Published in final edited form as:

Pediatr Radiol. 2009 February ; 39(0 1): S42–S45. doi:10.1007/s00247-008-1065-9.

What, Why, and When We Image: Considerations for Diagnostic Imaging and Clinical Research in the Children's Oncology Group

Gregory H. Reaman, M.D. [Professor of Pediatrics, Chairman, Children's Oncology Group]

The George Washington University, School of Medicine and Health Sciences, Division of Hematology Oncology, Children's National Medical Center, Washington, D.C.

Abstract

Success in improving treatment outcomes in childhood cancer has been achieved almost exclusively through multi-center and multi-disciplinary clinical and applied research over a series of several decades. [1,2] While biologically rational as well as empiric approaches have led to combination chemotherapy and multi-modality approaches to therapy, similar scientific rigor has not always been as evidently applied to modalities utilized to assess initial disease burden and, more importantly, response to investigational approaches to therapy. As the empiric approach to therapeutic advances has likely maximized its benefit, future progress will require translation of biologic discovery most notably from the areas of genomics and proteomics. [3,4] Hence, attempts to improve efficacy of therapy will require a parallel effort to minimize collateral damage of future therapeutic approaches, and such a parallel approach will mandate the continued dependence on advances in diagnostic imaging for improvements in staging methodologies to best define risk groups for risk adjusted therapy. [5] In addition, anatomic and functional assessment of response and surveillance for disease recurrence will require improved understanding of the biology, as well as natural history of individual diseases, which will hopefully better inform investigators in designing trials. [6] Clinical and research expertise is urgently needed in the selection of which specific imaging studies and their frequency are best utilized to assess a response as well as to define disease free intervals. Despite limited resources to develop sufficient infrastructure, emphasis on enabling early assessment of new technology to minimize risks associated with new treatment advances and with those critical diagnostic and staging procedures must continue to be a focus of pediatric cancer clinical research.

Introduction

Success in childhood cancer has been achieved in large part, and perhaps nearly exclusively, as a result of multi-center and multi-disciplinary clinical and applied research. The unique practice model in pediatric oncology, in large part academic medical center focused, and the strong integration of clinical research have resulted in a dramatic improvement in outcome results. Presently, nearly 80% of children diagnosed with cancer can anticipate prolonged event free survival or cure. Despite these advances, cancer is the fourth most common cause of death (after accidental injury, homicide, and suicide) among persons aged 1-19 years in the United States, and it continues to be the leading cause of death from disease. As advances in cancer therapy have improved and the prognosis of patients diagnosed with childhood malignancies has dramatically changed, increasing awareness of the

consequences of treatment, including all modalities, surgery, chemotherapy, radiation therapy, assumes increasing importance.

Improvements in outcome for childhood cancer by specific cancer diagnosis is demonstrated in Figure 1. These improvements have resulted from a series of successive randomized clinical trials developed to investigate whether selected intensification of therapy over best standard results in improvements in outcome or whether judicious reduction in therapy results in equally beneficial treatment effect with less acute and long term toxicity.[1]

As noted, specific diagnoses, including acute lymphoblastic leukemia, Hodgkin's Disease, Non-Hodgkin lymphoma, and Wilms' Tumor have enjoyed extraordinary success, and many cancer types which are commonly widespread beyond the site of origin at the time of diagnosis, and whose specific biologic characteristics result in resistance to current therapy remain problematic with respect to long term event free survival and likelihood of cure. In many of these high risk malignancies, further intensification of conventional therapies is not feasible as unacceptable risk benefit ratio considerations curtail further therapy intensification.

Future progress, therefore, will require translation of basic biologic discovery and exploitation of those genetic aberrations operational in the causation of pediatric cancer, and genomic approaches to molecular target identification, validation, and ultimately, drug discovery. Improvements in efficacy of therapy are expected from such targeted therapy approaches: equally anticipated is a substantial decrease in risk for collateral damage. In such future pediatric cancer therapeutic research, the implications for the pivotal role of diagnostic imaging remain for the anatomic and biologic (functional) staging of specific tumor types, response assessment to standard and investigational therapies, and surveillance for disease recurrence to objectively describe disease progression to define progression free intervals, and importantly, the detection of early and late sequelae of therapy. In addition, diagnostic imaging is expected to dramatically assist in multi-disciplinary approaches to improve the benefit: toxicity ratio of future therapy by improving staging methodologies, assisting with the refinement of risk group and risk adjusted therapy strategies, facilitating focused treatment delivery e.g. intensity modified radiation therapy (IMRT), and neo-adjuvant chemotherapy, for response definition and for response based therapeutic approaches to cancer management.[7]

In evaluating the diagnostic imaging guidelines of a number of current and recently completed COG clinical trials, it is apparent that major improvements are necessary in the communication, integration, and evidence of collaboration, of diagnostic imaging with other professional disciplines essential for clinical trial design and conduct in pediatric oncology. Specific examples of the need for better integration include the imaging guidelines in acute lymphoblastic leukemia protocols which include directions that either head CT or MRI are recommended for toxicity with recommendations to follow up as clinically required, however, no specific recommendations are provided to indicate a superiority or preference of one modality over another in any given clinical situation and the lack of detail in indications for repeated imaging as follow up are clearly lacking. Similarly, for the diagnosis of suspected avascular necrosis both skeletal plain films as well as MRI are mentioned, but

again, no recommendations with respect to which of these two modalities and at what specific point in time, would be preferred imaging modalities. Given the marked increase in incidence in therapy related avascular necrosis, specific imaging guidelines for both surveillance and diagnosis, as well as follow-up are sorely needed.

