Pediatric Liver Tumors: Hepatoblastoma

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Overview

An introduction to hepatoblastoma and salient issues

1. Epidemiology & associations
2. Management approach (‘how pediatric folks do it’)
3. Key current topics

Big Ideas

1. From diagnosing and treating a rare disease… to developing evidence-based management for a rare disease – globally

2. Management and decision making in a truly multidisciplinary manner

3. Unknown issues persist in pediatric liver tumor domain

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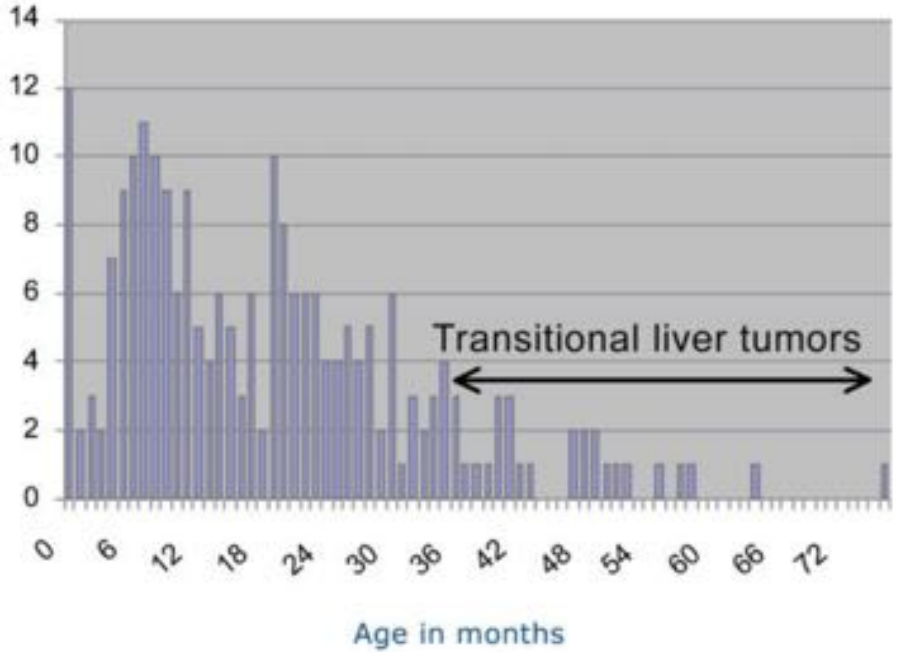
EPIDEMIOLOGY & ASSOCIATIONS

Epidemiology

Liver tumours rare in children

- Hepatoblastoma: 0.8 – 1.6 per million children
- HCC: even less common.

- 90% of liver tumours in children <4y are hepatoblastoma



Liver tumors in older chlidren

- Transitional liver tumors of childhood: features of hepatoblastoma & HCC (~4-10 yo)
- Embryonal sarcoma of liver (UESL) (>12 yo)
- HCC

Associations

Very low birth weight

- Suspected iatrogenic carcinogen hazards in NICUs, a/w neonates' decreased xenobiotic, antioxidant defenses
- Possible etiologies:
  - Ionizing radiation
  - High-fraction oxygen
  - TPN
  - di-(2-ethylhexyl)phthalate from plastic tubings (rodent hepatocarcinogen)

Site	n	Lowest BW	O.R. (95% CI)	Ref
Japan	543	<1,000 g	15.6 (7.6–31.1)	Tanimura. Cancer Res 1998.
UK	18	<1,500 g	69 (12.0–397.2)	Ansell. Eur J Cancer 2005.
US	273	<1,500 g	17.2 (7.5–39.5)	Spector. Pediatrics 2009.
China	87	<2,500 g	26 (14.0–65.7)	Pu. Zhonghua GZBZZ 2009.
Nordic	155	<1,500 g	9.5 (2.3–38.2)	de Fine Licht. Int J Cancer 2011.

- Maternal pre-eclampsia, poly-/oligohydramnios, obesity, IVF
- … but not associated with parental age

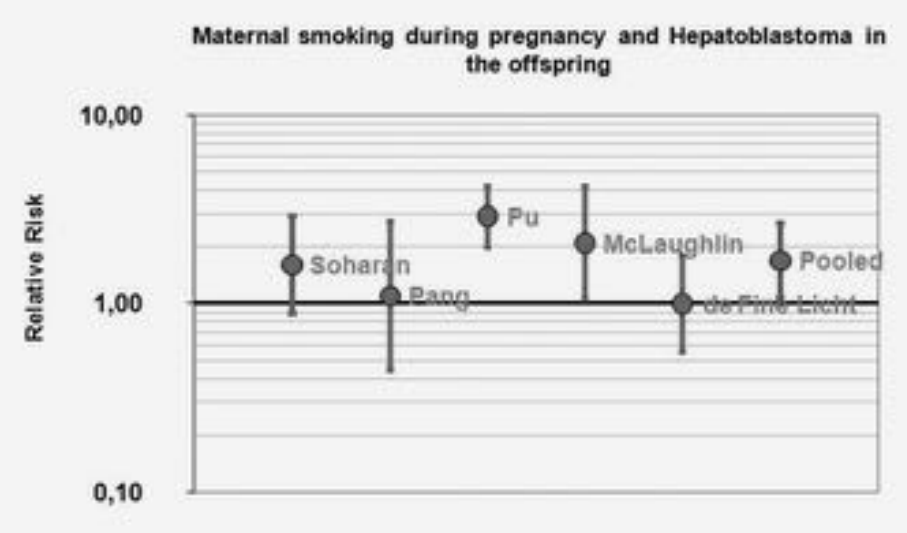
Associations

Parental tobacco use

- Associations with smoking by either parent
- Evidence with timing of exposure

- IARC declared parental tobacco smoking a carcinogen to fetal liver (2009) based on 4 studies

Maternal smoking during pregnancy



Both parents preconception smoking

O.R. (95% CI)	n (case/control)	Ref
4.7 (1.7-13.4)	27/6987	Pang. Br J Cancer 2003.
2.7 (1.2-6.1)	43/5777	Sorahan. Br J Cancer 2004.

