**Policy: Liver Transplantation for Hilar Cholangiocarcinoma**

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**Statement: 1. Activation date:** 04/01/2009

**2. Affected Department:** LiverTransplant Program

**3. Vision Strategy:** Patient Care

**4. Policy Statement:** The Emory Transplant Center will evaluate any patient with a diagnosis of hilar cholangiocarcinoma for the possibility of inclusion into the Liver Transplantation Protocol for Hilar Cholangiocarcinoma.

**5. Basis**: This policy will clarify the diagnosis of cholangiocarcinoma, Protocol inclusion criteria, neoadjuvant chemoradiation therapy regimen and Liver Transplantation for cholangiocarcinoma.

**6. Administrative Responsibility:** Section heads, physicians, practitioners, and staff are responsible for compliance with this policy.

**Scope/Procedure:**

**7. Protocol:**

**Liver Transplantation for Hilar Cholangiocarcinoma**

**A. BACKGROUND**

Cholangiocarcinoma (CCA) has been, until relatively recently, regarded as a contraindication to orthotopic liver transplantation (OLT). The initial experience in Nebraska and further expanded upon by the Mayo Clinic has permitted patients with hilar CCA to achieve a longer 5-year survival than if they were to undergo resection alone. Not all patients with hilar CCA are candidates for transplantation, however.
There are specific inclusion and exclusion criteria for patients to be considered for the hilar CCA protocol. These are outlined below. Please refer to the background info in the references section for additional information.

**B. DIAGNOSIS**

All patients being evaluated should have the following diagnostic tests performed prior to consideration for inclusion into the protocol:

1. Ca 19-9

2. ERCP with brushings for cytology

3. MR abdomen/pelvis

4. MR chest

5. EUS (endoscopic ultrasound) with hilar and celiac lymph node sampling for cytology

6. Other tests that may be considered include bone scan or PET scan

7. biopsy of the lesion ( except for those obtained via ERCP or PTC) is an absolute contraindication regardless of the modality of biospy

**Diagnostic criteria consistent with a diagnosis of hilar cholangiocarcinoma include:**

1. Positive transluminal biopsy for CCA

2. Positive or suspicious cytology

3. Dominant stricture with Ca 19-9 >100u/ml

4. Mass lesion on MR abdomen

5. Resectable Hilar cholangiocarcinoma in the setting of primary sclerosing cholangitis

**Indeterminate diagnostic criteria for hilar cholangiocarcinoma include:**

1. Indeterminate cytology (dysplasia)

2. Dominant stricture in absence of mass, positive cytology, positive biopsy or elevated Ca 19-9

**C. INCLUSION CRITERIA**

1. Otherwise reasonable Liver Transplant candidate.

2. Must not have had previous percutaneous biopsy, hilar exploration or attempted surgical resection.

3. Macroscopic disease must be proximal to the cystic duct insertion.

4. No evidence of extrabiliary spread, including negative lymph nodes.

5. Have the diagnosis established by criteria as establish above.

D. EXCLUSION CRITERIA

1. Vascular invasion (vascular encasement is not).

2. Extrahepatic disease (including LN involvement).

3. Intrahepatic metastases.

4. Prior radiation or chemotherapy.

5. Non-hilar CCA.

6. Uncontrolled infection.

7. Tumor size >3 cm in cross-sectional diameter.

8. Previous percutaneous biopsy, hilar exploration or attempted surgical resection

E. EMORY PROTOCOL ALGORITHM

Once a patient has been determined to meet the inclusion criteria, with no contraindications, then they are referred to Medical and Radiation Oncology. If they agree that the patient would tolerate therapy, the patient is then presented at Liver Transplant Selection Conference for formal approval. The patient would then initiate the neoadjuvant therapy.

a. *Neoadjuvant Chemoradiation*

4000 – 4500 cGy External Beam Radiation Therapy (EBRT), 5 days per week x 6 weeks (30 fractions) and 5-fluoruracil 500 mg/m2 qd x 3days at start of EBRT
2000 – 3000 cGy transcatheter Ir-192 wire, 2-3 weeks after completion of EBRT (performed via PTC or nasobiliary tube)
Capecitabine 2000 mg/m2 per day in 2 divided doses 2 out of every 3 weeks until transplant

b. *Application for MELD Exception*

1. UNOS Region 3 submission required. A MELD score equivalent to HCC exception status would be requested. The board has 21 days to reach a majority decision on the MELD exception upgrade.
2. Listed CCA patients should receive a MELD upgrade every 3 months, if not transplanted, equivalent to a 10% increase in 3 month mortality (increase by 2 points q 3 months).
3. List for Liver Transplant.

c. *Waitlist Monitoring*
1. MR abdomen/pelvis and Ca 19-9 q 2 months while on waitlist.
2. EUS with LN q2 months while on waitlist.

d. *Staging laparotomy at time of organ acceptance* thorough abdominal exploration biopsy celiac, hilar, choledochal, paraduodenal or other suspicious LN
examine caudate to determine whether caval-sparing OLT possible

Pathology must be available to process specimens submitted. A back-up recipient must be called in for every attempted OLT for CCA.
Extrahepatic metastases, LN metastases or local extension of disease to adjacent organs or tissues precludes transplantation.
Pathology must be available to process specimens submitted. A back-up recipient must be called in for every attempted OLT for CCA.
Extrahepatic metastases, LN metastases or local extension of disease to adjacent organs or tissues precludes transplantation.
The UNOS guidelines for MELD exception for patients with diseases not considered by the standard MELD formula state:

**“Cholangiocarcinoma and Biliary Dysplasia**
Recent neoadjuvant protocols that include operative staging for cholangiocarcinoma confined to the hepatic hilum have improved the previously dismal success rates for LT in patients with this condition.20 However, these results have only been achieved via rigorous application of well-designed protocols. Current evidence suggests that, for properly-selected patients with primary sclerosing cholangitis-associated cholangiocarcinoma in whom surgical resection is not possible, LT offers a reasonable chance at cure and that alternative therapies have little benefit. In addition, tumor recurrence rates are high for patients fulfilling protocol criteria who come to LT longer than 140 days after listing. Unfortunately, published reports do not describe pre-transplant
predictors of cancer recurrence other than waiting time. The results from these prospective, neoadjuvant protocols provide evidence for justification of increased priority for patients enrolled in these trials especially in light of the poorer results obtained when patients waiting longer. Though the recommended quantity of increased priority has not been calibrated to the risk of dropout as yet, this should become possible as more data accumulates…”

F. **POST TRANSPLANT MONITORING**

CA19-9, CT Chest and MRI every 6 months for 2 years, then yearly for years 3 to 5

**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. Pichlmayr R, Weimann A, Klempnauer J, et al. Surgical treatment in Proximal Bile Duct Canter. *Ann Surg*. 1996;224:628–638.

4. Meyer C, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. *Transplantation* 2000; 69: 1633–7.

5. Heimbach J, Haddock M, Alberts S, Nyberg S, Ishitani M, Rosen C, Gores G. Transplantation for hilar cholangiocarcinoma. Liver Trans; 2004, 10 (10): S65-S68.

6. Freeman R Gish R, Harper A, Davis G, Vierling J, Lieblein L, Klintmalm G, Blazek J, Hunter R, Punch J. Model for end-stage liver disease (MELD) exception guidelines: Results and recommendations from the MELD exception study group and conference (MESSAGE) for the approval of patients who need liver transplantation with diseases not considered by the standard MELD formula. *Liver Trans*; 2006, 12 (12): S128-S136

Approved by: Liver Transplant Leadership Group

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