Sultan Qaboos University Med J, February 2015, Vol. 15, Iss. 1, pp. e85–90, Epub. 21 Jan 15
Submitted 20 Mar 14
Revisions Req. 6 May & 3 Jul 14; Revisions Recd. 21 May & 5 Jul 14
Accepted 8 Jul 14

CLINICAL & BASIC RESEARCH

Hepatoblastomas in Oman
Unveiling success

*Fatma Rabah,[1] Nagwa El-Banna,[2] Dipali Bhuyan,[2] Ibrahim Al-Ghaithi,[2] Mohamed Al-Hinai,[2] Amal Al-Sabahi,[2] Nawal Al-Mashaikhi,[2] Ismail Beshlawi[1]

أورام الكبد الجنينيه في عمان
قصة نجاح

فاطمه رباح، نجوى البنا، ديبالى بويان، ، ابراهيم الغيثي، محمد الهنائي، امل الصباحية، نوال المشايخية، اسماعيل بشلاوي

abstract: ***Objectives:*** Primary malignant liver tumours account for more than 1% of all paediatric malignancies, with the most common form being hepatoblastomas (HB). Such malignancies among Arab populations have rarely been addressed in the literature. Using data from Oman's sole national referral centre for childhood solid malignancies, this study aimed to present the nationwide Omani experience with HB over the past 21 years. ***Methods:*** This retrospective study reviewed the medical records of all children with HB who were managed in the Royal Hospital, Muscat, Oman, between January 1991 and April 2012. Clinical, radiological and laboratory characteristics were examined as well as treatments and outcomes. ***Results:*** During the study period, 15 patients with HB were treated. Of these, 10 have survived to date. Nine of the survivors were no longer receiving treatment and one patient still had the disease but was in a stable condition. Of the remaining five patients, three did not survive and two were lost to follow-up. The survival rate among patients who completed therapy was 91%. ***Conclusion:*** HB has an excellent prognosis in Oman. The main obstacle to improving outcomes among Omani patients is non-compliance with therapy.

Keywords: Hepatoblastoma; Neoadjuvant Therapy; Hepatic Cancer; Oman.

الملخص: الهدف: تمثل أورام الكبد الخبيثة الأولية أكثر من 1% من جميع الأورام الخبيثة عند الأطفال واكثرها شيوعا الورم الجنيني. نادرا ماوصفت تلك الأورام بين السكان العرب في الأدبيات المنشورة. باستخدام بيانات مركز عمان الوحيد الوطني للأورام الخبيثة الصلبة في الأطفال، فإن هدف هذه الدراسة هو تقديم التجربة العمانية الوطنية مع أورام الكبد الجنينية منذ 21 سنة. **الطريقة:** استعرضت هذه الدراسة بأثر رجعي السجلات الطبية لجميع الأطفال الذين لديهم المرض وعولجو في المستشفى السلطاني في مسقط، سلطنة عمان، في الفترة من يناير 1991، وأبريل 2012. تم كذلك الفحص السريري، والخصائص الإشعاعية والمخبرية وكذلك العلاجات والنتائج لكل الحالات. **النتائج:** خلال فتره الدراسة عولج 15 طفلا لديهم ورم الكبد الجنيني. عشرة أطفال أتموا العلاج ووتعافوا حتى الآن. تسعة من الناجين لم يعودوا يتلقوا العلاج وطفل واحد لا زال عنده المرض ولكنه في حالة مستقرة. وبالنسبة للخمسة الباقين فثلاثة منهم توفوا واثنين فقدوا عند المتابعة. كان معدل البقاء على قيد الحياة لدى المرضى الذين أنهوا العلاج 91%. **الخلاصة:** علاج أورام الكبد الجنينية فى سلطنةعمان حقق نجاحا عاليا. العقبة الرئيسة أمام تحسين النتائج بين المرضى العمانيين هو عدم الالتزام بالعلاج.

مفتاح الكلمات: أورام الكبد الجنينية؛ العلاج المبدئي؛ سرطان الكبد؛ عمان.

