34. Plaschkes J, Perilongo G, Shafford E, *et al.* Childhood hepatoblastoma: an investigation into variables of prognostic relevance using data from the SIOP liver tumour study (SIOPEL-1) SIOP XXVII meeting abstract. *Med Ped Onc* 1995, **25**(4), 256.
35. Perilongo G, Brugieres, Plaschkes J, *et al.* SIOPEL 2 pilot study on hepatoblastoma—preliminary data. *Proc ASCO* 1998, abstract 1065.
36. Von Schweinitz D, Wischmeyer P, Leuschner I, *et al.* Clinicopathological criteria with prognostic relevance in hepatoblastoma. *Eur J Cancer* 1994, **30**, 1052–1058.
37. Van Tornout JM, Buckley JD, Quinn JJ, *et al.* Timing and magnitude of decline of alpha-fetoprotein levels in treated children with unresectable or metastatic hepatoblastoma are predictors of outcome: a report from the Childrens Cancer Group. *J Clin Onc* 1997, **15**, 1190–1197.

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Commentary

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PRIMARY TUMOURS of the liver occur rarely during childhood, comprising only 0.8–1% of all neoplasms in this age group. Most of these tumours are malignant. In fact, hepatoblastoma and hepatocellular carcinoma (HCC), growing from developing or adult hepatocytes, respectively, are the most important of these. Despite this fact, other entities are more common in some age groups, such as benign haemangioendotheliomas during the neonatal period.

In recent years, new insights into tumour biology and impressive improvement in clinical results have increased interest in hepatoblastoma as a typical malignancy of early childhood. Although it is true that the aetiology of hepatoblastoma is largely unknown, there exists increasing evidence that this tumour arises and differentiates from early hepatic progenitor cells, which in animal models are known as oval cells [1]. The reasons for malignant transformation of these immature liver cells, presumably during prenatal life, is not known. However, molecular genetic results indicate that several different genes act as putative tumour suppressor genes in the fetal liver, one of these being located at chromosome 11p 15.5, as has been mentioned in the Paediatric Update by Perilongo and Shafford above. Very recent findings have shown that stabilising and activating mutations of the β-catenin gene are important for the growth of many hepatoblastomas [2]. Interestingly, β-catenin is the target protein for the APC protein. This suggests that the molecular link between familiar polyposis coli and hepatoblastoma may be found here. Although far from being clear, these recent molecular findings make one suspect that there exist several biological 'types' of hepatoblastomas with different clinical behaviour, which are not clearly identified by conventional histology and immunotyping. Thus, prognostic groups are still most clearly defined by macroscopical findings, such as the growth pattern in the liver, vascular invasion and metastasising growth [3]. The recent finding mentioned in the Update, that very low birth weight may be associated with increased risk of hepatoblastoma, seems to be most important in this context. Further clinical analysis and biological research are important in order to clarify this aspect.

Alpha-fetoprotein is secreted by the majority of hepatoblastomas and is a typical serological marker for this tumour. Measuring this protein is very effective for monitoring therapy and the rate of decrease is a good indicator of patients' outcome. It has to be noted, however, that absolute values are not directly related to outcome, since both exceedingly high and normal low levels are associated with a poor prognosis [3].

The introduction of multi-agent neo-adjuvant chemotherapy had a dramatic effect on treatment results in hepatoblastoma. Therefore, currently cytotoxic drugs are an essential part of therapy protocols in all cooperative trials, and there is a strong trend towards increasing primary chemotherapy and delaying surgery. The new strategy of the SIOPEL protocol to reduce neo-adjuvant treatment to monotherapy with cisplatin, as mentioned in the Update, is being sceptically observed by many paediatric oncologists. It is known that hepatoblastomas develop resistance against cytotoxic drugs quite rapidly by upregulating several different molecular drug resistance mechanisms [4]. This is also the reason why not all groups follow the concept of prolonged neo-adjuvant chemotherapy for 'high risk' hepatoblastomas, but rather try to improve outcome of these patients by intensifying 'short term' chemotherapy, utilising high dose schedules and autologous stem cell rescue, to be followed by aggressive surgery or liver transplantation. The future will show which of these strategies will render superior results.

