Adjuvant chemotherapy after Liver Transplantation for Pediatric Hepatoblastoma

What we know and what we still need to learn

Jenna Allison, MD
Assistant Professor, Pediatrics
Director of Solid Tumors
University of Nebraska Medical Center
Children's Nebraska

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University of Nebraska Medical Center

Objectives

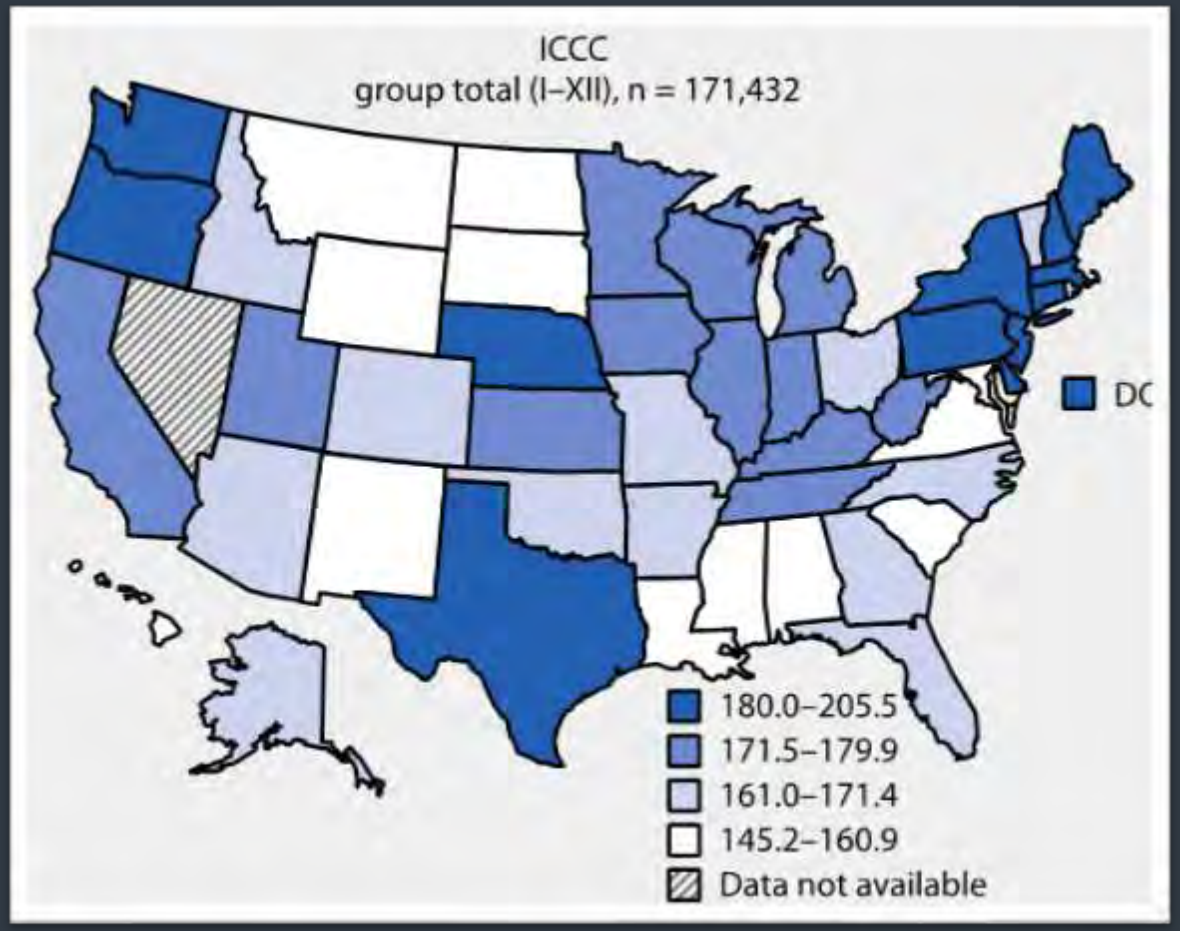
- Briefly review the incidence and prognostic factors in childhood hepatoblastoma
- Outline current treatment modalities, including chemotherapy and surgical options
- Define historical perspectives that inform our current treatments
- Review new, international trials that should assist in refining treatments in the future