Advances in Knowledge
- *This is the first study from Oman measuring the outcomes of childhood hepatoblastoma (HB) in terms of overall survival. There are very few studies of this kind in the Gulf Cooperative Council (GCC) region.*

Application to Patient Care
- *The results of this study will raise awareness among primary care physicians in the GCC region regarding the favourable outcomes for HB patients receiving treatment in Oman. An improved awareness of such positive outcomes would help improve patient counselling for chemotherapy and surgery.*
- *Raising awareness of these positive outcomes would also help reduce patient non-compliance with treatment as well as reduce the number of patients who choose to opt for treatment abroad.*

Approximately two-thirds of childhood liver tumours are malignant, with hepatoblastomas (HB) representing the most common type.[1–3] Other paediatric liver malignancies include sarcomas, hepatocellular carcinomas and germ cell and rhabdoid tumours.[1,4] HB accounts for 60–85% of all hepatic tumours in children, with an incidence of 0.5–1.5 per million.[2,3] HB is more frequent in males than females, with a median age at diagnosis of 18 months. Only 5% of patients present beyond

[1]Department of Child Health, Sultan Qaboos University Hospital; [2]Department of Paediatric Haemato-Oncology, Royal Hospital, Muscat, Oman
*Corresponding Author e-mail: fatmarabah@gmail.com

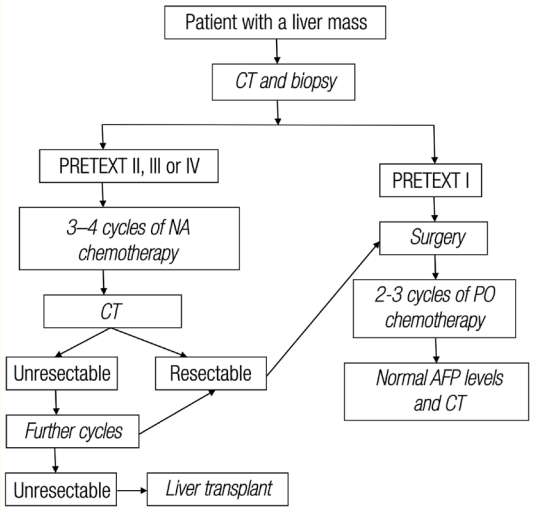

Figure 1: Flowchart identifying the process of paediatric hepatoblastoma management at the Royal Hospital in Muscat, Oman.

CT = computed tomography; PRETEXT = Pretreatment Extent of Disease staging system; NA = neoadjuvant; PO = postoperative; AFP = alpha-fetoprotein.

the age of four years. The right lobe of the liver is most commonly affected.[1] Histologically, HB is divided into either epithelial or mixed epithelial/mesenchymal tissue types, with the majority classified as epithelial and consisting of a mixture of embryonal and fetal cells.[3] Approximately 5% of HB cases are classified as small cell undifferentiated HB; this subtype is associated with a worse prognosis compared to other subtypes.[5–7]

The standard treatment for HB includes preoperative neoadjuvant chemotherapy, surgical resection and postoperative chemotherapy. The main determinants of clinical outcomes for patients with HB include the presence or absence of any metastatic disease and whether the tumour is resectable.[1–3] In addition, unique histological variants of HB, such as the small cell subtype, have been shown to adversely affect survival rates.[5–7] Conventional radical treatment (complete resection, neoadjuvant and adjuvant therapy and chemotherapy) is achievable in approximately 90% of patients, with 75–85% reportedly achieving long-term survival.[1–3] A liver transplant is the only remaining option for those patients with tumours that are rendered unresectable after a predetermined course of chemotherapy.[8]

Paediatric liver malignancies have been previously reported among the Omani population.[9] The current study aimed to present the nationwide Omani experience with paediatric HB over the past 21 years and to demonstrate the outcomes of standard treatment for HB in Oman.

Methods

This retrospective observational cohort study was undertaken at the Royal Hospital in Muscat, Oman. This large tertiary-level hospital is the only referral centre for paediatric solid tumours in the country. A retrospective review of the medical records of all children diagnosed with HB by pathological examination and managed at the hospital between January 1991 and April 2012 was undertaken. Data were collected from the records regarding patient demographics, clinical presentation, abdominal computed tomography (CT), magnetic resonance imaging (MRI), chest CTs (for pulmonary lesions), surgeries and pathology reports of biopsies. Alpha-fetoprotein (AFP) levels for each patient were recorded at diagnosis, before and after each chemotherapy course (neoadjuvant and postoperative), immediately after any operations and at the end of the therapy. Patients with other primary or secondary liver tumours were excluded from the study.

