

PEDIATRIC LIVER CANCER AND TRANSPLANTATION

**Analysis from the OPTN Pediatric
Transplantation Committee**

Scientific Registry of Transplant Recipients

SRTR

This presentation is reproduced on this site with the permission of the author(s). All opinions, research citations and analyses are those of the author(s) and may not reflect those of OPTN/UNOS committees or the OPTN/UNOS Board of Directors.

- **Hepatic tumors account for approximately 1% of childhood malignancies, with hepatoblastoma and hepatocellular carcinoma constituting the majority.**
- **Total hepatectomy and liver transplantation has been performed in a significant number of children whose hepatic tumors were not resectable.**
- **To better understand the role of liver transplantation for this patient group, a retrospective analysis of children listed for liver transplantation for primary hepatic malignancies was conducted.**

SRTR Analysis of Pre and Post Transplant Mortality for Pediatric Patients with Hepatic Malignancy

**Pediatric Transplantation
Committee**

May 14, 2002

SRTR

 **ustransplant.org**
Scientific Registry of Transplant Recipients

This presentation is reproduced on this site with the permission of the author(s). All opinions, research citations and analyses are those of the author(s) and may not reflect those of OPTN/UNOS committees or the OPTN/UNOS Board of Directors.

Study Question

- **What is the survival with or without a transplant for children listed with a diagnosis of liver tumors compared to all other children on the list?**

Methods

- **Pediatric patients registered on the liver waiting list (1/1/95-12/31/2000)**
- **Kaplan-Meier survival curves calculated for patients in four diagnosis categories**
 - **Malignant Neoplasm: Hepatoblastoma (HBL)**
 - **Malignant Neoplasm: Hepatocellular Carcinoma (HCC)**
 - **Malignant Neoplasm: Other**
 - **Other diagnostic categories**
- **Censored at removal from the waitlist, last expected transplant follow-up date, or end of study**

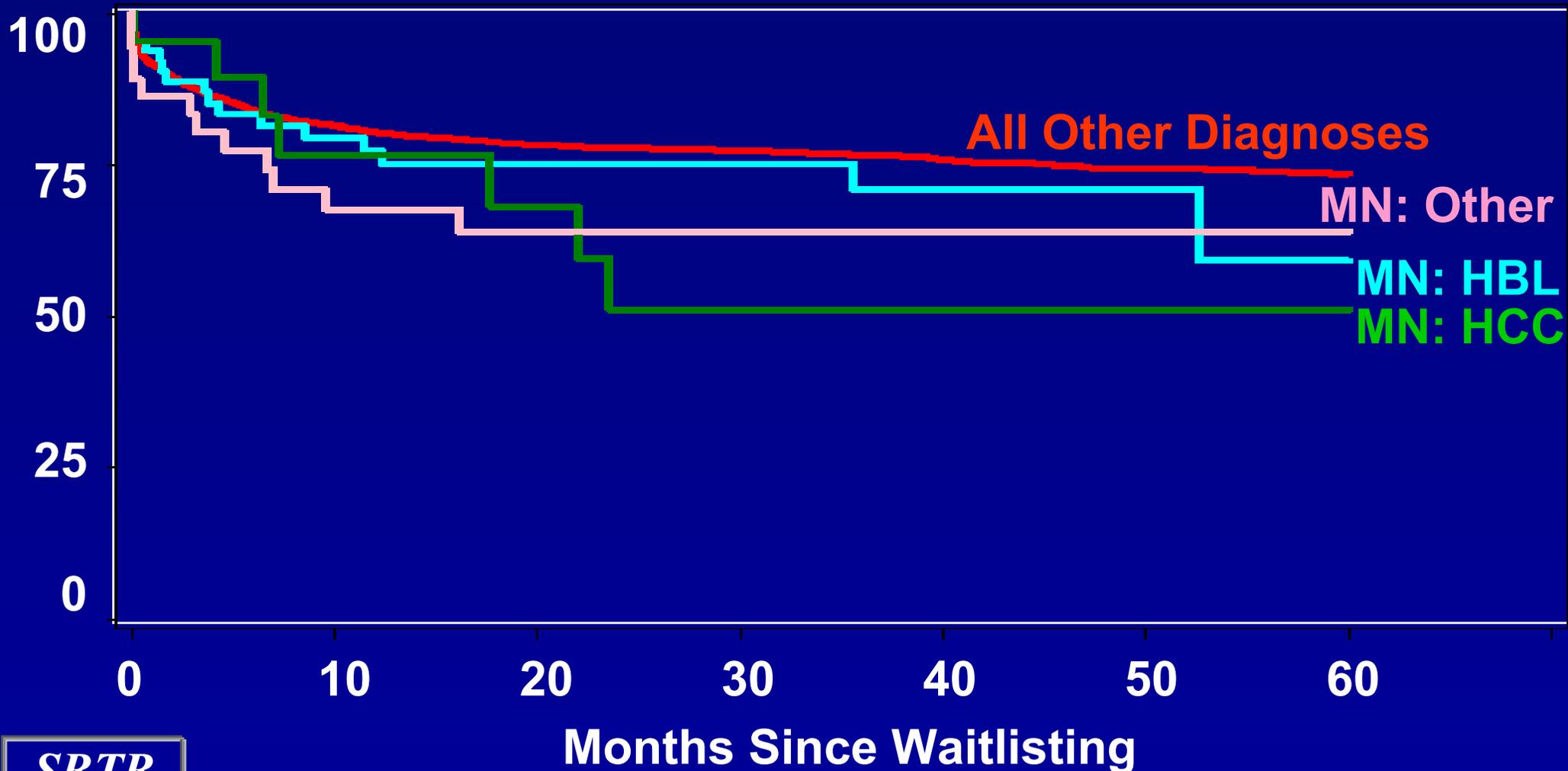
Counts of patients by diagnosis category

