Pergamon

*European Journal of Cancer*, Vol. 35, No. 6, pp. 953–959, 1999

Printed in Great Britain
0959-8049/99/$ - see front matter

PII: S0959-8049(99)00049-0

# Paediatric Update

# Liver Tumours

G. Perilongo[1] and E.A. Shafford[2]

[1]Division of Paediatric Haematology–Oncology, University of Padova, Italy; and [2]Department of Paediatric Oncology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE, U.K.

**Primary hepatic tumours in children represent an heterogeneous group of neoplasms. Malignant tumours are more common (60% of primary liver tumours), but account for only 1.2–5% of all paediatric neoplasms. There are two main types of malignant tumour, those of epithelial origin, hepatoblastoma (HB) and hepatocellular carcinoma (HCC), and the rarer mesenchymal tumours, e.g. rhabdomyosarcoma and undifferentiated sarcoma, (Weinberg AG, Finegold, MJ. Primary hepatic tumours of childhood. *Hum Pathol* 1983, 14, 512–532). Vascular tumours e.g. haemangioendotheliomas are the most common of the benign tumours followed by mesenchymal hamartoma and the rare hepatic adenoma and focal nodular hyperplasia. This article will concentrate on the malignant epithelial tumours.** © **1999 Elsevier Science Ltd. All rights reserved.**

**Key words: hepatoblastoma, hepatocellular carcinoma, chemotherapy, survival**
*Eur J Cancer*, Vol. 35, No. 6, pp. 953–959, 1999

## AETIOLOGY

THE INCIDENCE of hepatoblastoma (HB) throughout the world is fairly constant at 0.5–1.5 cases per million children. In most countries hepatocellular carcinoma (HCC) is less common than HB, but there is considerable geographic variation with rates ranging from 0.2 per million in England and Wales to 2.1 per million children in Hong Kong. In some populations e.g. Hong Kong and Taiwan HCC occurs more frequently than HB [2]. The aetiology of HB is largely unknown. It is considered to be an embryonic tumour whose genesis is thought to be related to a derrangement of the normal mechanism of cell proliferation and differentiation during hepatic organogenesis.

*Cytogenetic abnormalities*

Cytogenetic analysis of HB has been performed on a limited number of cases and only a few consistent chromosomal aberrations have been uncovered. Among these the most commonly found are trisomies of chromosome 20, 8 and of chromosome arm 2q (15–18), and the presence of double minute (3-D amplified genes) chromosomes (15, 17, 19) indicating gene amplification and possibly over-expression of oncogenes [3]. An unbalanced translocation between the long arm of chromosome 1 and 4, causing a partial trisomy of the large part of the long arm of chromosome 1 and a monosomy of the long arm of chromosome 4 has been reported by independent investigators. As many genes involved in cell growth regulation are located in the translocated 4p32 region and because this is the region of integration of the hepatitis B virus (HBV) in 10% of adult HCC, it is thought that this area may disclose important genes for HB development. Ten cases of HB with chromosome 1 abnormalities have been reported with a breakpoint at the 1q12-1q21 region.

*Molecular genetic abnormalities*

In HB, cytogenetic and loss of heterozygosity (LOH) analyses have uncovered frequent deletions of the short arm of chromosome 1 [4]. LOH on the distal part of chromosome lp with a common region mapped to 1p35-p36 has also been described in HCC. This may indicate that subsets of HB and HCC share a molecular pathway in their pathogenesis. Notably, neither patients with Beckwith-Wiedemann syndrome (BWs) nor patients with familial HB show LOH on chromosome 1. Deletions of the long arm of chromosome 1 have also been found with a common region of overlap in 1q31 and 1q42-3. Thus, the data suggest the location of several putative tumour suppressor genes in HB at both the long and the short arm of chromosome 1. Unlike many tumours of adulthood, including 25–30% of HCC, the *p53* gene has not been found to be altered in any of 50 independently studied HBs [5]. Loss of heterozygosity of chromosome 11p15.5

Correspondence to E.A. Shafford.
Received 1 Feb. 1999; accepted 3 Feb. 1999.

region, molecular genetic LOH and restriction fragment length polymorphism (RFLP) analyses have also indicated allelic loss of the chromosomal region 11p. This region is frequently altered in BWs patients. BWs is associated with a generally increased risk of developing embryonic tumours such as rhabdomyosarcoma, HB and Wilms' tumour (WT). LOH has been demonstrated at the 11p15.5 locus, which is also linked to BWs. HBs have been less intensively studied than WT, but frequent allelic loss in 11p15.5 has also been demonstrated in HB. Interestingly, LOH involved exclusively the maternal allele [6].