In Non-Hodgkin's lymphoma protocols imaging guidelines for staging include both chest x-rays, as well as CT scan, gallium scans, FDG-PET, and bone scan recommendations. Notably absent are any specific recommendation, based on concerns for repeated, and perhaps unnecessary, radiation exposure with specific modalities to be used, not only at the time of staging, but for response assessment following induction and the completion of therapy, and for bi-annual surveillance for two years following completion of therapy. [8] This concern is even more evident in protocol imaging guidelines and requirements in Hodgkin Disease protocols with chest x-rays, CT scan, gallium scans, FDG-PET, at the time of initial diagnosis for staging with response assessment utilizing CT and/or PET and/or CT/PET, and surveillance CT scans for two years, and annually for five years at the completion of therapy.

Commentary and Discussion

In evaluating guidelines for conventional imaging techniques for a series of COG clinical trials, it is unfortunately obvious that consistent and rational approaches to standardize recommendations within a specific diagnosis or across diagnoses is absent. In those clinical trials where specific therapeutic interventions are the variable to be assessed, and with a requirement for response assessment as endpoints, rational recommendations for imaging practice standards in both pediatric cancer care and clinical research are mandatory. Such standards should include issues related to technology and techniques and their availability and generalizability within the clinical research setting, and obviously with respect to potential risks, both short term and long term. [9,10] Standards should include whether response and surveillance is focused on functional and/or anatomic assessment, and whether specific technologies might be more appropriate in these settings. With respect to recommendations for optimal scheduling for both response assessment and metastatic surveillance, rational consideration of the natural history, biology, and effective therapy are needed in guiding the choice of a given technique. In addition, in that many of the new agents under consideration for use in targeted therapy of cancer are cytostatic rather than cytotoxic, designing clinical trials with timed progression endpoints is an increasingly likely consideration and rational recommendations for the frequency of imaging for progression assessment will require unprecedented collaboration between oncologists and diagnostic imagers.

In order to advance state of the art imaging in the science of childhood cancer clinical research, a paradigm shift may be in order in assuring that an evidence base exists to make rational recommendations for specific imaging technology in specific diseases. Going forward, pediatric cancer clinical trials should consider diagnostic imaging specific aims which may be integrated with primary endpoint evaluation, or could be considered as correlative biology and technology assessments. Such integrated questions would require the

same robust statistical power and sample size calculations to optimally address the questions posed.

Obvious logistical challenges exist, which may hamper progress. These include generalized access to new and emerging technologies, difficulties with scheduling, need for sedation and infusion access, and obvious economic considerations with respect to evaluating new technologies. It is important to note that within any highly effective clinical trials network, not all study sites are the same and specialized consortia can be developed where investigators have particular interest and expertise. Thus, it may be possible to develop an infrastructure for a critical mass of study sites to explore emerging technologies in a disease based and therapeutic intervention-based manner with a focus on technology evaluation. Such technologies could advance to a Phase III setting when a sufficient evidence base exists, and such initiatives will require resources to collect, submit, transfer, review, and archive images as well as correlate with clinical and outcome data. An investment in such an infrastructure is absolutely required as future progress and therapeutic research in childhood cancer requires maximal exploitation of both emerging biology and emerging technology. Before shifting to new technology, however, defining proof of principle in assuring superiority to current standard is necessary before incorporation of new technology and modalities in Phase II or Phase III clinical trials in pediatric cancer.

References

1. Reaman, GH. Pediatric Oncology: Principles and Practice in Cancer Medicine U 7. Kufe, DW.; Rast, RC., et al., editors. RC Decker Hamilton; 2006. p. 1914-1917.
2. MMWR Morbidity and Mortality Weekly Report. Vol. 56. Dept of Health and Human Services, Centers for Disease Control and Prevention; Dec. 2007 p. 1257-1261.
3. Unen A, Toretsky JA. Pediatric malignancies provide unique cancer therapy targets. *Curr Opin Pediatr.* 2005; 17:14–19.
4. Brodeur GM. Neuroblastoma: Biological insights into a clinical enigma. *Nat Rev Cancer.* 2003; 3:203–216. [PubMed: 12612655]
5. Anceci R, Reaman GH, Cohen A, Lampkin B. Position statement for the need to define pediatric hematology-oncology programs; a model of subspecialty care for pediatric chronic diseases. *J Pediatr Hem Onc.* 1998; 20:98–103.
6. Simone, Lyons J. The evolution of cancer care for adults and children. *J Clin Oncol.* 1998; 16:2904–05. [PubMed: 9738556]
7. Guillerman, RP.; Braverman, RM.; Panker, RR. Imaging studies in the diagnosis and management of pediatric malignancies. In: Pizzo, P.; Poplack, DG., editors. *Principles and Practice of Pediatric Oncology.* 5th. Lippincott; Philadelphia: 2006. p. 236-289.
8. Brenner DJ, Hall EJ. Current concepts-computed tomography- an increasing source of radiation exposure. *N Engl J Med.* 2007; 357:2277–2284. [PubMed: 18046031]
9. Slovis TL. The ALARA (as low as reasonably achievable) concept in pediatric CT intelligent dose reduction. Multidisciplinary conference organized by the Society of Pediatric Radiology. *Pediatric Radiology.* 2002; 32:217–317. [PubMed: 11956694]
10. da Losta e Silva EJ, da Silva GA. Eliminating unenhanced CT when evaluating abdominal neoplasia in children. *Amer J Radiol.* 2007; 189:1211–1214.

Overall Survival Data – COG Studies

Figure 1.
Overall survival data-COG studies