

**UPMC
STARZL TRANSPLANTATION INSTITUTE
LIVER TRANSPLANT POLICIES AND PROCEDURES**

**POLICY LT-CCA-0415
LIVER TRANSPLANTATION IN PATIENTS WITH HILAR CHOLANGIOCARCINOMA**

PURPOSE

This policy is intended to guide the management of liver transplant candidates with hilar cholangiocarcinoma.

BACKGROUND

Incidence

- 1-2/100,000
- 2% of all cancer diagnoses in US
- 15% of all liver cancers
 - Intrahepatic 2,600 cases/yr.
 - Extrahepatic 3,000 cases/yr.

Risk Factors

- Chronic biliary inflammation
- PSC, choledochal cysts
- Hepatitis B and C
- Cirrhosis
- ETOH
- Liver flukes
- Toxic exposure: thorium dioxide (Thorotrast®)

Cholangiocarcinoma (CCA) at one point was regarded as a contraindication to orthotopic liver transplantation (OLT). The initial experience in Nebraska (1) and further expanded upon by Mayo Clinic (2) has permitted patients with CCA to achieve a longer 5-year survival than if they were to undergo resection alone. Not all patients with CCA are candidates for transplantation, however.

INCLUSION and EXCLUSION CRITERIA

A. Inclusion Criteria

- otherwise appropriate transplant candidate
- unresectable hilar CA or CCA arising in the setting of PSC
- dx of CCA based on a malignant appearing stricture on cholangiography and *one* of the following:
 - a. Biopsy or cytology results demonstrating malignancy

- b. Carbohydrate antigen 19-9 greater than 100 U/mL in absence of cholangitis
- c. Aneuploidy

B. Exclusion Criteria

- extrahepatic disease, including LN involvement
- tumor size >3 cm
- previous attempted open biopsy or resection of tumor
- intrahepatic metastases (contiguous intrahepatic metastases permitted)
- Vascular encasement NOT a contraindication
- prior radiation therapy or chemotherapy
- uncontrolled infection
- peripheral CCA
- (?) extension of tumor below the cystic duct (req. Liver Tx and Whipple)

UNOS REQUIREMENTS FOR LISTING PATIENTS WITH CHOLANGIOCARCINOMA

Criteria must be met in accordance with UNOS Policy **9.3.F, Candidates with Cholangiocarcinoma:**

A candidate will receive the MELD/PELD exception in *Table 9-2: Specific MELD/PELD Exceptions for cholangiocarcinoma*, if the candidate's transplant hospital meets *all* the following qualifications:

1. Submit a written protocol for patient care to the Liver and Intestinal Organ Transplantation Committee that should include *all* of the following:
 - a. Candidate selection criteria
 - b. Administration of neoadjuvant therapy before transplantation
 - c. Operative staging to exclude any patient with regional hepatic lymph node metastases, intrahepatic metastases, or extrahepatic disease
 - d. Any data requested by the Liver and Intestinal Organ Transplantation Committee
2. Document that the candidate meets the diagnostic criteria for hilar CCA with a malignant appearing stricture on cholangiography and *one* of the following:
 - a. Biopsy or cytology results demonstrating malignancy
 - b. Carbohydrate antigen 19-9 greater than 100 U/mL in absence of cholangitis
 - c. Aneuploidy

The tumor should be considered unresectable because of technical considerations or underlying liver disease.

3. If cross-sectional imaging studies demonstrate a mass, the mass should be less than three cm.
4. Intrahepatic and extrahepatic metastases should be excluded by cross-sectional imaging studies of the chest and abdomen at the time of the initial application for the MELD/PELD exception and every three months before the MELD/PELD score increases.
5. Regional hepatic lymph node involvement and peritoneal metastases should be assessed by operative staging after completion of neoadjuvant therapy and before liver transplantation.

Endoscopic ultrasound-guided aspiration of regional hepatic lymph nodes may be advisable to exclude patients with obvious metastases before neo-adjuvant therapy is initiated.

6. Transperitoneal aspiration or biopsy of the primary tumor (either by endoscopic ultrasound, operative or percutaneous approaches) should be avoided because of the high risk of tumor seeding associated with these procedures.

