Photons or Protons for Non-Central Nervous System Solid Malignancies in Children: A Historical Perspective and Important Highlights

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OVERVIEW

Over the years, major advances have occurred in radiotherapy techniques, delivery, and treatment planning. Although radiotherapy is an integral treatment component of pediatric solid tumors, it is associated with potential acute and long-term untoward effects and risk of secondary malignancy particularly in growing children. Two major advances in external beam radiotherapy are intensity-modulated radiotherapy (IMRT) and proton beam radiotherapy. Their use in the treatment of children with cancer has been steadily increasing. IMRT uses multiple modulated radiation fields that enhance the conformality of the dose distribution to the target volume and avoid high doses to normal tissues. However, IMRT may be associated with increased volume of normal tissue that receives low doses and potential risk of secondary malignancy. Contrary to IMRT, proton beam radiotherapy uses a few beams and a fast dose fall-off distal to the target volume. Although both modalities require substantial personnel time and effort, the very high cost and limited availability of proton radiotherapy have constrained its widespread use. It is anticipated that both modalities may markedly improve tumor control and quality of life for long-term cancer survivors. Clinical trials with long-term follow-up are needed to confirm the premise that proton beam therapy will decrease late effects and secondary malignancies without compromising local control in pediatric patients with cancer.

Most pediatric solid tumor malignancies are treated with multimodality treatment including surgery, chemotherapy, and radiation therapy. Solid tumor malignancies outside the nervous system that are considered radiation-sensitive tumors include neuroblastoma, Wilms’ tumor, soft tissue sarcoma, and Ewing sarcoma. Although radiotherapy is an integral component of therapy for local tumor control, it is associated with potential acute and long-term untoward effects that can be problematic in children because of their developing organs and tissues. Radiation has been associated with increased risk of late mortality, development of second neoplasms, endocrine insufficiencies, organ dysfunction, growth abnormalities, and chronic health conditions.1-4 A recent report by the Children’s Oncology Group Radiation Oncology Discipline Committee highlighted some of the success areas and strategies being investigated to refine the role of radiation therapy and reduce complications in children with cancer.5 These strategies include (1) reduction of the prescribed radiation dose, (2) decreasing normal tissue exposure to radiation by reducing the margins of radiation therapy target volumes, (3) limiting the target volume to the postchemotherapy target volume when appropriate, (4) use of radiosensitizing chemotherapy, and (5) tailoring radiotherapy for individual tumor sites. Over the years, there have been major advances in radiation techniques, delivery, and treatment planning; perhaps the most significant recent ones are the use of IMRT and intensity-modulated proton radiotherapy. As the use of these two radiotherapy modalities has increased, questions have arisen as to which modality would be most appropriate to use for different patient case scenarios. Here we present a historic perspective on developments in radiation therapy and a summary of important aspects related to the use of photons versus protons in children with solid tumor malignancies arising outside the central nervous system.

HISTORIC PERSPECTIVE

X-rays were initially discovered by Wilhelm Röntgen in 1895, and within a year X-ray technology was applied to visualize fractures. Nobel Laureates Pierre and Marie Sklodowska Curie discovered radium, a naturally occurring radioactive element, in 1898. The first report of cancer treatment with radium was issued the next year. Unfortunately, Marie Curie died of aplastic anemia thought to be related to her radiation exposure. Notably, her daughter Irene Joliot Curie, Nobelist
for radiochemical research, died of a possibly radiation-induced leukemia.6

Modern clinical radiation therapy most commonly uses external beam delivery techniques with X-ray (photon) or electron fields. X-rays and electrons are forms of ionizing radiation which release energy and deliver radiation dose to the patient’s body. The standard unit of radiation dose is Gray (Gy) that was named after L.H. Gray, the British radiobiologist.7 In general, a patient treatment consists of multiple treatment fields that enter the patient from various strategic angles that are directed at the target area containing the tumor. Treatment planning is accomplished with the use of specialized computer algorithms that can calculate the radiation dose based on CT. MRI or other imaging information can be used, as needed, for tumor volume or normal tissue delineation. Computerized radiotherapy planning was initially reported more than 50 years ago. Three dimensional conformal radiotherapy (3DCRT) planning was first used clinically in 1978 with the introduction of the beam’s eye view (BEV) display. This display provides a view of the rays from the radiation source down to the anatomic structures and allows selection of beam orientations that optimizes tumor coverage while reducing normal tissue irradiation. The introduction of computerized scanning and its use in radiotherapy planning markedly improved the way patient anatomy can be specified in treatment planning.8,9 This technique takes patient anatomy dose restrictions and goals, as determined by the radiation oncologist, into consideration for computing the dose inside the patient. Between 1986 and 1989, 3DCRT planning systems started to be implemented,10-13 and their subsequent commercial availability led to the widespread use of three dimensional treatment planning in the clinic.14 Although the early IMRT concepts were developed several decades ago, it was not until the early 1990s that the delivery systems for modern IMRT began to become available.14

