Published in final edited form as:

Pediatr Blood Cancer. 2013 June ; 60(6): 1037–1043. doi:10.1002/pbc.24425.

Children's Oncology Group's 2013 Blueprint for Research: Radiation Oncology

Thomas E. Merchant, DO, PhD^{1,*}, David Hodgson, MD, MPH², Nadia N.I. Laack, MD, MS³, Suzanne Wolden, MD⁴, Danny J. Indelicato, MD⁵, and John A. Kalapurakal, MD⁶ on behalf of the COG Radiation Oncology Discipline Committee

¹St. Jude Children's Research Hospital, Memphis, Tennessee

²University of Toronto, Toronto, Ontario, Canada

³Mayo Clinic, Rochester, Minnesota

⁴Memorial Sloan-Kettering Cancer Center, New York, New York

⁵University of Florida, Jacksonville, Florida

⁶Northwestern University Feinberg School of Medicine, Chicago, Illinois

Abstract

Radiation therapy (RT) is used to treat children with CNS tumors, solid tumors or Hodgkin lymphoma. Pediatric radiation oncologists have provided critical input into the development and implementation of concepts for clinical trials to further define the modality's role and test newer methods to reduce side effects or intensify therapy. The quality of pediatric oncology clinical trials that include radiation therapy is linked to the quality of guidelines. Radiation oncology is an adult medical specialty; thus, pediatric radiation oncologists are uniquely positioned to work with adult cancer investigators in the reorganized US National Cancer Institute Clinic Trials Network.

Keywords

pediatric radiation oncologists; radiation oncology; radiotherapy

INTRODUCTION

Radiation oncology is integral to the design and conduct of clinical trials that include radiation therapy (RT) for children with cancer. Indications for and parameters of therapeutic irradiation are commonly primary objectives in pediatric clinical trials. Primary and secondary objectives often include the assessment of tumor and normal tissue responses. Clinical trial designs generally include one or more hypotheses that address the following radiation oncology tenets: (1) reduce the RT target volume to decrease side effects without affecting the rate of local tumor control or pattern of failure. (2) Concurrently administer

*Correspondence to: Dr. Thomas E. Merchant, DO, PhD, Division Chief, Radiation Oncology; Member, Department of Radiological Sciences, MS 220, St. Jude Children's Research Hospital, 262 Danny, Thomas Place, Memphis, TN 38105. thomas.merchant@stjude.org.

chemotherapy and RT to improve disease control with acceptable treatment-related toxicity in patients with high-risk malignancies. (3) Individualize the treatment of children with specific malignancies on the basis of prior trial results and prognostic factors to include or eliminate RT or reduce radiation doses. (4) The distribution of radiation dose to an at-risk organ will correlate with that organ's functional outcome.

In North America there are more than 250 treatment centers and 300 radiation oncologists who participate in clinical trials that include children. It is estimated that more than 1,500 children are treated annually at these centers using advanced methods of irradiation and supportive guidelines. Integration of centers that deliver radiation therapy to children requires specialized support. The Quality Assurance Review Center (QARC, www.qarc.org), the Radiological Physics Center (RPC, <http://rpc.mdanderson.org/RPC/home.htm>), and investigators within the radiation research program of the US National Cancer Institute support North American pediatric clinical oncology trials. Because RT has an established track record in the successful treatment of children with cancer, the quality of pediatric oncology clinical trials is linked to RT guidelines. Areas of recent success include reducing complications and refining the role of RT in the treatment of younger children, improving RT guidelines to implement new methods group-wide, completing the first generation of clinical trials using conformal RT and intensity-modulated RT for CNS and musculoskeletal tumors, and implementing the same approaches for solid tumors and lymphomas.

KEY INITIATIVES AND HYPOTHESES

With the advent of conformal radiation planning and delivery and an increased understanding that the side effects of RT limit the therapeutic ratio of many treatment regimens, reducing the target volume for RT has been a primary aim of pediatric clinical trials. The expectation is that newer methods of irradiation will decrease side effects without affecting the rate of local control or the pattern of failure.

