Journal of Pediatric Surgery 49 (2014) 233–240

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Journal of Pediatric Surgery Lecture

State of the art in oncology: High risk neuroblastoma, alveolar rhabdomyosarcoma, desmoplastic small round cell tumor, and POST-TEXT 3 and 4 hepatoblastoma

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ARTICLE INFO

Article history:
Received 29 October 2013
Accepted 9 November 2013

Key words:
Neuroblastoma
Alveolar rhabdomyosarcoma
Desmoplastic small round cell tumor
Hepatoblastoma

ABSTRACT

Despite advances in the treatment of pediatric cancers during the past few decades, high-risk neuroblastoma, alveolar rhabdomyosarcoma, desmoplastic small round cell tumor, and hepatoblastomas with 3 or 4 sector involvement after chemotherapy continue to present significant challenges. This review summarizes recent research on the management of these diseases, with a special focus on the use of surgical debulking, genetic analysis, immunotherapy, and chemotherapy in improving outcomes of patients with these solid tumors.

Pediatric oncology is a complex heterogeneous field that has benefitted greatly from a multidisciplinary approach to treatment, with resultant general improvement for children with cancer. Despite this progress, however, several challenging areas in pediatric oncology remain. Four of these, for which surgical intervention is particularly relevant, are (1) high risk neuroblastoma, (2) alveolar rhabdomyosarcoma (ARMS) with nodal metastases, (3) desmoplastic small round cell tumor, and (4) post-therapy extent of disease (POST-TEXT) 3 and 4 hepatoblastoma. Each of these diseases remains problematic, but patient outcomes can be favorably affected by selecting the appropriate surgical intervention. In the case of high-risk neuroblastoma, a major advance is the addition of monoclonal antibody therapy, while gross total resection greatly improves local control and correlates with better overall survival. In addition, a new approach to risk stratification uses pre-operative image-defined criteria. Survival is also improved in desmoplastic small round cell tumor after extensive de-bulking. R0 resection in extensive hepatoblastomas can sometimes be accomplished with complex resection techniques, thereby avoiding hepatic transplantation and subsequent lifelong immunosuppression. This article summarizes these state-of-the-art developments.

1. High risk neuroblastoma

Numerous studies have been published on the surgical management of neuroblastoma although comparison has been hampered by the incorporation of resection status into the International Neuroblastoma Staging System (INSS) criteria. For instance, a central abdominal tumor that encases the visceral arteries might be scored as a stage 3 at some centers, but after resection would be classified as stage 1 in others. To eliminate surgical intervention as a variable, the International Neuroblastoma Risk Group (INRG) Task Force has used pre-treatment imaging to enumerate specific image-defined risk factors that may more precisely define the local–regional extent of disease prior to intervention, thus facilitating comparison of differing therapeutic protocols [1,2]. Although initially applied to intermediate risk tumors, this system can also develop a picture of the primary tumor in high-risk neuroblastoma as well. In practice, individual image-defined risk factors, for the most part defined as vessel or nerve encasement, would be included and listed for each patient. The INRG survival tree is depicted in Fig. 1. Image-defined risk factors are now included in current Children's Oncology Group (COG) studies, and it is hoped that such factors will allow more uniform comparison of the loco-regional extent of disease across all neuroblastoma risk categories.

A second major development in neuroblastoma has been the improved survival of high-risk patients after treatment with an anti-GD2 monoclonal antibody [3]. This phase III study demonstrated a 20% survival advantage at 2 years for patients treated with the antibody plus granulocyte macrophage colony stimulating factor (GMCSF) and interleukin-2 (Fig. 2).

A controversial and highly charged issue remains the role of surgical resection of the primary tumor and involved regional lymphatics in high risk patients. A partial list of factors that confound analysis of its role includes: complete lack of prospective studies that assess the impact of a more complete resection on outcome until the recent SIOPEN study, a lack of assessment of the completeness of resection using imaging studies (operative reports are routinely used), the lack of agreed upon descriptors of the primary tumor, and the fact that surgical resections vary greatly with regard to technique and treatment center.

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0022-3468/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jpedsurg.2013.11.029

