The expanded future of pediatric radiation oncology

Sarah S. Donaldson

The new technologies in oncologic imaging and radiation therapy are designed to improve local-regional control, reduce treatment related morbidity, and are expected to bring about higher cure rates with improved quality of life. While these enhancements in tumor localization and radiation delivery are not age specific, they offer significant advantages to children and adolescents in whom early local tumor control is critical, and in whom late effects of cancer therapy can be severe.

Local failure accounts for the primary obstacle to cure in children with primary central nervous system tumors, intraocular tumors, bone and soft tissue sarcomas, and many other solid tumors (1,2). Radiation therapy is an effective modality to achieving local control, but high radiation doses to large treatment volumes, as delivered in the past, have been associated with significant late effects which, for some, have limited its effective use. The late effects of cancer therapy, as given several decades ago, are now being recognized. They include: impairment of soft tissue and bone growth; organ dysfunction including cardiac, pulmonary, gastro-intestinal, and renal; gonadal effects with potential infertility; endocrine sequelae; hearing and/or visual dysfunction; neuro-cognitive effects; psychosocial issues, and the induction of second tumors. Among these, secondary carcinogenesis and potential organ dysfunction are some of the most severe of the late effects from radiation therapy. The Childhood Cancer Survivor Study (CCSS) now has data from children who are at least 5-year survivors of their malignant disease, which report an approximate 5% cumulative incidence of second and subsequent cancers at 25 years following the diagnosis of the first cancer, and this incidence continues to rise. The large majority of these second malignancies occur in patients who received radiation as curative treatment for their first malignancy, with an approximate 6.6% cumulative incidence for those irradiated, as compared to an approximately 3.8% cumulative incidence for those non-irradiated, at 25 year follow-up (3,4). Among these secondary malignancies, breast cancer in Hodgkin’s disease and sarcoma survivors is most prevalent (5). In the CCSS study of long term survivors, girls receiving chest radiation for treatment of Hodgkin’s disease had a standardized incidence ratio (SIR) or relative risk of 26.3 of developing breast cancer. In addition, there is a dose related incidence of central nervous system glioma and meningioma after the diagnosis of a first brain tumor (6). The dose-response for the excess relative risk (ERR) of a brain tumor is estimated to be 0.33/Gy for glioma and 1.06/Gy for meningioma. For glioma, the ERR/Gy is highest among those exposed at ages under 5 years. The excess of glioma and meningioma is concentrated among children with leukemia or CNS cancer as their initial cancer. The standardized incidence ratio (SIR) for glioma is 8.7 overall, and the excess absolute risk (EAR) is 19.3 per 10,000 persons per year. The higher risk of subsequent glioma in children irradiated at a very young age may reflect greater susceptibility of the developing brain. However secondary thyroid cancers are not dose related beyond approximately 10 Gy. There is a linear relationship from about 0.05Gy to 0.1 Gy to 5Gy to 10 Gy, with an ERR of 7.7/Gy in thyroid cancer. The EAR is 4-5 thyroid cancers per 10,000 persons per year per Gy. (7). Organ dysfunction is also being recognized, but here the contribution from radiation is often difficult to separate from that of chemotherapy. It is important to remember that the serious late effects data, which impact all current treatment decisions, are reported among the cohort of children who were effectively treated for their first malignancy, often times with radiation, and who have survived long enough to suffer another
malignancy. These data usually do not account for genetic influences in carcinogenesis, an increasingly important predisposing factor for all (8, 9).

Standard of care today using radiation therapy for children and adolescents includes risk-adapted protocols, which recommend 3-dimensional conformal techniques when treating with curative intent (10). This therapy provides greatly improved radiation distribution over treatments of the past decades. Improved tumor localization and image acquisition using PET/CT as well as MR/CT fusion into treatment planning systems facilitate the planning and delivery of radiation. Cone beam CT and fluoroscopic imaging assist the verification and accuracy of these complex multi-dimensional systems. In select tumors, biologic and molecular imaging and treatment hold additional promise, and may be incorporated into specific treatment protocols.

Many centers are further investigating the use of very highly conformal radiation beams for specific anatomic sites such as delivered by intensity modulated radiation therapy (IMRT), stereotactic radiosurgery (SRS) and stereotactic radiation therapy (SRT), frame based or frameless (11-13). Brachytherapy for specific malignancies and anatomic sites has demonstrated utility in children and adolescents (14). Intraoperative radiation therapy (IORT) is useful in select situations (15-17). Targeted therapy with a bone-seeking radiopharmaceutical such as samarium-153 is being investigated in the treatment of osteosarcoma and bone metastases, and may have usefulness if the pancytopenia can be addressed with stem cell infusion (18-19). Image guided radiotherapy (IGRT) using 4-dimensional radiation therapy, respiratory gaiting, on-board imaging and tumor tracking, accounting for organ motion during treatment, is now being pioneered for specialized anatomic sites. Conformal proton beams and intensity modulated proton beams are planned in a few centers and are hoped to further enhance dose distribution, particularly for children with solid tumors (20-22). It is hoped that these highly conformal treatment fields will reduced late effects, specifically radiation-induced second cancers (23).

These new treatment techniques offer enormous potential for children and adolescents in whom the avoidance of normal tissue toxicity is an essential endpoint. However, they require close interaction between radiation oncologist, physicist, and biologist for complex technologic advances and biologic endpoints. These new technologies and research advances, being made in large cancer centers, currently apply to a disappointingly small number of children afflicted with malignant disease. From a global perspective, the number of children worldwide who will profit from these highly specialized technical advances will be just a small fraction of the world’s pediatric cancer problem. Nevertheless, these advances are an essential research step, as new technology offering improvement for a small proportion of children will advance the biology, physics, clinical research and patient care for all children with malignancy. During the past year reports have been published which demonstrate that in countries with limited, even very limited resources, more children with cancer have been cured than previously (24-25). However access to radiation therapy is very limited for the majority of children. In many countries, it is only in private institutions where one has access to radiotherapy, and it is limited to those who can afford the treatment. It has been estimated that <1% of all children who might benefit from radiation therapy actually receive this therapy. So, there are several issues of concern: one is limited availability world wide, and another is limited access even in developed countries. If even a few children with non-resectable, chemotherapy resistant, solid tumors can be effectively treated by these new treatment techniques, we will see further increases in the total numbers of children who will be cured of their cancer. However, the ultimate value of new technology in radiation therapy will require controlled clinical trials and cost effective analyses to define its use and applicability.

The possibility of cure without late effects is now a probability for those children and adolescents undergoing treatment with radiation. The vision of the expanded future for pediatric cancer confirms that never before has there been a more exciting time for pediatric radiation oncology than the present.
References