*Risk factors*

Most cases of HB appear to be sporadic but familial cases occasionally occur [7]. As well as the association between BW and HB mentioned above, there is known to be an association between familial adenomatous polyposis (FAP) and HB. FAP has been reported in relatives of children affected by HB as well as in some long-term HB survivors [8]. Patients with HB who later in life develop FAP also exhibit congenital hypertrophy of the retinal pigment epithelium (Gardner syndrome), which can be used as a marker for identifying carriers of the adenomatous polyposis coli gene.

Several recent papers have noted a possible association between very low birth weight and HB. In a review of the birth weights of all children with cancer enrolled into the Japanese Children's Cancer Registry from 1985 to 1993, there was an over-representation (58% of cases) of HB among children with cancer who had an extremely low birth weight [9]. Data from the U.S.A. shows a notable increase in the incidence of HB diagnosed among children less than 5 years of age during the period 1973–1992 [10]. This coincides with a period of marked improvement in survival of low birth weight infants. Further investigation is needed to determine whether factors associated with prematurity may play a role in the development of hepatoblastoma.

Hepatoblastomas almost always arise in an otherwise normal liver. Hepatocellular carcinoma, by contrast, is frequently associated with cirrhosis or another pre-existing parenchymal liver disorder [11]. The association of hepatitis B infection and HCC in adults has been well documented, and there are increasing numbers of reports of this association in children. Chen and colleagues demonstrated 100% positivity for HbsAg in 25 children with HCC in Taiwan [12]. Southeast Asia is a high prevalence area for HBV infection, but HbsAg in association with HCC in children has also been reported in Europe [13].

## PATHOLOGY

Hepatoblastoma is an embryonic tumour containing hepatic epithelial parenchyma and/or mesenchymal components. Based on the epithelial components, four major histological subtypes are identified (fetal, embryonal, macrotrabecular and undifferentiated), whereas the two mixed sub-types are distinguished by the presence or absence of teratoid features [14]. Epithelial components are frequently intermixed, but each may exclusively comprise a tumour. The significance of the histological subtype of HB as a prognostic factor is still under investigation [15, 16]. HCCs are of two main types, those resembling adult HCC with a trabecular pattern up to 20 layers of cells thick. The cells are usually larger than those of the surrounding liver, but vary markedly in size. Giant cells are common and mitoses frequent. Evidence of cirrhosis is seen in the non-tumorous liver in 10–70% of cases [17]. The fibrolamellar variant of HCC, which is probably a distinct clinicopathological entity, invariably arises in a non-cirrhotic liver. The two distinctive features of this epithelial tumour are: (i) tumour cells with eosinophilic cytoplasm; and (ii) broad fibrous septa dividing the hepatocytes into thin columns of cells or large nodules. Mitotic figures are rare [18].

## CLINICAL PRESENTATION, DIAGNOSIS AND STAGING

HB is a tumour of very young children. The median age of presentation is approximately 16 months; with congenital cases commonly included in every series so far published. However, cases in adolescents and adults have also been described. HCC, by contrast, is a tumour of older children with a peak incidence between 10 and 14 years. A male prevalence, especially for HCC, has been reported. HB may present as an asymptomatic abdominal mass. Weight loss, anorexia, vomiting and abdominal pain are usually a hallmark of advanced disease. Rare presenting features are pseudoprecocious puberty and the clinical stigmata of BWs [19]. HCC also presents as an abdominal mass or abdominal distension. Jaundice and abdominal pain may occur, especially in those patients with underlying liver disease.

