



Handbook for Children with Liver Tumors

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from the
Cancer Committee
of the
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NOTICE

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Attending physicians, residents, fellows, students and providers using this handbook in the treatment of pediatric patients should recognize that this text is not meant to be a replacement for discourse or consultations with the attending and consulting staff. Management strategies and styles discussed within this text are neither binding nor definitive and should not be treated as a collection of protocols.

1. INTRODUCTION

This handbook describes current surgical management of Liver Tumors. It is based on current literature, accepted practice, and the new recommendations for the upcoming AHEP1531 – Pediatric Hepatic International Tumor Trial (PHITT). This is managed and updated by the APSA Cancer Committee. It is designed to consolidate the most current and up to date material you need to know when treating your patient. Liver Tumor treatment is centered on the tumor cell type and the image based anatomy of the lesion.

This handbook begins with A One Minute Review, designed for use immediately before an operation that includes abbreviated staging, risk stratification, surgery guidelines, and tissue handling. There follows more descriptive sections for staging and surgical management, including diagrams for PRETEXT staging.

Enrollment on open Children’s Oncology Group protocols, both biology and clinical trials, is strongly encouraged.

COG Surgery Study members are listed below, and should be contacted for questions. Any and all suggestions for improvement are welcome.

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2. ONE-MINUTE REVIEW

PRETEXT Staging System:

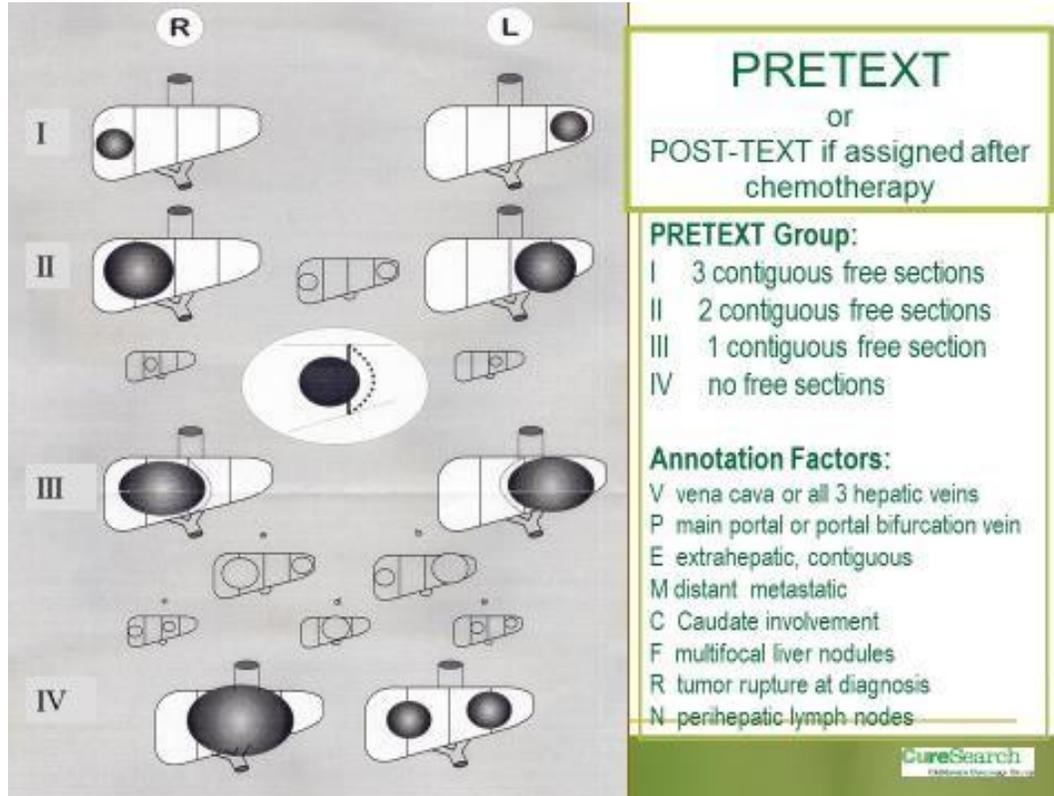
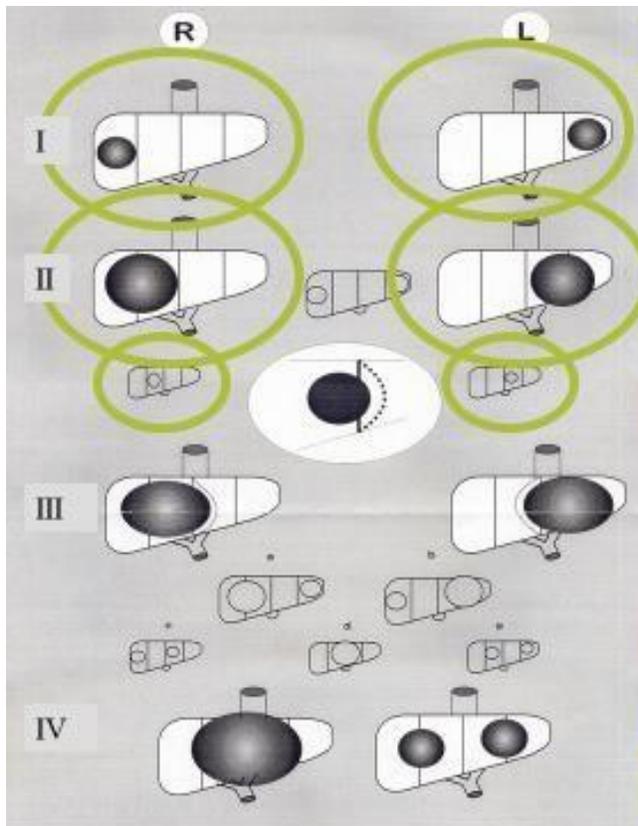