Completed studies of Ewing sarcoma have demonstrated improvement in disease control with the use of ifosfamide and etoposide and dose-intense chemotherapy [1, 2]. Because improvement in event-free survival (EFS) and overall survival (OS) were mostly attributed to improved local control, it is now hypothesized that contemporary chemotherapy regimens will enable radiation oncologists to reduce the margins of RT target volumes. AEWS1031 is the current Children's Oncology Group (COG) study of localized Ewing sarcoma. The clinical target volume margin for this trial is 1.0 cm, compared to 1.5–2.0 cm on prior trials. Reducing the radiation dose to normal tissues is further advanced in this trial for patients with microscopic positive margins who require adjuvant RT: the target volume will be limited to the post-chemotherapy target volume, rather than the larger pre-chemotherapy target volume in patients with good pathologic response (>90% necrosis). With improved imaging, treatment planning, and immobilization and verification, radiation oncologists have significantly decreased clinical target volume margins across soft-tissue sarcoma protocols from 2.0 to 1.3–1.5 cm in the current generation of cooperative group studies. Reductions in target volume margins are carefully evaluated by comparing local tumor control of current

trials with results from past trials, with consideration of further reductions in future studies, as image-guided RT becomes standard of care for children [3, 4].

New guidelines for the treatment of pediatric CNS tumors, solid tumors, and Hodgkin lymphoma are anticipated based on the results obtained from recently completed studies (Table I). The advancement of three-dimensional (3D) treatment planning and access to electronic data have positioned pediatric radiation oncology investigators, such as those participating in the COG, to compare outcomes across treatment eras, as shown in a recent publication in which highly conformal, intensity-modulated RT provided local control equivalent to that of three-dimensional conformal RT in rhabdomyosarcoma [5].

Administering chemotherapy concurrently with RT is not a new concept. However, in some clinical settings and with pediatric patients, combined-modality therapy has not been approached because of the risk of complications, both acute and long-term. Exploiting improvements in the environment of care and the concepts of target-volume reduction and highly conformal methods of irradiation, radiation oncology investigators believe that concurrently administered chemotherapy and RT may improve disease control with acceptable treatment-related toxicity in patients with high-risk malignancies.

Studies of Ewing sarcoma in which combined-modality treatment was used have shown excellent local control of more than 90% at 5 years [6]. Current intermediate-risk and completed high-risk rhabdomyosarcoma protocols have studied intensification of therapy using a combined-modality approach with radiosensitizing chemotherapy. The high-risk rhabdomyosarcoma study, ARST0431, was designed to determine the feasibility and immediate and short-term side effects of concurrent irinotecan and RT, whereas the intermediate-risk study, ARST0531, seeks to intensify therapy by including the sensitizer irinotecan and moving RT to earlier in the treatment regimen. This change in sequencing was made based on the finding that a small proportion of patients had early disease progression on chemotherapy [7]. There are sufficient data from prior Intergroup Rhabdomyosarcoma Group trials to demonstrate the advantage of early RT in this group of patients. Other examples include the aims of the completed soft-tissue sarcoma trial, ARST0332, which included neoadjuvant combined-modality therapy consisting of RT and chemotherapy for patients with eligible soft-tissue sarcoma, in an effort to improve the extent of surgical resection, local control, and OS. The current high-risk medulloblastoma study, ACNS0332, includes immediate, postoperative, concurrent carboplatin, and craniospinal irradiation. The current childhood nasopharyngeal carcinoma study, ARAR0331, includes neoadjuvant chemotherapy, and concomitant chemoradiotherapy using cisplatin and amifostine.

Radiation oncology investigators believe that the treatment of specific malignancies may be individualized based on prior trial results, prognostic factors, and imaging biomarkers to include or eliminate RT or to reduce radiation dose.