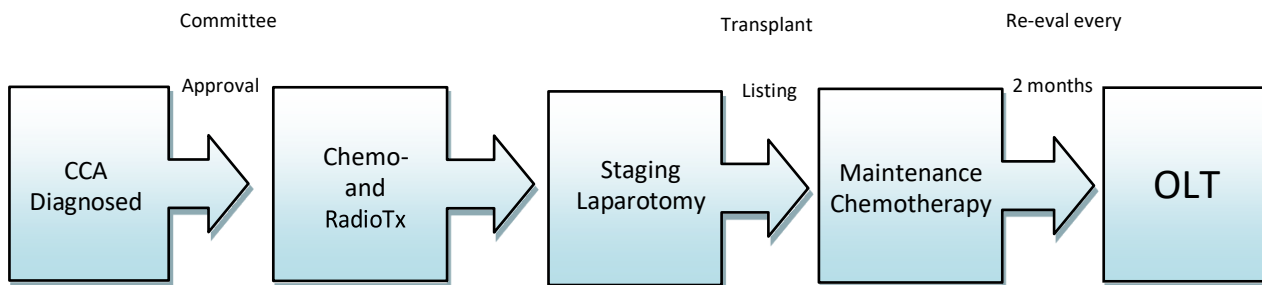
STAGING

Standard liver transplant evaluation protocol plus:

- ERCP with brushings
- Chest CT
- Abdominal MRI
- Bone scan/PET
- Ca 19-9
- EUS w/ LN biopsy (optional)

TREATMENT PROTOCOL OVERVIEW

Once the patient has met criteria for the protocol, they will receive *Neoadjuvant Chemoradiation, Exploratory Laparotomy, Application for MELD Exception and Listing for Transplantation*, followed by *Maintenance Chemotherapy* until time of transplant.



TREATMENT PROTOCOL

A. Neoadjuvant Chemoradiation

1. 4000 – 4500 cGy External Beam Radiation Therapy, 5 days per week x 6 weeks (30 fractions) and 5-fluoruracil 225 mg/m²/day or Capecitabine 850 mg/m² BID during XRT days. (ref: *J Clin Oncol* 32:5s, 2014 [suppl; abstr 4030])
2. 10-15 Gy external beam radiotherapy (EBRT) sequential boost (1.8-2.0 Gy per fraction)
3. For those patients who are eligible for transplantation after Exploratory Laparotomy:

Gemcitabine 1000mg/m² and Cisplatin 25 mg/m² on days 1 and 8 of every 21 days for 6 cycles or until transplantation, whichever comes first. (*ref. N Engl J Med 2010;362:1273-81.*)

If patients still on the waiting list after 6 cycles, then Capecitabine 1000 mg/m² bid for 14 days of every 21 days until transplantation.

B. Exploratory Laparotomy

1. Staging laparotomy 2-3 weeks after radiation
 - Thorough abdominal exploration
 - Biopsy celiac, hilar, choledochal, paraduodenal or other suspicious LN
 - Examine caudate to determine whether caval-sparing OLT possible
2. Extrahepatic metastases, LN metastases or local extension of disease to adjacent organs or tissues precludes transplantation
3. *Application for MELD Exception*
4. *List for Transplant*
5. Due to the possibility of disease progression between staging laparotomy and transplant laparotomy, the host OPO should be notified at time of organ acceptance so that a plan for a “back-up” recipient can be made. Our center should always call in a back-up patient whether or not we are “primary back-up.”

RADIATION THERAPY SPECIFICS

Radiotherapy regimen

- 40-45 Gy external beam radiotherapy (EBRT), delivered daily over 5-6 weeks (1.8-2.0 Gy per fraction)
- 10-15 Gy external beam radiotherapy (EBRT) sequential boost (1.8-2.0 Gy per fraction)

Radiotherapy treatment planning

- CT simulation with IV and PO contrast
 - MRI abdomen/liver may be used to assist with volume definition
 - 4DCT may assist with assessment of tumor motion
- Volume definition
 - GTV_{primary} + 1-1.5 cm = CTV_{primary}
 - GTV_{+LN} + 0.5-1.0 cm = CTV_{+LN}
 - Elective nodal regions (CTV_{-LN}) should include portohepatic, common hepatic and celiac nodal regions
 - Inclusion of the splenic, para-aortic and/or pancreaticoduodenal regions may be warranted based on initial nodal stage and involvement
 - PTV1 should encompass the CTVs with a 0.5-1.0 cm margin

