LIVER TRANSPLANTATION FOR HILAR CHOLANGIOCARCINOMA
Liver Transplantation for Hilar Cholangiocarcinoma

- Cholangiocarcinoma
- Protocol
- Results
- Special problems
- Living donor transplantation
- MELD score adjustment
- Challenges and controversies
The Emergence of Liver Transplantation for Hilar Cholangiocarcinoma

A Success Story of Team Care and Combination Therapy

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Julie Heimbach – Transplant Surgeon
Len Gunderson – Radiation Oncology
Mike Haddock – Radiation Oncology
Steve Alberts – Medical Oncology
David Nagorney – Hepatobiliary Surgeon
Jeff Steers – Transplant Surgeon
Eduardo Ramos – Transplant Fellow
Henk-Jen Mantel – Medical Student

Liver Transplant Team
Medical and Radiation Oncology
Cholangiocarcinoma

• Second most common primary malignant liver tumor
• Complication of primary sclerosing cholangitis
• Associated with hepatolithiasis, choledochal cysts, Caroli’s disease, biliary adenomata, parasite infections, and Thorotrast exposure
• Natural history of cholangiocarcinoma is poor, especially in the setting of primary sclerosing cholangitis
Hilar Cholangiocarcinoma

- Standard surgical resection has limited efficacy
  - Few tumors are resectable
  - Long term survival <35% with complete resection
- Results with liver transplantation alone are poor
- Lymph node metastases portend poor prognosis
- Radiation with chemosensitization affords palliation
- University of Nebraska protocol with neoadjuvant brachytherapy and liver transplantation
Cholangiocarcinoma
Cincinnati Transplant Tumor Registry
207 patients, 1968 - 1997

• PSC in addition to cholangiocarcinoma - 28%
  – No difference in survival
• Tumor recurrence - 51%
  – 84% within 2 years
  – 47% in allograft and 30% in lungs
  – Survival after recurrence less than 1 year
• No survival advantage for incidental tumors
• No advantage of postoperative adjuvant therapy

Transplantation 2000; 69:1633
Cholangiocarcinoma
Cincinnati Transplant Tumor Registry
207 patients, 1968 - 1997

Patient Survival, %

Year

Transplantation 2000; 69:1633
Cholangiocarcinoma
Spanish Liver Transplant Experience
36 patients, 1988 - 2001

• 36 hilar CCA transplants at 12 of 19 centers
• 13 of 36 with hepatic lymph node involvement
• 4 incidental tumors
• Patient survival:
  82% at one year
  53% at two years
  30% at three years
• 19 recurrences at mean of 21 months
  13 intraabdominal
• 17 of 23 deaths (47%) due to recurrent disease

Annals of Surgery 2004; 239:265
Incidental Cholangiocarcinoma
Canadian Transplant Experience
n=10

Hepatology 2002; 36:228A
Cholangiocarcinoma Complicating PSC
UCLA - Liver Transplant Experience

Patient Survival, %

Year

Annals of Surgery 1997; 225:472
Mayo Clinic Treatment Protocol

External beam radiation therapy

Brachytherapy

Protracted venous infusion of 5-FU

Abdominal exploration for staging

Liver transplantation
Hilar Cholangiocarcinoma
Mayo Clinic Approach
1993 to Present

• Appear resectable
  – Resection with excision of extrahepatic bile duct, regional lymphadenectomy, and right or left hepatectomy (+ caudate)

• Appear unresectable
  – Liver transplantation protocol

• Arising in setting of PSC
  – Liver transplantation protocol
Patient Eligibility

- Diagnosis of cholangiocarcinoma
  - transcatheter biopsy or brush cytology
  - CA-19.9 >100 mg/ml with a malignant appearing stricture on cholangiography
  - *Biliary ploidy by FISH with a malignant appearing stricture on cholangiography*

- Unresectable tumor above cystic duct
  - *Pancreatoduodenectomy for CBD tumors*
  - *Resectable CCA arising in PSC*

- Absence of intra- and extrahepatic metastases

- Candidate for liver transplantation
Fluorescence in situ hybridization of biliary brushing. A representative fluorescence photomicrograph of biliary brushings from a patient with cholangiocarcinoma is shown here. Each colored spot represents one chromosome, therefore, 2 spots per color are indicative of the normal diploid state. In this example, >2 spots are seen for more than one color (indicating more than one chromosome pair is abnormal), leading to a diagnosis of polysomy.
Exclusion Criteria

• Uncontrolled infection
• Prior radiation or chemotherapy
• Prior biliary resection or attempted resection
• Transperitoneal biopsy (including EUS)
• Intrahepatic metastases
• Evidence of extrahepatic disease
• History of other malignancy within 5 years
Radiation Therapy

• **External beam radiotherapy**
  - inclusion of primary tumor and regional (porta hepatis, celiac, and pancreatoduodenal) lymph nodes
  - window extended 3-5cm intrahepatically beyond ductal involvement
  - 4000 to 4500 cGy