Image © Rebecka Meyers, MD

LESIONS FOR PRIMARY RESECTION



COG Surgical Resection Guidelines

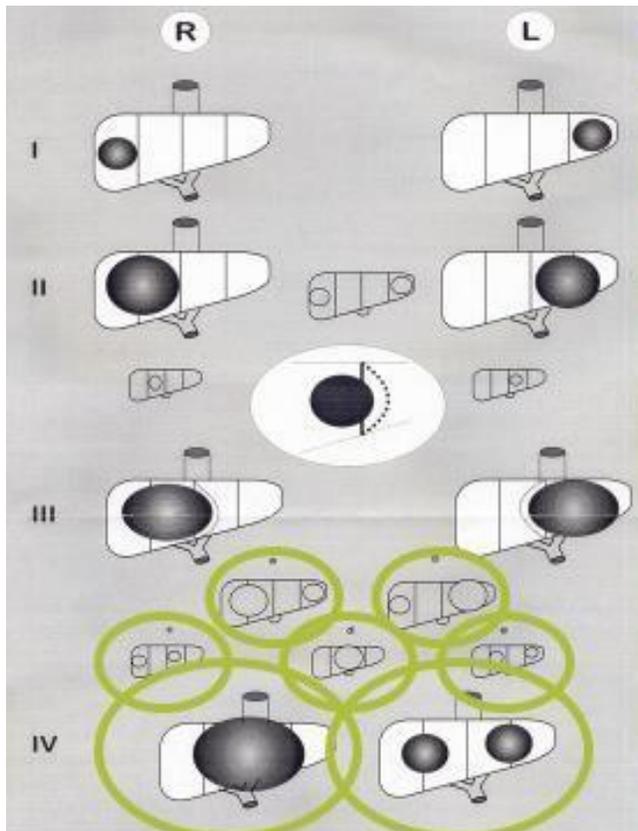
Resect at Diagnosis

- Rt or Lt lateral Segmentectomy or Hemi-Hepatectomy
- goal of ≥ 1 cm margin when resection is done **before** chemotherapy:
- PRETEXT I
- PRETEXT II

Diagnosis CT shows unifocal tumor with at least 1cm clear radiographic margin from middle hepatic vein and portal bifurcation

Image © Rebecka Meyers, MD

TUMORS TO BIOPSY AND REFER TO LIVER SPECIALTY CENTER AT DIAGNOSIS



COG Surgical Resection Guidelines

Biopsy and Refer to liver specialist at diagnosis or during first two cycles of chemotherapy

- Tumor might require complex liver resection or transplant
- multifocal PRETEXT III
 - PRETEXT III +V, +P, +E, +F, +R
 - any PRETEXT IV

Consultation with liver program to complete surgical evaluation and listing with goal of complex resection or transplant within 30 days of completion of four cycles preoperative chemotherapy

Image © Rebecka Meyers, MD

TUMORS TO BIOPSY AT DIAGNOSIS AND RESECT BY CONVENTIONAL SURGICAL TECHNIQUES AFTER 2ND OR 4TH CYCLE OF NEOADJUVANT CHEMOTHERAPY

