Liver Transplantation for Peri-Hilar Cholangiocarcinoma

Abbreviations

DFS: disease-free survival

ERCP: endoscopic retrograde cholangiopancreatography

EBRT: external beam radiation therapy

EUS: Endoscopic UltraSound

FISH: fluorescent in situ hybridization

FNA: fine needle aspiration

LT: liver transplantation

NCR: neoadjuvant chemoradiation

OS: overall survival

PD: pancreaticoduodenectomy

PHCC: peri-hilar cholangiocarcinoma

PSC: primary sclerosing cholangitis

PTC: percutaneous transhepatic cholangiogram

RCT: radiochemotherapy

TCB: tru-cut biopsy

UNOS: united network for organ sharing

1. Backgrounds and Literature

1.1. Definition

The term “peri-hilar cholangiocarcinoma” (PHCC) refers to cholangiocarcinoma arising from the left and/or right hepatic duct and/or at their junction, either in the duct itself or in the contiguous parenchyma. PHCC raises different diagnostic and therapeutic challenges than intrahepatic peripheral cholangiocarcinoma and extra hepatic bile duct cholangiocarcinoma.
These include:
- A high rate of lymph node invasion, associated with worse survival outcomes,
- Invasion of peri biliary plexus in 85% of the cases, hence a frequent underestimation of the biliary margin,
- Frequent invasion of the portal vein bifurcation and/or hepatic artery branches, as all anatomical elements of the pedicle are closely related to each other,
- The need to remove segment 1 and 4b of the liver in order to achieve curative surgery, because of these segments have multiple biliary canaliculi draining into the biliary confluence.

1.2. Assessment and diagnosis

Initial assessment of resectability includes chest-abdomen-pelvis CT scan with contrast enhancement (extra-hepatic disease, vascular involvement, hilar mass) and MR scan with MRCP (before any biliary drainage) for further evaluation of biliary and intra hepatic extension in the absence of extra hepatic disease.
PET-FDG has a sensitivity of 80-90% (less in case of biliary stent or underlying primary sclerosing cholangitis PSC) and can be performed to screen for extra-hepatic disease.
CA19-9 has a sensitivity and specificity of around 80%, but may be elevated in case of biliary obstruction, even of benign origin, especially when there is underlying biliary sepsis.
Endoscopic UltraSound (EUS) allows fine needle aspiration (FNA) or tru-cut biopsy (TCB) of regional lymph node and/or of the hilar mass (see below). In the event of endoscopic biliary drainage, endoscopic retrograde cholangiopancreatography (ERCP) will be performed with cholangiography, biliary brushings or endo-biliary biopsies.

1.2.1. Histological evidence

Ten percent of the peri-hilar masses and/or strictures are not cholangiocarcinoma. Other benign aetiologies include Mirizzi syndrome, pseudo-inflammatory tumours, post-cholecystectomy strictures, IgG4-related disease, sclerosing cholangitis and eosinophilic cholangitis. Hence, histological evidence of malignancy is required in before neoadjuvant treatment can be considered. Depending on the size and location of PHCC, histological evidence can be difficult to obtain.

The different options to obtain a specimen for pathological assessment include:

- Biliary brushings during drainage (either ERCP or percutaneous transhepatic cholangiogram PTC)
- Endo-biliary biopsies during cholangioscopy
- EUS-FNA or -TCB
- Percutaneous FNA

The sensitivity rates are approximately 60% for ERCP[1]. Applying fluorescent in situ hybridization (FISH) to detect aneuploidy allows a diagnosis in 60% of the cases with a negative standard cytology[2].

In the context of LT for PHCC, the united network for organ sharing (UNOS) protocol contra-indicates LT in case of "transperitoneal biopsy". This statement can be found in the two major papers from the United States[3,4] and in the United States guidelines in 2012 [2]. The only evidence in the literature is a paper from Heimbach *et al.* [5] where the authors describe a 83% rate of peritoneal metastases after FNA biopsy vs. 8% in patients who did not undergo a transperitoneal biopsy. In total, only 16 patients in this study had a transperitoneal biopsy (13 percutaneous and 3 EUS). Only 6/16 patients indeed had a FNA positive for adenocarcinoma.