• **Intraluminal brachytherapy**
  - 2-3 weeks after completion of external beam therapy
  - Iridium inserted through endoscopic or percutaneous tubes
  - 2000 to 3000 cGy delivered to a 1cm radius
Chemotherapy

- 5-FU daily bolus for three consecutive days at the beginning and end of external beam radiotherapy
- Protracted IV therapy begun with brachytherapy and continued until staging operation (daily for five weeks with one week off) and resumed afterward
- Oral capecitabine
Radiation and Chemotherapy Toxicity

- Nausea and vomiting
- Leukopenia
- Cholangitis
- Cholecystitis
- Gastroduodenal ulceration
- Gastroparesis
- Hepatic abscess
- Liver failure
Surgical Staging

• Completion of brachytherapy
  – Initially as time nears for deceased donor transplantation
  – Since September 2002: immediately after brachytherapy for those awaiting deceased donor transplantation
  – 2-7 days prior to living donor transplantation

• Thorough intraabdominal examination

• Palpation of liver

• Assess local extent of disease

• Regional hepatic lymph node biopsies
  – common hepatic artery lymph node
  – pericholedochal lymph node

• Hand-assisted laparoscopy for selected patients
Liver Transplantation

- Avoid hilar dissection
- Arterial interposition graft with deceased donor transplantation
- Low division of portal vein
- Portal vein interposition graft with living donor transplantation
- Caval replacement with caudate involvement
- Frozen section of cut common bile duct
  - *pancreatoduodenectomy if positive*
Cholangiocarcinoma Treatment Protocol
Results – March 2007

131 patients
- 11 deaths, debilitation, or disease progression
- 1 transplant elsewhere
- 2 deaths
- 24 (21%) positive
- 81 liver transplantation
- 60 deceased donor
- 20 living donor
- 1 domino donor

Irradiation + 5-FU

115 staging operation
- 5 awaiting transplantation
- 2 deaths
- 3 transplant elsewhere

81 liver transplantation
Patient Survival After Start of Therapy
1993 – 2007
n=131

55 ± 6%
Patient Survival After Transplantation
1993 – 2007
n=81

72 ± 7%
Disease-Free Survival After Transplantation
1993 – 2007
n=81

62 ± 8%
Staging Operation
n = 115

25 (22%) had findings precluding transplantation

- Regional lymph node metastases: 12
- Invasion of adjacent organs/tissues: 4
- Intrahepatic metastases: 3
- Peritoneal metastasis: 6
  - (Neuro-connective tissue): 1
  - (Gall bladder involvement): 1

*EUS transgastric aspiration site (primary tumor)
**Missed at staging, found at LD and DD transplantation
Cholangiocarcinoma Treatment Protocol

Results – 81 Transplants

17 (22%) deaths:

- 4 surgical complications, 2 – 5 months
- 1 GVHD, 4 months
- 1 hematological disease, 31 months
- 11 recurrent CCA
Deaths due to surgical complications – 4:

- Primary graft failure, HAT
  - 1
  - 5 months
  - HAT after retransplant, death during 2\textsuperscript{nd} retransplant
- Unexplained, possible HAT
  - 1
  - 3 months
- Complications of LDLT
  - 2
  - 2, 4 months
  - Bile leak (Wall stent), sepsis
  - HAT, retransplantation, bile leak, sepsis
### Recurrences After Liver Transplantation

**n=14**

<table>
<thead>
<tr>
<th>Site</th>
<th>Time</th>
<th>Status</th>
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<tbody>
<tr>
<td>Perihepatic</td>
<td>7, 13, 17, 27 mo</td>
<td>death at 9, 18, 24, 43 mo</td>
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<tr>
<td></td>
<td>10 mo</td>
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</tr>
<tr>
<td>Mediastinum</td>
<td>39 mo</td>
<td>death at 64 mo</td>
</tr>
<tr>
<td>Bone</td>
<td>7, 54 mo</td>
<td>death at 10, 83 mo</td>
</tr>
<tr>
<td></td>
<td>7 mo</td>
<td>alive at 28 mo</td>
</tr>
<tr>
<td>Brain, adrenal</td>
<td>46 mo</td>
<td>death at 47 mo</td>
</tr>
<tr>
<td>Remnant CBD</td>
<td>64 mo</td>
<td>death at 66 mo</td>
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**Mean time to recurrence – 26 months**
Timing of CCA Recurrence After OLT

11/65 (17%)
mean time = 29 months
median = 22 months
site = metastatic 8, regional 3
Special Problems

- Medical and neoadjuvant therapy problems
- Hepatic decompensation
- Technical problems
- Late vascular problems
Medical and neoadjuvant therapy problems

- DVT and PE
- Duodenal ulceration – perforation, bleeding
- Cholecystitis, gall bladder perforation
Special Problems

Hepatic decompensation

- Precluding staging
- After staging
# Recurrences After Liver Transplantation

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5 of 14 (36%) recurrences distant metastases
Special Problems