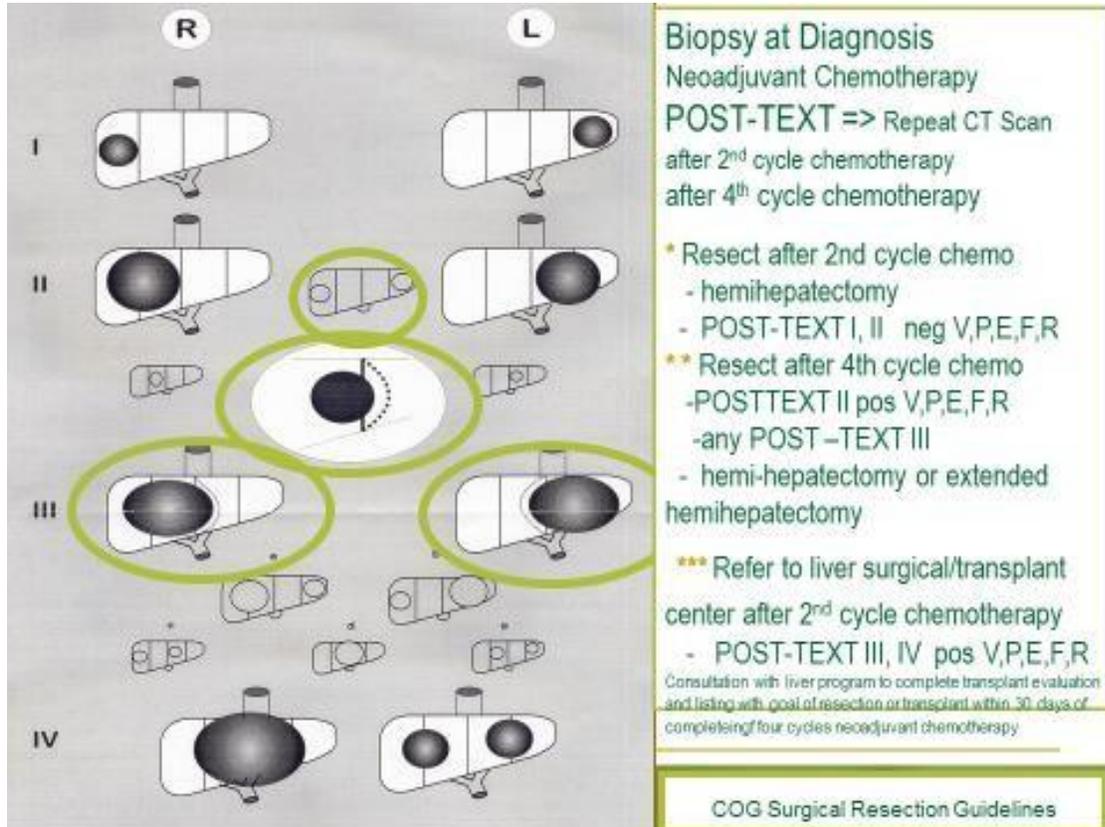


Image © Rebecka Meyers, MD

3. STAGING

PRETEXT

PRETEXT (PreTreatment Extent of Disease, assigned at diagnosis before any chemotherapy) or POST-TEXT (Post-Treatment Extent of Disease, assigned after chemotherapy) groupings. In the PRETEXT system, the liver is divided into four sections – the Right Posterior (Couinaud segments 6 and 7), Right Anterior (segments 5 and 8), Left Medial (segment 4) and Left Lateral (segments 2 and 3).

- PRETEXT I Tumor in 1 liver section, 3 sections free of tumor
- PRETEXT II Tumor in 2 adjoining sections, 2 sections free of tumor
- PRETEXT III Tumor in 3 adjoining sections; or 2 nonadjoining and 1 free in between; or the 2 medial sections involved (5,8 and 4a/4b)
- PRETEXT IV Tumor involves all 4 liver sections, no section free

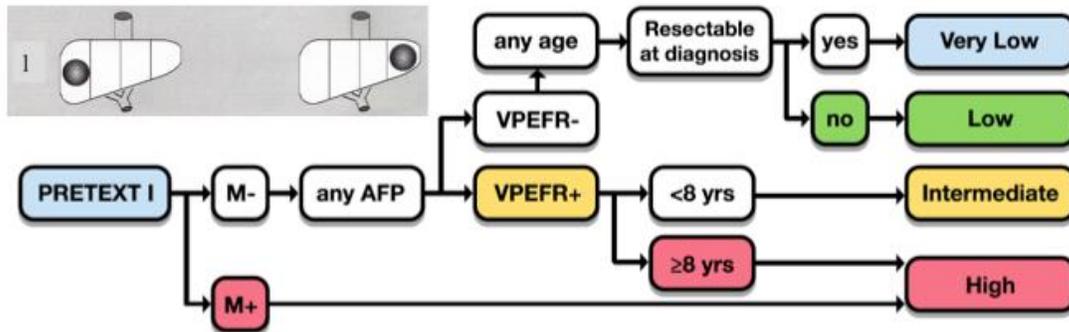
*Each PRETEXT group should be annotated with following modifiers, called PRETEXT Annotation Factors. For the upcoming PHITT trial, consensus determination of V and P+ will upstage patient and change chemotherapy treatment:

- +V > 50% circumferential involvement of all 3 major hepatic veins, and/or intrahepatic IVC; Tumor thrombus in major hepatic vein and/or IVC
- +P > 50% circumferential involvement both R and L portal veins and/or main portal vein; Tumor thrombus right, left, and/or main portal vein
- +E Extrahepatic contiguous tumor
- +F Multifocal tumor nodules within the liver
- +R Tumor rupture at diagnosis

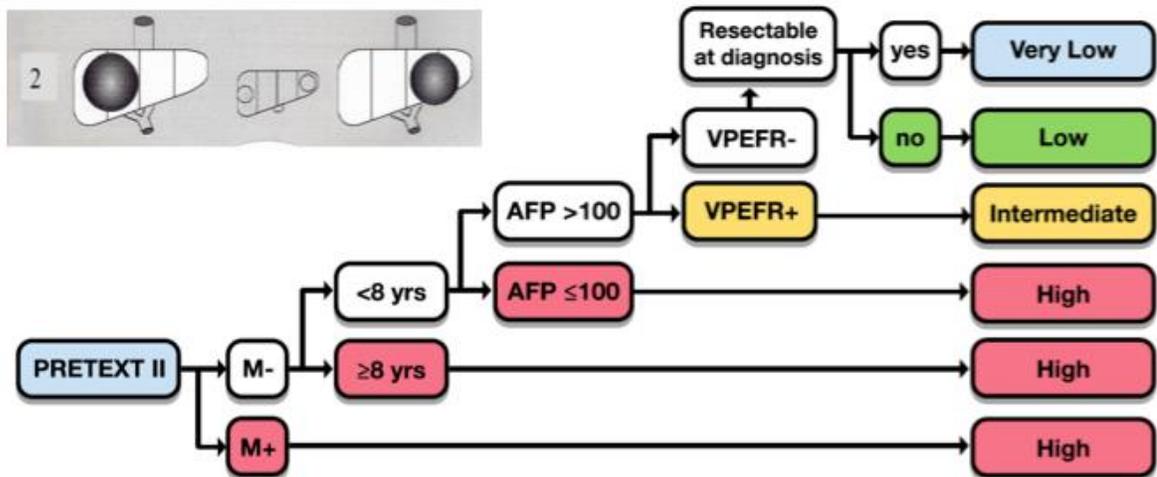
Children’s Hepatic Tumor International Collaboration (CHIC) Hepatoblastoma Risk Stratification:

The CHIC risk stratification system was just published in Meyers et al., *The Lancet Oncology*, 2017 vol. 18 (1) pp. 122-131. This is the most current consensus classification for defining risk groups for children with hepatoblastoma based on PRETEXT stage, age, annotation factors (VPEFR), AFP level, and presence of metastasis. These risk groups will be the basis for assigning the treatment groups within the PHITT trial as outlined in the next paragraph.