	Number of patients
Malignant Neoplasm:	
Hepatoblastoma	66
Hepatocellular Carcinoma	22
Other	37
Other diagnostic categories	4423
Total	4366

*** Pediatric patients registered on the liver waiting list (1995-1999)**

Kaplan-Meier Survival from Time of Waitlisting (1995-1999)

Survival with or without a Transplant



SRTR

This presentation is reproduced on this site with the permission of the author(s). All opinions, research citations and analyses are those of the author(s) and may not reflect those of OPTN/UNOS committees or the OPTN/UNOS Board of Directors.

Survival Probabilities by Selected Diagnoses, 1995-1999

Diagnosis	1 month	2 years	5 years
Malignant Neoplasm:			
HBL	94%	75%	59%
HC	95%	51%	51%
Other	86%	64%	64%
All other diagnoses	92%	78%	74%

(excerpt Table 4.1 from 5/14/02 Report)

Methods

- **Second analysis to look at benefit of transplantation for patients with liver tumors is restricted to 125 patients with liver tumors**
- **Cox regression models fit with a time dependent covariate at the time of transplant**
- **Time dependent Cox models adjusted for medical urgency status at waitlisting**
- **Censored at removal from the waitlist, last expected transplant follow-up date, or end of study**

Benefit of Transplantation for Pediatric Patients with Liver Tumors

	Before transplant	After Transplant
All MN Patients	1.00 (ref)	0.63 (p=0.31)
Stratified on MN diagnosis		
HBL	1.00 (ref)	0.60 (p=0.43)
HC	1.00 (ref)	0.18 (p=0.11)
Other	1.00 (ref)	1.14 (p=0.86)

* 125 pediatric patients with liver tumors (1995-1999)

Summary

- **No significant differences in mortality after transplant compared to on the waitlist within diagnosis group**

Request #1: Study Question

(Request #2 from the 9/20/01 Report)

- **Compare post-transplant mortality risk for pediatric liver transplant recipients with and without hepatic tumors**
- **Compute survival by cause of ESLD using biliary atresia as the reference group and splitting malignant neoplasm into 3 groups**
 - **Hepatoblastoma**
 - **Hepatocellular Carcinoma**
 - **Other**

Methods: Study Population

- **All pediatric patients who received liver transplants between October 1, 1987 and December 31, 1999**
- **Excluding patients who**
 - **had a previous liver transplant**
 - **received a multi-organ transplant**
 - **received a heterotopic transplant**

Methods: Diagnosis Classification

- **Patients classified by primary cause of ESLD**
 - **Biliary atresia**
 - **Metabolic disease**
 - **Acute hepatic necrosis (AHN)**
 - **Non-cholestatic cirrhosis**
 - **Cholestatic liver disease/cirrhosis**
 - **Malignant Neoplasm (MN): Hepatoblastoma (HBL)**
 - **Malignant Neoplasm: Hepatocellular Carcinoma (HC)**
 - **Malignant Neoplasm: Other**
 - **Other/Missing**