Several recent papers have shown the feasibility and high sensitivity rates of EUS-FNA of PHCC [1,6,7] with up to 98% sensitivity for combined ERCP+EUS-FNA and 94% for EUS-FNA alone. Therefore, although the diagnostic accuracy for EUS-FNA is high, the risk of transperitoneal seeding leading to post-transplant tumour recurrence remains uncertain.

EUS-FNA of regional lymph nodes is feasible in almost all patients and precluded 17% with unresectable PHCC from LT in a series from the United States [8].

1.2.2. Biliary drainage

Biliary drainage can be achieved with ERCP+plastic or metallic stents, or with PTC with external or internal/external drains. If the patient is aiming to LT, the biliary drainage should

be as effective, complete and comfortable as possible. Hence, ERCP metallic stents are preferred, but other modalities can be considered if the drainage is not sufficient (i.e. recurrent cholangitis, total bilirubin >3N).

1.3. Surgical resection

1.3.1. Resectability

Resectability is defined by the ability to remove the cancer and leave a future liver remnant with adequate volume (≈30%), sufficient inflow and outflow, and biliary drainage.

Principles of resection are the following:

- Resection of the main bile duct
- Removal of liver parenchyma: at least segments 1 and 4b (usually requires extended right or extended left hepatectomy)
- Removal of the portal bifurcation if there is tumour encroachment at surgery or on pre-operative imaging
- Aiming for a R0 distal and radial margin.

Arterial resection/reconstructions and associated Whipple procedure to achieve R0 resections are rare and only performed in highly selected patients.

1.3.2. Results

The main histological factors associated with worse overall survival (OS) after surgical resection are N1 status (the strongest factor), R1 status, perineural invasion, pTNM>T3, and poor differentiation of the tumour [9]. 5-y OS is between 20 and 30%, but can reach up to 41-67% in patients with N0R0 status [9,10].

1.4. Palliative treatment

If surgery (either resection or transplantation) is not feasible, median survival is between 9 and 15 months. Available therapeutic options are endo-biliary procedures to maintaining patency of biliary drainage and palliative chemotherapy (CISGEM, or gemcitabine alone if PS is 2). As second-line treatments, targeted therapies according to molecular screening can be proposed; if not FOLFOX or 5-FU alone may be proposed.

1.5. Liver transplantation

In non-metastatic patients, LT should be considered in non-resectable patients, either because of a too small liver remnant or underlying liver disease preventing from major liver resection (PSC, atrophy of the future liver remnant), or because an R1 resection is not achievable (eg: contralateral vascular encasement, bilateral biliary extension up to secondary biliary order).

Important publications: results from the Mayo clinic (Murad *et al*., Hepatology 2012 [11]), from 12 US centres (Murad *et al*., Gastroenterology 2012 [3]), one recent review from the Mayo clinic (Tan *et al*., JGIS 2020 [12]), and one recent meta-analysis (Cambridge et al., Ann Surg 2021[13]).