Technical problems
• Early hepatic artery thrombosis
• Caudate involvement
• Biliary Wall stents
• Adhesions
• Common bile duct involvement
Distal Cholangiocarcinoma

- Intrahepatic: 6%
- Perihilar: 67%
- Distal: 27%
Pancreatoduodenectomy and Transplantation

n = 9

- 8 of 50 (16%) PSC patients had positive CBD margins
  - 7 underwent pancreatoduodenectomy (4 DD, 2 LD, 1 AD)
    » 6 alive and disease-free at 8 years to 7 days after transplantation
    » 1 death at 3 months from presumed HAT
  - 1 adhesions precluded pancreatoduodenectomy
    » alive with disease at 2 years

- 2 PSC patients with prior biliary operations underwent en bloc pancreatoduodenectomy
  - Alive and disease-free
Common Bile Duct Involvement
Pancreatoduodenectomy
Late vascular problems

• Overall incidence – 40%

• Portal vein stenosis and thrombosis
  – 22% with both living and deceased donor livers
  – Percutaneous angioplasty and stent insertion

• Hepatic artery stenosis and thrombosis
  – 21% with living donor grafts
  – Avoided by routine use of iliac graft with deceased donor livers
Living Donor Liver Transplantation

• Appears attractive for cholangiocarcinoma
• Enables better timing of therapy
  – neoadjuvant therapy
  – staging operation
  – transplantation
• Obviates problems with deceased donor organ availability and UNOS Regional Review Board appeals
  – status 2B prior to change in allocation system
  – no standard score assignment with MELD/PELD system
Revisiting Living Donor Liver Transplantation for Cholangiocarcinoma

• Conservative inclusion criteria
• Strict exclusion criteria
• Adjustment of neoadjuvant therapy
• Timing of staging operation
• Preferential avoidance of iliac artery graft
Patient Survival After Transplantation

2004 – 2006

- Living Donor Transplant (12)
- Deceased Donor Transplant (24)

83 ± 15%
79 ± 15%

Years after transplantation
Cholangiocarcinoma Treatment Protocol

Key Questions

• Efficacy?
• Appropriate use of donor organs?
• Resection or transplantation?
• Prioritization for deceased donor liver allocation?
Cholangiocarcinoma Treatment Protocol
Key Questions (update efficacy data)

• Efficacy?
  – 55% five-year survival overall
  – 73% five-year survival after transplantation
  – 62% five-year disease-free survival after transplantation

• Appropriate use of donor organs?
• Resection or transplantation?
• Prioritization for deceased donor liver allocation?
Cholangiocarcinoma Treatment Protocol

Key Questions

• Efficacy?
• Appropriate use of donor organs?
• Resection or transplantation?
• Prioritization for deceased donor liver allocation?
Patient Survival After Transplantation
CCA Versus Other Diagnoses

% Survival over Years after Transplantation

- CCA (28)
- HCC (70)
- HCV (147)
- PSC (131)

ATC 2004
Years after transplantation
Cholangiocarcinoma Treatment Protocol

Key Questions

• Efficacy?
• Appropriate use of donor organs?
• Resection or transplantation?
• Prioritization for deceased donor liver allocation?
Survival after Operation

- Transplantation (n=38)
  - 92% at 1 year
  - 82% at 3 years
  - 82% at 5 years

- Resection (n=26)
  - 48% at 1 year
  - 21% at 5 years

ASA 2005
Survival after Operation
Patients *Without* PSC

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Transplantation (n=16)</th>
<th>Resection (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>83%</td>
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</tr>
<tr>
<td>3</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>18%</td>
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ASA 2005
Survival from Start of Therapy

**Transplant protocol (n=71)**
- 82% at 1 year
- 79% at 2 years
- 61% at 3 years
- 58% at 4 years
- 21% at 5 years

**Resection (n=26)**
- 48% at 1 year
- 21% at 2 years

ASA 2005
Cholangiocarcinoma Treatment Protocol

Key Questions

- Efficacy?
- Appropriate use of donor organs?
- Resection or transplantation?
- Prioritization for deceased donor liver allocation?
Summary

- Combined chemoradiation therapy and liver transplantation achieves excellent results for highly selected patients with early stage disease - 73% patient survival at 5 years
- Operative staging is essential - findings preclude transplantation for ~20% of patients
- Morbidity is significant but not prohibitive
- Living donor transplantation is an attractive option for patients with cholangiocarcinoma
Summary

• Patient survival after liver transplantation with this protocol exceed results reported with resection for hilar CCA

• Results compare favorably with survival after liver transplantation for chronic liver disease and hepatocellular carcinoma

• Results warrant due consideration for deceased donor liver allocation by UNOS Regional Review Boards
Liver transplantation with neoadjuvant therapy has emerged as an effective treatment for patients with localized, regional lymph node negative, hilar cholangiocarcinoma