Protons are positively charged subatomic nuclear particles that were identified by Nobel Laureate Ernest Rutherford (1871–1937) in 1917.15 Interestingly, in 1904 William Henry Bragg (1862–1942, Nobel prize winner 1915), through his studies of alpha particles emitted from radium, described the Bragg peak, which is the characteristic profile of the sharp energy deposition of all charged particles.16 In the 1930s, particle accelerators were refined, and further studies of particle beam and energy deposition took place. It was recognized early on that there was a potential benefit of charged particle radiation because the lack of an exit dose distal to the target volume because of the Bragg peak. This property is the fundamental difference between proton and photon irradiation. Because the Bragg peak was not clinically useful as a result of the extreme sharpness, technologies were developed to create a spread out Bragg peak allowing a clinically useful energy deposition (Fig. 1).

In 1946, Robert R. Wilson suggested that proton therapy could be an effective therapy for patients with cancer. The first patients were treated at the Lawrence Berkeley Laboratory, California, in 1954 and Uppsala, Sweden in 1957. Between 1961 and 2002, over 9,000 patients were treated with proton therapy at the Harvard Cyclotron Laboratory, Massachusetts. Because of the technological infrastructure required for the accelerators, much of the early work was restricted to physics research facilities. In 1990, the first hospital-based proton facility was established at Loma Linda Medical Center in California.17 Since then, with technological advances and smaller accelerators, more hospital-based systems have been developed. Computer based planning technologies and 3DCRT approaches were used consistently throughout this time. Currently, there are 10 functioning proton centers in

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**KEY POINTS**

- The fundamental difference between intensity-modulated radiation therapy (IMRT) and proton radiotherapy is a result of the characteristics of the X-ray/tissue and proton/tissue atomic interactions.
- Both IMRT and proton radiotherapy offer substantial advantages in terms of radiation delivery precision and improved tumor control.
- Proton radiation therapy is considered the state-of-the-art technique for achieving precise dose localization in a tumor and reducing normal tissue irradiation.
- The excellent dose distributions and benefit of no exit dose make proton beam radiotherapy an excellent choice for the treatment of tumors located next to critical structures and for pediatric malignancies.
- Clinical trials with long-term follow-up are needed to confirm the premise that proton beam therapy will decrease late effects and secondary malignancies without compromising local control.
the United States with at least five others in development. Internationally, particle therapy centers using proton or carbon ions are being developed in many different countries.

Advances in radiation therapy include the use of a modern linear accelerator with enhanced capabilities such as daily imaging, high dose rate, multileaf collimation, electronic record and verification systems, and very high mechanical precision allowing complete control of the delivery of the radiation dose to the patient. Three dimensional imaging is fundamental for modern radiotherapy treatment planning. Imaging techniques such as magnetic resonance imaging and PET-computed tomography improve the definition of volumes of interest in the patient (tumor, positive nodes, and organs at risk). Image-guided radiotherapy and four dimensional planning have allowed incorporation of patient and organ motion in the treatment planning and delivery.

Both IMRT and proton therapy include advances in treatment planning and delivery approaches that are mentioned above. The fundamental difference between these two modalities is a result of the characteristics of the X-ray/tissue and proton/tissue atomic interactions.

BIOLIGIC AND CLINICAL CONSIDERATIONS
Radiation induces damage to the DNA in tumor cells causing unrepaired or misrepaired double-strand breaks, which lead to cell killing.7 Tumor response to radiation depends on the sensitivity of the tumor to radiation, its oxygen status, and the position of tumor cells in the cell cycle and their capacity to repair radiation damage and to repopulate. Radiotherapy is delivered in multiple fractions given on a daily basis. The daily fraction size and number of fractions vary according to the clinical need. The use of fractionation improves the therapeutic index with a reduction of normal tissue toxicities as a result of the repair of sublethal damage that occurs between fractions. The typical daily fraction size for pediatric malignancies is 1.8 – 2.0 Gy per day given 5 days a week. The relationship between radiation dose and probability of tumor control displays a sigmoidal dose response curve. Parameters that can be varied during a course of treatment include the volume irradiated, the total dose, the fraction dose, and the dose rate used at each treatment session. The total dose required for tumor control is largely dependent on the number of tumor cells present, the type of the tumor, and fractionation. Whereas 10.8 Gy given in six fractions will provide excellent control in favorable histology Wilms’ tumor, doses of greater than 50 Gy given in more than 25 fractions are required for sarcomas.19-21 The reasons(s) for the disparity in tumor response to radiotherapy among the different cancer types remain unclear.