Hepatoblastoma Incidence

Hepatoblastoma is the most common malignant liver neoplasm in children

Annual incidence in the United States has increased from 0.8 (1975–1983) to 2.3 (2020) cases per 1 million children less than 19 years of age

- Perhaps related to improved survival of VLBW infants and pre-term infants



Siegel et al. Geographic Variation in Pediatric Cancer Incidence - US, 2003–2014. *MMWR*, 2018

Prognostic Factors

Main determinants of outcome are metastasis at diagnosis and local control (likelihood of tumor resection)

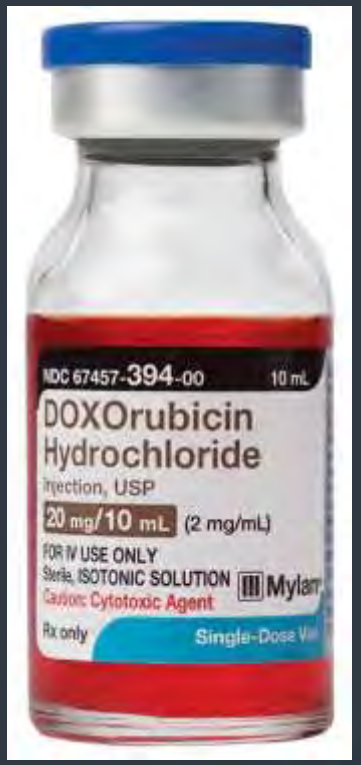
- Other prognostic factors include higher PRETEXT group, positive PRETEXT annotation factors, low AFP, and increased age

Complete surgical resection of the primary tumor is essential for cure. Three surgical options include:

- Initial surgical resection (alone or with adjuvant chemotherapy).
- Delayed surgical resection (with neoadjuvant chemotherapy).
- Orthotopic liver transplant (with neoadjuvant chemotherapy).

Purpose of Chemotherapy

- Provide disease control after presentation
- Confirms chemosensitivity of primary and metastatic lesions
- Establishes proof of “unresectability” for eventual liver transplant
- Reduces recurrence after liver transplant