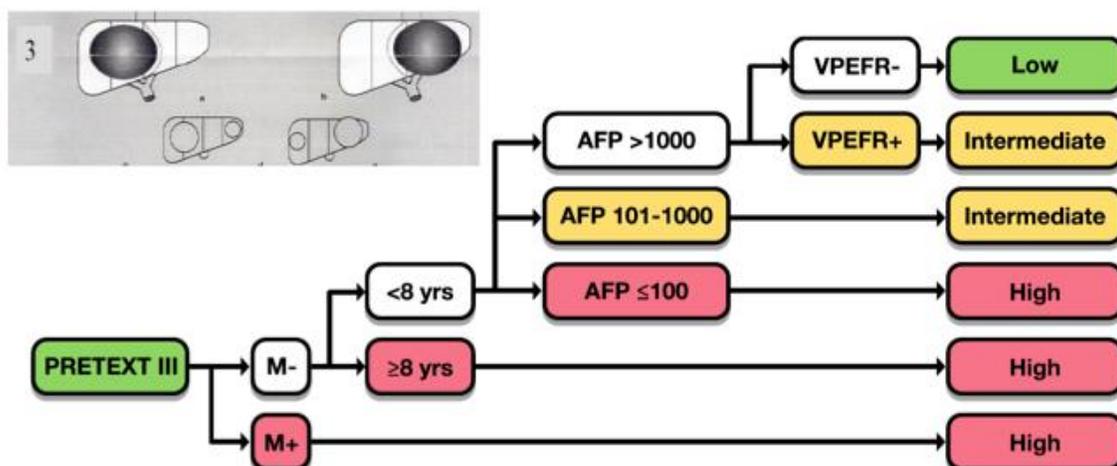
PRETEXT I



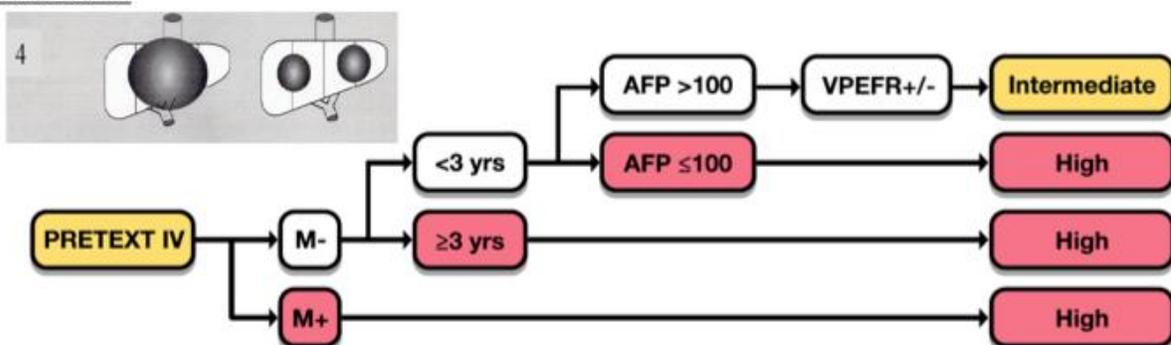
PRETEXT II



PRETEXT III



PRETEXT IV



PHITT/AHEP1531 TREATMENT GROUPS

GROUP A (HB, Very Low Risk)- completely resected at diagnosis

GROUP B (HB, Low Risk)- biopsied at diagnosis, not resectable at diagnosis, PRETEXT I-III with negative annotation factors VPEFR

GROUP C (HB, Intermediate Risk)- biopsied at diagnosis, not resectable at diagnosis and VPEFR+

GROUP D (HB, High Risk)- biopsied at diagnosis, not resectable at diagnosis, VPEFR+, and other high-risk features- age >8yrs, metastatic disease, AFP<100

GROUP E (HCC)- completely resected at diagnosis

GROUP F (HCC)- unresectable at diagnosis or metastatic disease

We strongly encourage surgeons and oncologists to enroll their patients on available collaborative trials. Current treatment planning recommendations are taken from PHITT which will soon be opening in Europe, Japan, and North America.

4. RADIOGRAPHIC IMAGING AND INTERVENTIONAL TECHNIQUES

- **CT SCAN.** All CT scans should be done with technical factors using the lowest radiation exposure possible (ALARA principle) that allow optimal image quality. This includes clear visualization of the vascular structures. Studies done without IV contrast are of limited value. CT slice *acquisition* thickness should be 1.5 mm or less. Post-contrast IV enhanced portal venous phase abdominal and pelvic CT should be performed from just above the diaphragm to the symphysis pubis. Dual phase (arterial and portal venous) abdominal CT is strongly recommended.
- **MRI.** Axial images and coronal images of the liver tumor should be acquired with at least two pulse sequences, including T1 and either fat-suppressed T2, STIR, or fat-suppressed fast/turbo imaging. Gadolinium should be given if appropriate and if there is normal renal function. After contrast administration T1W, fat-suppressed, axial images should be obtained. Based on patient age, images may be non-breath-hold or breath-hold, including respiratory triggered or respiratory gated. Dual phase MRI may be performed at the discretion of the local radiologist. To perform dual phase MR, gadolinium-enhanced imaging is performed in combination with dynamic gradient echo sequences. After contrast agent injection, images are obtained through the liver during the arterial phase (20 to 30 seconds post injection), portal venous phase (60 to 80 seconds after injection), and at equilibrium (3 to 5 minutes after injection). Delayed images can be obtained if needed for further lesion characterization.
- **Metastatic Site Imaging.** Chest CT is required to evaluate metastatic disease. Chest CT may be performed without intravenous contrast material. The diameter of a "measurable" nodule should be at least twice the reconstructed slice thickness. Smaller nodules are considered detectable, but will be counted as "non-measurable. Bone scan is not required but should be considered in symptomatic patients with bone pain or bone lesions. Metastatic disease to bone and bone marrow is extremely rare and should only be considered if the patient is symptomatic with unexplained bone pain or unexplained cytopenias.
- **Hepatic Arterial Chemoembolization (HACE) TransArterial Chemoembolization (TACE).** Experience is less in children than adults, but this modality is increasingly used for HCC that is unresectable and in children not candidates for transplant due to metastatic disease. Although complications with the older lipiodol technique were frequent, chemoembolization is now possible with doxorubicin-eluting beads and yttrium-theraspheres. Anecdotal reports of success where resection was facilitated with this modality are encouraging.
- **Pre-Operative Portal Venous Embolization.** Preresection portal venous embolization has been used in adults with HCC to induce hypertrophy of the remaining liver remnant and results of this technique have been reported in children. This technique may be particularly useful in children with large unifocal tumors with limited remaining normal liver. The portal venous branch on the side of the tumor is embolized with polyvinyl alcohol and coils. This has the dual effect of alcohol thrombosis of the embolized tumor and compensatory hypertrophy of the unharmed opposite liver lobe increasing the hepatic functional reserve.