Most pediatric cancer regimens incorporate the use of chemotherapy and radiation either sequentially or concurrently. Certain chemotherapeutic agents can potentiate the radiation effect on the tumor and may be used as radiosensitizers; however, strong radiosensitizers such as dactinomycin and doxorubicin are usually given at the start of radiotherapy and omitted during radiotherapy to avoid severe toxicity to normal tissue. In addition, they can cause radiation recall with recurrence of prior radiation reaction even when given 3 weeks after radiation therapy. Cisplatinum and carboplatin may also act as radiosensitizers.

The treatment of childhood cancer presents several challenges that may be particularly addressed by the concepts of 3DCRT. It is common for pediatric solid tumors to have large, irregular volumes close to critical normal structures. The acquisition of detailed CT images at the time of simulation, along with the use of three-dimensional reconstruction and BEV capabilities, have greatly improved tumor targeting and allowed more selective blocking of normal structures.22 In addition, compared with adults, children have a longer anticipated life span and an increased sensitivity of their developing organs and tissues to radiation which puts them at higher risk of late effects and secondary malignancy. The use of CRT offers promise to provide high rates of local tumor control with low rates of late effects, such as impairment of growth and development and injury to organ function. The ability to use novel beam arrangements and to evaluate radiotherapy treatment plans with quantitative tools, such as dose-volume histogram analysis or probabilities of normal tissue complications, should enable the use of treatment programs with a lessened risk of late effects.22

### TABLE 1. Comparison of IMRT to Proton Radiotherapy

<table>
<thead>
<tr>
<th>Feature</th>
<th>IMRT</th>
<th>Proton Therapy</th>
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<tbody>
<tr>
<td>Radiation source</td>
<td>Photons</td>
<td>Protons</td>
</tr>
<tr>
<td>Radiation fields</td>
<td>Multiple</td>
<td>Few</td>
</tr>
<tr>
<td>Dose distribution</td>
<td>Low dose to normal tissue</td>
<td>Limited to tumor</td>
</tr>
<tr>
<td>Scatter</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Availability</td>
<td>Widely available</td>
<td>Limited to selected centers</td>
</tr>
<tr>
<td>Personnel time and effort</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Cost</td>
<td>High</td>
<td>Very high</td>
</tr>
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INTENSITY-MODULATED RADIATION THERAPY
The introduction of IMRT is a fundamental development in radiation oncology. IMRT uses multiple modulated radiation fields resulting in enhanced conformality of the dose distribution to the target volume when compared with conventional photon radiotherapy. The ability to modulate or control the radiation intensity and dose within each beam over the field area allows improved control of the actual dose delivered to the patient. Treatment planning uses computer-based algorithms that take into account the geometric shape and location of the target volume and other critical structures as well as the doses to each structure. IMRT requires the use of 3DCRT planning capabilities, such as defining target volumes and organs at risk in three dimensions by drawing contours on cross-sectional images (i.e., CT, MRI) on a slice-by-slice basis as opposed to drawing beam portals on a simulator radiograph.14 IMRT can reduce the radiation dose to normal
tissues and create concave dose distributions to reduce the dose to a critical structure that indents the target volume. IMRT offers substantial advantages in terms of radiation delivery precision and improved tumor control, but its highly complex techniques increased the time and effort required by the radiation oncologists, medical physicists, and radiation therapists.

The IMRT Collaborative Working Group formed by the National Cancer Institute published its consensus guidelines and recommendations for implementation of IMRT and for further research in 2001. The group highlighted the need for research to facilitate the implementation of IMRT and to model the clinical outcomes to allow truly automated solutions, to improve the IMRT delivery systems, and to establish instrumentation and methods for IMRT quality assurance procedures and testing. They concluded that IMRT has significant potential for improving the therapeutic ratio and reducing toxicity, and that its full development should improve the overall efficiency of the planning and delivery of external beam radiotherapy and potentially lower costs of radiotherapy.