*Laboratory findings*

Many patients are anaemic at diagnosis and thrombocytosis is common, especially in HB. The platelet count may be $> 1000 \times 10^9/1$, probably due to production by the tumour of a circulating 'thrombopoietin' [20]. Alpha fetoprotein (αFP) is produced by the normal fetal liver and, although present in decreasing amounts in the serum of babies up to 6 months old, is not normally detected in the serum of older children and adults [21]. An elevated level of serum αFP is found in more than 90% of cases of HB and 60–90% of HCC. It is a very sensitive tumour marker but not specific to hepatoma as elevated levels are also found in patients with malignant germ cell tumours, especially those containing yolk sac elements and some immature teratomas. Rarely HB cells secrete human chorionic gonadotrophin hormone (βHCG) causing virilisation in boys [22]. In patients with the fibrolamellar variant of HCC, serum αFP is normal but unsaturated vitamin B12 binding capacity is a useful tumour marker [23].

*Radiological findings*

The universal finding is a solid, usually non-cystic, intrahepatic mass documented by abdominal ultrasound, computer tomography scan (CT) and magnetic resonance imaging (MRI). Usually, on abdominal ultrasound, hepatocellular tumours are hyperechoic compared with the surrounding normal parenchyma. Abdominal CT scanning delineates the tumour which is characteristically of low attenuation compared with the surrounding liver. Involvement of the hepatic veins, inferior vena cava or portal vein is best seen after contrast enhancement. MRI gives definition of tumour and hepatic veins without intravenous (i.v.) contrast and permits assessment of the segmental extent of the tumour [24]. Lung CT scanning may reveal metastases not visible on chest X-ray. Bone metastases are so rarely reported at diagnosis that a bone scan is not usually part of the initial investigations.

*Diagnosis*

The combination of the clinical findings of young age (between 6 months and 3 years), elevated serum αFP,

thrombocytosis and an intrahepatic abdominal mass is considered almost pathognomonic of HB. Thus, many investigators argue that in these circumstances a surgical biopsy is not necessary to confirm the diagnosis. In fact in this age group, only anecdotal cases of intrahepatic primary malignant germ cell tumours or of HCC can be considered in the differential diagnosis of an αFP-producing intrahepatic mass. For patients less than 6 months or over 3 years of age histological diagnosis is always recommended. In the very young child (less than 6 months of age) αFP can be physiologically elevated; furthermore, other tumour types should be considered, mainly mesenchymal hamartoma (though this tumour is usually cystic) or haemangioendothelioma (even though this tumour usually has typical radiological findings); in children older than 3 years biopsy is necessary to distinguish between HB and HCC.

*Staging*

A universally accepted staging system for childhood hepatocellular tumours does not exist. This reflects the different approach to treatment adopted by the different study groups. The North American Co-operative Study Groups on HB favour a therapeutic approach based on primary surgery. They use a staging system based on the results of the initial attempt at complete resection of the tumour mass. Thus, four stages are identified: stage 1 complete resection, no microscopic residual disease, stage II microscopic residual, stage III macroscopic residual disease; and stage IV distant metastases.