All patients diagnosed with HB before 2005 were classified according to the staging system of the North American Cooperative Group on HB.[10] Four stages were identified: stage I (complete resection with no microscopic residual disease); stage II (microscopic residual disease); stage III (macroscopic residual disease), and stage IV (distant metastases).[10] All patients diagnosed after 2005 were classified according to the Pretreatment Extent of Disease (PRETEXT) staging system.[11,12] Except for those classified as PRETEXT I, all patients were initially started on a neoadjuvant chemotherapy course to ensure safe and complete resection [Figure 1]. This chemotherapy course was repeated 3–4 times a week. After approximately 3–4 courses, patients were reassessed for tumour resectability. Once a tumour was deemed resectable, a standard anatomical resection with clear margins was attempted. Following this, postoperative chemotherapy was commenced. Upon completion of a determined number of chemotherapy courses and the normalisation of the patient's AFP levels, a CT was performed to confirm the response of the tumour and to inform decisions to end the therapy.

This study was approved by the Royal Hospital Ethical Committee.

Results

A total of 15 patients were diagnosed with HB during the study period. The mean age at diagnosis was 20.5 months (range: 5–68 months) with a male predominance of 3:2. A palpable mass in the abdomen was the main presenting symptom in 12 patients

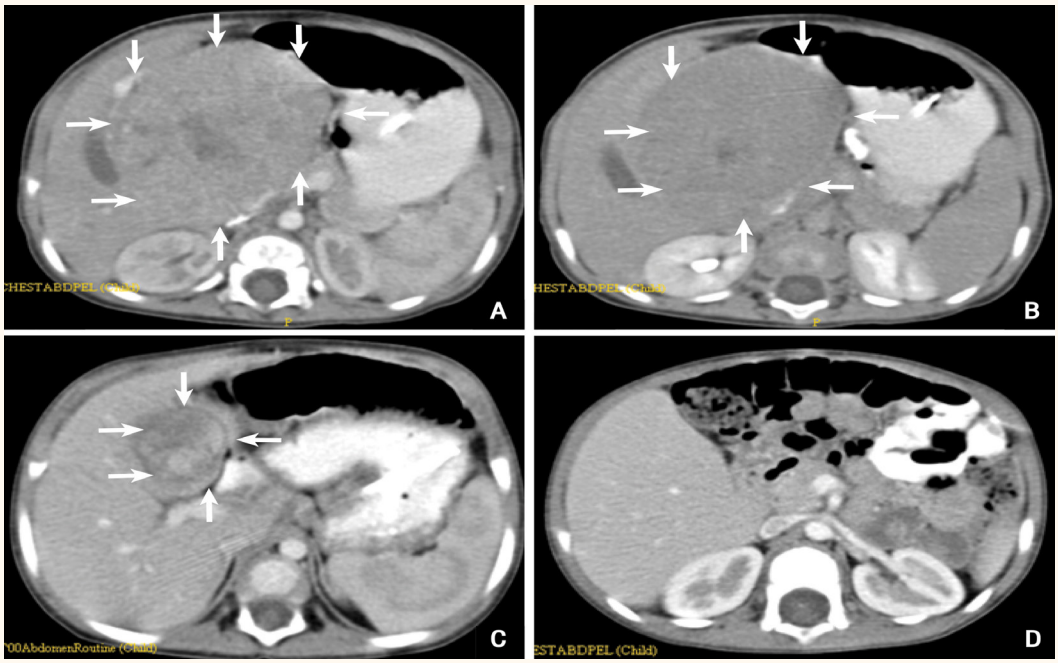

Figure 2A–D: Computed tomography (CT) scans of **(A)** a hepatoblastoma tumour arising from segment 4b of the liver as a heterogeneous mass with hypodense areas of central necrosis and **(B)** the same tumour post-contrast. Subsequent CT scans showed **(C)** a marked decrease in the size of the tumour after five courses of neoadjuvant chemotherapy and **(D)** the successful treatment of the tumour with a left lobectomy. The tumour was thus rendered resectable after neoadjuvant chemotherapy.

(80%). Of the remaining three patients, one presented with constipation, fever, irritability and excessive crying, the second had had a fever of unknown origin of one month's duration and the third patient presented with acute abdomen pain due to a ruptured tumour. One ex-preterm child with a congenital heart defect (tetralogy of Fallot) died before treatment could be administered. AFP levels were elevated in all but one of the patients. With the exception of two patients who were diagnosed by excisional biopsy, all cases of HB were diagnosed by a percutaneous needle biopsy of the liver.

