Cholangiocarcinoma: Not an Indication for Hepatic Transplantation

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Objectives

1. Very brief overview of cholangiocarcinoma
2. Review current standards of care for patients with perihilar cholangiocarcinomas
3. Current statistics regarding OLT in the US, actuarial estimates of survival
4. Review of historical data of orthotopic liver transplantation (OLT) for cholangiocarcinoma
5. Neoadjuvant therapy for cholangiocarcinoma
Cholangiocarcinoma

Malignancy of biliary duct system\(^1\)
- Intrahepatic
- Extrahepatic – Perihilar 60%-80%
- Distal 10-30%

Perihilar (Klatskin) classified by anatomic location\(^2\):
I. Confined to common hepatic duct
II. Bifurcation w/o secondary intrahepatic duct involvement
III. a) Right intrahepatic duct extension
III. b) Left intrahepatic duct extension
IV. Both intrahepatic duct involvement
Cholangiocarcinoma: AJCC TNM Staging

T1 Tumor confined to bile duct
T2 Tumor invades beyond the wall of the bile duct
T3 Tumor invades the liver, gallbladder, pancreas, and/or unilateral branches of the portal vein (right or left) or hepatic artery (right or left)
T4 Tumor invades any of the following: main portal vein or its branches bilaterally, common hepatic artery, or other adjacent structures, such as the colon, stomach, duodenum, or abdominal wall

N0 No regional lymph node metastasis
N1 Regional lymph node metastasis
M0 No distant metastasis
M1 Distant metastasis

Stage Grouping
IA T1 N0 M0
IB T2 N0 M0
IIA T3 N0 M0
IIB T1 N1 M0, T2 N1 M0, T3 N1 M0
III T4 Any N M0
IV Any T Any N M1
Cholangiocarcinoma: Current surgical therapy

Types I and II without vascular involvement:
Local tumor excision + Portal lymphadenectomy + Cholecystectomy + CBD excision + Bilateral ReY hepaticojejunostomies

Types IIIa and IIIb: All of the above including appropriate hepatic lobectomy

Type IV: No curative surgical therapy – palliation with or without surgery.
UNOS/OPTN Data for Liver Transplantation\textsuperscript{5}

Kaplan-Meier Patient Survival Rates 1997-2004:

<table>
<thead>
<tr>
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<th>Malignant neoplasms</th>
<th>All</th>
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<tbody>
<tr>
<td>1 Year</td>
<td>86.3%</td>
<td>82.5%</td>
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<tr>
<td>3 Year</td>
<td>70.0%</td>
<td>73.5%</td>
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<tr>
<td>5 Year</td>
<td>57.3%</td>
<td>67.2%</td>
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Burden of proof of studies relies on survival rates versus figures listed above.

Only malignancy that is indication for OLT is HCC
OLT for Cholangiocarcinoma

1997 Meyer et al.⁶ – Retrospective review of Cincinnati Transplant Tumor Registry.
- 207 pts transplanted for cholangiocarcinoma
- 34% living at date of publication
- 51% recurrence, 4% survival with recurrence
- 1, 2, & 5 yr survival estimates 72, 48, & 23%
OLT for Cholangiocarcinoma

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1998 Iwatsuki et al.\textsuperscript{7} – Retrospective analysis of Univ of Pittsburg experience of hepatic resection vs OLT
- n=72, 38 w OLT
- 1, 3, 5yr survival: 60, 32, 25\%. 
OLT for Cholangiocarcinoma

2000 Figueras et al.⁸ – Spanish retrospective analysis
-n=28, 20 resections, 8 OLT
-5 YSR of 36% w OLT
OLT for Cholangiocarcinoma

2000 Figueras et al.\textsuperscript{8} – Spanish retrospective analysis
- n=28, 20 resections, 8 OLT
- 5 YSR of 36\% w OLT