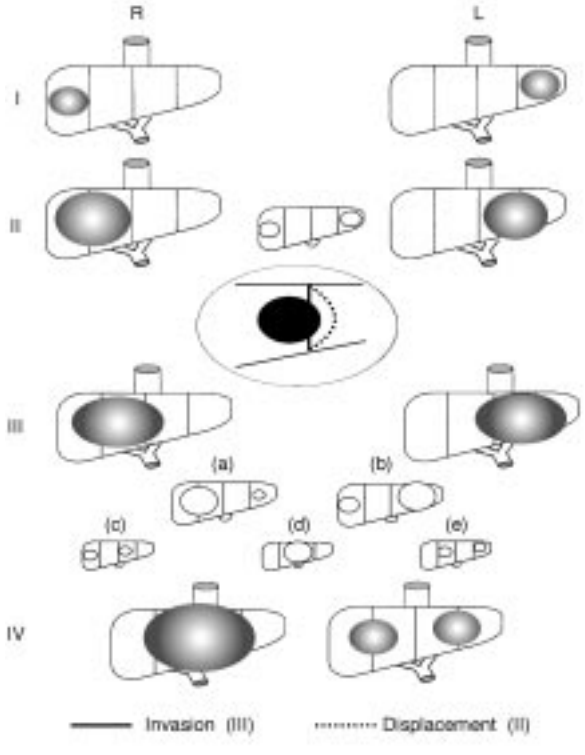


**Figure 1. The PRETEXT Pretreatment Extent of Disease system for staging paediatric liver tumours.**

This surgical staging system is in contrast to that used by the Liver Tumour Study Group of the International Society of Paediatric Oncology (SIOPEL), whose therapeutic strategy is based on primary chemotherapy. The PRETEXT system (pre-treatment extension of disease) describes the site and size of the tumour, invasion of vessels, and distant spread, as judged by pretreatment imaging with ultrasound, CT scans and MRI (Figure 1). The system identifies four PRETEXT categories (I–IV) which reflect the number of sections of the liver that are free of tumour, and describes the extension of the disease beyond the liver using the following letters, 'V' if the tumour extends into the vena cava and/or all three hepatic veins, 'P' if the main and/or both left and right branches of the portal vein are involved by tumour, 'E' if there is evidence of extra hepatic intra-abdominal disease and 'M' if there are distant metastases [25].

## MANAGEMENT AND PROGNOSIS

For both HB and HCC only complete resection of the tumour offers a chance of cure. However, surgery alone will cure very few patients. More than half of the patients present with unresectable primary tumours or distant metastases. In the early series of patients treated with surgery alone, there was a 30% relapse rate in those patients whose tumour could be completely resected [26]. Evidence that HB is a chemosensitive tumour began to accumulate in the early 1970s when responses were seen to combinations of cyclophosphamide, vincristine, 5-fluorouracil and actinomycin-D [27], but not until the introduction of cisplatin- and doxorubicin-containing regimens was there a major impact on survival. Chemotherapy may reduce tumour volume making the tumour resectable and may lead to the complete disappearance of lung metastases. The tumour response rate to the present cisplatin-containing chemotherapy regimens varies from 70 to 90% according to the different series [28–32]. Chemotherapy not only makes the tumour 'smaller' and consequently more likely to be completely resected, but also more solid, less prone to bleed and more demarcated from the remaining healthy liver parenchyma. Because of all these reasons some study groups currently recommend starting treatment, after biopsy, with preoperative chemotherapy, deferring definitive surgery until after 2 to 3 months of therapy. This is the treatment philosophy adopted by the SIOP Liver Tumour Group. In the SIOPEL 1 study [31] 134 HB patients were treated with preoperative chemotherapy (cisplatin, CDDP and doxorubicin, DOX), 113 of them (85%, 95% CI (confidence interval) 78–90%) had a tumour volume reduction, subsequently 95 had complete tumour resection upon delayed surgery (69%, 95% CI 61–77%). The complete resection rates of other modern series vary between 60 to 90% [29, 30, 32]. In contrast to the SIOP approach, the North American Study Groups still recommend primary surgery, whenever possible, as initial treatment. No controlled comparison has been done between the two therapeutic strategies, primary chemotherapy versus primary surgery, in terms of overall survival rates. However, the present survival rates of the different study groups are comparable, projecting 3-year overall survival rates, regardless of the first therapeutic modality used, of 62 to 70%. The different chemotherapy regimens used by the various study groups, with the respective survival data reported, are summarised in Table 1.

All groups give doxorubicin as a continuous i.v. infusion over 24–72 h in the hope of reducing cardiotoxicity.

*Table* 1. *Treatment results of the principal prospective cooperative studies of childhood hepatoblastoma*

| Study group [Ref.] | Years | Number of patients | Main treatment strategy CT regimen | Partial response to CT | Macroscopic complete resection | Survival |
|---|---|---|---|---|---|---|
| CCG-823 [29] | 1986–1989 | 33 Stage II 8, stage III 15, stage IV 10 | Primary surgery Cisplatin Doxorubicin | 76% | 70% Primary and 2nd look surgery | 2-year estimated survival 66.6% |
| POG ♯8697 [30] | 1986–1989 | 60 Stage I (UH) 16, II 5, stage III 31, IV 8 | Primary surgery Cisplatin, vincristine 5-fluorouracil | 92% Stages III and IV | 77% Primary and 2nd look surgery | 3-year DFS stage I (UH) and II 91% stage III 67% stage IV 12.5% |
| Intergroup Hepatoma Study [33] | 1989–1992 | 173 Stage I, 42, stage II 7, stage III 82, stage IV 42 | Primary surgery Cisplatin, vincristine 5-fluorouracil versus cisplatin, doxorubicin | Not known | Not known | 3-year OS 71% 3-year ES 63% |
| GPOH HB89 [32] | 1989–1993 | 72 Stage I 21, stage II, 6, stage III 38, stage IV 7 | Primary surgery Ifosfamide, cisplatin, doxorubicin | 98% Stages III & IV | 91% Primary and 2nd look surgery | DFS (median follow up 64 m) stage I 100% stage II 50% stage III 71% stage IV 29% |
| SIOPEL 1 [31] | 1990–1994 | 155 Pretext I 8% Pretext II 36% Pretext III 37% Pretext IV 19% | Primary chemotherapy Cisplatin, doxorubicin | 83% | 69% delayed surgery | 2-year OS 79% |