With regards to CT findings, the tumour was observed to occupy the entire liver in seven patients, the right lobe only in four patients and the left lobe only in the remaining four patients. Pulmonary metastasis, in the form of multiple metastases in the left lung, was present in one patient at the time of diagnosis. After a preliminary work-up was completed, 12 patients received preoperative chemotherapy for 3–4 cycles starting within 7–10 days of the diagnosis. Upon parental request, one patient received a fifth cycle as a bridge therapy until surgery could be performed abroad. Postoperative chemotherapy was given in 2–5 cycles for 11 patients.

Patients underwent the following surgical procedures. One patient classified as PRETEXT I underwent a right hepatectomy which was not preceded by chemotherapy while another patient had an immediate surgical excision due to a ruptured tumour. Four patients had no surgical excisions, three were lost to follow-up and one was deemed unfit for surgery. One patient (PRETEXT IV) received chemotherapy followed by a liver transplant for bilateral multifocal HB; this procedure was performed overseas as such services are not currently offered in Oman. For the remaining nine patients, neoadjuvant chemotherapy rendered the tumours resectable [Figures 2A–D].

For follow-up surveillance after the patients were discharged, AFP levels were monitored monthly during the first year and then every three months for the following three years. Abdominal imaging using CT and ultrasound scans was done every three months for the first three years and on a yearly basis thereafter. Recurrence was detected by imaging results and the serial increment of AFP levels.

Of the 15 patients examined, 10 have survived to date following the completion of therapy. The median follow-up period was 74 months (range: 1–288 months). The Kaplan-Meier probability of survival estimate is shown in Figure 3. Event-free survival ranged from 1–20 years in nine of the patients, while one patient still had the disease but was in a stable condition at the time of writing. Among the five remaining patients, there were three fatalities. As mentioned earlier, one patient died from a cardiac comorbidity (tetralogy of Fallot) prior to treatment. Another patient defaulted twice on their treatment and later died of advanced

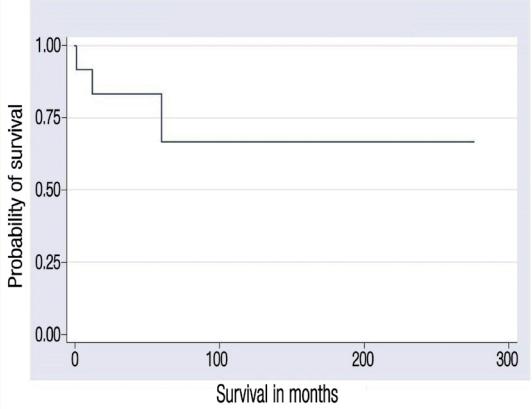

Figure 3: Kaplan-Meier probability of survival estimate curve for the paediatric hepatoblastoma cases identified over a 21-year period (N = 15).

refractory disease and the third patient died after multiple recurrences despite receiving therapy within the recommended timeframe. The remaining two patients were non-compliant with treatment and their outcome was unknown as contact was lost during the follow-up period. Of the 11 patients who completed therapy, there was a single mortality, resulting in a survival rate of 91%.

Discussion

This study presented the nationwide Omani experience with paediatric HB over a 21-year period. The results of this study mirror previous research on cancer treatment in Oman, where the outcomes of patients with early stages and fewer adverse prognostic factors are comparable to those reported in the international literature.[13] However, it is important to note that the management of HB in Oman has some unique characteristics. In some cases, patient treatment may be delayed for a number of reasons, for example if families wish to seek a second opinion or prefer treatment with traditional medicine (herbs and cautery). Choices such as these could be the result of social pressure from extended family. Moreover, one parent may request that either the other parent and/or the child being treated are not informed of the diagnosis and its implications. Patient non-compliance during HB treatment was a striking feature observed during this study; this type of behavior may have many negative repercussions. Parents may be reluctant to allow their child to continue chemotherapy or proceed with surgical resection after their child is in remission. This reluctance may be due to a fear of chemotherapy, which could potentially be aggravated when parents of children with the same condition socialise amongst themselves. As a result, one patient's morbidity or mortality might negatively affect treatment decisions for another when these parents share their experiences.