Liver transplant for Hepatoblastoma

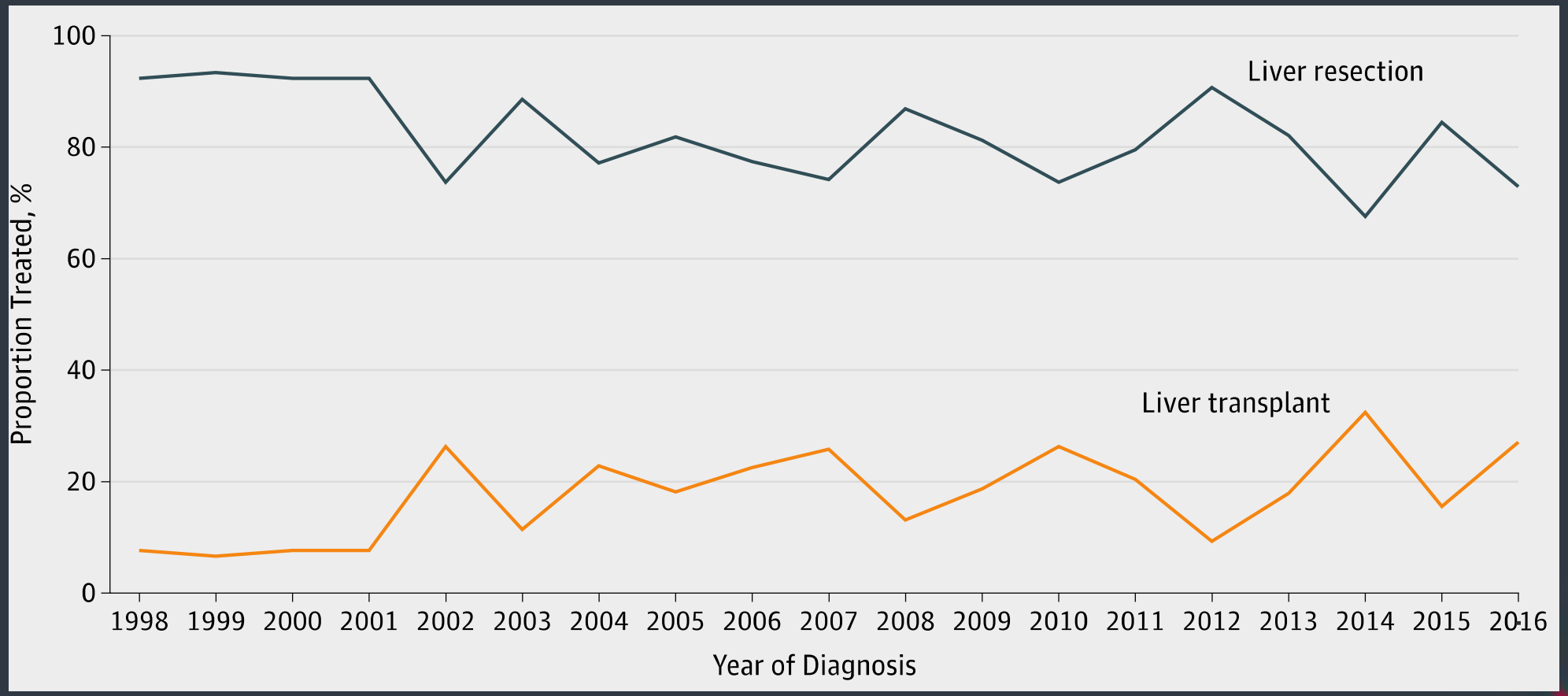
First report of American experience in 1991

- 12 children from 10 centers
- 6 survived up to 70 months
- 3 died of recurrent disease

Dr. Byers Shaw Jr.

Liver Transplantation is increasing in frequency

Trends in Liver Transplant versus Liver Resection For Pediatric Hepatoblastoma Patients



Feng et al.Assessment of Survival of Pediatric Patients with Hepatoblastoma who received Chemotherapy following Liver Transplant or Liver Resection. *JAMA Network Open*, 2019

Post transplant chemotherapy appears to reduce recurrence

Recurrence after LT for HBL presents as metastatic disease and is encountered in as high as 40% of post transplant patients

- SIOPEL studies show a reduction in recurrence and improved survival with post transplant chemotherapy, but numbers are small
  - A review of all SIOPEL cases from France from 1990 – 2017 only had 12 total transplant patients (Illiano et al, 2021)
- A study of 14 patients who received post-transplantation chemotherapy had 100% survival compared with 56% without chemotherapy (Browne et al 2008)

Potential issues with the science

Table 1 The neoadjuvant and adjuvant chemotherapy cycles in all 14 patients as well as their PRETEXT staging retrospectively assigned based on patient records and pathology findings and review of imaging files at the time of the transplant