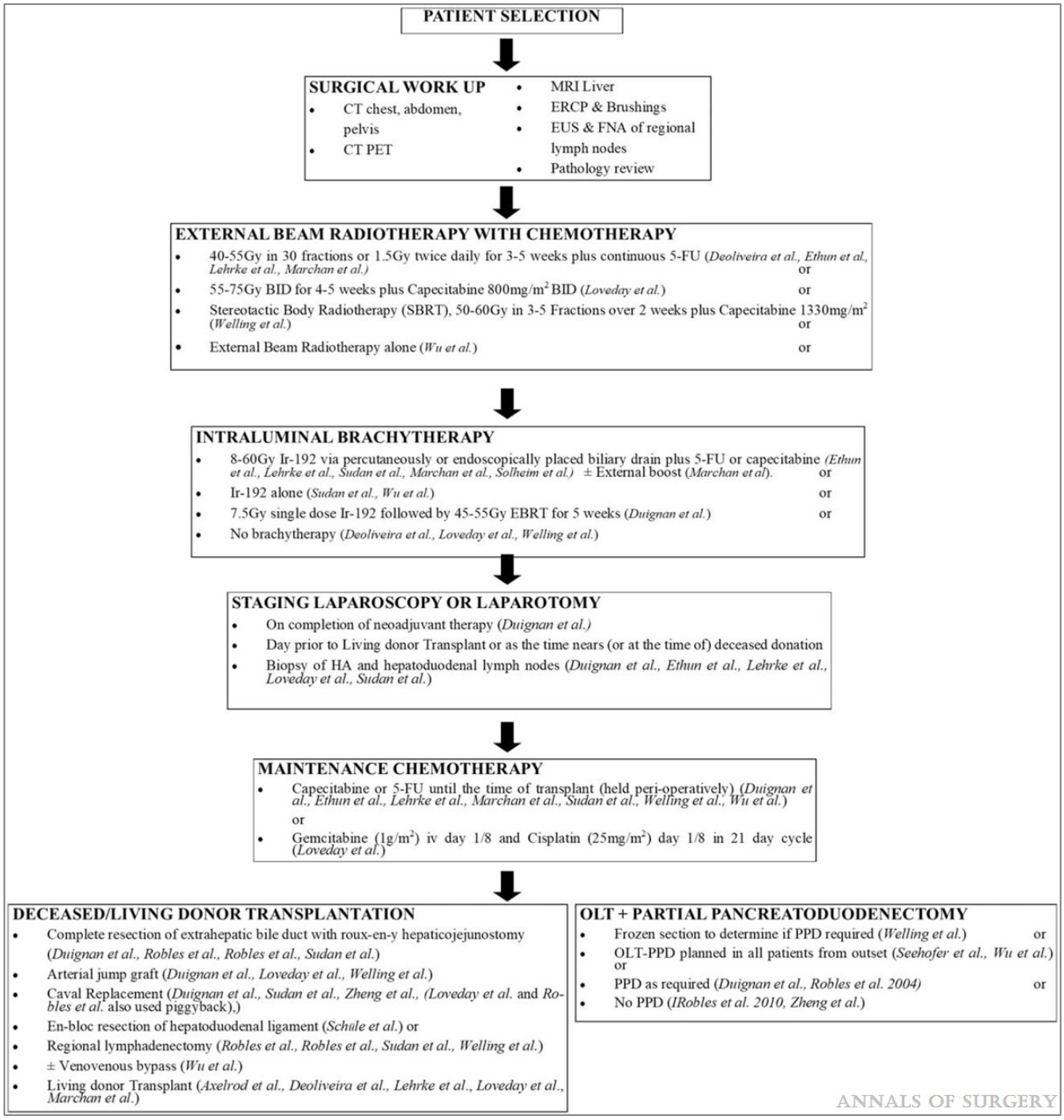
1.5.1. Mayo protocol and modifications

The publication of good survival outcomes after LT for PHCC after neoadjuvant chemoradiation (NCR) by the Nebraska group [14] and the Mayo clinic [15] in 2000 prompted units to re-evaluate PHCC as an indication for LT. The most frequently utilized neoadjuvant regimen is referred to as the "Mayo protocol" [16].

Mayo protocol

- NCR consists of external beam radiation therapy (target dose of 45 Gy in 30 fractions) over a 3-week period
- Intra-venous 5-FU given at 500 mg/m^2 as a daily bolus for the first 3 days at the initiation of the external beam radiation therapy (EBRT), then continuous infusion for the duration of EBRT
- At 2-3 weeks after completion of EBRT, an intraluminal radiation boost delivered using a fluoroscopically guided catheter loaded with Iridium^{192} seeds (initially, target dose of 20 Gy over 24h using low-dose-rate brachytherapy; now, high-dose brachytherapy of either 12-16 Gy in 2 to 4 fractions)
- Thereafter, oral Capecitabine (3mg/day) for 2 out of every 3 weeks while awaiting LT
- A staging laparotomy or hand-assisted laparoscopy is performed upon completion of NCR with complete exploration and biopsy of regional lymph nodes.