OS, overall survival; DFS, disease-free survival; EFS, event-free survival; CT, chemotherapy; UH, unfavourable histology.

However, continuing concern over the potential cardiotoxicity of doxorubicin, especially when given to infants, led to the POG 8697 study using cisplatin in combination with vincristine and 5-fluorouracil (CDDP/VCR/5-FU) [30]. This was followed by an Intergroup randomised study comparing this regimen to the cisplatin/doxorubicin (CDDP/DOX) combination used by the CCSG in the early 1980s [29].

The results, so far published only in an abstract format, have failed to show any differences in terms of overall and disease-free survival between the two arms, but with a definite advantage for the CDDP/VCR/5-FU arm in terms of reduced toxicity, especially anthracycline-related cardiotoxicity [33]. The SIOP Liver Tumour Study Group in their first study (SIOPEL 1) [31] using preoperative CDDP/DOX did not experience the same toxicity reported by the American Study Groups, perhaps due to a slightly lower total dose of doxorubicin.

HCC does not appear to be as chemoresponsive as HB although response to CDDP/DOX chemotherapy has been documented. 8 of 14 patients with HCC in the CCSG study had a partial response to this chemotherapy, although only 2 then achieved a complete resection [29]. In the SIOPEL 1 study 50% of patients showed some shrinkage of tumour and 58% showed a $>1$ log fall in αFP in response to CDDP/DOX. 35% of these patients had complete resection of primary tumour [31].

## WHAT THE FUTURE HOLDS

Very few clinical characteristics have been universally accepted as prognostic factors for childhood HB, but all groups agree that intrahepatic tumour extent and distant metastases are prognostic factors. In the SIOPEL 1 study patients were grouped into one of four PRETEXT categories according to whether one, two, three, or four hepatic sections were involved by tumour. Three-year event-free survival for patients with PRETEXT IV tumours was 44% compared with 100, 83 and 59% for patients with PRETEXT I, II, and III tumours, respectively. Presence of metastases at diagnosis was also associated with a worse prognosis, with 28% 3-year event-free survival compared with 77% for those without metastases [34]. As a result of these findings, in the SIOPEL 3 study, patients with HB are treated according to 'risk' category. Patients with localised HB (PRETEXT I-III), without evidence of extrahepatic disease (standard risk) are randomised to receive preoperative chemotherapy CDDP/DOX or CDDP alone. The monotherapy arm was piloted in 35 HB patients in the SIOPEL 2 study [35]. In this study, a response rate of 77.8% has been obtained. 'High risk' HB patients, those with PRETEXT IV tumours or evidence of extrahepatic disease, are treated with an intensive regimen based on a 15 day regimen of carboplatin/doxorubicin alternating with CDDP.

Other clinical characteristics have been proposed as possible negative prognostic factors, including a normal or exceedingly high (over 1 000 000 μg/l) αFP at diagnosis, vascular invasion and the tumour growth pattern within the liver (i.e. solitary nodule or multifocal tumour) [36]. All these factors need further investigation. The timing and magnitude of αFP decrease, in children with unresectable or metastatic HB, have also been correlated with long term outcome. Van Tornout and colleagues found that those children who had less than a 2 log decrease of the initial serum αFP value during preoperative chemotherapy and before surgery had a much worse outcome compared with children with a more significant reduction in the αFP value [37]. These findings need confirmation by other groups.