European Ewing sarcoma trials have shown that histologic response is a positive predictor of survival [8]. The AEWS1031 trial will confirm this result for North American chemotherapy regimens. A secondary objective is to evaluate the impact of local surgical margins and

histologic response on EFS in patients with localized Ewing sarcoma tumors. Along with the analysis of histologic response, new treatment recommendations based on histologic response have been proposed. As noted earlier, in patients with microscopic positive margins requiring adjuvant RT, the volume will be individualized based on response such that post-chemotherapy volume will be targeted in patients with good pathologic response (>90% necrosis), and the larger pre-chemotherapy volume will be targeted for poor responders. For children with rhabdomyosarcoma, the margin definitions have been revised such that widely negative margins are not required for patients with favorable responses to chemotherapy. This change in margin definition should reduce the number of patients with favorable responses receiving postoperative RT.

For those with rhabdomyosarcoma involving the hands or feet, recent analysis showed that local control was 100% with definitive RT, and functional outcome was good; therefore, amputation is not necessary in this subgroup [9]. In the next generation of rhabdomyosarcoma trials, response-adjusted radiation doses may be administered after delayed surgical resection. FDG-PET is highly useful for rhabdomyosarcoma staging as noted on the intermediate-risk rhabdomyosarcoma study ARST0531. Future analyses will seek to determine whether FDG-PET findings may replace technetium bone scans, bone marrow biopsies, and/or sentinel lymph node biopsies. PET analysis of early response may help to identify patients for whom alterations in radiation dose and/or volume may be tested.

The location of the primary tumor is highly prognostic in rhabdomyosarcoma and there is evidence that can local therapy be specifically tailored for individual sites. For instance, D9602 and ARST0331 tested whether RT could be eliminated in female patients with tumors of the vagina; this approach resulted in an unacceptable local failure rate [10]. RT is now recommended for all females with non-resected rhabdomyosarcoma of the vagina. Another study of extremity rhabdomyosarcoma showed a high risk of in-transit nodal failures, indicating that initial lymph node staging and regional RT is essential to prevent relapse [9]. The completed low-risk rhabdomyosarcoma trial, ARST0331, studied radiation dose reduction from 45 to 36 Gy for those patients with negative lymph node assessment, microscopic residual disease, and gross residual orbital tumors. Preliminary results support the use of 36 Gy for those with resected, lymph node negative, microscopic residual tumors in a favorable site. Their failure rate was 15% with a median follow-up of 4.8 years [11]. The completed non-rhabdomyosarcoma soft-tissue sarcoma trial (ARST0332) omitted adjuvant RT for all patients with negative margins and a select subgroup of patients with positive margins.

Radiation oncologists who design protocols for children with Hodgkin lymphoma are building on prior studies that have demonstrated the effectiveness of a response-based paradigm for selecting patients to receive RT. Future protocols may advance the use of clinical risk factors identified by in earlier trials to stratify patients into low-, intermediate- or high-risk groups. Patients with low-risk Hodgkin lymphoma will be treated with minimal chemotherapy and response-based assignment of RT. Novel targeted agents may be evaluated in future trials in conjunction with further reductions in the proportion of children who require RT and the volume of normal tissue irradiated: among patients receiving RT, normal tissue exposure will be further reduced by transitioning from involved-field to

involved-nodal irradiation. The use of functional imaging (e.g., changes in glycolytic PET-avid tumor volume) will be combined with CT to assess response and further direct treatment intensity.

Similar to world-wide strategies [12, 13], craniospinal irradiation will continue to be omitted for children with favorable-risk CNS disease and those considered vulnerable to the long-term adverse effects of RT (i.e., children with CNS embryonal tumors or CNS germ cell tumors including non-germinomatous germ cell tumors). The ACNS1123 phase II trial for CNS germ cell tumors will omit craniospinal irradiation for all patients with localized tumors. A report in which early focal irradiation was used to treat children with nonmetastatic medulloblastoma showed a remarkable advance. The pattern of failure was clearly associated with the timing of RT (P9934). Failure to control local disease predominated during 4 months of induction chemotherapy, and failures were largely metastatic post-irradiation and limited to the volume of the brain receiving <12–15 Gy over the course of a 6-week treatment [14].