Genetic Factors

Beckwith-Wiedemann syndrome

- IGF2-H19 locus on chromosome 11p15: defective imprinting, uniparental disomy (UPD)

- Hepatoblastoma: 2,280-times population risk (95% CI: 928–11,656)

- Macrosomia
- Macroglossia
- Omphalocele
- Hemihypertrophy

Sparago A. Hum Mol Genet 2007.
DeBaun MR. J Pediatr 1998;132:398–400.

Genetic Factors

Familial Adenomatous Polyposis (FAP)

- Inactivating APC gene mutations
- Hepatoblastoma: 847-times population risk (95% CI: 230–2,168)

Congenital anomalies

- 6.4–41%

Overgrowth syndromes

- Simpson–Golabi–Behmel syndrome (GPC3)
- Sotos syndrome (NSD1)

Isolated syndromic associations

- Prader–Willi syndrome
- Kabuki syndrome
- Neurofibromatosis type 1
- Fanconi Anemia, Tyrosinemia type 1
- Noonan syndrome
- DiGeorge syndrome

Narod SA. Am J Hum Genet 1997.
Spector LG. Br J Cancer 2008.
Ansell P. Eur J Cancer 2005.

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MANAGEMENT APPROACH

Management Approach

Multidisciplinary management… from the beginning

Clinical:

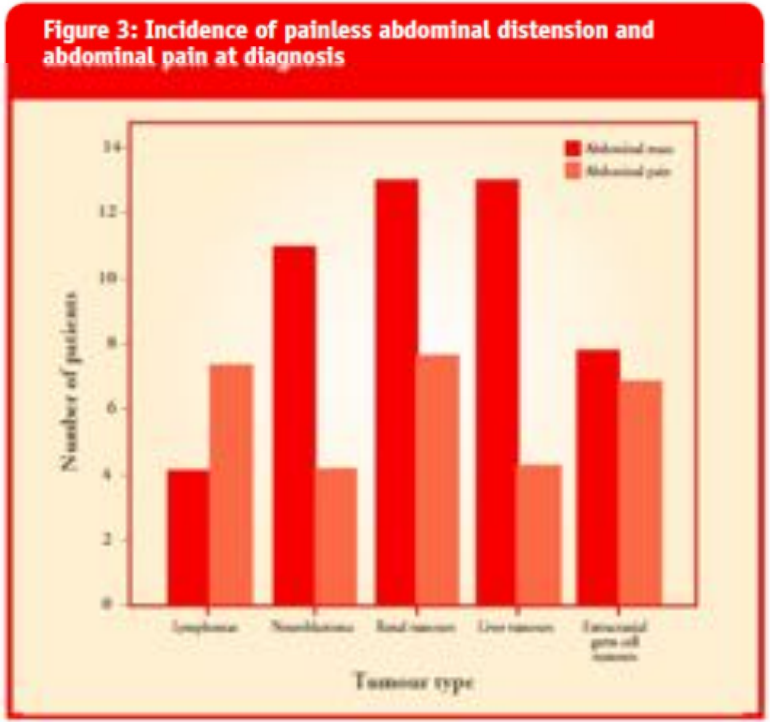
- Silent… the painless abdominal mass

Imaging (primary site):

- A lot can be told from just US
- MRI preferred, but requires GA
- Triphasic phases of CT not helpful

Tumor markers

- AFP sensitive and specific



Chua JHY, et al. JPOG. 2010.

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Management Approach

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Loh AHP, et al. J Pediatr Hematol Oncol. 2009.

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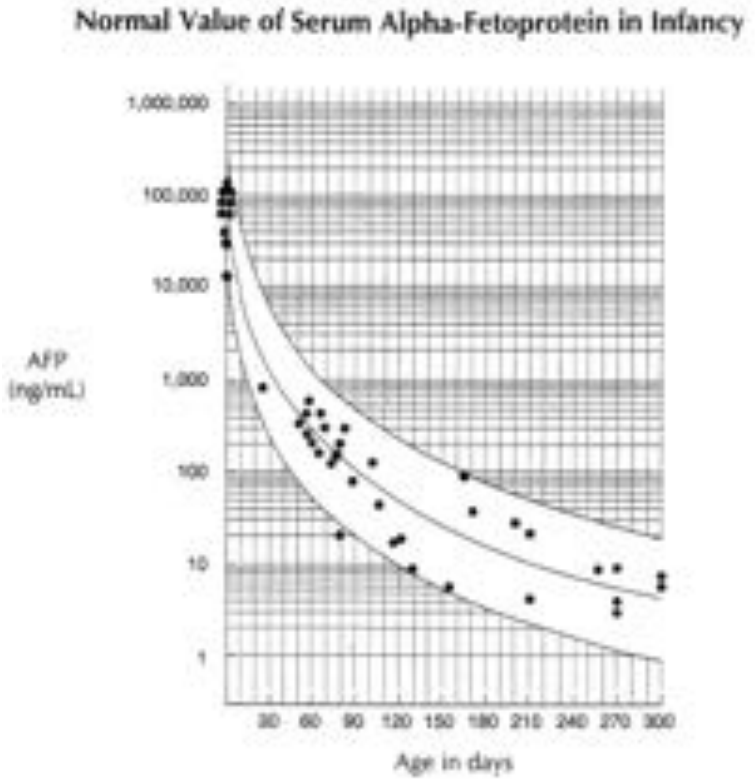

Loh AHP, et al. J Pediatr Hematol Oncol. 2009.