The role of orthotopic liver transplantation in the treatment of HB and HCC also needs to be clarified. In the SIOPEL 1 study 11 children affected by HB have been transplanted. Out of these 11 children, 9 are presently alive without evidence of disease at a median follow-up from diagnosis of 46 months (range 28–54), 2 died, 1 of tumour recurrence and the other from vascular complications after transplant. The patient who died of tumour was the only one transplanted at the time of (the first) tumour recurrence. 2 children with HCC were transplanted, 1 because of a PRETEXT IV tumour and the other because of underlying metabolic liver disease. Both patients are alive with no evidence of disease at 55 and 40 months, respectively. Orthotopic liver transplantation should be considered for patients who respond to chemotherapy but whose tumour remains unresectable. Owing to the shortage of donor organs, patients should be selected with extreme care and the procedure carried out in a quaternary referral centre. Some centres are using living related donors.

The prognosis for most patients with HCC remains poor and more effective chemotherapy is needed for those patients who present with unresectable disease at diagnosis. Some centres in Japan and the U.S.A. advocate the use of intra-arterial chemotherapy or chemoembolisation, but there is no evidence in children that this form of treatment is more effective than i.v. therapy with the same drugs. Co-operation with adult studies may be the way forward for this rare childhood tumour.

Much progress has been made in the past two decades in the treatment of children with these tumours, especially HB. This has been brought about by national and international cooperation of paediatric oncology centres. It is only through a continuation of this collaboration, gathering information from a large number of patients, that we will be able to increase our knowledge of the behaviour of these tumours and so improve our care of these children.


