Strategies to Overcome Late Complications from Radiotherapy for Childhood Head and Neck Cancers

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KEYWORDS

• Radiotherapy • Intensity-modulated radiotherapy • Proton therapy • Radiation-induced neoplasms • Image-guided radiotherapy

KEY POINTS

- Radiotherapy is administered with increasing frequency given the increasing rates of pediatric head and neck cancer and improved long-term survival rates.
- Long-term radiation morbidities include abnormal tooth development and decay, bone and soft tissue hypoplasia, hypopituitarism, and damage to visual and auditory organs.
- Radiation increases the risk of second malignancies, which are associated with adverse outcomes.
- Approaches have been developed to reduce the risk of late radiation toxicities, including improvements in the delivery of radiation that more precisely targets tumors and that uses newer technologies, including proton beam therapy and image-guided radiotherapy.

INTRODUCTION: THE PROBLEM OF RADIATION MORBIDITIES IN CHILDREN

Even though pediatric cancer is the second leading cause of death in children aged 5 to 14 years,[1] the 5-year overall survival for childhood cancers has increased to 83% for patients diagnosed from 2003 to 2009 compared with 56% for those diagnosed from 1974 to 1976.[2,3] Of the children surviving 5 years or more, approximately 80% were treated with radiotherapy.[4] Furthermore, radiotherapy for head and neck pediatric cancers is becoming increasingly common, as shown by an analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER). This analysis showed that the incidence of pediatric head and neck cancers (overall 12% of all pediatric cancers) was increasing faster than pediatric cancers overall.[5] For cancers involving the head and neck area, the most common pathologic types include lymphomas (Hodgkin lymphoma and non-Hodgkin lymphoma); neural tumors (neuroblastoma and retinoblastoma); and soft tissue sarcomas, including rhabdomyosarcomas.[5]

Because various types of pediatric cancers can arise in the head and neck region, radiation treatments vary widely based on the histologic type and site of disease. Specific cancer types are treated with different radiation doses, and the

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intensity of the dose is a major determinant of long-term treatment-related morbidities. Radiation doses are prescribed in units of Gray (Gy), which denotes the amount of energy that is absorbed per unit mass in the radiated tissue. Radiation doses tend to be low (usually <15 Gy) for patients with leukemia receiving total body irradiation (TBI) in preparation for stem cell transplantation. Likewise, doses tend to be low (generally 20–40 Gy) in lymphomas and neuroblastomas, which require localized radiotherapy to specific disease sites. Nonetheless, these patients are at risk for developing hypopituitarism, cataracts, and secondary cancers. By contrast, soft tissue sarcomas and other solid tumors, such as squamous cell carcinomas, require considerably higher radiation doses of 50 Gy or more. In these cases, patients are at risk for dental damage, bone hypoplasia, and hearing and vision toxicities.

Given these risks, this article reviews approaches to minimize the toxicities from pediatric head and neck radiotherapy. The first part of this article discusses current and emerging approaches to minimize radiation-induced toxicities. The second part discusses the long-term morbidities from radiation therapy, specifically addressing the recent advances that minimize these risks of head and neck radiotherapy in children.

THERAPEUTIC OPTIONS TO MINIMIZE RADIATION MORBIDITIES

Several groups have sought to reduce the risks of late radiation morbidities by using modalities such as proton beam radiotherapy (PBR) and intensity-modulated radiotherapy (IMRT). Compared with conventional radiotherapy, these modalities offer the potential to deliver radiation plans that better conform to the targeted tumor. Image-guidance techniques ensure more reproducible delivery of radiation plans. In addition, medical approaches such as radiation protectors and mitigators may help to minimize radiation toxicities. These approaches to avoid radiation toxicities in pediatric patients with cancer are detailed later.

Overview of Radiation Therapy and Planning

The radiation therapy planning process begins by defining the tumor target and susceptible normal tissues. The process then involves arranging the radiation beams such that they cover target tissues while minimizing exposure to the adjacent normal organs. Radiation therapy planning begins with a process called simulation, which uses computed tomography (CT) to image the patient and tumor. Secondary imaging studies including MRI and PET scans are aligned with the treatment-planning CT in order to delineate the tumor target, which is termed gross tumor volume (GTV; see red outline, **Fig. 1**). Additional margins are included to account for microscopic tumor spread, resulting in an expanded structure termed the clinical target volume (CTV). An additional volumetric expansion is added to account for daily variations in tumor motion and in patient positioning, which is termed the planning target volume (PTV; magenta outline **Fig. 2**). The physician then works with dosimetrists and medical physicists to develop an optimal radiation delivery plan, optimally covering the tumor target and minimizing dose to the normal organs (see **Fig. 2**). The resulting plan is used to deliver a prescribed radiation dose.

Radiation Modalities: Protons Versus Photons

Pediatric cancers have been treated with photon-based radiotherapy using three-dimensional (3D) conformal radiotherapy (3D-CRT) or IMRT and, more recently, with proton-based therapy. Photon radiotherapy likely provides more skin sparing compared with traditional proton beams. By contrast, proton therapy probably provides more

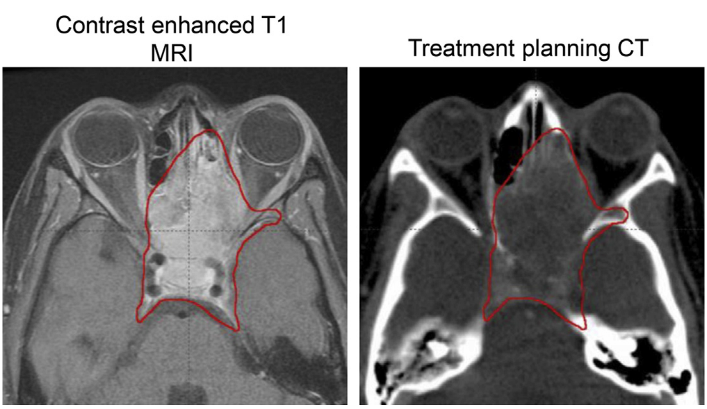

Fig. 1. Radiation therapy planning to define radiation therapy targets. A pediatric patient with a parameningeal rhabdomyosarcoma and brain invasion underwent radiation therapy simulation consisting of treatment-planning CT. The contrast enhanced MRI was fused to the treatment-planning CT. The GTV is delineated in the red outline using both the MRI and treatment-planning CT images.