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Management Approach

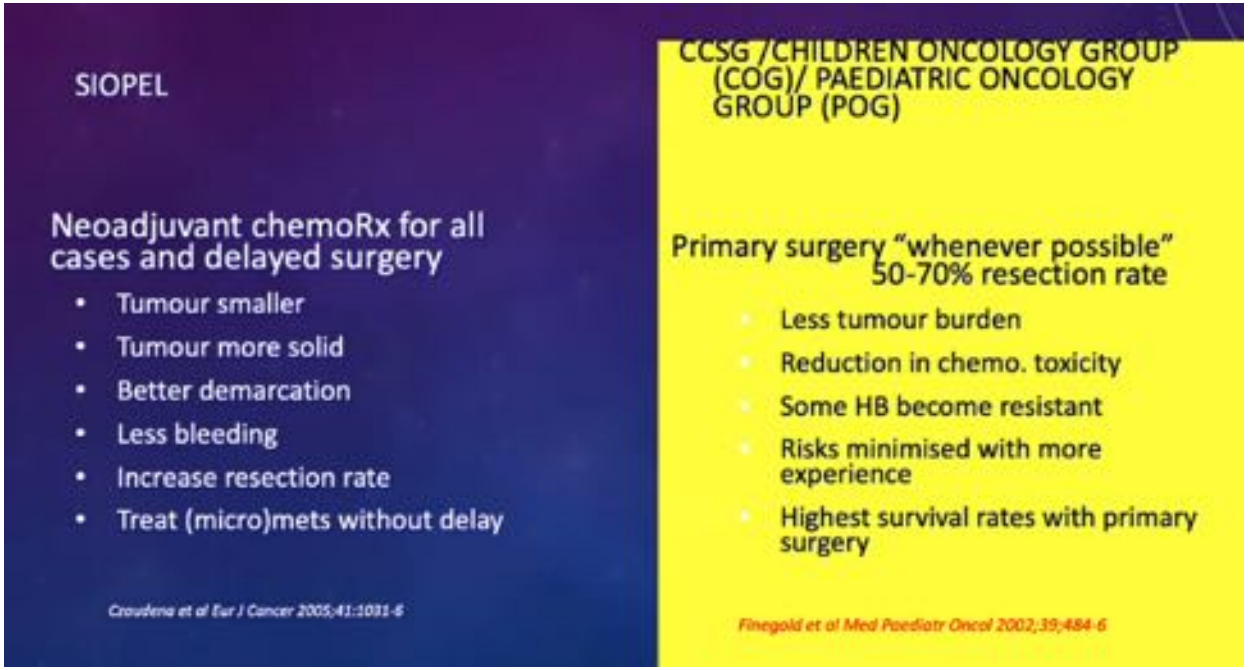
Multidisciplinary management… from the beginning

Key factors affecting decision making:

1. Resectability, especially at diagnosis
2. Risk factors (PRETEXT, PRETEXT annotation factors, age, AFP, histology), and…
   Risk classification
3. Response to initial treatment

Principles of Management (historical)

Two sides of the same divide



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Principles of Management (historical)

Pediatric Hepatic International Tumor Trial group (PHITT)

Pediatric Radiology (2018) 48:536–554
https://doi.org/10.1007/s00247-018-4078-z

REVIEW

2017 PRETEXT: radiologic staging system for primary hepatic malignancies of childhood revised for the Paediatric Hepatic International Tumour Trial (PHITT)

Alexander J. Towbin[1] · Rebecka L. Meyers[2] · Helen Woodley[3] · Osamu Miyazaki[4] · Christopher B. Weldon[5] · Bruce Morland[6] · Eiso Hiyama[7] · Piotr Czauderna[8] · Derek J. Roebuck[9] · Greg M. Tiao[10]

… because pediatric liver tumors are so rare – 1 in a million!

Largest and only international pediatric liver tumor trial

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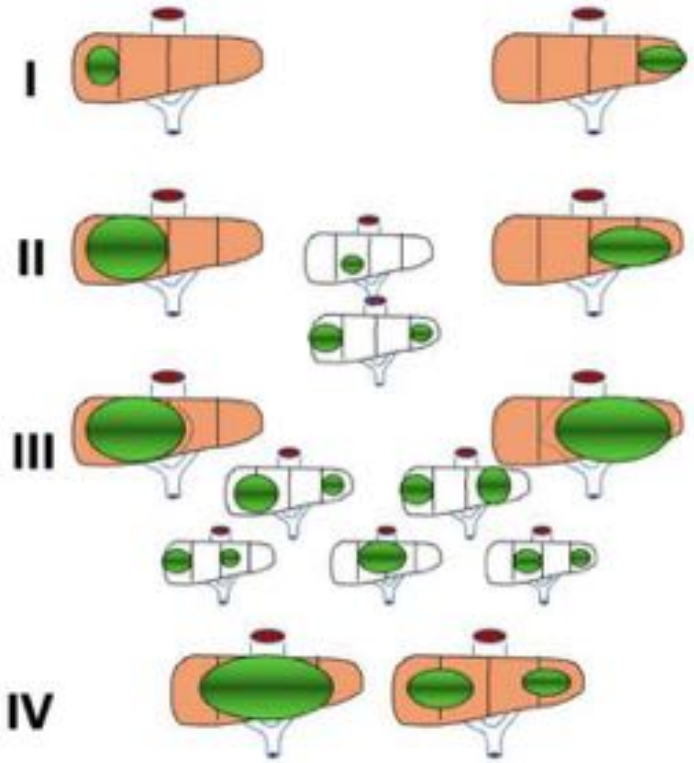
Principles of Management (historical)

Childhood Hepatic tumour International Consortium (CHIC)

- Combined the clinical data from 8 prior multicenter trials (1988–2010) conducted by COG, SIOPEL, GPOH, and JPLT
- Analyzed joint database of 1,605 patients.
- Identified risk factors, associated with varying EFS:

❑ – PRETEXT group
❑ – Age at diagnosis
❑ – AFP level
❑ – Presence of a PRETEXT annotation factor

Risk Factors: PRETEXT & Annotation Factors



PRETEXT Group, *Pre*treatment *Ext*ent of Disease
Extent of parenchymal involvement at diagnosis
POST-TEXT Group, *Post*treatment *Ext*ent of Disease,
Extent of parenchyma involvement after chemotherapy

I ... 3 contiguous sections tumor free
II ... 2 contiguous sections tumor free
III ... 1 contiguous sections tumor free
IV ...no contiguous sections tumor free

2017 PRETEXT Annotation Factors[34]

V ...involvement all 3 hepatic veins or retrohepatic vena cava and/or tumor thrombus in any one or more of the hepatic veins
P ...tumor involvement of the portal bifurcation, both right and left portal veins, and/or tumor thrombus in either the left or right portal
E ...contiguous organ involvement such as diaphragm, abdominal wall, colon, stomach
F ....multifocal tumor nodules
R ... tumor rupture prior to diagnosis
C ...caudate lobe
N ... enlarged lymph nodes
M ...metastasis, distant extrahepatic tumor (usually lung nodules)

APSA Cancer Committee AHEP1531

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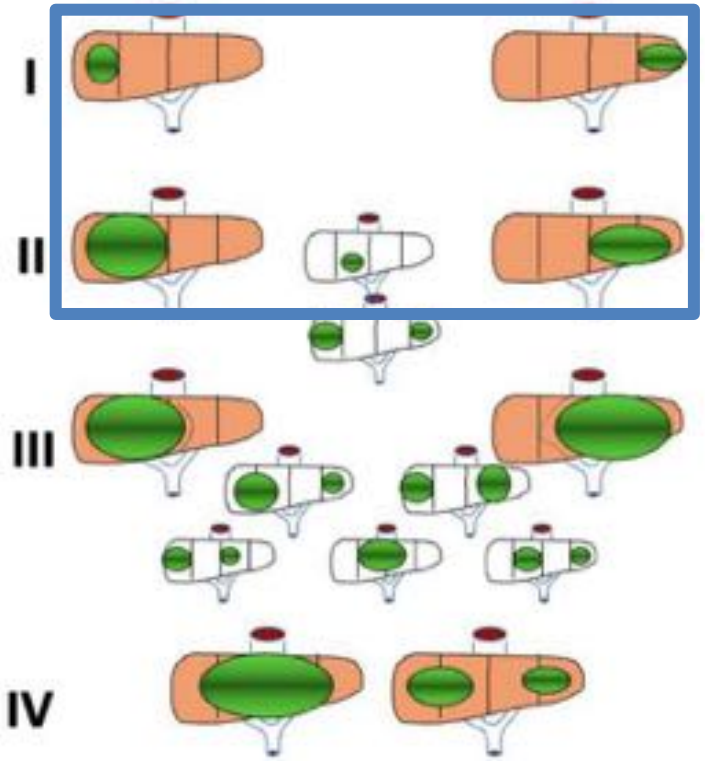
Risk Factors: PRETEXT & Annotation Factors



CONSIDER UPFRONT RESECTION

PRETEXT I, II unifocal tumors with ≥1cm margin from MHV & portal bifurcation on initial imaging

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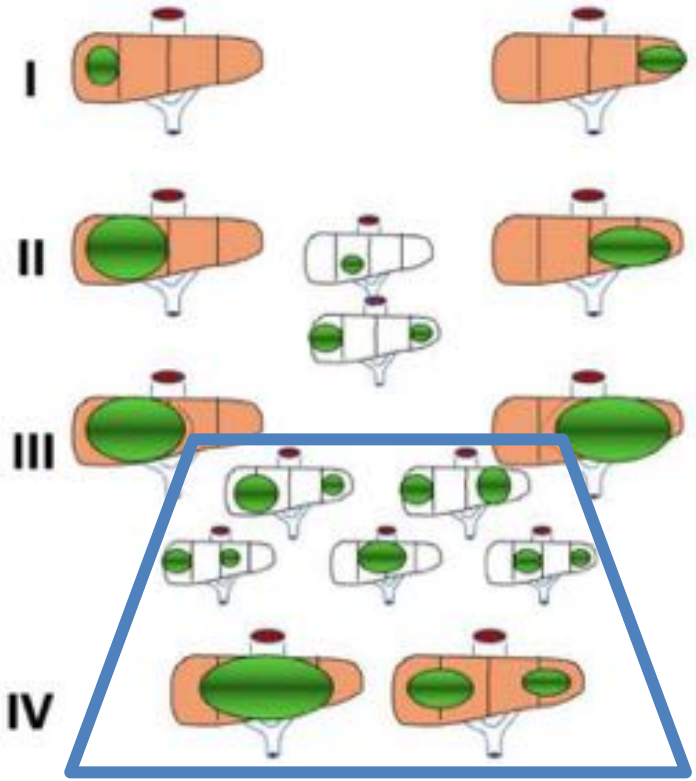
Risk Factors: PRETEXT & Annotation Factors



May require extended resection or transplant

BIOPSY AND REFER TO LIVER CENTER
(at diagnosis or within first 2 cycles)
PRETEXT III multifocal
PRETEXT III +ve annotation factors
PRETEXT IV