Methods: Analysis

- **Kaplan-Meier survival calculated by primary cause of ESLD as time from transplant to death for**
 - **All patients, 1987-1999 (N=5,140)**
 - **More recent patients, 1995-1999 (N=2,169)**
- **Patients followed for up to 5 years censoring at last known follow-up or December 31, 2000**

Patient Count by Primary Diagnosis

Primary Diagnosis	Count (%)			
	1987-99		1995-99	
Biliary Atresia	2528	(49.2%)	958	(44.2%)
Metabolic Diseases	651	(12.7%)	262	(12.1%)
AHN	641	(12.5%)	301	(13.9%)
Non-Cholestatic Cirrhosis	469	(9.1%)	203	(9.4%)
Cholestatic Liver Dis/Cirrhosis	165	(3.2%)	86	(4.0%)
MN: HBL	77	(1.5%)	39	(1.8%)
MN: HC	20	(0.4%)	8	(0.4%)
MN: Other	46	(0.9%)	29	(1.3%)
Other/Missing	543	(10.6%)	283	(13.1%)
TOTAL	5140	(100.0%)	2169	(100.0%)

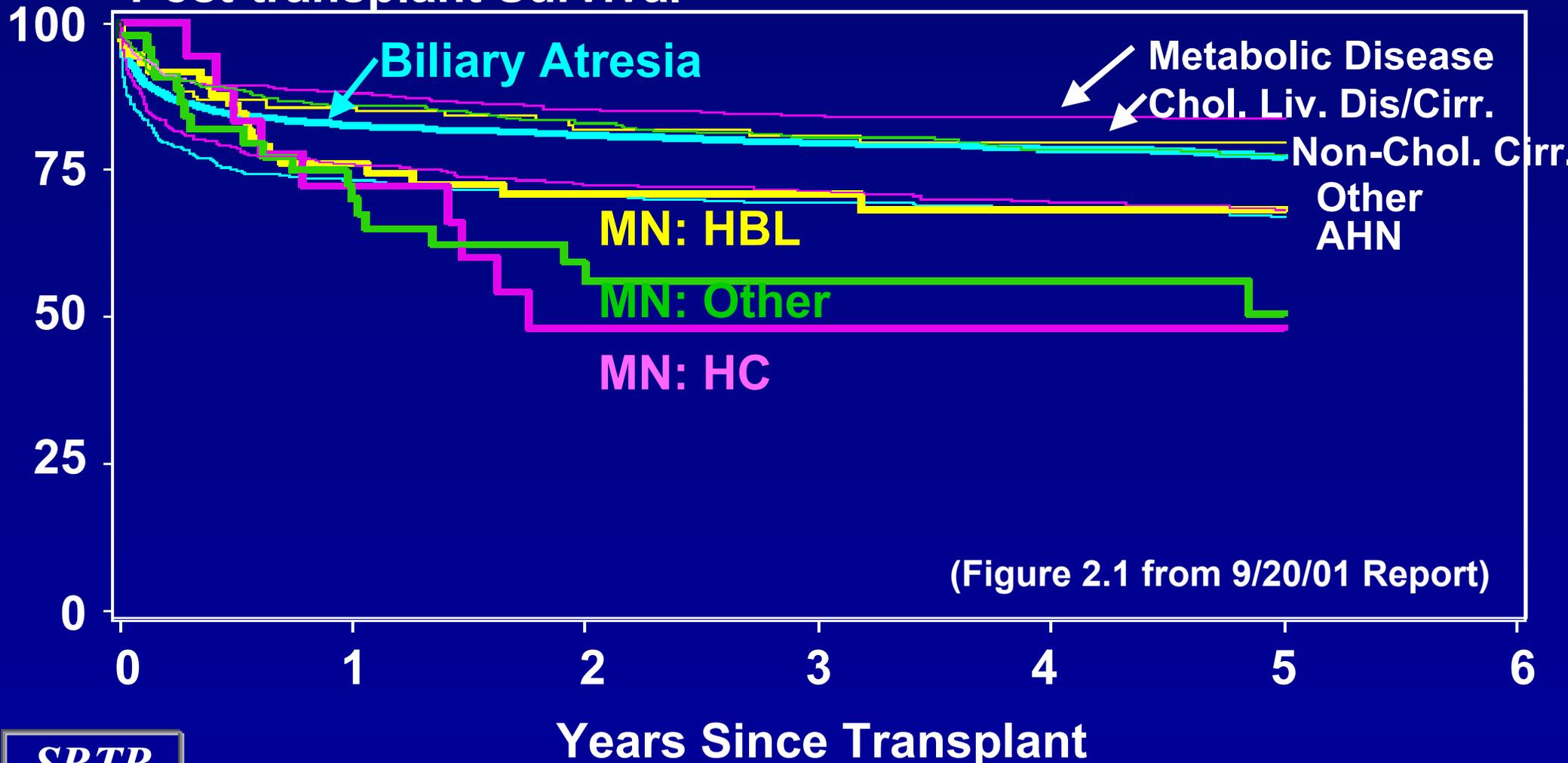
(Table 2.1 from 9/20/01 Report)