Summary of the different NCR protocols (from Cambridge *et al.* [13])

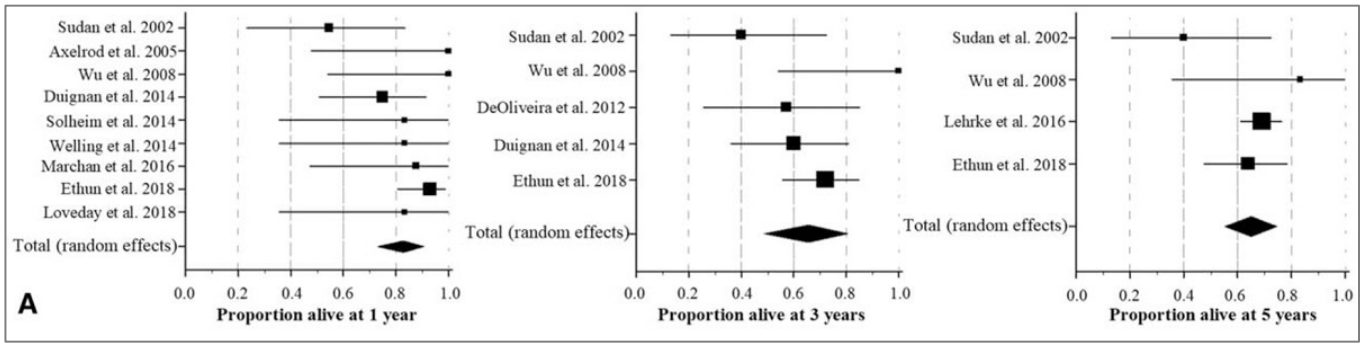


In some US centres[11], an extra boost of EBRT (10-15 Gy) is given instead of brachytherapy.

1.5.2. Results

In the study from the Mayo clinic[11], 199 patients were included with 131 proceeding to LT. Patients with tumour >3cm in radial diameter or N1 status were excluded; 38% of the patients had underlying PSC. Vascular encasement and stricture/mass extension along the biliary tree were not contra-indications. The dropout rate was 31%, and factors associated with dropout were: size>3cm (longitudinal), initial positive biopsy, elevated CA19-9 (>100 and >500). Staging surgery found 20% of metastases at staging. Median time to LT was 7 months, and 47% of specimens contained residual tumour. **At 5 years, OS after LT was 71% (53% in intention-to-treat), and DFS was 68%.** Factors associated with recurrence after LT were: (i) at enrolment: elevated CA19-9>500, vascular encasement, (ii) residual tumour on the specimen. Waitlist time was not associated with increased recurrence.

In the recent meta-analysis from Cambridge et al.[13], **OS rates after NCR followed by LT were 83% [73-91%] at 1y, 65.5% [49%-80%] at 3y, and 65% [55%-74%] at 5y.** 5y OS rates were not significantly different between Mayo and other centres. The recurrence rate at 3y was 24% [18%-31%].



Patients with PSC:

In the initial Mayo experience [4], patients with PSC experienced a better survival, but this effect disappeared in multivariate models. This advantage in survival may be due to patients having a more favourable profile with younger age, less mass formation, less weight loss, less vascular encasement, and lower CA19-9 levels. Patients with PSC also have a lower drop-out rate (15%).

Concomitant pancreaticoduodenectomy (PD):

Only 32 patients were reported in the literature with concomitant PD+ LT[13]. PD was planned either before surgery, or intra operatively because of positive frozen sections.

LT for resectable PHCC:

At this point in time LT has not been proven to offer better OS than resection in patients with resectable PHCC (TRANSPHIL protocol in France, prematurely stopped and [17]).

2. Patients selection

2.1. Indications

At enrolment:

- Age≤65y
- Tumour≤3cm in radial diameter
- Unresectable PHCC (see 3.3 diagnosis of PHCC)
- M0/N0
- CA19-9<1000 UI/mL *without major cholestasis/cholangitis*
- Patient otherwise fit for LT

For listing, M0/N0 status should be confirmed at staging surgery (see 5.2.).

If the longitudinal extent of the tumour exceeds 3cm along the biliary tree, this is classically not a contra-indication, although it is associated with an increased risk of drop out[11].

CA19-9>100 and >500 UI/mL is a risk factor for dropout; CA19-9>500 UI/mL at enrolment is an independent risk factor for recurrence after LT[11]. Although a CA19-9 threshold is not a classical criteria in other protocols, we decided to exclude patients with CA-199>1000 UI/Lm in the absence of ongoing major cholestasis and/or cholangitis.