A recent Children’s Oncology Group study found that highly conformal, IMRT provided local control equivalent to that of 3DCRT in rhabdomyosarcoma. A review of published data by Palm and Johansson found that compared with conventional radiotherapy, IMRT improves the dose distribution in the target volume, which may increase the probability of tumor control. In addition, IMRT could increase the out-of-field low dose distribution and the irradiated non-target volume, leading to a potentially increased risk of radiation-induced secondary malignancy, while decreasing the dose to normal tissues close to the target volume and reducing the normal tissue complication probability. This issue should be considered particularly in children who are more susceptible than adults to effects of any dose of irradiation and have relatively long life expectancy.

**PROTON RADIATION THERAPY**

Proton radiation therapy is considered the state-of-the-art technique for achieving precise dose localization in a tumor and reducing normal tissue irradiation. Protons are charged particles that damage the DNA of cells, ultimately causing their death. Their biologic effects in tissue are comparable to those of high-energy X-rays used in conventional radiation therapy. However, protons have a very rapid energy loss in the last few millimeters of penetration, which results in a sharply localized peak of dose, or the Bragg peak. Contrary to IMRT, proton beam radiotherapy uses a few beams and a fast dose fall-off distal to the target volume. Because of the defined range of protons, dose distributions can be designed that conform more closely to a tumor volume. This advantage results in a much greater ability to reduce radiation dose to nontarget normal tissues and allows greater dose to be delivered to the tumor. The excellent dose distributions and benefit of no exit dose make proton beam radiotherapy an excellent choice for the treatment of tumors located next to critical structures such as the spinal cord, eyes, and brain, as well as for pediatric malignancies. Its effectiveness was initially demonstrated in patients with uveal melanoma and other eye lesions, and chondrosarcoma and chordomas of the skull base. Because of the high capital required to establish a proton treatment facility, this modality is available only at selected institutions. Currently, all 10 active proton centers in the United States provide proton beam radiotherapy for children, but it is anticipated that the number of

FIG 2. Comparison of radiation therapy dose distribution between proton radiation (left panel) and intensity-modulated radiotherapy (right panel) in a patient with a retroperitoneal Ewing sarcoma.
facilities and the number of patients treated with this technology will increase.

Proton radiotherapy is an emerging modality that holds great promise to reduce the treatment-related late effects in long-term survivors by sparing dose to normal tissues. Dosemetric studies of proton radiotherapy compared with best available photon-based treatment show significant dose sparing to developing normal tissues.26,27 Furthermore, clinical data are now emerging that begin to quantify the benefit in decreased late treatment effects while maintaining excellent cancer control rates.28 Various techniques of 3DCRT, electrons, IMRT, and proton therapy including IMPT, are useful in the treatment of many pediatric tumors. Proton therapy has been found to be useful treating retinoblastomas, medulloblastomas (craniospinal and the tumor bed boost), and pelvic sarcomas. Protons deliver superior target dose coverage and sparing of normal structures. Because dose-volume parameters are expected to correlate with acute and late toxicity, proton therapy should receive serious consideration as the preferred technique for the treatment of pediatric tumors.26 The review by Palm and Johansson found that protons show no or only minor advantage on the dose distribution in the target volume and the conformity index compared with IMRT.18 However, proton beam therapy substantially decreases the organs at risk average dose compared with conventional radiotherapy and IMRT because of the reduction of the volume of mid and low dose irradiation. It is also clear that protons provide an improved dose distribution in non-target tissues compared with the other two techniques.18 As shown in Fig. 2, proton beam radiation and IMRT allow delivery of a highly conformal dose to a target with notable differences in radiation dose to normal tissue. In children with Ewing sarcoma, neuroblastoma, and rhabdomyosarcoma, proton therapy showed encouraging preliminary outcomes in terms of local control, adverse events, and normal tissue sparing.27,29,30

CONCLUSION

The use of IMRT and proton beam radiotherapy to treat children with cancer is increasing. It is anticipated that both modalities may markedly improve tumor control and quality of life for long-term cancer survivors.18 Comparative studies and clinical trials with long-term follow-up are needed to confirm the premise that proton beam therapy will decrease late effects and secondary malignancies without compromising local control in pediatric patients with cancer. The rarity of pediatric cancer presents a major challenge for the conduct of such trials. The Quality Assurance Review Center (www.qarc.org) can be instrumental in facilitating cooperative group research and providing radiotherapy quality assurance to ensure the validity of data across multidisciplinary cooperative group trials. The future for radiation therapy is promising with further advancement in radiation delivery techniques and refinement of dosimetry and treatment planning. It is expected that such advancements would help alleviate radiotherapy late effects and possibly avoid the need for very morbid and disfiguring surgeries.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.


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