Supratentorial Primitive Neuroectodermal Tumors in Young Children

To the Editor: In the April issue of the Journal of Clinical Oncology, Timmermann et al suggest that radiotherapy plays a major role in the treatment of young children with supratentorial primitive neuroectodermal tumors (stPNET) and conclude that a delay in irradiation may compromise survival.2 Although stPNET are undeniably aggressive brain tumors and results of treatments are still disappointing, the conclusions of Timmermann et al should be considered with caution.

Twenty-nine children younger than 37 months were diagnosed with stPNET and were registered in these consecutive multi-institutional protocols. The protocols used two different chemotherapy regimens, and recommendations regarding radiation were fundamentally different between HIT-SKK87 (all patients received systematic radiation at the age of 3 years, or earlier with progression) and HIT-SKK92 (radiation for patients > 18 months old with recurrence/progression). The 3-year overall survival and progression-free survival of 17.2% and 14.9% of patients, respectively, are in agreement with previous reports from cooperative groups. Five children were disease-free survivors (including four who received craniospinal irradiation [CSI]), and radiation therapy was a statistically significant factor for survival. Based on their experience, the authors recommend whole CNS irradiation (54 Gy to the tumor bed, 35 Gy CSI) and also advise limiting the delay of radiation to a maximum of 6 months.

The arguments of Timmermann et al3 are based on solid evidence that stPNET in infants has an aggressive behavior. However, their conclusions regarding the role of prophylactic radiation may be flawed, as they analyzed the impact of radiation after the fact. Almost every child whose parents, or treating physicians, refused irradiation for their children had early disease progression (14 of 15 patients). Conversely, the median time to progression was longer in the group that underwent radiation. Prophylactic radiation was offered for 10 children in remission at completion of chemotherapy. This certainly represents a subgroup of patients whose tumors behaved unusually, and one may wonder whether some of these patients who received radiation may have been overtreated. Only intent-to-treat statistics may help to refine the conclusions of this study.

In addition, detailed information on the five survivors is lacking, in particular their neurocognitive assessments. The morbidity related to CSI in very young children is well documented. Walter et al2 reported a median IQ of 62 (44 to 86) at 5 years in a cohort of 19 young children with medulloblastoma who received CSI at a median age of 3.3 years. As stPNET are located supratentorially, concerns regarding long-term effects of radiation are even more important, as the size of these tumors is often considerable3 and the morbidity of a boost greater than 50 Gy is a major issue. In the absence of measurable data on neurointellectual outcome, the conclusions and recommendations of Timmermann et al1 should be considered with extreme caution, since the decision to avoid or delay standard-dose CSI in infants is primarily based on the unacceptable long-term morbidity of this treatment modality in this specific population.

Long-term survival without radiation therapy has been reported using intensive or high-dose chemotherapy with stem cell rescue.4,5 Although the success observed with chemotherapy only is still low, new strategies are currently under investigation to improve these results. The recommended use of standard-dose CSI may represent a step back after 20 years of experience using and developing “baby brain” strategies.

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References

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The authors indicated no potential conflicts of interest.

In Reply: We appreciate the interest of Dr Larouche and colleagues in our report on very young children with supratentorial primitive neuroectodermal tumors (stPNET), and we would like to accentuate the conclusions of our initial report and the rationale behind them.

First, we agree completely that radiotherapy (RT) in young children with brain tumors is potentially harmful. In fact, we tried to emphasize the undisputable high risk of serious late effects associated with RT in young children. Herein lies the rationale for our approach of delaying or even avoiding RT in young children by introducing intensive chemotherapeutic regimen. Our conclusions on RT are based on a retrospective analysis, limiting the conclusiveness of our studies’ results. Nevertheless there is no clear indication that patients who received prophylactic radiation were overtreated, especially because reports on sustained tumor control without RT are limited to very small patient numbers in the respective age group so far.
Comparing children in remission who received prophylactic radiation (n = 10) with children in remission who received no prophylactic RT (n = 4; two without any RT, two receiving salvage RT), only three of 10 prophylactically radiated children survived. Furthermore, none of the four children in remission without prophylactic radiotherapy survived.

In addition, we consider the distinct differences in the results for the various tumor types treated by the same multimodal treatment protocols to be noteworthy. Despite the limited case numbers, evidence for a positive effect of radiotherapy on survival was observed in all subgroups of children with stPNET—children older than 3 years of age in the HIT88/91 study, children younger than 3 years in the HIT-SKK/92 study, as well as the subgroup of children suffering from pineoblastoma.\(^1,3\) In contrast, results were far better in children with early childhood medulloblastoma without radiotherapy,\(^4\) and complete tumor resection and initial tumor stage had higher impact than radiotherapy on survival in patients with ependymoma.\(^5,6\)

To our view, there is little evidence that radiotherapy can be avoided at present to achieve sustained tumor control in young children with stPNET. Trying to implement less intensive radiotherapy, we have increased the initial age for standard therapy from 3 to 4 years in the ongoing studies of the HIT group, and craniospinal irradiation is limited to 24 Gy. Clearly, craniospinal radiotherapy of 35 Gy is not recommended in any case for the treatment of very young children, as was alleged by Larouche et al.

We hope that effective “baby brain” strategies with further reduced, delayed, or omitted radiotherapy will be found in the future. We are also confident that increasing international cooperation in the research of rare pediatric tumors will contribute to improving the fate of our young patients.

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**Perioperative CA19-9 Levels Can Predict Stage and Survival in Patients With Resectable Pancreatic Adenocarcinoma**

**TO THE EDITOR:** In the June 20, 2006, issue of the *Journal of Clinical Oncology*, Ferrone et al\(^1\) propose to include the preoperative tumor marker CA19-9 concentration into a treatment decision model.

The authors have shown in their retrospective analysis of patients with serum bilirubin less than 2 mg/dL, that tumor burden correlates with CA19-9 concentrations. However, presentation of data not only as median values, but, for example, together with minimum and maximum values, would have shown the broad range of CA19-9 concentrations in individual patients.\(^2,3\) A low individual CA19-9 concentration in locally advanced or metastatic disease may underestimate tumor stage. Therefore, in the individual patient, the preoperative CA19-9 concentration is of limited value for treatment decision. In contrast, the change of CA19-9 concentration in the individual patient during serial measurements is of prognostic value in the perioperative and the metastatic situation. A falling CA19-9 concentration is associated with a significantly better prognosis.\(^4\) On the other side, increase of CA19-9 concentration after resection of the tumor or during chemotherapy correlates with recurrence and progression of the disease, respectively, and is associated with an extremely poor prognosis.\(^4\)

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