Survival Probabilities and 95% CI for Selected Diagnoses, 1987-99

Diagnosis	1 month	2 years	5 years
Malignant Neoplasm:			
HBL	94.6% (89.4%, 99.7%)	70.9% (60.1%, 81.8%)	68.2% (56.5%, 79.9%)
HC	100% (100%, 100%)	48.1% (24.5%, 71.8%)	48.1% (24.5%, 71.8%)
Other	97.8% (93.6%, 100%)	56.1% (40.5%, 71.7%)	50.5% (33%, 68%)
Biliary Atresia	91.0% (89.9%, 92.2%)	80.9% (79.3%, 82.5%)	77.2% (75.4%, 78.9%)

Post-transplant Survival Curves by Diagnosis, 1987-99

Post-transplant Survival



Summary

- **Survival is highest for patients without MN**
- **Patients with HCC have a survival similar to patients without MN until 2 years after listing**
- **Patients with HBL have a survival similar to patients without MN until 4 years after listing**
- **None of the differences are statistically significant**

Summary: Post-transplant Survival by Diagnosis Group, 1987-99

- Confidence intervals for the MN diagnoses are relatively wide, due to the small number of patients with these diagnoses
- Diagnoses divide roughly into three main groups:
 - Group 1 (metabolic, cholestatic/cirrhosis, non-cholestatic and biliary atresia)
 - Group 2 (MN:HBL, AHN and Other/Missing)
 - Group 3 (MN:HC and MN:Other)