5. BIOPSY GUIDELINES

Tumor biopsy only at diagnosis for PRETEXT II with *less than* 1 cm radiographic margin, PRETEXT III, PRETEXT IV, any V+/P+, or metastatic disease.

- The type of biopsy procedure performed will be at the discretion of the treating institution. However, in general, an **image-guided, co-axial core needle biopsy (CNB) is the preferred method of tumor sampling**, particularly in the case of HCC where minimizing spill and tract contamination is important.
- The recommended amount of *tumor* tissue to be retrieved for diagnostic purposes and for biologic studies is:
 - a. $\geq 1\text{cm}^3$ for ‘wedge’ biopsies regardless of procedure route (laparotomy v laparoscopic)
 - b. ≥ 7 cores with CNB technique using a 16 gauge core needle gun at a 20-30mm core length (or equivalent quantity with other size CNB devices).
- The recommended amount of *normal* liver to be retrieved for diagnostic purposes and for biologic studies is:
 - a. Small wedge biopsy of normal liver if open biopsy is performed.
 - b. ≥ 2 cores with CNB technique using a 16 gauge core needle gun at a 20-30mm core length (or equivalent quantity with other size CNB devices).
 - c. Ideally, sample acquired from normal liver that will be resected with the tumor
- **BIOPSY APPROACH SHOULD NOT RESULT IN CONTAMINATION OF LIVER UNINVOLVED WITH TUMOR AS THIS COULD RESULT IN SEEDING OF LIVER THAT WILL BE SPARED AT THE TIME OF CONVENTIONAL RESECTION**
- If feasible, sampling from multiple different areas of the primary tumor should be acquired during the biopsy procedure to better evaluate for heterogeneous foci of small-cell undifferentiated (SCU) tumor- worse prognosis.
- Especially important to obtain tumor for biologic study in patients with atypical presentation or age greater than 4 years, patients with metastatic disease, or +V, +P, +E, +F, or +R

6. SURGICAL GUIDELINES

Surgical Resection of Liver tumor At Diagnosis (HB, GROUP A; HCC, GROUP E):

- Liver resection at diagnosis **DONE WITHOUT BIOPSY INDEPENDENT OF SUSPECTED CELL TYPE** (segmentectomy or hemi-hepatectomy, > 1 cm margin desired for resections done prior to chemotherapy) for PRETEXT I or PRETEXT II with >1 cm radiographic margin on the middle hepatic vein, the retrohepatic IVC, or portal bifurcation (negative V, negative P).

Surgical Resection of Liver tumor After Biopsy:

- For Hepatoblastoma, GROUP B and C patients:
 - Following 2 cycles chemotherapy: Hemi-hepatectomy for all POST-TEXT I, POST-TEXT II with $>1\text{cm}$ margin and negative–V, -P, -E, -F, - R after 2 cycle
 - Referral to surgical center with expertise in pediatric liver transplantation and “complex” liver resection ***no later than*** after 2 cycles for any POST-TEXT +V, +P, +P, +E, +F, +R or POST-TEXT IV. Goal is complete resection or transplantation within 4 weeks of completion of the 4th cycle
 - Following 4 cycles of chemotherapy: Hemi-hepatectomy (independent of distance from middle hepatic vein) or extended hemi-hepatectomy for all tumors
 - Assistance required from surgical center with expertise in pediatric liver transplantation and complex liver resection for any POST-TEXT +V, +P, +P, +E, +F,