Sufficient evidence supports the concept that the distribution of radiation dose to an organ-at-risk correlates with its functional outcome [15–17]. The standard-risk medulloblastoma study ACNS0331 has two primary objectives: First, to determine whether reducing the craniospinal dose of RT from 23.4 to 18 Gy in children aged 3–7 years significantly reduces EFS or OS. Second, to determine whether reducing the irradiated volume of the primary site tumor boost from the whole posterior fossa to the tumor bed only will compromise EFS or OS. The primary objectives for the first- and second-generation conformal RT trials for ependymoma, ACNS0121 and ACNS0831, include estimating the local control and pattern of failure for pediatric patients with localized ependymoma treated with 3D-conformal RT using anatomically confined, clinical target-volume margins. The primary objectives for the completed low-grade glioma study, ACNS0221, include estimating the overall progression-free survival, EFS, and OS of pediatric patients with recurrent, progressive or symptomatic low-grade glioma after treatment with reduced-field conformal RT. In all cases, these trials are coupled with secondary evaluations to measure the impact of therapy on neurologic, endocrine, and cognitive function and quality of life.

Investigators have standardized concurrent chemotherapy and RT for high-risk CNS tumors including brainstem glioma, high-grade glioma, and high-risk medulloblastoma. The latter includes the ACNS0332 protocol, in which concurrent carboplatin and high-dose craniospinal irradiation are uniquely administered. CNS diseases are a major focus of radiation oncologists and an area of significant advancement.

The AEWS1031 trial will be the first to systematically study surgical and RT techniques and volumes in relation to musculoskeletal complications and functional outcomes. The secondary objectives from the current study include the following: (1) To evaluate the effect of local therapy modality (surgery, RT or a combination) and the type of surgical reconstruction on musculoskeletal complications. (2) To compare the differences in musculoskeletal impairments, physical performance, and health-related quality of life among children and young adults treated with surgery alone versus RT alone versus a combination of radiation and surgery. (3) To evaluate other predictors of musculoskeletal impairments

and physical performance limitations (e.g., type of surgery, tumor size at diagnosis, tumor location, age at diagnosis, sex, and baseline function). (4) To evaluate the associations between physical performance limitations and physical, emotional, and social dimensions of health-related quality of life. In CNS trials, normal-tissue dose information from first-generation, volume-reduction trials (ACNS0121, ACNS0221, and ACNS0331) are being used to refine guidelines for collateral normal-tissue irradiation and determine the association between radiation dose and functional outcomes.

THE ROLE OF THE RADIATION ONCOLOGIST IN PEDIATRIC CLINICAL TRIALS

Radiation oncology investigators play a primary role in protocol design and treatment of children enrolled on studies of various CNS and solid tumors, testing the risks and benefits of reduced-volume irradiation, the appropriate and safe treatment of young children, and the use of combined-modality therapy in a number of disease settings. They supported randomized trials comparing chemotherapy alone with combined-modality therapy in patients with Hodgkin lymphoma who experienced complete response to induction chemotherapy found that combined-modality therapy is associated with superior EFS; no significant difference in OS was detected [18].

An important consideration in pediatric Hodgkin lymphoma is the impact of salvage therapy on fertility and other late effects and the potential for anthracyclines-related cardiotoxicity to emerge at lower doses than typically seen among adult patients with Hodgkin lymphoma. Consequently, investigators have been reluctant to accept higher relapse rates or to substantially intensify chemotherapy. Although the COG AHOD0031 trial demonstrated that early chemotherapy response can be used to identify patients who did not benefit from RT, RT remains a standard component of treatment among patients with slow early response or in limited-stage relapsed disease. Improvements in imaging and linear accelerator technology allow much better delineation of target volumes and avoidance of normal tissues than was previously possible. By more precisely targeting at-risk nodal areas, investigators hope to improve the therapeutic ratio for those receiving RT, and by implementing response-based risk assessment for some patients.