The incidence and survival rate of HB among Arab populations has rarely been discussed in the literature. One report from the United Arab Emirates (UAE) detailed 11 HB cases with a mortality rate of 45% following the death of five patients.[14] The current study noted a survival rate of 91% in Oman, a comparison which is favourable against that of the UAE. This rate is consistent with previously reported studies among other countries.[1,5,8] However, it is remarkable that this rate was achieved despite the fact that bilateral lobar involvement of the liver was most prevalent among the current study's patient population. This is in contrast to other research which indicates that right lobar involvement is most common.[1,2,8,7]

A study performed in El Salvador found that the severity of neutropaenic fever episodes in paediatric patients was associated with a low socioeconomic status or residence in rural areas.[15] Gavidia *et al*. reported significant relationships between maternal illiteracy, low household income and anticipated travel time to the hospital on the outcomes of febrile neutropaenia.[15] Similarly, the number and severity of febrile neutropenia episodes in the current study population were influenced by parental education, socioeconomic status and travel time.

Although HB is rare, it has gained attention in recent decades due to its incidence, which has increased by 5% annually.[8] As can be seen by the minimal number of HB patients observed in the present study despite the lengthy study period, the incidence of HB in Oman is low. However, the real incidence of this disease in Oman may be underestimated. Some patients may have died before diagnosis, while others may have been treated overseas. Nevertheless, considering a population of approximately three million,[16] the incidence of HB in Oman is almost identical to reported annual incidence rates of 0.5–1.5 cases per million.[2,3,8] However, the findings of the current study did not match those of other researchers regarding average patient age at presentation (20.5 versus 18 months in other studies).[1–3,5] It is likely that this difference is attributable to a delay among families seeking medical advice for their child.

There is mounting evidence suggesting an association between HB and prematurity.[1,17,18] The present study provides further evidence to support this association as one of the studied patients was an ex-preterm infant. Interestingly, several studies have observed that ex-preterm infants do not present with tumours at a younger age than term infants.[17,18] It has been theorised that observed increases in HB incidence could partly be due to increasing survival

rates among extremely premature infants.[1] Moreover, increases in HB incidence could also be a result of the adverse effects of neonatal intensive care.[17,18]

Regarding the laboratory findings at diagnosis, only one case in the present study had low AFP levels at presentation with histopathology indicating small undifferentiated cell HB. It has been found that this pathological subtype constitutes 5% of HB cases and has a poor prognosis, especially when coupled with low AFP levels at diagnosis.[5,6,19,20]

Chemotherapy played a pivotal role in inducing tumour resectability in the current study. A total of 10 patients had tumours that were initially inoperable. However, preoperative neoadjuvant chemotherapy enabled the tumours to be resected in nine of these patients. Surgical resection is the mainstay of HB therapy.[1,6] Approximately 10–20% of all HB cases involve the entire liver, are extensively multifocal or exhibit macrovascular invasion. Such cases require a liver transplant to achieve long-term survival, which ranges from 55–100% as reported in several single centre series.[8,21]

Although the HB survival rate in Oman was determined to be 91%, this good prognosis is not well known among primary care physicians. Thus, some families of HB patients may opt for overseas treatment or default on therapy without realising the significant impact this may have on the patient's chances of survival. A greater awareness of the success rate for HB therapy in Oman is required among treating physicians and their patients. The families of survivors should be encouraged to share their experiences with successful HB treatment in Oman.

Conclusion

Patients diagnosed with HB in Oman have an excellent prognosis, with the results of this 21-year study demonstrating a 91% survival rate. However, there is a need for greater awareness of this positive prognosis among primary care physicians in Oman in order to overcome patient non-compliance. Prevention of patient non-compliance could have a significant impact on the disease outcome and may be accomplished in collaboration with the families of survivors.

ACKNOWLEDGEMENTS

The authors are grateful to all the physicians, nurses and staff who participated in the care of the patients in this study, with special thanks to Dr. Anil Pathare.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