Unresectability should be assessed and confirmed by at least 2 HPB surgeons in collaboration with a radiologist. The potential for inclusion in a transplant pathway should be confirmed at an MDM, in presence of at least two HPB surgeons, one transplant surgeon, a radiologist, a medical oncologist, and a radiation oncologist.

2.2. Non-indications and Contra-indications

- Resectable PHCC
- Age>65y
- Extra-hepatic disease
- Tumour>3cm in radial diameter
- N1 on imaging or at staging surgery, including in the hepatic pedicle
- CA19-9>1000 UI/mL *without major cholestasis/cholangitis*
- Invasion of the duodenum
- Previous surgery with violation of the tumour plane

- Vascular invasion (but not vascular encasement)
- Transperitoneal aspiration or biopsy of the primary tumour in the last 12 months, including EUS-FNA (see 3.3 below).
- Any contra-indication to LT or RCT (including DPD deficit, previous radiation of the abdomen)

2.3. Drop-out criteria

- Proof of metastatic disease after inclusion
- Failure of transplant assessment
- Positive nodes at staging laparotomy
- Disease progression on treatment
- Failure to complete NCR
- CA19-9>1000 UI/mL in absence of major cholestasis/cholangitis

3. Initial assessment and management

The aims of the initial assessment are to assess the general condition of the patient, establish the diagnosis of PHCC, rule out the differential diagnoses (PSC, auto-immune cholangitis, eosinophil cholangitis, ischemic cholangitis, post-cholecystectomy bile duct injury), to screen for extra-hepatic disease, assess non-resectability, and assess the suitability for NCR-LT. Nutritional support and adequate biliary drainage should be provided throughout the patient's management.

3.1. General assessment

- Clinical assessment: performance status score, ASA score, nutritional assessment, assess for an underlying hepatopathy, including PSC.
- Biological: FBC, platelets, basic metabolic panel, LFTs, CRP, albumin, serologies for HIV/HBV/HCV, CA19-9, ACE, Beta-HCG for women, IgG4.

3.2. Imaging

A four-phase CAP-CT scan and a **gadolinium-enhanced liver MR scan with MRCP** should be performed to assess local invasion and resectability. A hepatobiliary agent will be added during MR scan only in case there is a suspicious lesion within the liver parenchyma. Both CT and MR scans should be performed *before* any biliary drainage. An **^{18}FDG-PET-CT scan** should be performed to look for extra-hepatic disease (HB2 category).
The following elements will be assessed/searched for:

- Signs of chronic hepatopathy/biliary disease
- Dilatation of the main pancreatic duct or mass in the head of the pancreas
- Peri-hilar mass>3cm in radial diameter
- Distant metastases, including: liver parenchyma, lungs, lymph nodes, and peritoneum
- Description of the vascular anatomy, encasement or invasion of portal vein branches or artery branches
- In case a liver resection could be considered, volume of the future liver remnant
- Invasion of the duodenum

3.3. Diagnosis of PHCC

All patients will have **ERCP and spyglass.**

Histological evidence of PHCC may be obtained (see 1.2.1.) with ERCP + biliary brushings or spyglass + biopsy. **EUS-FNA and EUS-TCB are contra-indicated if transplant is being considered.** There is no solid data regarding the risk of peritoneal dissemination (see 1.2.1.) but neither are there data on long-term follow-up after EUS-FNA or EUS-TCB of the mass in the transplantation setting. To remain consistent with what is done in almost all centres, we will not do EUS-FNA or EUS-TCB and will rely on the diagnostic criteria described below.

Definitive diagnostic criteria:

- Endoscopic biopsy positive for cancer
- Biliary brushings with unequivocal cytological features of malignancy
- Mass lesion on cross sectional imaging with malignant appearing stricture
-Malignant appearing stricture + CA19-9>100UI/mL (in the absence of un-stented obstructive jaundice and/or cholangitis).
- Malignant appearing stricture with suspicious cytology and/or FISH polysomy.

