Pediatr Radiol (2009) 39 (Suppl 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

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Received: 15 October 2008 / Accepted: 30 October 2008 / Published online: 16 December 2008
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Abstract Success in improving treatment outcomes in childhood cancer has been achieved almost exclusively through multicenter and multidisciplinary clinical and applied research over several decades. While biologically rational as well as empirical approaches have led to combination chemotherapy and multimodality approaches to therapy, which have given rise to evidence-based practice standards, similar scientific rigor has not always been as evidently applied to modalities utilized to assess initial disease burden and, more important, response to investigational approaches to therapy. As the empirical 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. 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. 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 one hopes will better inform investigators in designing trials. Clinical and research expertise is urgently needed in the selection of specific imaging studies and frequencies that best 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 treatment advances and with those critical diagnostic and staging procedures must continue to be a focus of pediatric cancer clinical research.

Keywords Children's Oncology Group · Pediatric oncology · Imaging

Introduction

Success in childhood cancer has been achieved in large part, and perhaps nearly exclusively, as a result of multicenter and multidisciplinary clinical and applied research. The unique practice model in pediatric oncology, in large part focused on academic medical centers, and the strong integration of clinical research have resulted in a dramatic improvement in outcomes. 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 people age 1–19 years in the United States, and it continues to be the leading cause of death from disease. As advances in cancer therapy improve and the prognosis of patients diagnosed with childhood malignancies dramatically changes, increasing awareness of the consequences of treatment, including all modalities, surgery, chemotherapy, and radiation therapy, assumes increasing importance.

Improvements in childhood cancer outcomes by specific diagnosis are demonstrated (Fig. 1). These improvements have resulted from a series of randomized clinical trials developed to investigate whether selected intensification of

Dr. Reaman has no relevant financial relationships or potential conflicts of interest related to the material to be presented.

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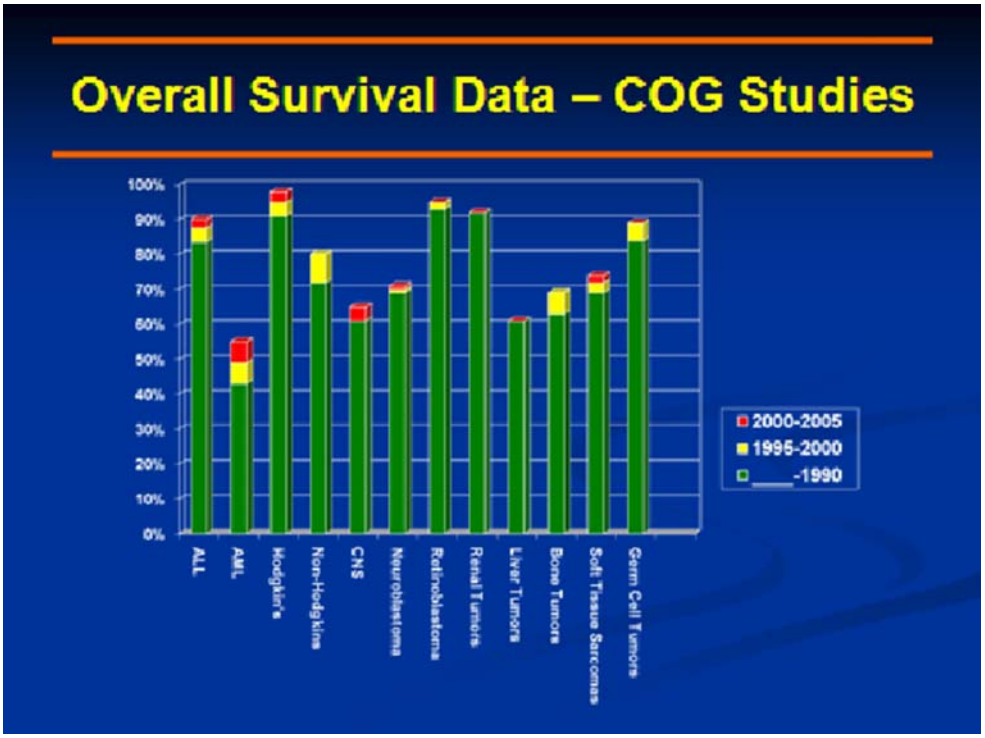

Fig. 1 Overall survival data—COG studies

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, 2].

As noted, there has been extraordinary success in treatment of specific diagnoses including acute lymphoblastic leukemia, Hodgkin disease, non-Hodgkin lymphoma, and Wilms tumor; however, many cancers that are commonly widespread 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, unacceptable risk-benefit ratio considerations curtail intensification of conventional therapies.

Progress, therefore, will require translation of basic biologic discovery and exploitation of those genetic aberrations that cause pediatric cancer, genomic approaches to molecular target identification and validation, and, ultimately, drug discovery [3, 4]. Improvements in efficacy of therapy are expected from such targeted therapy approaches: equally anticipated is a substantial decrease in risk for collateral damage [5]. In such future research of pediatric cancer therapy, 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 multidisciplinary approaches to improve the benefit-to-toxicity ratio of future therapy by improving staging methodologies, assisting with the refinement of risk group and risk-adjusted therapy strategies, and 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 [6, 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 that include directions that either head CT or MRI is 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 radiographs and MRI are mentioned, but again, no recommendations are made with respect to which of these modalities and at what specific point in time. Given the marked increase in incidence in therapy-related avascular necrosis, specific imaging guidelines for surveillance, diagnosis, and follow-up are sorely needed.

In non-Hodgkin lymphoma protocols, recommended imaging guidelines for staging include chest radiograph as well as CT scan, gallium scans, FDG-PET, and bone scan. Notably absent are any specific recommendations 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 therapy and for twice-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, with chest radiograph, CT scan, gallium scans, and FDG-PET at the time of initial diagnosis for staging, and with response assessment utilizing CT and/or PET and/or CT/PET, and surveillance CT scans for 2 years, and annually for 5 years at the completion of therapy.

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 are 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 ability to be generalized within the clinical research setting, as well as potential risks, both short-term and long-term [9, 10]. Standards should include whether response and surveillance is focused on functional 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.

Conclusion

In order to advance state-of-the-art imaging science in childhood cancer clinical research, a paradigm shift might 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 goals that might 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 might 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 is 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 would 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 progress and therapeutic research in childhood cancer requires maximal exploitation of both emerging biology and emerging technology. 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.

Acknowledgement This work is supported in part by grant U10-CA98543.

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