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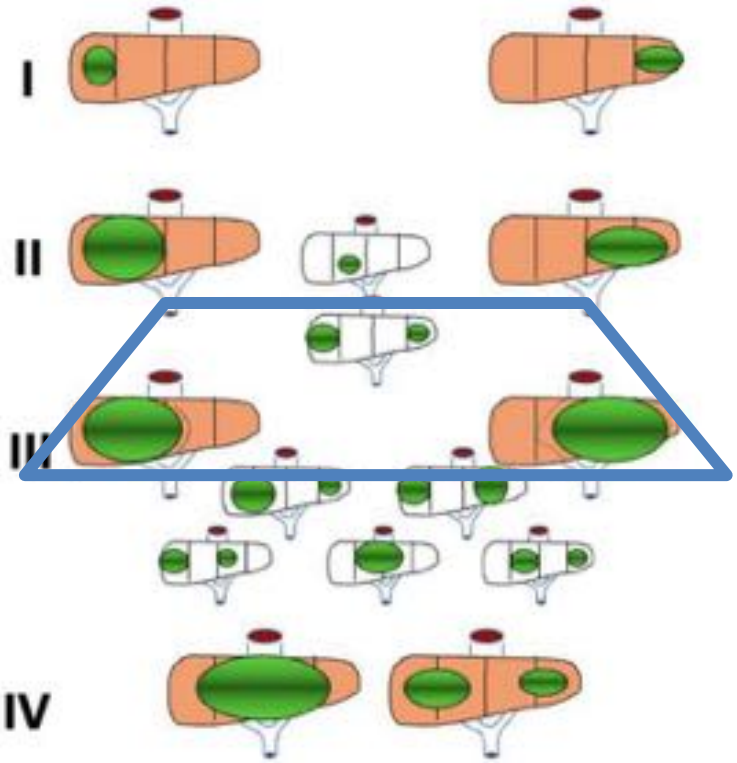
Risk Factors: PRETEXT & Annotation Factors



BIOPSY, NEOADJUVANT CHEMO-THERAPY, DELAYED RESECTION

PRETEXT II multifocal

PRETEXT III unifocal

POSTTEXT

I
II –ve annotation factors
➢ *after 2 cycles*

II +ve annotation factors III
➢ *after 4 cycles*

III
IV
➢ *refer liver center after 2 cycles*

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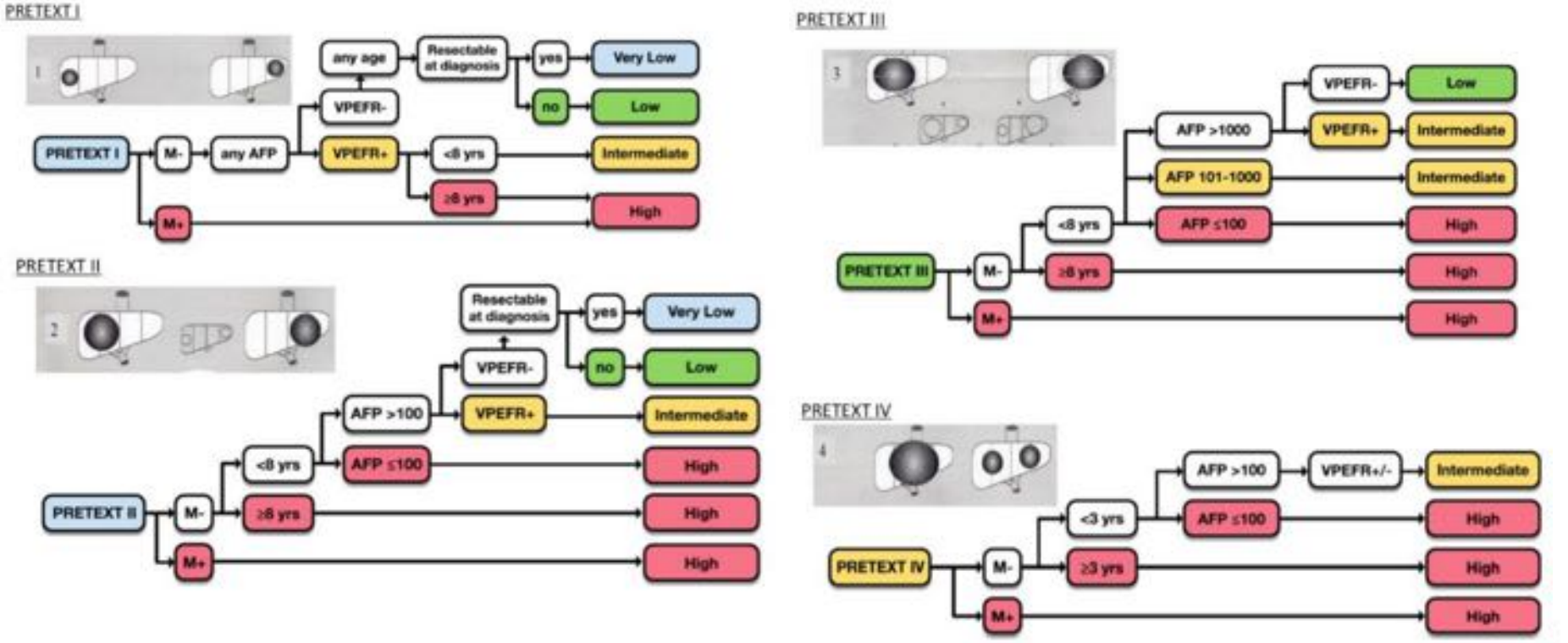
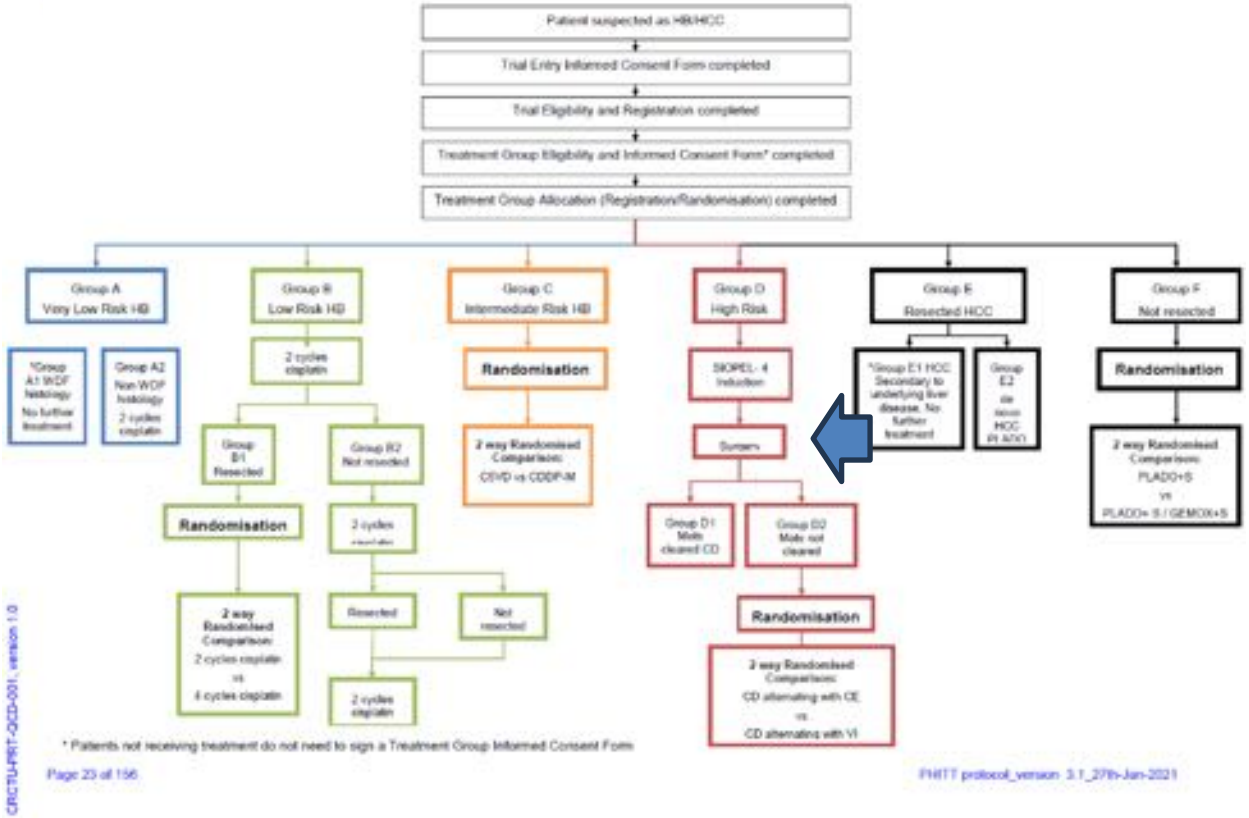
Risk Stratification: CHIC



