Seminars in Pediatric Surgery 25 (2016) 265–275

Contents lists available at ScienceDirect

Seminars in Pediatric Surgery

journal homepage: www.elsevier.com/locate/sempedsurg

Malignant tumors of the liver in children

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ARTICLE INFO

Keywords:
Pediatric liver tumors
PRETEXT/POST-TEXT
Liver resection
Pediatric liver transplantation
Pathology
Risk stratification

ABSTRACT

This article aims to give an overview of pediatric liver tumors; in particular of the two most frequently occurring groups of hepatoblastomas and hepatocellular carcinomas. Focus lays on achievements gained through worldwide collaboration. We present recent advances in insight, treatment results, and future questions to be asked. Increasing international collaboration between the four major Pediatric Liver Tumor Study Groups (SIOPEL/GPOH, COG, and JPLT) may serve as a paradigm to approach rare tumors. This international effort has been catalyzed by the Children's Hepatic tumor International Collaboration (CHIC) formation of a large collaborative database. Interrogation of this database has led to a new universal risk stratification system for hepatoblastoma using PRETEXT/POSTTEXT staging as a backbone. Pathologists in this international collaboration have established a new histopathological consensus classification for pediatric liver tumors. Concomitantly there have been advances in chemotherapy options, an increased role of liver transplantation for unresectable tumors, and a web portal system developed at www.siopel.org for international education, consultation, and collaboration. These achievements will be further tested and validated in the upcoming Paediatric Hepatic International Tumour Trial (PHITT).

Introduction

Although rare, hepatoblastoma (HB) is the most frequent of the malignant pediatric liver tumors. After neuroblastoma and nephroblastoma, HB is the third most common *abdominal* solid tumor in very young children. Hepatocellular carcinoma (HCC) is most often seen in older children and adolescents.[1] An interesting hybrid tumor, HB with features of HCC variably called transitional or "not-otherwise-specified" (NOS), exists on the age continuum between HB and HCC. In Asia and Africa, hepatocellular carcinoma (HCC) occurs more frequently than HB, which is probably a consequence of the higher prevalence of hepatitis B infection on those continents. Interestingly, the incidence of HCC seems to have decreased in some countries as a consequence of wide spread vaccination programs against hepatitis B infection in these areas.[2] In today's age of electronic communication, the possibility of collaboration on an international scale has increasingly facilitated treatment and research of these rare tumors. For example, in addition to international cooperative research and education services, advice on treatment of difficult cases is now possible with the support of a consultation service which can be accessed under the *virtual consultation service* tab on the international pediatric liver tumor website (www.siopel.org). This virtual consultation service gives any interested treating clinician, some of whom may see a pediatric liver tumor only once every few years, real time access to expert opinion from an international panel of pediatric liver tumor oncologists, pathologists, radiologists, and surgeons.

Hepatoblastoma (HB)

The treatment of hepatoblastomas has been one of the success stories of pediatric oncology. From a disease with a dreadful outlook with survival rates around 35% in the seventies of the last century, survival has now reached over 90% for patients with standard risk tumors, and 45–80% for patients with metastatic disease.[3–7] Progress has been made due to improved surgical technique and better risk stratified chemotherapy based on increasingly refined risk factors. In addition, sharing of accumulated experience through improved international collaboration has lead to an increase in our understanding of the tumor biology in the past decade. Promising new results from our collaborating biology laboratories are now beginning to identify poor molecular

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http://dx.doi.org/10.1053/j.sempedsurg.2016.09.002
1055-8586/

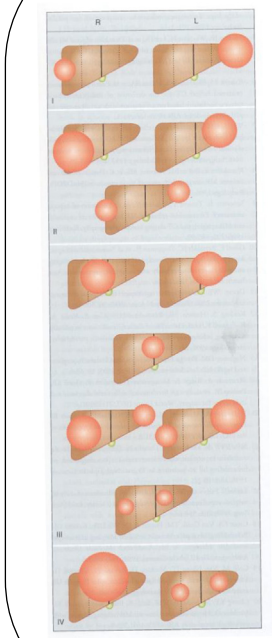
prognostic factors such as the NFR2 mutation and a high risk 12 gene signature.[8–12] These may open the way to the development of new personalized targeted therapies in the future.