- PTV2 (boost) will include CTV_{primary} with a 0.5-1.0 cm margin
- Constraints
 - Liver (Mean dose <20 Gy)
 - Bilateral kidneys (Mean dose <18 Gy)
 - Small bowel (contoured as cavity 2 cm above and below PTV, (Max dose ≤55 Gy, V45 Gy <195 cc)
 - Duodenum (V45 Gy <30 cc, V55 Gy <15 cc)
 - Stomach (V45 Gy <75 cc, Max dose ≤50 Gy)
 - Spinal cord (Max dose ≤45 Gy)

Radiotherapy technique

- 3D conformal or intensity-modulated radiotherapy is encouraged
- 4DCT simulation should be applied to enable gating if primary tumor motion is >5 mm
- Image-guidance in the form of cone-beam CT and/or kV imaging should be conducted

AT TIME OF TRANSPLANT

Intraoperatively, the abdomen should be explored for any evidence of metastatic disease, including peritoneal and omental implants. Additionally, a section of common bile duct should be sent for frozen section analysis to ensure a negative margin can be achieved prior to proceeding with any vessel ligation as part of the hepatectomy.

POST-TRANSPLANT MONITORING

Biphasic abdominal CT scans q 3-, 6-, 12-, 18-, and 24-months and then yearly. Ca 19-9 q month x 6 months and then concomitant with CT scans.

REVIEW OF SINGLE-INSTITUTION DATA

- **Mayo**
 - Neoadjuvant regimen
 - EBRT 45 Gy @ 1.8 Gy/fraction with continuous 5-FU 225 mg/m²/day (or Xeloda)
 - LDR brachytherapy (20-30 Gy with Ir-192 wire)
 - Results
 - Rea et al. Ann Surg 2005
 - Retrospective, n=71
 - 26 patients (37%) proceeded to curative resection and liver transplant
 - 88% R0, 12% R1 (hepatic duct margin)
 - pCR 42.1%
 - 12% 30-day mortality
 - Transplant patients
 - 5-year recurrence rate 12%
 - 5-year OS: all patients 58%, liver transplant 82%

- **Univ. of Nebraska**
 - Neoadjuvant regimen
 - LDR brachytherapy alone (60 Gy over 55-60 hrs with Ir-192 wire)
 - With continuous infusion 5-FU (300 mg/m²/day)
 - Results
 - Sudan et al. Am J Transplant 2002
 - Retrospective, n=17
 - 11 patients (65%) proceeded to curative resection and liver transplant
 - 91% R0, 9% R1 (dysplasia at margin)
 - pCR 27.1%
 - Overall survival 30% (?crude rate)
- **Emory**
 - Neoadjuvant regimen
 - EBRT (conventional or VMAT) 45 Gy @ 1.8 Gy/fraction
 - With continuous infusion 5-FU 225 mg/m²/day or Xeloda 1 gm/m² BID x 2 weeks with 1 week break (3 week cycles)
 - EBRT or Ir-192 HDR boost
 - Results (unpublished, RSNA 2012)
 - Retrospective, n=10
 - **6/10 received EBRT boost**; 4/10 received HDR boost
 - 8 completed and proceeded to surgery
 - pCR 38%
 - 25% required Whipple due to positive margins
 - 2-year OS 67% for all, 87.5% for those undergoing surgery (OLT)
 - 2-year LC for patients undergoing OLT 100%
- **Thomas Jefferson**
 - Neoadjuvant regimen
 - Mean dose 46 Gy EBRT → Ir-192 ribbon (mean 25 Gy)
 - Chemotherapy: CI 5-FU +/- doxorubicin, MMC or paclitaxel
 - Results (Heron et al., Am J Clin Oncol 2003)
 - Retrospective, n=36 that received surgery
 - Median survival 32 months after GTR

OTHER REFERENCES

1. Sudan D, DeRoover A, ChinnaKotla S, et al. Radiochemotherapy and transplantation allow long-term survival for non-metastatic hilar cholangiocarcinoma. *Am J Transplantation*. 2002; 2:774 - 779.

2. Rea DJ, Heimbach JK, Rosen CB, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. *Ann Surg* 2005; 242: 451 -61.
3. Gregory J. Gores, Sarwa Darwish Murad, Julie K. Heimbach, Charles B. Rosen. Liver Transplantation for Perihilar Cholangiocarcinoma. *Dig Dis* 2013;31:126–129.