Nevertheless, it should be pointed out that surgery is still the mainstay of therapy in hepatoblastoma. It has been shown in all cooperative trials that after chemotherapy, the majority of all tumours are resectable, with a relatively low risk of severe surgical complications. Clinical and recent experimental data from our laboratory indicate that postresectional regeneration of the liver may induce growth of vital residual hepatoblastoma tissue presumably under the influence of cytokines. Therefore, resections of untreated tumours should not be attempted because of the risk of residual tumour or

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metastasis. It should be kept in mind that some hepatoblastomas, which are thought to be unresectable by non-specialised general or paediatric surgeons, could be radically removed by specialised liver surgeons utilising specific techniques. Thus, only very few children can be considered candidates for liver transplantation, which has been shown to render equally good results in hepatoblastoma as conventional surgery [5]. Furthermore, surgery also has an important role in the treatment of metastatic disease, as even children after repeated resections of pulmonary metastases have a chance of cure [6].

In order to facilitate a direct comparison for trial results, the introduction of common definitions are urgently needed [7]. To date, the different national and international study groups use their own staging system. One of these, the SIOPEL-PRETEXT grouping is presented in the Update. Yet, the prognostic impact of this system has not been definitively confirmed by all groups. Alternatively, the pTNM-system used for liver carcinoma could be used for this purpose, since it can be applied irrespective of therapeutic strategies and has been proved to be of high prognostic value in hepatoblastoma [3]. There is hope that a closer cooperation of the working groups on an international level will result in the application of a common staging system.

In contrast to hepatoblastoma, the mechanisms of tumorigenesis of HCC are different. Although not thoroughly understood, these tumours seem to arise from initially normal hepatocytes under the influence of transforming factors. Among these, hepatitis B and C viruses have been identified to be the most important ones in endemic areas, such as South-east Asia, Africa and South America. Thus, HCC usually occurs not only at an older age than hepatoblastoma but also displays a different biological behaviour. As stated by Perilongo and Shafford, HCC often grow multifocally in the liver and metastasise early. These tumours respond poorly to chemotherapy, which may be due to their expression of drug resistance mechanisms.

Therefore, therapy results are still disappointing and future treatment strategies cannot be the same as for hepatoblastoma. The very few patients with resectable HCC will benefit from primary surgery. This, however, is not applicable in the majority of patients. Many different treatment concepts tried in adults have not brought a breakthrough. Up to now, there exist no large cooperative therapeutic trials on HCC. Furthermore, it is not proven that treatment of HCC in adults will be as equally effective in children. Since childhood HCC is very rare in Western countries, an internationally organised trial is urgently needed, including countries with relatively high HCC prevalence in children. This could ideally be launched by the International Society for Pediatric Oncology (SIOP), which includes treatment centres from these countries and initiates activities to support paediatric oncology in the developing world. Yet, the problem still exists, which treatment elements should be combined in a strategy to make it most effective and, at the same time, keep costs low. A first important step has been taken in recent years in Taiwan, where the incidence of HCC in childhood was reduced by 50% after the introduction of a general hepatitis B virus vaccination programme for all infants [8]. Political steps and financial support are mandatory to transfer this experience to less developed countries with a high incidence of hepatitis B and C virus infection during childhood.

1. Ruck P, Xiao JC, Pietsch T, *et al*. Hepatic stem-like cells in hepatoblastoma. Immunohistochemical and immuno-electron-microscopic investigations with OV-1 and OV-6, and antibodies against cytokeratin 7 and albumin. *Histopathology* 1997, **31**, 324–329.
2. Pietsch T, Koch A, Denkhaus D, *et al*. Childhood hepatoblastomas frequently carry a mutated degradation targeting box of the β-catenin gene. *Cancer Res* 1999, **59**, 269–273.
3. von Schweinitz D, Hecker H, Schmidt-von Arndt G, *et al*. Prognostic factors and staging systems in childhood hepatoblastoma. *Int J Cancer* 1997, **74**, 593–599.
4. Bader P, Fuchs J, Wenderoth M, *et al*. Altered expression of resistance genes in hepatoblastoma xenografts incorporated in mice following treatment with doxorubicin and cisplatin. *Anticancer Res* 1998, **18**, 3127–3132.
5. Achilles OA, Brist JL, Kelly DA, *et al*. Unresectable hepatic tumours in childhood and the role of liver transplantation. *J Pediatr Surg* 1996, **31**, 1563–1567.
6. Black CT, Luck SR, Musemeche CA, *et al*. Aggressive excision of pulmonary metastases is warranted in management of childhood hepatic tumours. *J Pediatr Surg* 1991, **26**, 1082–1086.
7. Shafford EA, Pritchard J. Hepatoblastoma—a bit of a success story?. *Eur J Cancer* 1994, **30A**, 1050–1051.
8. Chang M-H, Chen C-J, Lai M-S, *et al*. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *N Engl J Med* 1997, **336**, 1855–1859.