current research and opportunities for their patients. Nurses involved in all areas of pediatric oncology, especially those working with brain tumor patients undergoing radiation therapy, should be familiar with new treatment options to serve as a resource and an advocate. An increasing number of patients will require help navigating the system as more options for treatment and studies become available. Patients and families frequently look to their nurses for answers and guidance to make better, more informed decisions. Because this technology is still relatively new, proton beams may have side effects that have not yet been reported and clinical nurses will need to be aware of the novelty of this treatment in order to be vigilant in monitoring for possible new adverse effects as well as educating their patients.

Conclusion

The future of pediatric cancers, and subsequently CNS malignancies, continues to look brighter as more treatment options, surgical advancement and research become available. Although current science has been able to drastically improve survival rates for these patients, additional resources are necessary to ensure the highest probability of cure with the least number of long-term adverse effects. Proton beam therapy is a newer alternative to standard radiation treatment and to date has shown promising results in the treatment of pediatric malignancies. By decreasing the integral dose to healthy tissues as well as precisely targeting the tumor site, patients may be able to achieve greater possibility of cure with less long-term effects. Preserving a child's intelligence, growth, and healthy organs must continue to be a chief priority when deciding on the best treatment options presented to each patient. As further research becomes available and additional centers are opened, the true capabilities and limitations of proton beam therapy will become more evident.

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