- +R or POST- TEXT IV. Goal is conventional resection or transplantation within 4 weeks of completion of the 4th cycle of chemotherapy.
- For Hepatoblastoma, GROUP D patients:
 - Following induction chemotherapy (cycle A1-A3): Hemi-hepatectomy, extended hemi-hepatectomy, or extreme hepatectomy for all tumors.
 - Assistance required from surgical center with expertise in pediatric liver transplantation and complex liver resection for any POST-TEXT III +V, +P, +P, +E, +F, +R or POST- TEXT IV tumor.
 - High risk stratified tumors that are *unlikely* to be resectable after cycle A3 *should* be referred to or discussed with a transplant center (with expertise in extreme liver resection) at initial biopsy/diagnosis. This early referral is HIGHLY RECOMMENDED.
- For HCC, GROUP F patients:
 - Following induction chemotherapy (3-4 cycles of chemotherapy): Hemi-hepatectomy, extended hepatectomy, or extreme hepatectomy should be considered for resection.
 - Strong consideration should be made for adjuvant procedures such as TACE/HACE, Y90, or RFA for unresectable lesions.
 - Liver transplant can ONLY be considered for these lesions if there is NO evidence of extrahepatic/metastatic disease and vascular invasion.
 - Assistance required from surgical center with expertise in pediatric liver transplantation and complex liver resection for any POST-TEXT +V, +P, +P, +E, +F, +R or POST- TEXT IV.
- For Undifferentiated Embryonal Sarcoma of the Liver (UESL):
 - Resectability criteria similar to HB should be followed for these tumors.
 - Hemi-hepatectomy can be performed at diagnosis if it is safe to remove the tumor with negative margins.
 - If extended hepatectomy or extreme hepatectomy is required, some authors recommend a trial of neoadjuvant chemotherapy (2-4 cycles, sarcoma chemotherapy) prior to attempted resection.
 - Transplant is a viable option for unresectable tumors.
- For Rhabdoid Tumor of the Liver:
 - Aggressive surgical approach as these tumors will metastasize early and have a poor prognosis
 - If extended hepatectomy or extreme hepatectomy is required, some authors recommend a trial of neoadjuvant chemotherapy (2-4 cycles, sarcoma chemotherapy) prior to attempted resection.
 - Transplant has been performed in a few cases reported in the literature.
- For Angiosarcoma of the Liver:
 - One should consider extended hepatectomy or extreme resection since these tend to be chemo-insensitive. If there is no evidence of metastatic disease, orthotopic liver transplantation can also be performed with evidence of success in the literature.
- For Biliary Rhabdomyosarcoma:
 - Hilar biliary RMS- the MAJORITY of these can be treated effectively with chemotherapy and XRT and do not require surgery
 - Parenchymal RMS- similar resectability criteria should be followed for RMS as stated above. These are highly chemosensitive; therefore, careful consideration should be made as to the need of resection.

7. SURGICAL MANAGEMENT OF PULMONARY METASTASIS:

For Hepatoblastoma, Group D patients:

- Resection of pulmonary mets should be performed after induction chemotherapy. In patients with tumors that require liver transplantation to achieve local control, metastectomy has to be completed soon after induction as transplant teams may not consider them to be candidates until after a period of extra hepatic free disease has been demonstrated. In patients who are candidates for conventional resection metastectomy can be staged according to the discretion of the treating team
- Staged thoracotomy or thoracoscopy can be performed with one cycle of chemotherapy in between procedures for bilateral disease. Simultaneous thoracotomy, sternotomy, or bilateral thoracoscopy can be performed at the discretion of the treating surgeon.

For other histologies:

- Resection of pulmonary mets can be performed for persistent lesions after resection of primary and no evidence of disease progression.

8. LIVER TRANSPLANT AND EXTREME RESECTION GUIDELINES

Liver Transplantation Guidelines for Hepatoblastoma:

- **Chemotherapy.** Patients should be treated with standard on-study chemotherapy protocols with the same number of cycles of chemotherapy, before and after transplant, as patients submitted to partial hepatectomy. Extended courses of chemotherapy aimed at alleviating the need for transplantation *are not* recommended. Extended and prolonged preoperative exposure to chemotherapy risk the induction of chemotherapy resistance genes, a well described phenomenon in HB.
- **Multifocal PRETEXT IV.** Even with good response to chemotherapy accompanied by POST-TEXT down-staging, total hepatectomy followed by liver transplantation is the only way to ensure clearance of all microscopic foci. Radiographic clearance of a section *does not* guarantee total obliteration of microscopic residual in multifocal disease, and any residual disease may be stimulated by hepatocyte growth factors after major resection (33).
- **Solitary POST-TEXT IV.** Large, solitary, PRETEXT IV tumors may occasionally downstage to a POST-TEXT III and become resectable. When the ability to preserve adequate normal liver is in question, the decision for transplant versus resection should be made by a liver specialty team with the capability of liver transplantation.
- **Vascular Invasion, PRETEXT III +P, +V.** With macroscopic vascular invasion the tumor may *not* become resectable, even after a good response to chemotherapy. Central tumors involving Couinaud's segments 4,5,8 can have close contact with the main portal vein, portal bifurcation and all three hepatic veins. Central hepatectomy, or "meso-hepatectomy" may be possible in experienced centers, but should not be attempted without the full support and safety net of a transplant team. Resection when the tumor abuts major venous structures may be possible. Resection when the tumor invades major venous structures runs the risk of uncontrolled bleeding, tumor residual, and compromise of vascular inflow and/or outflow. Radiographic imaging cannot always reliably distinguish between the two situations. With either a resection or a transplant, invaded areas of retrohepatic vena cava should be resected en bloc and reconstructed either with autologous internal jugular vein, donor iliac vein, or a preserved cadaveric whole organ with donor IVC.