Indeterminate diagnostic criteria that requires repeat FISH, cytology, CA19-9 and imaging at 3 months:

- FISH with single locus gain; high grade or low-grade dysplasia on biliary biopsy
- FISH polysomy in the absence of a malignant appearing stricture
- Malignant appearing stricture in the absence of mass lesion, positive cytology/biopsy, elevated CA19-9, or FISH polysomy.

In case of suspicious cytology where there are abundant atypical cells for testing, FISH will be performed by the LabPlus FISH team on cell block.

3.4. Biliary drainage

If the patient is on a potential LT pathway, the biliary drainage should be as effective, complete and comfortable as possible. Plastic stents can be placed in the beginning to allow re-ERCP and biopsies. If metal stents are placed, they should be covered, or if not, short enough to allow the surgeon to divide the bile duct just above the pancreas at the time of

transplant without going through the stent. In doubt, the type of drainage should be discussed with the NZLTU.

3.5. Initial staging laparoscopy

To prevent patients from entering a long treatment protocol before the staging surgery, an initial staging laparoscopy can be performed after the initial imaging to look for sub-capsular liver metastases or peritoneal disease in case of doubtful imaging, but is not mandatory.

3.6. EUS-FNA of regional lymph nodes

A EUS-FNA for sampling of regional lymph nodes will be performed before inclusion in the NCR-LT pathway (NB: EUS-FNA or EUS-TCB must not be performed if LT is being considered – see 3.3 above).

3.7. Suitability for NCR-LT

A **DPD deficiency** should be searched for; a mutation in DPD is a contra-indication to the protocol.
A whole **LT assessment** should be performed *before* inclusion in the transplant pathway to look for general contra-indications.

At the end of this first assessment, if the patient can be included in the NCR-LT pathway, he or she will sign a written consent to the protocol.

SUMMARY OF THE INITIAL ASSESSMENT

Mandatory:

- FBC, platelets, basic metabolic panel, LFTs, CRP, albumin, serologies for HIV/HBV/HCV, CA19-9, ACE, Beta-HCG for women, IgG4, DPD deficiency
- CAP-CT scan
- MR scan with MRCP
- PET-CT scan
- ERCP with spyglass, biliary brushings and biopsies
- EUS-FNA of regional lymph nodes

Optional:

- Bone scan
- Initial staging laparoscopy

Contra-indicated:

- EUS-FNA or EUS-TCB of the primary rumour

4. Neo-adjuvant treatment

4.1. Radiotherapy

EBRT will be performed over 4-5 weeks with a target dose of 45Gy, with an extra-boost of an extra boost of 10-15Gy.

A special circumstance is for patients with hilar cholangiocarcinoma planned to be treated with radiation and chemotherapy, followed by chemotherapy, as a bridge to liver transplant. These patients will be screened first by the transplant team, and if found eligible (GTV < 3 cm), radiation therapy will consist of 2 phases:

- The first will treat local-regional nodes to 45 Gy in 1.5 Gy bd with capecitabine,
- The second will treat only the GTV with a small margin to a dose of 60 – 75 Gy in 1.5 Gy bid, with capecitabine (with the upper limit based on normal tissue constraints.).

Please see Appendix for full radiation protocol.

4.2. Chemotherapy

Patients will receive chemosensitisation with Capecitabine 800 mg/m2 orally twice daily continuously while on radiation.

4.3. Maintenance chemotherapy

Once the N0 status is confirmed at staging laparotomy (see below), patients will receive maintenance chemotherapy: Capecitabine 1000 mg/m2 orally twice daily on days 1-14 as part of 3 weekly cycles (median maintenance chemotherapy 3 cycles), while awaiting LT.

5. Re-assessment after neo-adjuvant treatment

Re-assessment, including routine blood tests + LFTs + CA19-9, will be performed 4 to 6 weeks after completion of NRC.

5.1. Imaging

A four-phase CAP-CT scan and a gadolinium-enhanced liver MR scan with MRCP will be performed 4 weeks after completion of RC. A MR scan with hepatobiliary agent will be performed only in case of suspicious lesion in the liver parenchyma. A PET-scan will be performed on specific occasions (eg, suspicious lesion that cannot be easily assessed during laparotomy) if the primary lesion was PET-avid.

