Pediatric Liver Tumors and Transplantation

- Northwest Regional Pediatric Liver Disease Symposium, Seattle WA, April 12, 2008
Liver transplantation for primary liver tumours in children

• WHEN?
  - patient selection
  - tumour types
  - contra-indications

• HOW?
  - timing
  - techniques
  - chemotherapy
Liver transplantation for primary liver tumours in children

One Concept:

Large unresectable tumour (ben/mal)
No malignant active extra-hepatic disease

→ Radical resection by total hepatectomy

Two Strategies

- Elective transplant  (Pre-emptive selection)
- Rescue indications  (incomplete resection or recurrence)
Liver transplantation for primary liver tumours in children

Tumour types

Benign
- Haemangiomas
- Others

Low grade malignancy
- Epitheloid Haemangioendothelioma

Malignant
- Hepatoblastoma
- Hepatocarcinoma
- Other carcinomas
- Sarcomas
Benign liver tumours

- Haemangioma
- Infantile haemangio-endothelioma
- Other
Hepatic Vascular Tumours in Children

- Haemangioma
- Haemangio-endothelioma
  - Infantile type Type I
  - Infantile type Type II
  - Epitheloid type
- Angiosarcoma
Benign liver tumour

Should we consider selected cases for transplant?  
Yes / No

When?
Benign liver tumour Haemangioendothelioma
Case Study: Hemangioendothelioma

- 8 month old girl (presented at age 2 months)

- Large non-metastatic hepatic mass, ? Hemangioma

- Treatment: steroids/interferon hepatic artery embolization tracheostomy

- Problems: - massive untreatable hemangioendothelioma - respiratory compromise - sepsis
Liver transplantation for primary liver tumours in children

**Benign liver tumour**

- Huge Mesenchymal Hamartoma
- Recurrent after 2 resections
- Growth failure
- Refractory ascites
- Hospital dependant
- 1- Re-attempt and transplant if secondary liver failure
- 2- liver transplant
Benign liver tumour

Should we consider selected cases for transplant?

- as RESCUE? after failure of previous other treatment including “last chance” resection?
  
  ... Rescue = suboptimal treatment ...

- PRIMARY IF Complicated, Unresectable and Refractory to conventional treatments
Liver transplantation for primary malignant liver tumours in children

**Low grade malignancy**

Epitheloid Haemangioendothelioma

- 11 Yrs old
- Abdominal pain
- Hepato-splenomegaly
- Multifocal liver EHE
- Lung metastases

Not considered for transplant
  ➔ Chemotherapy

At one year:
- Reduced Liver tumour mass
- Stable lung nodes
- No pain
- 1 grade I oesophageal varix

Options for future management?
Liver transplantation for primary liver tumours in children

**Primary Malignancies**

- Hepatoblastoma
- Hepatocarcinoma
- Other carcinoma and Sarcomas
Liver transplantation for primary malignant liver tumours in children

**CONDITIONS**

- No extrahepatic active disease
- Radical resection by total hepatectomy

**CONDITIONS?**

- Effective adjuvant therapy available
- Chance of success > 50% at 5 years
Hepatoblastoma

Indication for transplantation =

Unresectable after chemotherapy
Liver transplantation for primary liver tumours in children

Hepatocarcinoma
RARE in children

**Presentation A:** small HCCA on diseased livers
- HBV
- Biliary atresia
- Tyrosinemia

**Presentation B:** large HCCA on normal liver
(2 fibrolamellar type)
Liver transplantation for primary liver tumours in children

Results of Transplantation For HB and HCCA:

1- UNOS
2- SIOPEL
3- World review
## Patient Count by Primary Diagnosis

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

(Table 2.1 from 9/20/01 Report)
# Survival Probabilities and 95% CI for Selected Diagnoses, 1987-99

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

(excerpt Table 2.2 from 9/20/01 Report)
Post-transplant Survival Curves by Diagnosis, 1987-99

(Figure 2.1 from 9/20/01 Report)
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
Waiting List Survival Curves by Diagnosis, 1995-99

(Figure 3.1 from 9/20/01 Report)
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.
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:

<table>
<thead>
<tr>
<th>Stage</th>
<th>(n)</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>2</td>
<td>100%</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>IVA</td>
<td>6</td>
<td>100%</td>
</tr>
<tr>
<td>IVB</td>
<td>6</td>
<td>50%</td>
</tr>
</tbody>
</table>

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, PTLD 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.
Pediatric Liver Cancer & Present Allocation

- Hepatoblastoma – Regional Status I
- Hepatocellular Carcinoma – included in adult HCC schema
Median Lab MELD/PELD Among HCC Recipients at Cadaveric Transplant by Region

