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Predictors of survival after resection of children with hepatoblastoma: A single Asian center experience

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Abstract

Aim: The aim of this study is to investigate and identify the predictors associated with the prognosis of patients with hepatoblastoma (HB).
Methods: We retrospectively reviewed 112 children with HB (58 female, 54 male) managed in our institution between May 1st, 2001 and January 30th, 2012. Prognostic factors were evaluated using Kaplan–Meier curves and Cox proportional hazards models.
Results: For the entire cohort of 112 patients, the overall median survival was 83.5 months, and the 5-year EFS and OS rates were 57.1% and 63.4%, AFP<100 or >1000 (ng/ml)(HR:2.454, $P = 0.013$), multifocality (HR:2.852, $P = 0.012$), vascular invasion (HR:2.272, $P = 0.026$), metastases (HR:2.654,$P = 0.005$) and PRETEXT stage (HR:2.817, $P = 0.005$) were associated with an adverse prognosis in the univariate and multivariable adjusted analysis. Based on these findings, a prognostic scoring system was developed that allotted one point each for these factors. Patients with HB could be stratified into 3 distinct prognostic groups (median and 5-year EFS, respectively): 0 points (105.1 months, 94.1%), 1–2 point (85.8 months, 60.2%), and 3–4 points (31.8 months, 13.5%) ($P < 0.001$).
Conclusions: We have confirmed the HB prognostic factors associated with survival in the Asian population and established a simple prognostic scoring system.

Keywords: Hepatoblastoma; Survival; Prognosis; Liver tumor

Introduction

Hepatoblastoma(HB) is the most common primary malignant hepatic tumor in young children, representing 0.8%–2.0% of all pediatric malignancies.[1,2] Survival outcome had improved over the past decades due to the advent of efficacious chemotherapy and the innovation of surgical techniques.[3] Children with HB respond well to chemotherapy and have a high cure rate (3-year overall survival (OS):70%). Although children with HB is generally thought to have a good prognosis, the survival outcomes following surgical resection may vary, as several factors are associated with the prognosis of HB, including completeness of tumor removal (the most important prognostic factor), serum alpha-fetoprotein (AFP) levels, tumor size, tumor multifocality and distant metastases, etc.[4,5] The standard treatment of HB includes preoperative (neoadjuvant) chemotherapy, surgical resection, and postoperative chemotherapy.[6,7]

At present, based on the Pre Treatment Extent of Disease staging System (PRETEXT), the Liver Tumor Study Group of the International Society of Pediatric Oncology (SIOPEL) group stratified patients with HB into two categories: the standard and high risk groups.[8] The standard risk group encompassed patients with a primary tumor completely confined to the liver and involving no more than three hepatic sections (PRETEXT I, II or III).[9] Patients were included in the high risk group if they presented with a tumor involving all four sections of the liver (PRETEXT

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IV) and/or the portal vein, both of the right and left branches (P+) and/or all three hepatic veins or the inferior vena cava (V+) and/or intra-abdominal extrahepatic disease (E+) and/or metastases (M+) and/or serum alpha-fetoprotein (AFP) less than 100 ng/ml. In addition, children suffered from tumor rupture at diagnosis were allocated to the high risk group since 2004.[10]

In this study, we investigated the clinical and tumor characteristics of children with HB to identify the predictors associated with the prognosis of HB in a large Asian cohort of a single institution (Capital Institute of Pediatrics, Beijing. China). We also built a prognostic scoring system, which was based on the characteristics of Chinese patients, to predict the survival of children with HB after hepatic resection.

Patients and methods

Patients

We retrospectively reviewed 112 children with HB (58 female, 54 male) managed in our institution between May 1st, 2001 and January 30th, 2012. Tumor extension was graded using the PRETEXT system (based on the revised version by D. J. Roebuck).[11] Ethics approval from the Ethics Committee of Capital Institute of Pediatrics was obtained. Written, informed consents were obtained from the parents of HB patients before the study.

Diagnosis and treatment

After a detailed history and a thorough physical examination, blood was collected for liver function test and tumor markers including alpha-fetoprotein (AFP), carbohydrate antigen 19-9 (CA19-9), and carcinoembryonic antigen (CEA). Other routine investigations included chest X-ray, upper gastrointestinal endoscopy, abdominal ultrasound, contrast-enhanced computerized tomography (CT) and/or magnetic resonance imaging (MRI). In recent years, positron emission tomography (PET) was added to the investigation in patients with clinical or radiological suspicion of intrahepatic or extrahepatic metastases.

Liver resection was carried out, taking note of the tumor diameter, location, tumor extension and estimated volume of the remaining liver. Liver resection was performed following Couinaud's segments, sectors and hemilivers.

Histopathological study of the resected specimens were carried out independently by three pathologists and by consensus should there be any disagreement.

Follow-up

Postoperative serum AFP and abdominal ultrasound were carried out in all patients monthly. Patients received abdominal contrast-enhanced CT scan or MRI once every 3 months in the first two years after surgery, and once every 6 months thereafter. Further investigations were carried out when clinically indicated or when tumor recurrence was suspected.

Outcome definitions: Complete resection was defined as resection of all tumor sites on the basis of surgical findings and postsurgical images. Overall survival (OS) was defined as the period from the date of surgery until death or last contact. Patients who did not experience an event were censored on the date of last contact. Event-free survival (EFS) was defined as the period from the date of surgery until an occurrence of event (progressive disease, death, diagnosis of a second malignant neoplasm) or last contact, whichever occurred first.

Statistical methods

Continuous variables were expressed as mean ± SD (standard deviation) and compared using a two-tailed unpaired Student's t test; categorical variables were compared using $\chi 2$ or Fisher analysis. The cut-off of AFP level was defined by the receiver-operating characteristic (ROC) curve analysis.[12] Predictive performance of the prognostic systems was measured using the Area Under ROC Curve (AUC). Life-table estimates of survival time were calculated according to the Kaplan and Meier methodology.[13] The Greenwood formula was used for the standard deviation. A Cox proportional hazards regression approach[14] was chosen for the evaluation of EFS as the primary endpoint. Potential prognostic variables were analyzed both univariately with one factor taken at a time, and then in a multivariate model combining all factors. Results were showed as hazard ratios (HR) and their 95% confidence intervals (CI) An HR > 1 indicated an elevated risk with respect to the reference category. A confidence interval which did not include the value 1 indicated statistical significance at the 5% level. It should be noted that this was a retrospective evaluation and therefore statistical significance should be interpreted with caution. All statistical evaluations were carried out using SPSS software(Statistical Package for the Social Science, version 15.0, SPSS Inc,Chicago, IL). A value of $p < 0.05$ was considered to be statistically significant in all the analyses.

Results

Patients' characteristics

One hundred and twelve children were recruited into the study from the Capital Institute of Pediatrics. The median follow-up was 5.2 years (range 7.4 months–10.5 years). The baseline characteristics of patients at diagnosis were summarized in Table 1. Overall, these patients had a median age of 1.6 years. The gender distribution was roughly equal (M:F = 48.2%:51.8%). The PRETEXT status of most patients were PRETEXT III(37.5%), and PRETEXT IV(45.5%). Most patients had solitary tumors (85.7%),