Meyers et al., The Lancet Oncology, 2017

PHiTT Clinical Trial Schema



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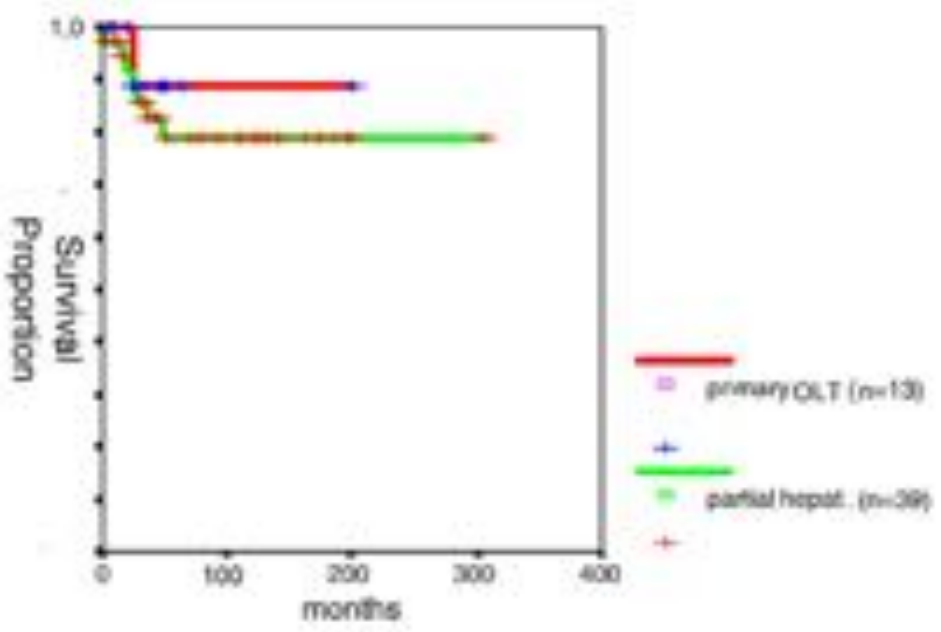
KEY CURRENT ISSUES

Extreme Resection vs Liver Transplant

Historical experience with OLT in hepatoblastoma

- Primary tumor control: equivalent outcomes with resection
- Rescue: inferior to primary OLT

	SIOPEL 1 10-yr OAS (n)	World 6-yr OAS (n)
primary OLT	85 % (7)	82 % (106)
« rescue » OLT	40 % (4)	30 % (41)

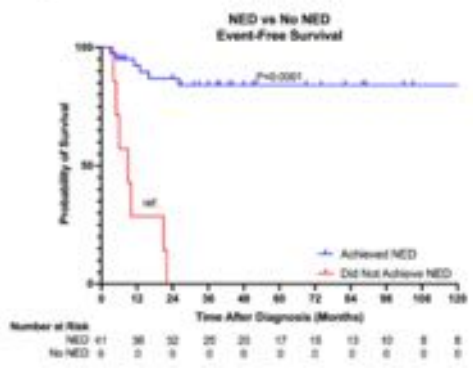


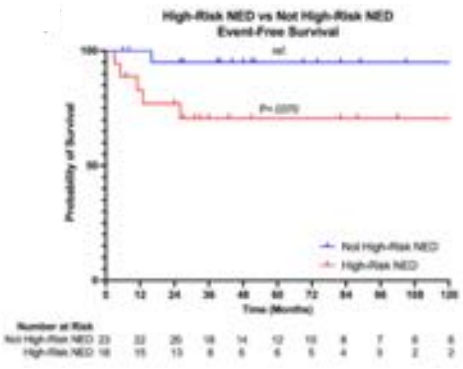
Otte. Cancer Treatment Rev. 2010.