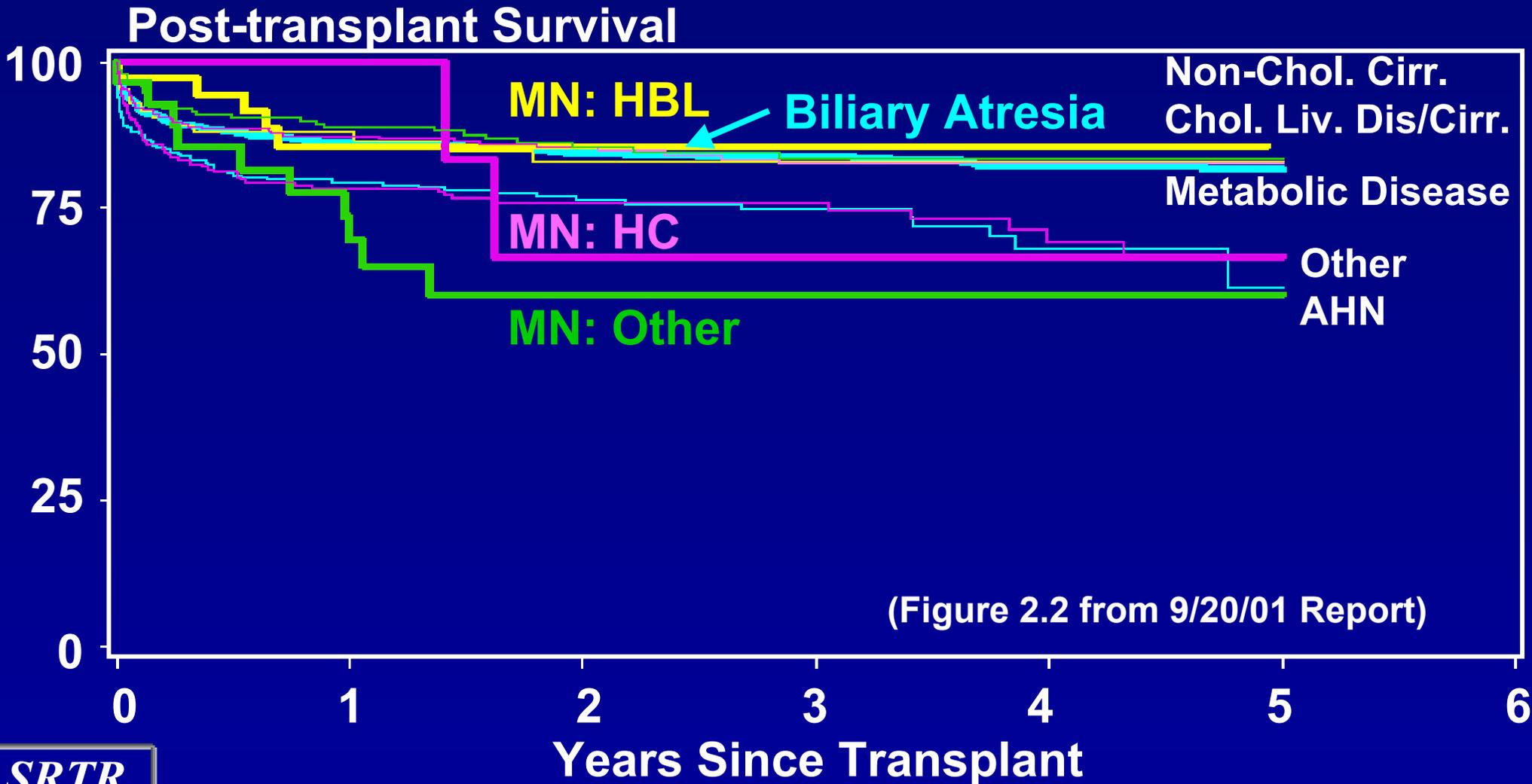
Summary: Post-transplant Survival by Diagnosis Group, 1987-99

- **At 1 month:**
 - survival probability is significantly higher for MN:HC and MN:Other than for biliary atresia, AHN or Other/Missing
- **Survival probability for MN:HC and MN:Other drops off drastically during the 2 years after transplant**
- **At 2 and 5 years:**
 - Group 1 has the best survival, and is statistically different than MN:HC and MN:Other, which has the lowest survival
- **Group 2 diagnoses fall between and are not significantly different from the other groups**

Survival Probabilities and 95% CI for Selected Diagnoses, 1995-99

Diagnosis	1 month	2 years	5 years
Malignant Neoplasm:			
HBL	97.4% (92.3%, 100%)	85.5% (73.8%, 97.3%)	-- --
HC	100% (100%, 100%)	66.7% (28.9%, 100%)	66.7% (28.9%, 100%)
Other	96.6% (89.9%, 100%)	60.1% (40.6%, 79.7%)	60.1% (40.6%, 79.7%)
Biliary Atresia	93.0% (91.4%, 94.6%)	84.5% (82.1%, 86.9%)	81.6% (78.5%, 84.7%)

Post-transplant Survival Curves by Diagnosis, 1995-99



Summary: Post-transplant Survival by Diagnosis Group, 1995-99

- Number of patients with each diagnosis is even smaller, and patterns are harder to detect.
- Survival probability for MN:HC and MN:Other drops off drastically in the first 18 months after transplant.
- At year 2:
 - MN:Other has statistically worse survival than non-cholestatic, metabolic, and biliary atresia
 - Biliary atresia is statistically better than AHN and Other/Missing

Summary: Post-transplant Survival by Diagnosis Group, 1995-99

- At year 5:
 - non-cholestatic, metabolic, and biliary atresia are statistically better than AHN and Other/Missing
 - there is not enough data to assess the MN diagnoses at this time.