	Neoadjuvant therapy	No. of cycles	PRETEXT at transplant	Chemotherapy after transplant	No. of cycles
1	DR, CiP, VP16, IF, CaP	8	II v3	None	
2	DR, CiP	6	IV m1	None	
3	CiP, DR, V, 5FU	8	III m1 (recurrent disease)	None	
4	CiP, V, 5FU, DR	10	II-III v3	None	
5	CiP, V, 5FU, CaP, DR, VP16	6	IV v3, p1	None	
6	CiP, V, 5FU	4	III v3	None	
7	Unknown	–	IV(recurrent disease)	Irinotecan	
8	CiP, BL, DR, ET	5	IV	CiP, BL, DR, ET	2
9	CiP, 5FU, V, AM	5	II. p2	CiP, 5FU, V, AM	1
10	CiP, DR, CaP	6	III p2	CiP, DR, CaP	3
11	CaP, AM, CiP, VB	6	III v3 (residual disease)	CaP, AM, CiP, VB	1
12	DR, CiP	2	IV	None	
13	CiP, 5FU, CaP, V	2	IV (recurrent disease)	None	
14	AM, CiP, V, 5FU	6	III v3	CiP, V, 5FU	2

Patients 2 and 3 had pulmonary metastases at the time of the initial diagnosis but not at the time of the transplant. CiP indicates *cis*-platinum; VB, vinblastine; ET, etoposide; 5FU, 5 fluorouracil; AM, Amifostine; DR, doxorubicin; BL, bleomycin; VP, VP16; CaP, carboplatinum; V, vincristine; IF, ifosfamide.

Browne et al. Liver Transplantation for Hepatoblastoma. *Jrnl Peds Surg*, 2008

How much post transplant chemotherapy ?

Some European surgical groups are still struggling with this decision

- Chemotherapy and immunosuppression have overlapping toxicities
- At the time of SIOPEL-1, the world experience with transplant for hepatoblastoma included 65 patients who received post-LTX chemotherapy and 82 who did not.
  - Overall survival rates (77% and 70%, respectively) were not statistically different.

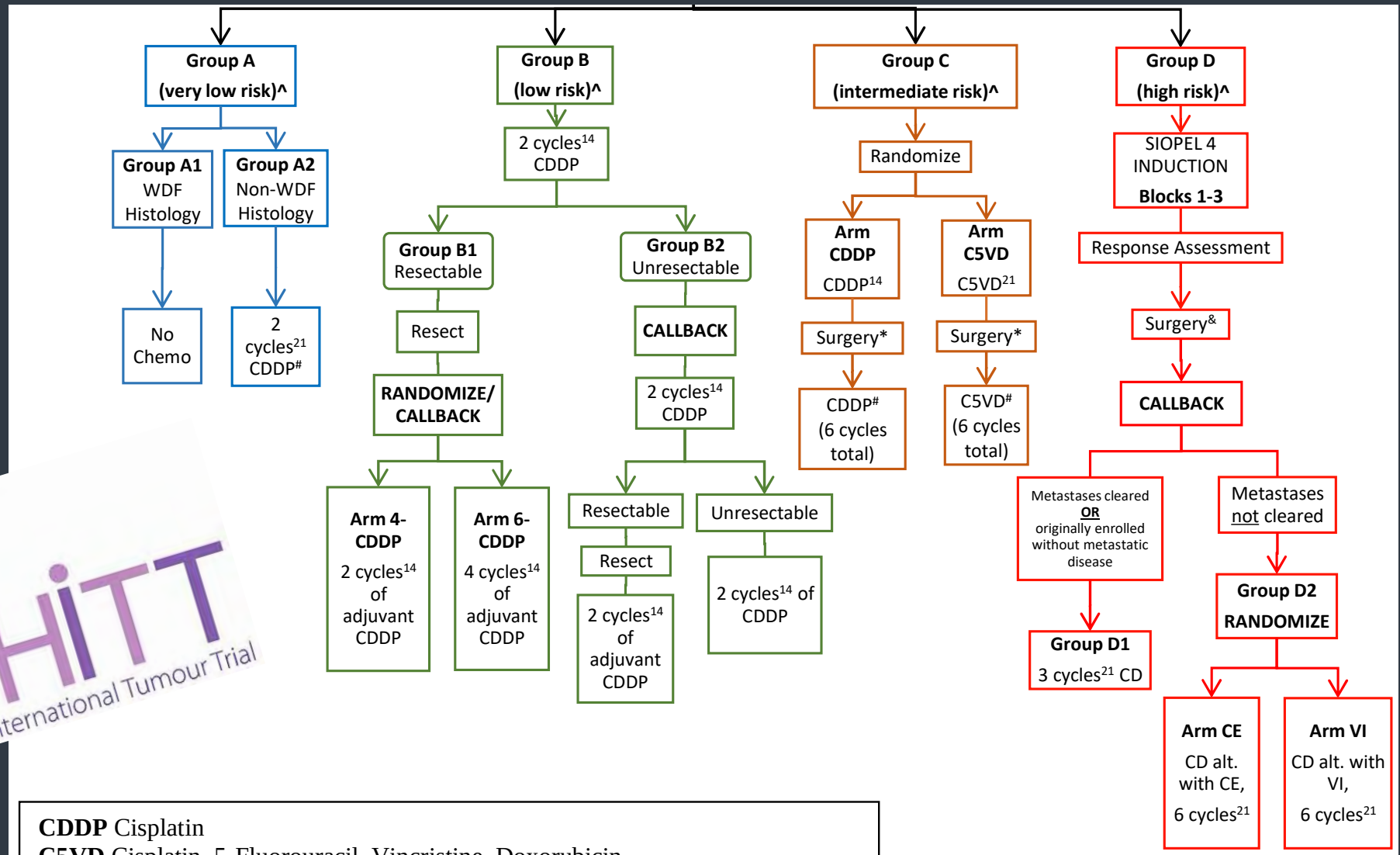
Previous trials did not utilize uniform definitions, dosing, or treatment cycles to inform adjuvant therapy decision making.