RADIATION ONCOLOGY RESEARCH

Contemporary hypotheses being tested in CNS protocols designed to include RT in children test the idea that reducing the target volume of RT will decrease side effects without affecting the rate of local control or pattern of failure (ACNS0121, ACNS0221, ACNS0831, ACNS0331, and ACNS1123); concurrently administered chemotherapy and RT may improve disease control with acceptable treatment-related toxicity in patients with high-risk malignancies (ACNS0332 and ACNS0927); treatment of specific malignancies in children may be individualized based on prior trial results and prognostic factors to include or eliminate RT or reduce radiation doses (P9934); the distribution of radiation dose to an at-risk organ correlates with functional outcome.

The Quality Assurance Review Center (QARC, www.qarc.org) has been used to capture data on normal tissue exposure to radiation in patients treated with RT. This information will be expanded to create a data source that may improve our predictive modeling of late effects and provide a better understanding of the biologic variability in tumor response and normal tissue response to RT. Radiation oncology investigators have been conducting subset analyses of AHOD0031 data to examine patterns of relapse and clinical factors that distinguish those who benefit from RT from those who do not.

Beyond protocol-specific, disease-control objectives, which are a combined disease-discipline-committee objective, further associating the distribution of radiation dose to an at-risk organ with a functional outcome would significantly improve the ability to refine indications for RT and prove the value of more advanced RT methods. Reducing radiation dose and volume or eliminating RT from the treatment regimens of selected patients is a primary objective for many protocols. The rationale for this objective is based on the premise that increasing radiation dose and volume of irradiated tissues are directly linked and inversely proportional to the acute and late effects of treatment.

Pursuant to the goal of reducing side effects, there is global interest in researching the correlation between radiation dose and specific functions. Understanding the relation between radiation dose and side effects may improve our ability to design risk-adapted treatment regimens, optimize RT planning, and mitigate the consequences of treatment when the severity and time to onset of specific side effects can be predicted. Radiation dose and functional outcome correlations may be used to compare the relative benefits and risks of different treatment-planning methods, protocol-targeting guidelines, normal tissue-dose constraints, and the newer method of proton beam therapy.

Future Hodgkin lymphoma trials world-wide will focus on reducing the number of irradiated patients based on early chemotherapy response. This will represent a substantial investment to go beyond the German GPOH protocol in which 70% of patients with favorable-risk disease were irradiated [19]. Normal tissue exposure may be further reduced as the group transitions from involved-field to involved-node/site irradiation. The latter has been evaluated retrospectively and prospectively [20] and found to reduce irradiation of normal tissues, especially heart, lung, and breast. In addition, proton beam therapy guidelines will be implemented for upcoming Hodgkin lymphoma trials to further reduce dosing to normal tissues in selected patients (Fig. 1).

RT continues to play a vital role in the modern multidisciplinary management of pediatric renal tumors. The present indications for RT in Wilms' tumor administered through COG clinical trials include local tumor control in the flank and/or abdomen and management of metastatic disease in the lungs, liver, bone, and brain. An important goal has been to explore new RT methods, such as intensity-modulated RT, to reduce the dose of radiation to the heart or kidneys in children who require whole-lung or whole-liver irradiation, respectively [21, 22]. The implementation and integration of these novel treatments in the multimodality treatment of children with lung or liver metastasis will be an important objective in the next generation of renal tumor protocols in COG (Fig. 2).

Radiation oncologists will continue to work closely with other specialists to improve the survival and quality of survival of irradiated patients especially adolescents and young adults. Analyses have shown that the progress in survival prolongation as a function of age is correlated with both the number and proportion of patients enrolled on a clinical trial. RT plays a recognized role in the most common cancers diagnosed in this age group, including bone tumors (Ewing sarcoma), CNS tumors, Hodgkin lymphoma, soft-tissue sarcoma, cervical cancer, and breast cancer. Unfortunately, irradiation is associated with an increased risk for late mortality; development of second malignancies; endocrine, pulmonary, and cardiac dysfunction; growth abnormalities; and other various chronic health conditions [23]. Cranial RT specifically has been associated with neurocognitive difficulty and poor physical functioning, which contribute to lower rates of employment, independent living, and marriage among these cancer survivors.

