

UNIVERSITY OF CINCINNATI CHOLANGIOCARCINOMA TRANSPLANT PROTOCOL

Inclusion criteria:

- unresectable hilar (perihilar) cholangiocarcinoma after review at University of Cincinnati Medical Center Hepato-Biliary conference
- hilar (perihilar) cholangiocarcinoma in the setting of primary sclerosing cholangitis (PSC)

Diagnosis of cholangiocarcinoma¹⁻³: at least 1 of the following:

- intraluminal brush cytology or biopsy positive for adenocarcinoma
- radiographic malignant stricture and serum CA 19.9 > 100 ng/ml
- radiographic malignant stricture in setting of PSC
- biliary aneuploidy in fluorescent in situ hybridization (FISH)

Staging:

- CT chest, abdomen
- Bone scan
- Endoscopic ultrasound (EUS) with fine needle aspiration of suspicious lymph nodes
- Laparoscopy for staging if suspicion of extrahepatic disease

Exclusion criteria:

- mass > 3cm^{4,5}
- extrahepatic disease (including regional lymph node involvement)
- previous operation or attempted resection of the tumor
- uncontrolled infection

Neoadjuvant Therapy

- Fractionated chemoradiation will be provided to the primary tumor and regional lymphatics to a dose of 45 Gy at 1.8 Gy per fraction with a concurrent fluoropyrimidine based sensitizer.
- This will be followed by a conformal, hypofractionated 20 Gy boost to the primary tumor (4Gy x 5 fractions)

Staging operation

- performed 4 weeks after completion of neoadjuvant therapy.
- laparoscopy or laparotomy
- biopsy of lymph nodes overlying common hepatic artery and common bile duct (GDA and BD node)
- biopsy of any abnormal lymph nodes/mass
- Patients with negative staging will be listed for transplant.
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Maintenance Chemotherapy

- Patients will receive 3 cycles Cisplatin/gemcitabine based chemotherapy .

- Patients will go on to receive additional maintenance Capecitabine until the time of transplant.

Imaging Surveillance:

- Contrast CT scans of the chest, abdomen, and pelvis will be obtained every 3 months after the time of restaging operation until transplant or the development of metastatic disease.

Transplant

- hilar structures are divided as low as possible close to the duodenum
- frozen section of the bile duct margin
- pancreatoduodenectomy in case of bile duct involvement
- caval-sparing hepatectomy and piggy-back implantation unless caudate involvement is suspected (caval interposition with bicaval anastomosis in case of caudate involvement)
- Aorto-hepatic jump graft with conduit
- Roux-en-Y hepatico-jejunostomy

Schedule

Start time	
0	Staging: CT or MRI abdomen/pelvis, CT chest, EUS, DSE, Social worker
0	Neoadjuvant chemoradiation
11th week	Staging laparoscopy or laparotomy, MultiD clinic and listing for liver transplant
13th week	Initiate 3 cycles of Gemcitabine/cisplatin
19th week	Maintenance capecitabine chemotherapy

Post-transplant follow-up

- CT chest non-contrast, CT biphasic abdomen, Ca 19.9 every 6 months for years 1 and 2
- CT chest non-contrast, CT biphasic abdomen, Ca 19.9 annually for years 3, 4, and 5

Reported Outcomes

- survival rate after liver transplantation: 91% at 1 year, 82% at 5 years²
- recurrence-free survival after transplantation: 78% at 2 years, 65% at 5 years⁴
- recurrence rate: 12% at 5 years²
- mean time to recurrence : 40 months²
- drop-out rate (from enrollment to transplantation): 25%⁴

References

1. Rosen CB, Darwish Murad S, Heimbach JK, Nyberg SL, Nagorney DM, Gores GJ. Neoadjuvant therapy and liver transplantation for hilar cholangiocarcinoma: is

- pretreatment pathological confirmation of diagnosis necessary? *Journal of the American College of Surgeons*. Jul 2012;215(1):31-38; discussion 38-40.
2. Rea DJ, Heimbach JK, Rosen CB, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. *Annals of surgery*. Sep 2005;242(3):451-458; discussion 458-461.
 3. Welling TH, Feng M, Wan S, et al. Neoadjuvant stereotactic body radiation therapy, capecitabine, and liver transplantation for unresectable hilar cholangiocarcinoma. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society*. Jan 2014;20(1):81-88.
 4. Darwish Murad S, Kim WR, Harnois DM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. *Gastroenterology*. Jul 2012;143(1):88-98 e83; quiz e14.
 5. Gores GJ, Gish RG, Sudan D, Rosen CB. Model for end-stage liver disease (MELD) exception for cholangiocarcinoma or biliary dysplasia. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society*. Dec 2006;12(12 Suppl 3):S95-97.
 6. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *The New England journal of medicine*. Apr 8 2010;362(14):1273-1281.