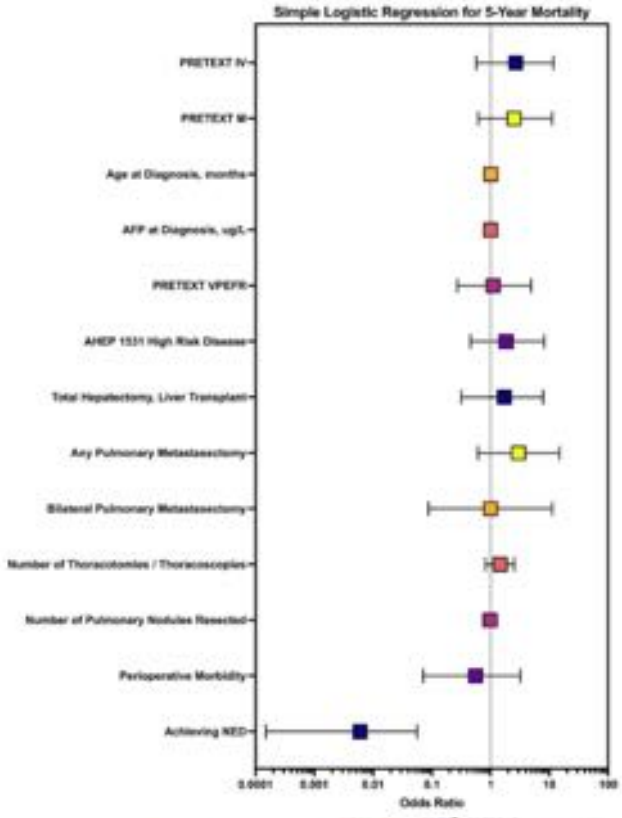
Extreme Resection vs Liver Transplant

Primary disease clearance is necessary for survival

- Trends toward permitting upfront resection for low-risk disease
- Systemic cisplatin-based chemotherapy has improved rates of tumor resectability
- Achieving NED status associated with 10Y OS, EFS





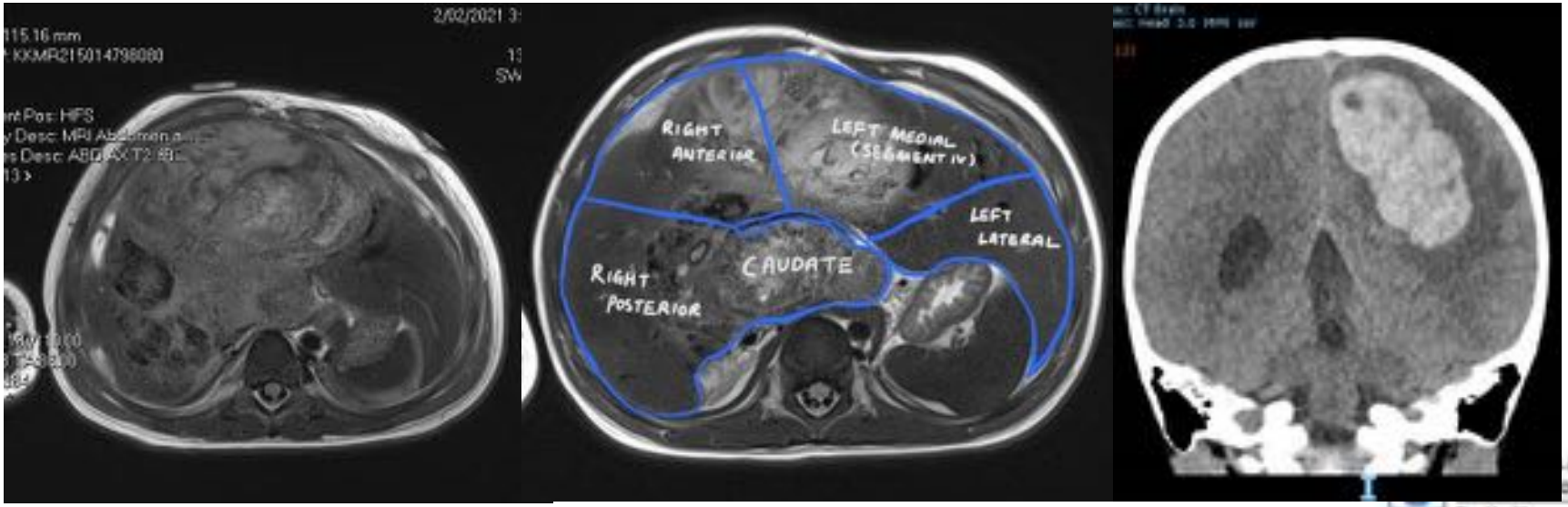


Fleming. J Pediatr Surg, 2023.