Request #2: Study Question

(Request #3 from the 9/20/01 Report)

- **Compare waiting list mortality risk for pediatric liver candidates with and without hepatic tumors splitting malignant neoplasms into 3 groups:**
 - Hepatoblastoma
 - Hepatocellular Carcinoma
 - Other

Methods: Study Population

- All pediatric patients registered on the liver transplant waiting list between January 1, 1995 and December 31, 1999
- Patients classified by primary cause of ESLD
 - Malignant Neoplasm (MN): Hepatoblastoma (HBL)
 - Malignant Neoplasm: Hepatocellular Carcinoma (HC)
 - Malignant Neoplasm: Other
 - All other diagnostic categories

Methods: Analyses

- **Kaplan-Meier survival calculated by primary cause of ESLD as time from registration until removal due to death, deteriorated medical condition, or medically unsuitable**
- **Patients followed for up to 2 years censoring at the earliest of**
 - **transplant**
 - **removal from the waiting list (for reasons other than deteriorated medical condition or medically unsuitable)**
 - **last known follow-up**
 - **December 31, 2000**

Patient Count by Primary Diagnosis

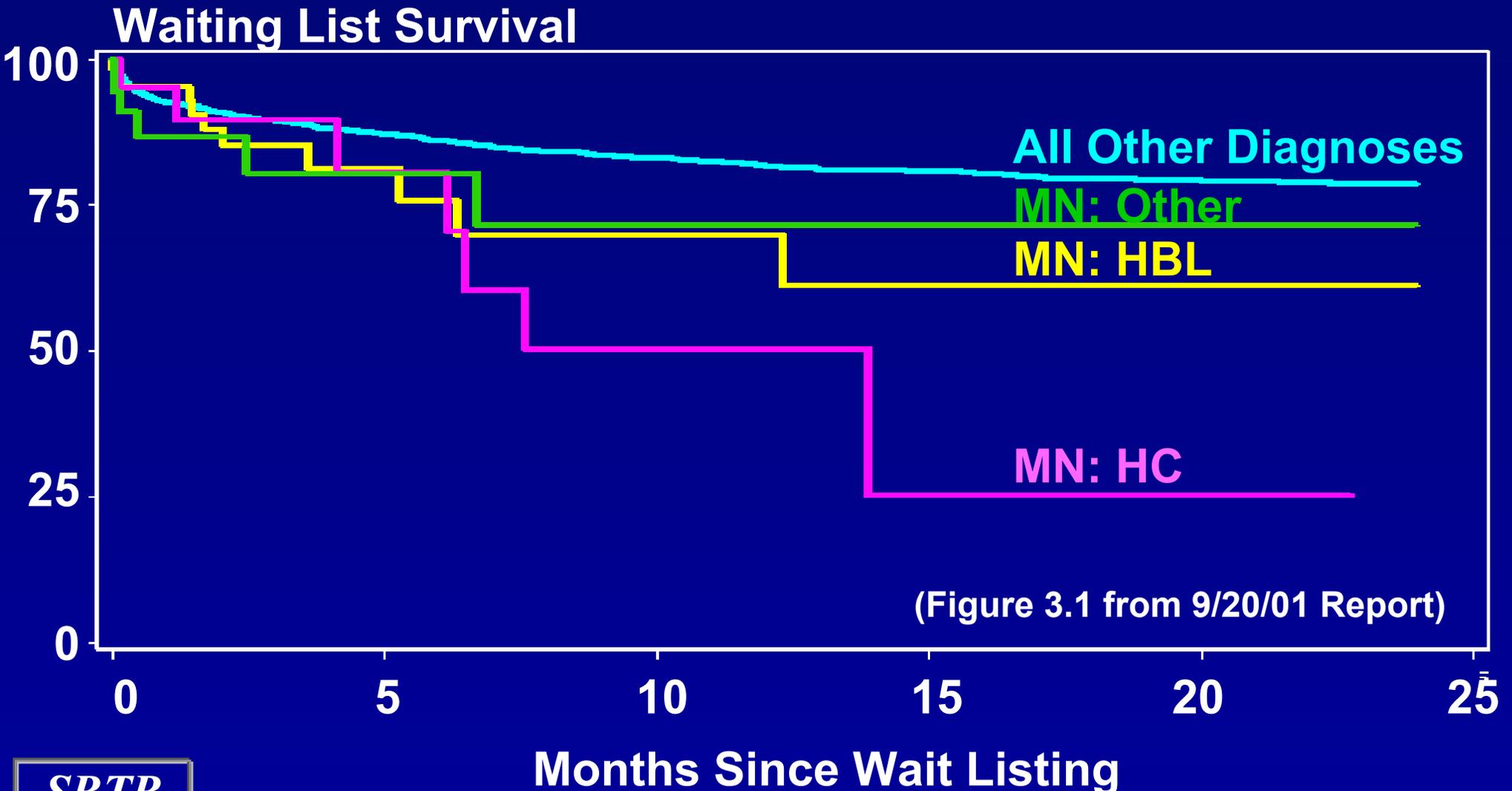
Primary Diagnosis	N	%
MN: HBL	66	1.4
MN: HC	22	0.5
MN: Other	37	0.8
All Other Diagnoses	4,431	97.3
TOTAL	4,556	100