PROTON THERAPY IN PEDIATRIC CLINICAL TRIALS

The capacity for children to receive proton beam therapy has expanded world-wide since 2007. Less than a decade ago, only two centers in the United States offered proton therapy for children. There are currently 10 US-based proton beam centers that treat children with cancer. Diagnoses treated with proton therapy include medulloblastoma, low-grade glioma, Ewing sarcoma, rhabdomyosarcoma, soft-tissue sarcoma, Hodgkin disease, neuroblastoma, and retinoblastoma (Fig. 3). Both the number of patients treated and the breadth of trials allowing proton therapy for children have markedly increased yearly, demonstrating the acceptance of proton therapy by oncologists across all disciplines and the growing availability of this technology. The increased use of proton beam therapy is an extension of the hypotheses that reducing the target volume will decrease side effects without affecting the rate of local control or pattern of failure. Increased use of proton therapy is envisioned. As additional proton beam centers open, thereby increasing the availability and access to this modality, the goal will be to enroll eligible children in clinical trials and focus on standardization, and quality assurance.

COOPERATIVE GROUP INTEGRATION

Because many pediatric radiation oncologists who participate in pediatric cooperative groups are also members of the adult cooperative groups and professional societies that span the treatment of adult and pediatric cancers, the seamless integration of protocol guidelines for those diseases and treatment sites that span the ages is expected as the US National Cancer Institute develops its new Clinic Trials Network. Radiation oncologists have initiated efforts to align guidelines for clinical trials affecting a number of diseases and treatments. Potential examples of integrated protocols include a high-risk non-rhabdomyosarcoma soft-tissue sarcoma trial and a trial that will include stereotactic body RT for patients with newly diagnosed metastatic Ewing sarcoma (Fig. 4).

REFERENCES

1. Granowetter L, Womer R, Devidas M, et al. Dose-intensified compared with standard chemotherapy for nonmetastatic Ewing sarcoma family of tumors: A Children's Oncology Group Study. *J Clin Oncol*. 2009; 27:2536–2541. [PubMed: 19349548]

2. Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. *N Engl J Med*. 2003; 348:694–701. [PubMed: 12594313]
3. Beltran C, Krasin MJ, Merchant TE. Inter- and intrafractional positional uncertainties in pediatric radiotherapy patients with brain and head and neck tumors. *Int J Radiat Oncol Biol Phys*. 2011; 79:1266–1274. [PubMed: 20605345]
4. Pai Panandiker AS, Sharma S, Naik MH, et al. Novel assessment of renal motion in children as measured via four-dimensional computed tomography. *Int J Radiat Oncol Biol Phys*. 2012; 82:1771–1776. [PubMed: 21621338]
5. Lin C, Donaldson SS, Meza JL, et al. Effect of radiotherapy techniques (IMRT vs 3D-CRT) on outcome in patients with intermediate-risk rhabdomyosarcoma enrolled in COG D9803—A report from the Children's Oncology Group. *Int J Radiat Oncol Biol Phys*. 2012; 82:1764–1770. [PubMed: 21470795]
6. Yock TI, Krailo M, Fryer CJ, et al. Local control in pelvic Ewing sarcoma: Analysis from INT-0091—a report from the Children's Oncology Group. *J Clin Oncol*. 2006; 24:3838–3843. [PubMed: 16921035]
7. Minn AY, Lyden ER, Anderson JR, et al. Early treatment failure in intermediate-risk rhabdomyosarcoma: Results from IRS-IV and D9803—a report from the Children's Oncology Group. *J Clin Oncol*. 2010; 28:4228–4232. [PubMed: 20713850]
8. Schuck A, Ahrens S, Paulussen M, et al. Local therapy in localized Ewing tumors: Results of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials. *Int J Radiat Oncol Biol Phys*. 2003; 55:168–177. [PubMed: 12504050]
9. La TH, Wolden SL, Su Z, et al. Local therapy for rhabdomyosarcoma of the hands and feet: Is amputation necessary? A report from the Children's Oncology Group. *Int J Radiat Oncol Biol Phys*. 2011; 80:206–212. [PubMed: 20646853]
10. Walterhouse DO, Meza JL, Breneman JC, et al. Local control and outcome in children with localized vaginal rhabdomyosarcoma: A report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *Pediatr Blood Cancer*. 2011; 57:76–83. [PubMed: 21298768]
11. Breneman J, Meza J, Donaldson SS, et al. Local control with reduced-dose radiotherapy for low-risk rhabdomyosarcoma: a report from the Children's Oncology Group D 9602 study. *Int J Radiat Oncol Biol Phys*. 2012; 83:720–726. [PubMed: 22104356]
12. Grundy RG, Wilne SH, Robinson KJ, et al. Primary postoperative chemotherapy without radiotherapy for treatment of brain tumours other than ependymoma in children under 3 years: Results of the first UKCCSG/SIOP CNS 9204 trial. *Eur J Cancer*. 2010; 46:120–133. [PubMed: 19818598]
13. Calaminus G, Alapetite C, Frappaz D, et al. Malignant CNS germ cell tumors (GCTs): Interim analysis after 5 years of SIOP CNS GCT 96. *Proc Am Soc Clin Oncol*. 2003; 22
14. Ashley DM, Merchant TE, Strother D, et al. Induction chemotherapy and conformal radiation therapy for very young children with nonmetastatic medulloblastoma: Children's Oncology Group Study P993. *J Clin Oncol*. 2012; 30:3181–3186. [PubMed: 22851568]
15. Hua C, Shukla HI, Merchant TE, et al. Estimating differences in volumetric flat bone growth in pediatric patients by radiation treatment method. *Int J Radiat Oncol Biol Phys*. 2007; 67:552–558. [PubMed: 17097831]
16. Merchant TE, Nguyen L, Nguyen D, et al. Differential attenuation of clavicle growth after asymmetric mantle radiotherapy. *Int J Radiat Oncol Biol Phys*. 2004; 59:556–561. [PubMed: 15145176]
17. Merchant TE, Kiehna EN, Li C, et al. Modeling radiation dosimetry to predict cognitive outcomes in pediatric patients with CNS embryonal tumors including medulloblastoma. *Int J Radiat Oncol Biol Phys*. 2006; 65:210–221. [PubMed: 16472938]
18. Kung FH, Schwartz CL, Ferree CR, et al. POG 8625 a randomized trial comparing chemotherapy with chemoradiotherapy for children and adolescents with stages I IIA, IIIA1 Hodgkin disease: A report from the Children's Oncology Group. *J Pediatr Hematol Oncol*. 2006; 28:362–368. [PubMed: 16794504]

19. Mauz-Korholz C, Hasenclever D, Dorffel W, et al. Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: The GPOH-HD-2002 study. *J Clin Oncol*. 2010; 28:3680–3686. [PubMed: 20625128]
20. Paumier A, Khodari W, Beaudre A, et al. Intensity-modulated radiotherapy and involved-node concept in patients with Hodgkin lymphoma: Experience of the Gustave-Roussy Institute. *Cancer Radiother*. 2011; 15:709–715. [PubMed: 22116023]
21. Kalapurakal JA, Zhang Y, Kepka A, et al. Cardiac-sparing whole lung IMRT in children with lung metastasis. *Int J Radiat Oncol Biol Phys*. 2012 [Epub ahead of print].
22. Kalapurakal JA, Pokhrel D, Gopalakrishnan M, et al. Advantages of whole-liver intensity modulated radiation therapy in children with Wilms tumor and liver metastasis. *Int J Radiat Oncol Biol Phys*. 2012 [Epub ahead of print].
23. Green DM, Grigoriev YA, Nan B, et al. Congestive heart failure after treatment for Wilms' tumor: A report from the National Wilms' Tumor Study group. *J Clin Oncol*. 2001; 19:1926–1934. [PubMed: 11283124]

Fig. 1. Involved-field radiation therapy (**left**) irradiates uninvolved lymph node chains by convention. Involved-nodal radiation therapy (**right**) irradiates only involved lymph nodes.