1. Weinberg AG, Finegold MJ. Primary hepatic tumours of childhood. *Hum Pathol* 1983, **14**, 512–532.
2. Parkin DM, Stiller CA, Draper GJ, Bieber CA. The international incidence of childhood cancer. *Int J Cancer* 1988, **42**, 511–520.
3. Mascarello JT, Jones MC, Kadota RP, Krous HF. Hepatoblastoma characterised by trisomy 20 and double minutes. *Cancer Genetics and Cytogenetics* 1990, **47**, 243–247.
4. Kraus JA, Albrecht S, Wiestler OD, *et al*. Loss of heterozygosity on chromosome 1 in human hepatoblastoma. *Int J Cancer* 1996, **67**, 467–471.
5. Debuire B, Paterlini P, Pontisso P, *et al*. Analysis of the p53 gene in European hepatocellular carcinomas and hepatoblastomas. *Oncogene* 1993, **8**, 2303–2306.
6. Albrecht S, von Schweinitz D, Waha A, *et al*. Loss of maternal alleles on chromosome 11p in hepatoblastoma. *Cancer Res* 1994, **54**, 5041–5044.
7. Fraumeni JF Jr, Rosen PJ, Hull EW, *et al*. Hepatoblastoma in infant sisters. *Cancer* 1969, **24**, 1086–1090.
8. Kingston JE, Herbert A, Draper GJ, Mann JR. Association between hepatoblastoma and polyposis coli. *Arch Dis Child* 1983, **58**, 959–962.
9. Ikeda H, Matsuyama S, Tanimura M. Association between hepatoblastoma and very low birth weight: a trend or a chance? *J Pediatrics* 1997, **130**, 557–560.
10. Ross JA, Gurney JG. Hepatoblastoma incidence in the United States from 1973 to 1992. *Med Ped Onc* 1998, **30**, 141–142.
11. Lack EE, Neave C, Vawter GF. Hepatocellular carcinoma. Review of 32 cases in childhood and adolescence. *Cancer* 1983, **50**, 1500–1515.
12. Chen WJ, Lee JC, Hung WT. Primary malignant tumour of the liver in infants and children in Taiwan. *J Pediatr Surg* 1988, **23**, 457–461.
13. Leuschner I, Hams D, Schmidt D. The association of hepatocellular carcinoma in childhood with hepatitis B infection. *Cancer* 1988, **62**, 2363–2369.
14. Weinberg AG, Finegold MJ. Primary hepatic tumours in childhood. In Finegold M. ed. Pathology of neoplasia in Children and Adolescents: Major Problems in Pathology. Philadelphia, WB Saunders, 1986, 333–372.
15. Haas JE, Muczynski KA, Kralio M, *et al*. Histopathology and prognosis in childhood hepatoblastoma and hepatocellular carcinoma. *Cancer* 1989, **64**, 1082–1095.
16. Conran RH, Hitchcock CL, Waclwiw MA, *et al*. Hepatoblastoma: the prognostic significance of histologic type. *Pediatr Pathol* 1992, **12**, 167–183.
17. Exelby PR, Filler RM, Grosfeld JL. Liver tumours in children with particular reference to hepatoblastoma and hepatocellular carcinoma: American Academy of Pediatrics Surgical Section Survey—1974. *J Pediatr Surg* 1975, **10**, 329–337.
18. Craig JR, Peters RL, Edmonson HA, Omata M. Fibrolamellar carcinoma of the liver. *Cancer* 1980, **46**, 372–379.
19. Stringer MD, Hennayake S, Howard ER, *et al*. Improved outcome for children with hepatoblastoma. *Br J Surg* 1995, **82**, 386–391.
20. Nickerson HJ, Silberman TL, McDonald TP. Hepatoblastoma thrombocytosis and increased thrombopoietin. *Cancer* 1980, **45**, 315–317.
21. Wu JT, Book L, Sudar K. Serum alpha fetoprotein (αFP) levels in normal infants. *Pediatr Res* 1981, **15**, 50–52.
22. Nakagawara A, Ikeda K, Tsureyoshi M, *et al*. Hepatoblastoma producing both fetoprotein and human chorionic gonadotrophin. *Cancer* 1985, **56**, 1636–1649.
23. Paradinas FJ, Melia WM, Wilkinson ML, *et al*. High serum vitamin B 12 binding capacity as a marker of the fibrolamellar variant of hepatocellular carcinoma. *Br Med J* 1982, **285**, 840–842.
24. Finn JP, Hall-Craggs MA, Dicks-Mireaux C, *et al*. Primary malignant liver tumours in childhood: assessment of resectability with high-field MR and comparison with CT. *Paediatr Radiology* 1990, **21**, 34–38.
25. Vos A. Primary liver tumours in children. *Eur J Surg Oncol* 1995, **21**, 101–105.
26. Feusner JH, Kralio MD, Haas JE, *et al*. Treatment of pulmonary metastases of initial stage 1 hepatoblastoma in childhood. *Cancer* 1993, **71**, 859–864.
27. Evans AE, Land VJ, Newton WA, *et al*. Combination chemotherapy (vincristine, adriamycin, cyclophosphamide, and 5-fluorouracil) in the treatment of children with malignant hepatoma. *Cancer* 1982, **50**, 821–826.
28. Ninane J, Perilongo G, Stalens JP, *et al*. Effectiveness and toxicity of cisplatin and doxorubicin (PLADO) in childhood hepatoblastoma and hepatocellular carcinoma: a SIOP pilot study. *Med Ped Onc* 1991, **19**, 199–203.
29. Ortega JA, Kralio MD, Haas JE, *et al*. Effective treatment of unresectable or metastatic hepatoblastoma with cisplatin and continuous infusion doxorubicin. A report from the Children's Cancer Study Group. *J Clin Oncol* 1991, **9**, 2167–2176.
30. Douglass EC, Reynolds M, Finegold M, *et al*. Cisplatin, vincristine and fluorouracil therapy for hepatoblastoma: a Pediatric Oncology Group Study. *Clin Oncol* 1993, **11**, 96–99.
31. Plaschkes J, Perilongo G, Shafford E, *et al*. Pre-operative chemotherapy—cisplatin (PLA) and doxorubicin (DO) PLADO for the treatment of hepatoblastoma and hepatocellular carcinoma—results after 2 years' follow-up. *Med Ped Onc* 1996, **27**, 256, abstract O182.
32. Von Schweinitz D, Byrd DJ, Hecker H, *et al*. Efficiency and toxicity of ifosfamide, cisplatin, and doxorubicin in the treatment of childhood hepatoblastoma. Study committee of the Cooperative Paediatric Liver Tumour Study HB89 of the German Society of Paediatric Oncology and Haematology. *Eur J Cancer* 1997, **33**, 1243–1249.
33. Ortega JA, Douglass E, Feusner J, *et al*. A randomised trial of cisplatin/vincristine/5fluorouracil vs cisplatin/doxorubicin iv continuous infusion for the treatment of hepatoblastoma. Results from the Pediatric Intergroup Study (CCG-8881/POG-8945). *ASCO Abstracts J Clin Oncol* 1994, **13**, 416.

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.

**PII: S0959-8049(99)00093-3**

# Commentary

D. von Schweinitz

Department of Paediatric Surgery, University Children's Hospital, Basel, Switzerland

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

Received 17 Mar. 1999; accepted 24 Mar. 1999.