2001 Shimoda et al.\textsuperscript{9} – Los Angeles retrospective analysis of all OLT at 2 sites: UCLA and Cedars Sinai
- n=25, 1 & 3 year survival rates of 71 & 35\%
- 1&3 year disease-free survival 67 and 42\%
- Affecting disease-free survival: tumor size (>3cm), extension to other organs, single versus multiple nodules.
OLT for Cholangiocarcinoma

2003 Robles et al.\textsuperscript{10} – Spanish retrospective multicenter study.

- $n=36$ OLT for hilar cholangiocarcinoma
- $53\%$ recurred. 1, 3 & 5 YSR of 82, 53 & 30\%
OLT for Cholangiocarcinoma

2003 Robles et al.\textsuperscript{10} – Spanish retrospective multicenter study.
- n=36 OLT for hilar cholangiocarcinoma
- 53% recurred. 1,3 & 5 YSR of 82, 53 & 30%

2005 Ghali et al.\textsuperscript{11} – Canadian retrospective study
- n=10 during period during 1996 to 2003
- All stage I or II, none w +LN
- 2/10 survived, actuarial 3 yr SR of 30%
Neoadjuvant therapies: Chemo/Radiotherapy

2002 Sudan et al. Prospective trial of intraluminal bile duct irradiation (6000 cGy) and systemic chemotherapy (5-FU), followed by OLT.

- Neoadjuvant therapy provided daily until transplant.
- n=17, 6 inoperable, 11 OLT. Mean age 45
- Median waiting time 87d (15-792 days).
Neoadjuvant therapies: Chemo/Radiotherapy

2002 Sudan et al.
- 5 of 11 patients (45.5%) alive at end of study
- mean survival 4.2 years
- mean survival of 6 pts who died: 0.6 years
Chemotherapy and radiotherapy preceding OLT represents a significant contribution to early postoperative fatality.
Neoadjuvant therapies: Chemo/Radiotherapy


n=71

+External beam rad 4500cGy
+IV 5-FU 1st 3d of EBR: chemosensitization
+Ir-192 brachytherapy 3 weeks after EBR

1 awaiting lap
9 pts excluded

staging laparotomy

38 OLT
9 Awaiting

14 excluded
2005 Rea et al.

1, 3 & 5 YSR of all 71 pts 79, 61, and 58%

1, 3 & 5 YSR of 38 OLT pts 98, 86, and 81%
Neoadjuvant therapies: 
Chemo/Radiotherapy

2005 Rea et al. Problems with study

1. Mean age disparity in control vs OLT group
   - 63 years old versus 48

2. 16/38 explanted livers free of residual tumor

3. Establishment of diagnosis in treatment group
   made by brush cytology OR CA 19-9 greater
   than 100ng/ml w radiographic malignant stricture

4. 5 year actuarial survival estimates of 14 patients
   treated nonsurgically greater than that of
   resection patients.
Neoadjuvant therapies: Chemo/Radiotherapy

2005 Rea et al. Critical conclusions

1. Control resection group was retrospective review of resection during same time period
2. Chemo- and radiation therapy without resection better than resection.
3. No attempt at using neoadjuvant therapy in combination with resection – may be unrealistic.
4. Burden of imposing operable share of 4000 cases of cholangiocarcinoma diagnosed annually.¹
UNOS/OPTN Data for Liver Transplantation$^5$

7/01/2005 to 6/30/2006 – National figures

• On waitlist – 17,492
• Total OLT – 6,550
• Transplant rate 38%
• Died on waitlist without transplant within one year of listing 9.4% = 1047 people.
Conclusions

• Prior studies prove failure of cholangiocarcinoma as an indication for OLT
• Neoadjuvant therapies in combination with OLT have shown success, but no trials to date with Mayo protocol and resection
• Our burdened organ transplantation system will be taxed by cholangiocarcinoma as new indication for OLT
• Is there a Milan Criteria/UCSF Criteria extractable from Mayo Study?
References


References