Incidence, clinical features, and risk factors

Hepatoblastoma comprises 1% of all pediatric malignancies. It occurs equally in males and females most often presenting in infants and young children between 6 months and 4 years of age, with a median age of onset of 18 months; it is rare after 5 years of age and seems to behave more aggressively in children over 8 years.[13] Cases in neonates and adolescents have also been reported. The annual incidence is fairly constant with 1.0–1.5 cases per million children per year younger than 15 years of age in Western countries, with a small increase reported in the USA and Europe. Children most commonly present with slowly progressive abdominal distension or an asymptomatic abdominal mass. Occasionally a young infant may present with the clinical features and abdominal signs of an acute abdomen due to acute intra-tumor hemorrhage, either from spontaneous or traumatic tumor rupture. These infants may become very unwell from bleeding and associated fluid volume loss with a risk of death from hemorrhagic shock. Hepatoblastoma most commonly disseminates to the lungs and very rarely to the local abdominal lymph nodes, neither of which are associated with symptoms or clinical signs. A clinical presentation of acute or chronic liver dysfunction is unusual and liver function is preserved until very late stage disease. Most cases are sporadic but some are associated with genetic cancer syndromes like Beckwith–Wiedemann syndrome, Familial Adenomatous Polyposis or trisomy 18/Edwards syndrome and suggest a role in the pathogenesis of HB for chromosomes 5, 11, and 18, respectively.[14] Also prematurity and very low birth weight have been associated with hepatoblastoma, and increases in premature birth rates have been postulated to drive an increase in hepatoblastoma incidence.[15,16]

Radiographic imaging, staging (including PRETEXT), and risk stratification

As staging and treatment have become more and more dependent on imaging, good quality radiographic imaging is of vital importance. Either contrast enhanced computed tomography (CT) or MR is recommended. Many radiologists feel that MR angiography enhanced by hepatocyte specific contrast agents such as eovist gadolinium may improve differential diagnosis and detection of small disease deposits that can be seen with multifocal disease.[17,18] It has been one of the earliest achievements of the SIOPEL group to produce a preoperative staging system (Pretreatment Extent of Disease or PRETEXT), based on radiological imaging. A non-surgical, radiographic system had to be developed when SIOPEL began treating all patients with primary chemotherapy in the 1980s. The North American approach at this time was surgical staging based on attempted resection at diagnosis. Over the years it has become clear that while small localized tumors may be amenable to up-front resection, patients with extensive tumors may benefit from preoperative chemotherapy and the PRETEXT staging groups (I, II, III, IV) which define extent of liver parenchyma involvement have stood the test of time (Figure 1). The PRETEXT annotation factors which help to define the extent and nature of any extrahepatic disease have evolved over time. Initially just V, P, E, and M, these factors now include V, P, E, F, R, N, C, and M defined as tumor involvement of the hepatic veins or retrohepatic vena cava (V); main portal or portal bifurcation (P); contiguous organ such as diaphragm, abdominal wall, bowel, etc. (E); multifocal tumor nodules (F); tumor rupture at diagnosis (R); lymph nodes (N); caudate lobe (C); and distant metastatic (M). PRETEXT group is highly predictive of outcome and this system has been adopted as the common international language for hepatoblastoma staging now used in some form by all major multicenter trial groups.[19–21] The current COG study AHEP-0731 has used PRETEXT to POST-TEXT (Post-treatment



PRETEXT/POSTTEXT

The tumor is classified into one of the following four PRETEXT stages depending on the number of liver sectors that are invaded by tumor :

PRETEXT I, one sector invaded

PRETEXT II, two sectors invaded (or one sector invaded in each hemi-liver)

PRETEXT III, three sectors invade (or two sectors in one hemi-liver and one nonadjacent sector in the other hemi-liver)

PRETEXT IV, all four sectors invaded

Additional criteria (annotation factors):

V	Involvement of the IVC and/or hepatic veins
P	Involvement of the portal vein
E	Extrahepatic abdominal disease
F	Tumour focality
R	Tumour rupture or intraperitoneal haemorrhage
N	Lymph node metastases
C	Caudate lobe involvement
M	Distant metastases

Fig. 1. PRETEXT groups I, II, III, and IV, and PRETEXT Annotation Factors (V, P, E, F, R, N, C, and M).