Waiting List Survival Probability by Primary Diagnosis

Survival Probability by Time Point (95% confidence interval)

Diagnosis	1 month	1 year	2 years
Malignant Neoplasms:			
HBL	95.4% (90.2%, 100%)	70% (51.9%, 88.1%)	61.3% (38.7%, 83.8%)
HC	95.2% (86.1%, 100%)	50.4% (20.4%, 80.4%)	--
Other	86.7% (74.3%, 99.2%)	71.6% (49.5%, 93.7%)	71.6% (49.5%, 93.7%)
All other diagnoses	92.7% (91.9%, 93.5%)	81.7% (80.2%, 83.3%)	78.7% (76.8%, 80.5%)

Waiting List Survival Curves by Diagnosis, 1995-99



Summary

- **Waiting list survival experience for the malignant neoplasm diagnoses is lower after 1 year, compared to all other diagnoses.**
- **Because of small numbers in the malignant neoplasm diagnoses groups, the differences are not statistically significant.**

Single Center Experience

964 total pediatric liver transplant recipients
(1981 – 2003)

36 primary malignancies (3.7%).

Hepatoblastoma (n=15)

Stage II-2, III-I, IVA-6, IVB-6

Hepatocellular Carcinoma (n=21)

Stages: I-1, II-4, IVA-10, IVB=3

Associated liver disease 14/21:

Tyrosinemia	4
Familial cholestasis	3
Hepatitis B	3
Autoimmune hepatitis	2
Neiman Pick Type C	1
Wilson's disease	1

Treatment Regimen

Pre-transplant systemic chemotherapy 23 pts

Pre-transplant intra-arterial chemotherapy 10 pts

Total Hepatectomy: 5 were hepatic dysfunction

Unresectable tumor

- **Multi-focal disease**
- **Bilobar disease**
- **Centrally located disease**
- **Previous resection with persistent or recurrent disease**

Follow-up ranged from 1 - 230 months

Survival

Hepatoblastoma – 15 patients

Alive and disease free – 13 patients
(1, 3, 5 year survival 93, 93, & 87% respectively)

Died and tumor – 2 patients
(stage IVA D+-1 mos, Stage IVB DT – 38 mos)

Disease free survival by stage:

Stage II (n=2) 100%

Stage IVA (n=6) 100%

Stage III (n=1) 100%

Stage IVB (n=6) 50 %

Intra-arterial chemotherapy was effective in all patients treated.

Survival

Hepatocellular Carcinoma – 21 patients

Alive and disease free – 13 patients

(1, 3, 5 year survival 86, 76, 67% respectively)

Died with tumor – 6

Died free of tumor – 3 pts. (neurologic complications of original disease n=1, PTLN n=1, sepsis n=1)

Disease free survival by stages:

Stage I (n=1) 100%

Stage IVA (n=10) 60%

Stage II (n=4) 100%

Stage IVB (n=3) 33%

Stage III (n=3) 100%

Median time to tumor death was 19.5 mos (range 6 to 58 mos)

Intra-arterial chemotherapy was effective in 3/5 pts.

Factors Influencing Tumor Recurrence

Hepatoblastoma – metastatic disease

Hepatocellular carcinoma

Major vascular invasion

Lymph node involvement

Tumor size

Gender (male)

Conclusion

- **Liver transplantation for unresectable HBL and HCC can be curative.**
- **Risk factors for recurrence were significant only for HCC and followed the factors found in the adult HCC/transplant population except for number of lesions.**
- **More advanced stages in the HBL group were amenable to cure.**
- **These findings raise the speculation regarding the impact of pre-transplant chemotherapy and resection of clinical “down staging” and post-transplant survival.**

Pediatric Liver Cancer & Present Allocation

- **Hepatoblastoma – Regional Status I**
- **Hepatocellular Carcinoma – included in adult HCC schema**