Fig. 2. Example of cardiac-sparing whole-lung radiation therapy for Wilms' tumor. Dose distributions are shown as blue line (950 cGy), green line (750 cGy), and yellow line (500 cGy). Anterior (light blue) and posterior (red) cardiac structures are outlined.

Fig. 3. Example (individual columns) of photon conformal radiation therapy (3DCRT), photon intensity-modulated radiation therapy (IMRT), and conformal proton therapy (3DCPT) for a case of Ewing sarcoma involving the temporal bone. Axial (**upper**), coronal (**middle**), and sagittal (**lower**) images show high-dose (red-orange), intermediate-dose (green), and low-dose (blue) regions by method.

Fig. 4. Example of stereotactic body radiotherapy plan for vertebral body metastasis from Ewing sarcoma. The radiation dose distribution (contour lines) displayed on the axial CT scan is shaped to minimize dose to the spinal cord. Liver (light green) and left kidney (orange) are shaded.

TABLE I

COG Studies Registered on the National Clinical Trials Network

Clinical Trials.gov identifier	COG identifier	Study title	Date and status
NCT01231906	AEWS1031	Combination chemotherapy in treating patients with non-metastatic extracranial Ewing sarcoma	11/10—active
NCT00354744	ARST0431	High-dose combination chemotherapy and radiation therapy in treating patients with newly diagnosed metastatic rhabdomyosarcoma or ectomesenchymoma	7/06—06/08
NCT00354835	ARST0531	Combination chemotherapy and radiation therapy in treating patients with newly diagnosed rhabdomyosarcoma	12/06—active
NCT00346164	ARST0332	Observation, radiation therapy, combination chemotherapy, and/or surgery in treating young patients with soft tissue sarcoma	02/07—2/12
NCT00392327	ACNS0332	Chemotherapy and radiation therapy in treating young patients with newly diagnosed, previously untreated, high-risk medulloblastoma or supratentorial primitive neuroectodermal tumor	03/07—active
NCT00274937	ARAR0331	Radiation therapy, amifostine, and chemotherapy in treating young patients with newly diagnosed nasopharyngeal cancer	02/06—active
NCT00002995	D9602	Combination chemotherapy with or without radiation therapy in treating patients with newly diagnosed rhabdomyosarcoma	09/97—09/04
NCT00075582	ARST0331	Vincristine, dactinomycin, and cyclophosphamide with or without radiation therapy in treating patients with newly diagnosed low-risk rhabdomyosarcoma	09/04—09/11
NCT01602666	ACNS1123	Chemotherapy followed by radiation therapy in treating younger patients with newly diagnosed localized central nervous system germ cell tumors	05/12—active
NCT00006461	P9934	Combination chemotherapy followed by second-look surgery and radiation therapy in treating children with nonmetastatic medulloblastoma or primitive neuroectodermal tumor	10/00—06/06
NCT00085735	ACNS0331	Comparison of radiation therapy regimens in combination with chemotherapy in treating young patients with newly diagnosed standard-risk medulloblastoma	04/04—active
NCT01096368	ACNS0831	Maintenance chemotherapy or observation following induction chemotherapy and radiation therapy in treating younger patients with newly diagnosed ependymoma	03/10—active
NCT00027846	ACNS0121	Observation or radiation therapy and/or chemotherapy and second surgery in treating children who have undergone surgery for ependymoma	08/03—11/07
NCT00238264	ACNS0221	Radiation therapy in treating young patients with gliomas	11/05—12/10
NCT00387790	ACNS0222	Motexafin gadolinium and radiation therapy in treating young patients with pontine glioma	06/07—11/08
NCT00025259	AHOD0031	Chemotherapy with or without additional chemotherapy and/or radiation therapy in treating children with newly diagnosed Hodgkin's disease	09/02—10/09