Region

HCC1

HCC2

1
11
15

2
13
15

3
12
15

4
13
14

5
12
14

6
12
15

7
13
15

8
16
15

9
15
15

10
7
15

11
8
14

All
12
12

HCC1

HCC2
90-Day Mortality Rate by HCC Exception Status

*Unadjusted Cox model of time to death, censoring at removal from the waitlist for reasons other than death (including transplant).
Proportion of Cadaveric Transplants with an HCC Exception by Region

Percent of All Transplants

Region

% HCC 1 % HCC 2
SIOP E Pre-T-Ext Staging

I

II

III

IV

Size matters
SIOPEL – Outcome of liver resection for Hepatoblastoma

Standard risk  N=67  Stage I, II, III  No Metastases
High risk  N=59  Stage IV  or Metastases  or Vasc invasion  or extrahepatic ext

Cum Survival

Years
SIOPEL I  1990-1994

12 LIVER TRANSPLANTS
7 “primary” LT
5 “rescue” LT

8/12 LONG-TERM SURVIVORS

10 Yrs survival
85% for “primary” LT
40% for “rescue” LT

N = 154
At diagnosis:
- Lung metastases = 8%
- Vascular invasion = 18%

N = 147
World experience review – Prof JB Otte / SIOPEL

82% survival rate after primary liver transplantation (LTX) for 106 patients.

30% survival rate after rescue liver transplantation (LTX) for 41 patients with incomplete resection or recurrence.

(years)
# Liver transplantation for hepatoblastoma in children

## SIOPEL 2 - 126 Hepatoblastomas

<table>
<thead>
<tr>
<th></th>
<th>67 standard risk</th>
<th>59 high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastases</td>
<td>0</td>
<td>42 %</td>
</tr>
<tr>
<td>Vasc. Invasion</td>
<td>0</td>
<td>21 %</td>
</tr>
<tr>
<td>Extrahepatic ext.</td>
<td>0</td>
<td>10 %</td>
</tr>
<tr>
<td>Macrosc. resection</td>
<td>96 %</td>
<td>66 %</td>
</tr>
<tr>
<td>Event free survival</td>
<td>89 %</td>
<td>47 %</td>
</tr>
</tbody>
</table>
67 standard risk  SIOPEL
106 primary LTX
59 high risk  SIOPEL
41 rescue LTX
Liver transplantation for hepatoblastoma in children

- Primary transplantation allows radical resection of “unresectable” hepatoblastomas.

- Good long-term survival rates are achieved even in patients with previous metastases if they cleared during chemotherapy.

- Outcome is poor if transplantation is done
  - after incomplete resection
  - or for recurrence of disease.
34 children with hepatoblastoma
Actuarial survival *

- Includes 2 patients who were not operated and 10 primary transplants
- All surviving patients currently with Nl AFP
- F-Up > 18 months in 90 % of patients
Liver transplantation for hepatoblastoma in children

**Strategy**

Selection of patients
- no active lung metastases
- no extrahepatic disease
- ? chemosensitive tumours

Adequate first choice
- avoid incomplete resection
- straight primary Tx when appropriate
- early referral to expert surgical team
Liver transplantation for primary malignant liver tumours

STRATEGY?

- timing
- technique
- chemotherapy
Liver transplantation for primary malignant liver tumours

STRATEGY?

- timing
  . Avoid long waiting time?
  . Living / cadaveric donor?
Liver transplantation for primary malignant liver tumours

STRATEGY?

- technique
  . IVC replacement?
  . Lymphadenectomy?
  (? Aggressive resection)
Liver transplantation for primary malignant liver tumours

STRATEGY?

- Pre-Op chemotherapy
  . Downstaging
  . Selecting patients?

- Post-Tx chemotherapy?
  . Cumulative toxicity!
  . Modified IS protocol
14 month old boy
Multifocal liver masses, Pretext 3, No extra-hepatic extension
Chemo: good decrease in size
decreasing then plateauing AFP

At diagnosis

After 4 chemo courses
16 month old boy
Large liver mass, Pretext 3,
Lung mets,
Portal vein thrombosis
Chemo: downstaged
decreasing AFP

CT at diagnosis

![CT scan at diagnosis](image1)

After 4 chemo courses

![CT scan after 4 chemo courses](image2)
16 month old girl
Multifocal liver masses, Pretext 4,
Portal vein thrombosis
Non AFP secreting
Chemo: good decrease in size

CT at diagnosis

After 4 chemo courses
QUESTIONS:

1. Patient selection
2. Pre & post-transplant therapy
3. “Down-staging” of tumors
4. Medical urgency/priority
5. Segmental transplantation: with/without preservation of IVC