Intrahepatic Cholangiocarcinoma Liver Transplant Protocol

I. Scope
Patients with Stage I-II intrahepatic cholangiocarcinoma (i.e. those without perforation of visceral peritoneum, invasion of adjacent structures, periductal invasion or lymph node involvement) without macrovascular invasion, regardless of size, demonstrating stable disease with neoadjuvant therapy > 6 months are candidates for liver transplant.

II. Diagnosis
• Candidates must satisfy the following diagnostic criteria for intrahepatic cholangiocarcinoma (CCA)
  – Malignant-appearing mass with imaging characteristics consistent with intrahepatic CCA on CT or MRI and at least one of the following criteria:
    o Biopsy or cytology results demonstrating malignancy
    o Carbohydrate antigen 19-9>100 U/mL
  – The tumor must be unresectable on the basis of technical considerations or underlying liver disease (e.g. primary sclerosing cholangitis)
  – If imaging studies (CT scan, ultrasound, MRI) demonstrate an intrahepatic mass, patient has demonstrated stability with neoadjuvant therapy for at least 6 months at evaluation
  – No evidence of concurrent hepatoma or mixed pathology
  – No extrahepatic disease
  – Remote attempted surgical resection is allowed if patient has had subsequent sustained response to neoadjuvant therapy for at least 6 months following most recent intervention
  – Transperitoneal aspiration or biopsy of the primary tumor (endoscopic ultrasound, operative or percutaneous approaches) should be minimized but are not exclusionary
  – Biliary sepsis, if historically present, must be controlled.
• The following high-risk tumor characteristics are exclusions for liver transplant consideration:
  – Presence of extrahepatic metastases
  – Lymph node involvement
  – Invasion or encasement of major hepatic vascular structures
  – Perforation of the visceral peritoneum
  – Invasion of extrahepatic structures
– Invasion of perihilar fat
– Periductular invasion

III. Staging

• CT of the chest, abdomen, and pelvis and MR bone survey to exclude intra- and extrahepatic metastases. Liver MR may be substituted

• FDG-PET should be supplemented for patients with elevated serum CA 19.9 levels who do not demonstrate metastatic disease on other imaging

• Radiologically suspicious regional hepatic lymph nodes, endoscopic ultrasound-guided aspiration biopsy should be performed to exclude regional nodal metastases before neoadjuvant therapy is initiated (if possible)

• Suspicious extrahepatic lesions, such as lung nodules or bone lesions, should be biopsied to exclude extrahepatic disease

• Pretransplant laparoscopy may be selectively utilized in questionable cases

IV. Patient Selection Procedures

All patients who meet criteria for this protocol will undergo standard liver transplant evaluation to include surgical, hepatology, oncologic, psychosocial, nutrition and financial screening for Patient Selection Committee approval. Patients who meet oncologic criteria for the protocol and who would otherwise qualify for liver transplantation will initiate therapy under this protocol.

V. Pre-Transplant [Induction] Treatment

Treatment

• All patients who meet initial selection criteria will initiate biliary cancer chemotherapy with platinum and gemcitabine-based systemic therapy or other standard chemotherapy at the discretion of the treating oncologist (e.g. FOLFOX/FOLFIRI or gem/Xeloda)

• Additional biologic or targeted therapy may be considered

• Locoregional therapy other than external-beam radiation therapy may be utilized (e.g. TACE, RFA, Y-90) but should not be the sole pretransplant therapy, except in cases of solitary tumor <3 cm in size

Monitoring

• All patients will be restaged with contrasted CT of chest/abdomen/pelvis and MR bone scan every 3 months to identify disease progression that would contraindicate transplantation. Regional hepatic lymph node involvement and peritoneal metastases will be assessed by operative staging at the time of liver transplantation.
VI. Listing Procedures
Patients completing protocol chemotherapy with no evidence of disease progression will be listed for liver transplantation with United Network for Organ Sharing (UNOS).

VII. Intraoperative (OLT) Management

Explant Pathology
• Following transplantation a complete histopathologic analysis of the explant specimen will be made. All pathologic specimens will be additionally sent for genomic mutation analysis

VIII. Adjuvant Post-Transplant Therapy with Complete Pathologic Response

Low Risk Patients
• Complete remission achieved by pretransplant treatment with initial low risk features (no active malignant disease on explant)
• Treatment
  a. Completion of adjuvant chemotherapy after transplant for a total of 6 months

IX. Adjuvant Post-Transplant Therapy with Incomplete Pathologic Response

Moderate Risk Patients
• Active disease on explants with all of the following characteristics:
  – No vascular invasion
  – Single lesion, less than 3 cm in size
  – Moderate or well-differentiated disease
  – Clean resection margins, including bile duct
  – Negative lymph nodes
• Treatment
  a. Completion of induction chemotherapy after transplant for total of 6 months
  b. If disease progression, consider alternative biliary cancer chemotherapeutic agents as adjuvant therapy for 4-6 months

High Risk Patients
• Active disease on explants with ANY of the following characteristics:
  – Single lesion ≥6 cm
  – Vascular invasion
  – Poorly differentiated
Mixed cholangiocarcinoma/hepatocellular carcinoma
- Multifocal disease (any size)
- Positive lymph nodes on explants
- Residual disease at cut margins

Treatment
a. Complete induction chemotherapy for a total of 6 months if pathologic response seen.
b. If no pathologic/clinical response observed, give alternative biliary chemotherapy or novel agent for 4 to 6 months

R2 Disease
- Residual disease amenable to full dose radiation or surgical therapy
  - Resection should be treated with surgery and or radiation
  - Completion of induction chemotherapy after transplant for total of 6 months
  - If disease progression, consider alternative biliary cancer chemotherapeutic agents as adjuvant therapy for 4-6 months
- Residual disease not amenable to full dose radiation or surgical therapy
  - Disease is considered metastatic and should be treated according to the current National Comprehensive Cancer Network (NCCN) guidelines

Mixed Pathology
- Patients should undergo at least 4-6 months of adjuvant therapy. Patients should be followed according to the mixed tumor protocol

X. Immunosuppression Therapy
- Rapid withdrawal of steroids will be performed
- Immunosuppression will be minimized
- Patients will be considered for transition to mTOR inhibitor immunosuppression at 4 weeks following transplantation as per institutional protocols

To refer a patient, please call 713.441.8839 or fax 713.791.5033.