- **Transplant in Patients with Metastatic Tumor at Diagnosis.** If metastases clear after chemotherapy or surgical resection children are still eligible for transplant. Conversely, persistence of viable extrahepatic tumor nodules after neoadjuvant chemotherapy, if not amenable to surgical resection, is an absolute contraindication to transplantation. Some have recommended manual palpation of lungs pre-transplant. Others have recommended very high resolution CT, and even PET-CT, with very meticulous preoperative scrutiny of the lungs. Unresponsive or progressive metastatic disease in the face of neoadjuvant chemotherapy is a relative contraindication to transplant because even if the nodules can be surgically resected microscopic foci of chemo resistant tumor are highly probable.
- **Rescue Transplant for Relapse vs Persistent Tumor.** Multiple series have shown superior outcome after primary transplant (about 80% overall survival) when compared to rescue transplant (about 35% overall survival). Although detailed data are missing, a distinction should be made between two distinct types of “rescue” transplant. When gross residual tumor persists after a failed attempt at partial hepatectomy, prompt progression to a rescue transplant may have a favorable outcome with the assumption that adjuvant chemotherapy may control any spillage of malignant cells outside of the liver. In contrast, local tumor relapse remote from the initial resection suggests possible chemotherapy resistance and debilitated patient status and transplant results may be inferior.

Liver Transplantation Guidelines for HCC:

- Currently, Milan criteria is followed for children/adolescents with HCC. One of the study questions being looked at through the PHITT trial is to see whether adult Milan criteria is applicable to children since many children are transplanted outside of Milan criteria. Many published series report better overall survival with transplantation for HCC over primary resection.

Extreme Resection Guidelines for Hepatoblastoma/HCC:

- Extreme liver resection can be used to extirpate challenging PRETEXT III and IV tumors that may not be otherwise eligible for OLTxp due to extrahepatic disease/metastasis.
- Extreme liver resection is defined as:
 - Any resection requiring a vascular reconstruction of the hepatic veins, portal veins, inferior vena cava or hepatic artery.
 - Residual liver parenchyma volume less than 1% liver mass weight (g)-to-patient weight (kg) as assessed by volumetry on preoperative imaging (e.g., less than 700g of remaining liver in a 70 kg person).
 - 180 encasement of the remnant hepatic vein or portal vein.
 - Trisectionectomy with wedge resection/ablative procedure of a lesion(s) in the remnant liver.
- Extreme liver resection SHOULD only be performed in a center with extensive expertise in pediatric liver resections of this kind and have access to pediatric liver transplantation.

9. SURGEON RESPONSIBILITIES

Surgeons should fill out surgical CRFs

- Dictated operative report by the operating surgeon should optimally include all of the following information:
 - Preoperative assessment of PRETEXT and/or POST-TEXT group (I, II, III or IV) and positive annotation factors (V,P,E,F,R,C,N,M) .

- Postoperative assessment of PRETEXT and/or POST-TEXT group (I, II, III or IV) and positive annotation factors (V,P,E,F,R,C,N,M) based upon the surgeons' findings at resection.
- Procedure performed:
 - a) Segmentectomy (one Couinaud's segment removed)
 - b) Sectionectomy (three sections remain at the end of the procedure)
 - c) Hemihepatectomy (two sections remain, resect middle hepatic vein)
 - d) Trisectionectomy/Extended hemihepatectomy (one section remain, resect the middle hepatic vein)
 - e) Central resection/Mesohepatectomy of left medial and right anterior sections
 - f) Orthotopic liver transplantation (OLTxp) and type (e.g. whole-organ, split, etc.)
- Concern for margin
 - a) Location
 - b) Was a frozen section of surgical margin sent?
- Vascular inflow to the remaining liver remnant
- Vascular outflow of liver remnant
- Estimated volume of the remnant liver