References

1. Mueller BU, Lopez-Terrada D, Finegold MJ. Liver tumors. In: Pizzo PA, Poplack DG, Eds. Principles and Practice of Pediatric Oncology, 5th ed. Houston, Texas, USA: Lippincott Williams & Wilkins, 2006. Pp. 887–904.
2. Stringer MD. Liver tumors. Semin Pediatr Surg 2000; 9:196–208. doi: 10.1053/spsu.2000.18844.
3. Litten JB, Tomlinson GE. Liver tumors in children. Oncologist 2008; 13:812–20. doi: 10.1634/theoncologist.2008-0011.
4. Allan BJ, Wang B, Davis JS, Parikh PP, Perez EA, Neville HL, et al. A review of 218 pediatric cases of hepatocellular carcinoma. J Pediatr Surg 2014; 49:166–71. doi: 10.1016/j.jpedsurg.2013.09.050.
5. Haas JE, Feusner JH, Finegold MJ. Small cell undifferentiated histology in hepatoblastoma may be unfavorable. Cancer 2001; 92:3130–4. doi: 10.1002/1097-0142(20011215)92:12<3130::AID-CNCR10115>3.0.CO;2-#.
6. Trobaugh-Lotrario AD, Tomlinson GE, Finegold MJ, Gore L, Feusner JH. Small cell undifferentiated variant of hepatoblastoma: Adverse clinical and molecular features similar to rhabdoid tumors. Pediatr Blood Cancer 2009; 52:328–34. doi: 10.1002/pbc.21834.
7. Perilongo G, Shafford E, Maibach R, Aronson D, Brugières L, Brock P, et al. Risk-adapted treatment for childhood hepatoblastoma: Final report of the second study of the International Society of Paediatric Oncology SIOPEL 2. Eur J Cancer 2004; 40:411–21. doi: 10.1016/j.ejca.2003.06.003.
8. Emre S, Umman V, Rodriguez-Davalos M. Current concepts in pediatric liver tumors. Pediatr Transplant 2012; 16:549–63. doi: 10.1111/j.1399-3046.2012.01704.x.
9. Ministry of Health Oman. Cancer Incidence in Oman: Report of 2010. Muscat, Oman: Ministry of Health. Pp. 86.
10. Malogolowkin MH, Katzenstein HM, Krailo M, Meyers RL. Treatment of hepatoblastoma: The North American Cooperative Group experience. Front Biosci (Elite Ed) 2012; 4:1717–23. doi: 10.2741/492.
11. Brown J, Perilongo G, Shafford E, Keeling J, Pritchard J, Brock P, et al. Pretreatment prognostic factors for children with hepatoblastoma: Results from the International Society of Paediatric Oncology (SIOP) study SIOPEL 1. Eur J Cancer 2000; 36:1418–25. doi: 10.1016/S0959-8049(00)00074-5.
12. Czauderna P, Otte JB, Aronson DC, Gauthier F, Mackinlay G, Roebuck D, et al. Guidelines for surgical treatment of hepatoblastoma in the modern era: Recommendations from the Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL). Eur J Cancer 2005; 41:1031–6. doi: 10.1016/j.ejca.2005.02.004.
13. Burney IA, Al Moundhri MS, Rizvi AJ, Ganguly SS, Al Abri R, Ashrafi RA. Outcome as a measure of quality of care in oncology: Experience at Sultan Qaboos University Hospital, Oman. Sultan Qaboos Univ Med J 2008; 8:27–36.
14. Nawaz A, Matta H, Jacobsz A, Mpofu C, Al-Salem A. Unresectable hepatoblastoma: The role of preoperative chemotherapy. Ann Saudi Med 1999; 19:553–6.
15. Gavidia R, Fuentes SL, Vasquez R, Bonilla M, Ethier MC, Diorio C, et al. Low socioeconomic status is associated with prolonged times to assessment and treatment, sepsis and infectious death in pediatric fever in El Salvador. PLoS One 2012; 7:e43639. doi: 10.1371/journal.pone.0043639.
16. Sultanate of Oman. Demographics. From: www.omansultanate.com/demographics.htm Accessed: Jul 2014.
17. Reynolds P, Urayama KY, Von Behren J, Feusner J. Birth characteristics and hepatoblastoma risk in young children. Cancer 2004; 100:1070–6. doi: 10.1002/cncr.20061.
18. Spector LG, Feusner JH, Ross JA. Hepatoblastoma and low birth weight. Pediatr Blood Cancer 2004; 43:706. doi: 10.1002/pbc.20122.

19. De Ioris M, Brugieres L, Zimmermann A, Keeling J, Brock P, Maibach R, et al. Hepatoblastoma with a low serum alpha-fetoprotein level at diagnosis: The SIOPEL group experience. Eur J Cancer 2008; 44:545–50. doi: 10.1016/j.ejca.2007.11.022.

20. Jassem N, Jones CM, Briscoe T, Horner JH. The hook effect: A need for constant vigilance. Ann Clin Biochem 2006; 43:314–17. doi: 10.1258/000456306777695726.

21. Hishiki T, Matsunaga T, Sasaki F, Yano M, Ida K, Horie H, et al. Outcome of hepatoblastomas treated using the Japanese Study Group for Pediatric Liver Tumor (JPLT) protocol-2: Report from the JPLT. Pediatr Surg Int 2011; 27:1–8. doi: 10.1007/s00383-010-2708-0.