A starting point for assessing the role of resection is a comprehensive literature review. At Memorial Sloan-Kettering Cancer Center, we conducted a literature search that yielded 33 non-redundant studies with adequate surgical data for analysis of survival [4–36]. Thirteen of these studies presented additional data enabling an evaluation of local control. (Complete details of the literature search strategy, study inclusion/exclusion criteria, and methods of data analysis are presented in the Appendix.) A total of 2599 patients were included in the survival analysis and 412 in the analysis of local progression. A meta-analysis was performed, and an overall odds ratio was computed for various subsets analyzed. Data for various subsets are summarized in Table 1. The effect of extensive resection of the primary neuroblastoma in stage 3 and 4 on the aggregate patient cohort is depicted in Fig. 3. The relative risk of mortality for patients who underwent > 90% resection was 0.67 (95% CI 0.59–0.77) compared to those who underwent a lesser resection. Data for stage 4 patients alone are depicted in Fig. 4A and the relative risk was 0.75 (95% CI 0.62–0.92). Similarly, only stage 3 patients are shown in Fig. 4B, and the relative risk associated with ≥ 90% resection was 0.42 (95% CI 0.30–0.58). Finally, the relative risk of local recurrence or progression was 0.38 (95% CI 0.27–0.53) for those undergoing extensive primary site resection compared to those who did not. The results of this analysis are presented in Fig. 5 and favor more complete resection of the primary tumor in stage 3 and 4 neuroblastoma. One must not forget that the primary effect of resection is local control and the results of our comprehensive literature review regarding this endpoint are depicted in Fig. 3. It should be noted that analysis of the German prospective clinical neuroblastoma trial (NB97), showed no impact of > 90% resection on either event-free survival or local control. However, the surgical question was retrospectively and not prospectively analyzed, and the overall event-free survival rate was comparatively low relative to other cooperative group studies. Although not yet published, initial results from the High Risk Neuroblastoma Study 1 (1.5) of SIOP-Europe (SIOPEN) (NCT01704716), in which the role of surgery was prospectively analyzed, showed a significantly improved event-free survival at three years (Keith Holmes, SIOPEN Surgery Subcommittee, personal communication, August 2013).

2. Alveolar rhabdomyosarcoma

Most patients with ARMS are classified as high risk. An important development in this field is the recognition of a specific fusion gene that occurs in most patients with ARMS [37,38]. Subsequent work has shown that it is the translocation rather than the histopathologic appearance (reminiscent of pulmonary alveoli) that determines biological aggressiveness in alveolar rhabdomyosarcoma [39,40]. This has been examined in a recent analysis showing that both overall survival and event-free survival were worse for fusion-positive alveolar rhabdomyosarcoma, while fusion-negative disease behaved like embryonal rhabdomyosarcoma (Fig. 6) [41]. Additionally, the proportion of patients with metastases was higher in fusion-positive but not fusion-negative ARMS. Thus, genetic events associated with fusion positivity more closely correlate with metastatic potential and prognostic risk. These data underline the importance of obtaining an adequate amount of tissue for molecular analysis when performing diagnostic biopsies.

Further, there are data that suggest that regional lymph node involvement in patients with alveolar rhabdomyosarcoma indicates a prognosis similar to patients with distant metastases [42] (Fig. 7). This finding suggests an expanded role for regional lymph node biopsy in patients with alveolar rhabdomyosarcoma. The state of the art for patients with ARMS includes a biopsy adequate to determine the existence of one of the specific translocations, as well as assessment of regional lymph nodes, by surgical means if necessary.

3. Desmoplastic small round cell tumor

Desmoplastic small round cell tumor is a relatively recently described, highly malignant polyphenotypic tumor with unknown cell of origin and an extremely poor prognosis [43]. As with alveolar rhabdomyosarcomas and many other sarcomas, there is a

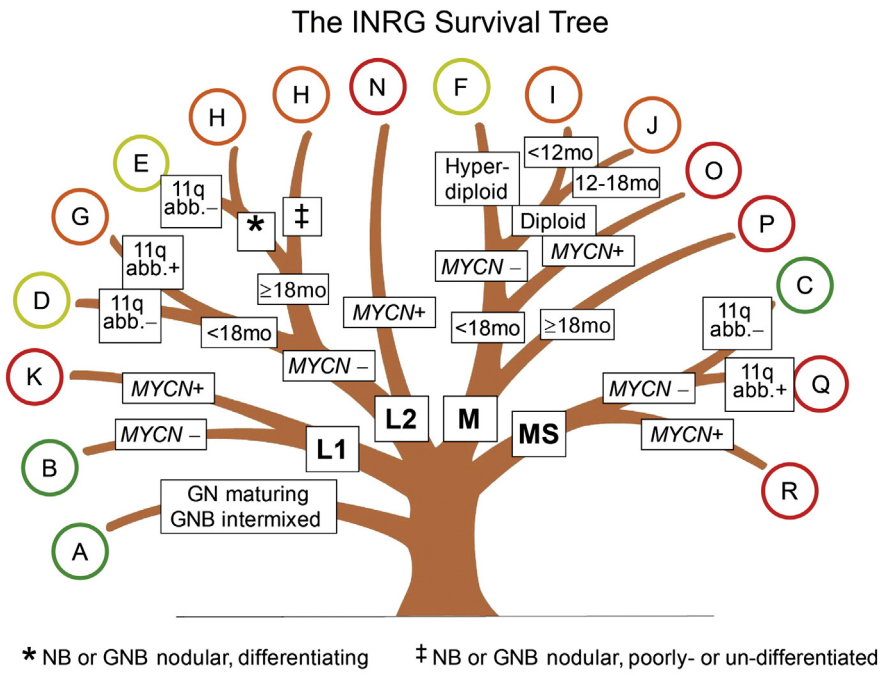

Figure courtesy of Tom Monclair, MD, PhD. Used with permission.

Fig. 1. This decision tree depicts the International Risk Group (INRG) staging system. Notation of the number and kinds of image-defined risk factors would be made for individual patients. Figure courtesy of Tom Monclair, MD, PhD. Used with permission.