Recent SPLIT Experience

	Hepatoblastoma transplants				
	Subjects with death, retransplant, or Recurrence ($n = 30$)	Surviving subjects ($n = 127$)	Hazard ratio	95% CI	p
Number of neoadjuvant chemotherapy cycles[b]	5.0 ± 1.8	4.7 ± 1.6	1.12	0.88–1.42	.36
Number of adjuvant chemotherapy cycles[b]	3.6 ± 4.3	1.8 ± 1.5	1.16	1.06–1.26	.001
Duration (days) between last neoadjuvant cycle and transplant[b]	17.7 ± 11.3	23.5 ± 15.3	0.97	0.93–1.01	.09
Duration (days) between transplant and first adjuvant cycle[b]	33.0 ± 14.9	36.0 ± 17.3	0.99	0.96–1.02	.48

- 157 liver transplants for Hepatoblastoma from 2011 – 2019
  - 3-year Event Free Survival was 81 %
- Transplant patients were twice as likely to have a GFR < 90 ml/min/m^2 in the year following transplant

Boster et al. Predictors of survival following liver transplantation for pediatric hepatoblastoma and hepatocellular carcinoma: Experience from the Society of Pediatric Liver Transplantation (SPLIT). Am J Transplant. 2022;22:1396–1408



PHITT
Paediatric Hepatic International Tumour Trial

CDDP Cisplatin
C5VD Cisplatin, 5-Fluorouracil, Vincristine, Doxorubicin
SIOPEL 4 Induction Cisplatin, Doxorubicin
CD Carboplatin/Doxorubicin
CE Carboplatin/Etoposide
VI Vincristine/Irinotecan
WDF Well-Differentiated Fetal histology
[21]21 day cycle
[14]14 day cycle

Conclusions

- The incidence of childhood hepatoblastoma is increasing.
- Surgery is required for cure in childhood hepatoblastoma.
- Neoadjuvant chemotherapy allows for disease control and evaluation of potential surgical interventions.
- Adjuvant chemotherapy after liver transplantation appears to reduce recurrence, but questions remain regarding timing and quantity.
- Current international trials should inform how much adjuvant chemotherapy is required to maintain survival for pediatric hepatoblastoma patients.

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