Extreme Resection vs Liver Transplant

2 yo PRETEXT III stage IV pulmonary metastases with intracardiac thrombus

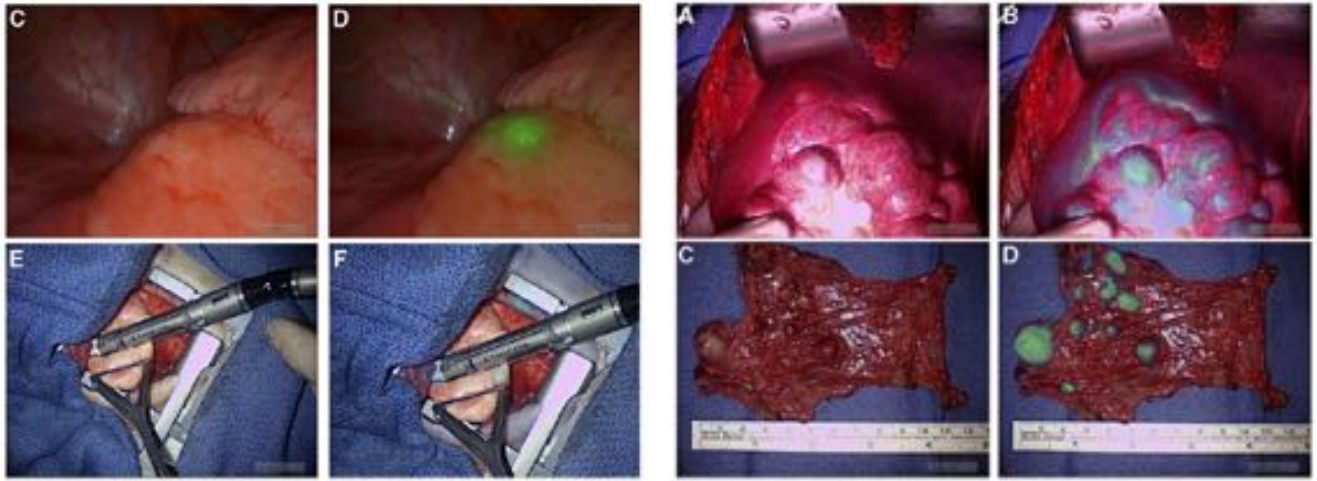
- Extended left hepatectomy with caval thrombectomy and IVC reconstruction on ECMO
- Now relapse 7, EFS 2.5 years



ICG

Established usage in adult liver tumor resections

- More recent experience in children
- Only established utility in classic primary and metastatic tumor indications

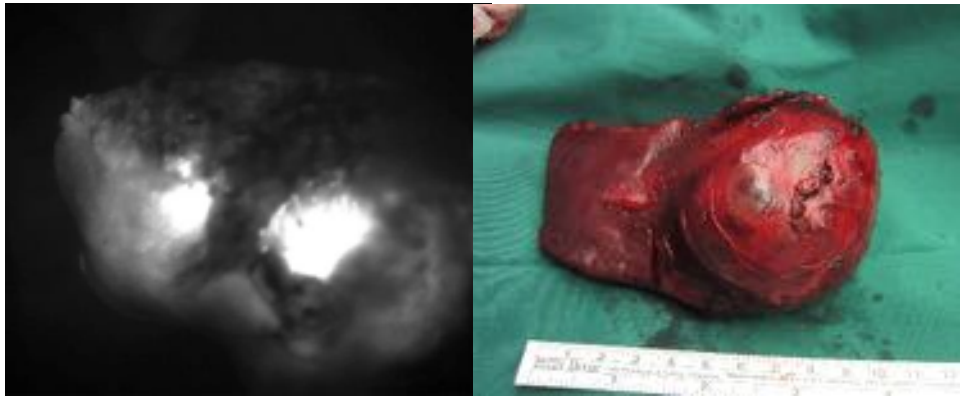


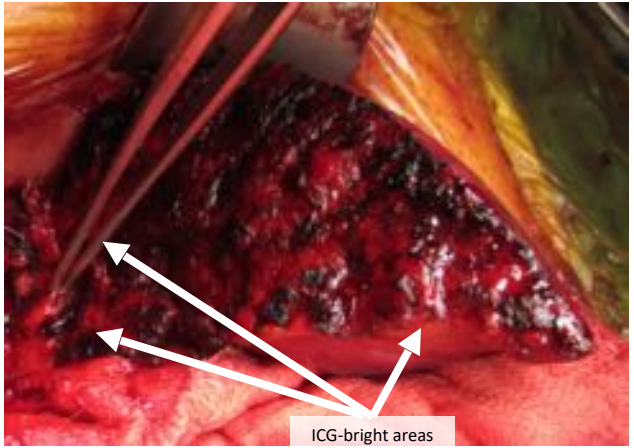
Abdelhafeez, Front Pediatr 2021.

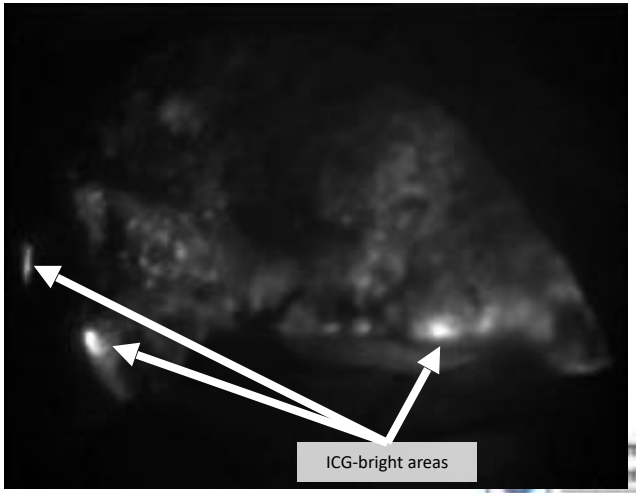
ICG

- Less data on pharmacodynamics in pediatric tissues
- Unknown interpretation in context of metastatic disease
- Recent failed clinical trial for use of ICG in pediatric tumor pulmonary nodules

2yo PRETEXT I hepatoblastoma







Questions?