5.2. Staging laparotomy

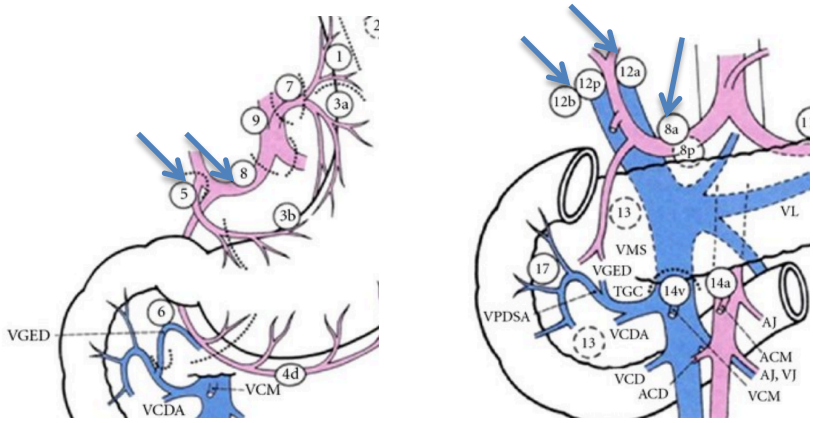
An exploratory and staging laparotomy will be performed after imaging (so 6 to 8 weeks after completion of NCR). The aims are:

- To search for sub capsular liver metastases and peritoneal carcinomatosis
- To search for an invasion of the duodenum
- To do biopsies of any suspicious tissue
- To perform a lymphadenectomy of the hepatic pedicle (as specified below), in order to exclude patients with any lymph nodes involvement.

If the patient is too sick to have the staging operation as a separate procedure, it can be performed immediately before transplant (frozen section assessment of lymph nodes required, with reduced diagnostic accuracy).
The lymphadenectomy specimen will be searched for lymph nodes. All nodes will be bisected, or trisected depending on size, and examined histologically to search for metastases.

<u>Lymphadenectomy</u>:
Lymph nodes from stations 12a (left hepatoduodenal), 12b,p (posterior hepatoduodenal), 5 (suprapyloric), 8a (anterior common hepatic artery), and 8b (posterior common hepatic

artery (according to the Japanese classification) should be removed and sent for definitive pathological analysis.



6. Liver transplantation

6.1. Criteria for enrolment

After reassessment, only patients with the following criteria will be listed for LT:

- N0 status on definitive pathological analysis
- M0 status
- Completion of the NCR protocol
- CA1-9<500 UI/L

The minimal time between completion of NCR and LT should be 4 weeks.

6.2. Graft allocation

Patients who fulfil all criteria for LT will be prioritized on the waiting list and attributed the median MELD from the time of listing.

While waiting patients will receive maintenance chemotherapy with Capecitabine and will have follow-up with CAP-CT scan and CA19-9 every 3 months.

6.3. LT procedure

DCD donors should be avoided because of the high rate of vascular complications in LT for PHCC (21% of late arterial and 22% of late portal vein complications [12]).

A back-up patient will be required. Start with exploratory laparotomy.

During hepatectomy the portal vein and common bile duct should be divided as close as possible to the pancreas.

Arterial anastomosis should be performed outside of the radiation field. Options can be either an anastomosis to the recipient proximal common hepatic artery, the splenic artery, or an arterial conduit from the aorta or iliac artery (conduits should be avoided if possible because of the increased later HAT rate). Roux-en-Y biliary reconstruction is performed. Frozen biopsy on the distal bile duct (expect 10% of positivity: then re-excise lower, or consider associated Whipple). Only invasive carcinoma, but not dysplasia/atypical changes, will be considered.

Consider aspirin at discharge for indefinite time.

The tumour within the explant will be reported according to the College of American Pathologists report template for PHCC, including AJCC 8th edition staging and tumour regression grade according to Lehrke et al.[18].

6.4. Post LT management

Adjuvant chemotherapy with Capecitabin (Capecitabine 1000 mg/m2 orally twice daily on days 1-14 as part of 3 weekly cycles for 24 weeks/8 cycles) will be discussed at MDM in case of residual viable tumour in the specimen plus adverse histological features such as perineural invasion, vascular invasion, or encasement on the specimen (or any other pathological factor associated with high recurrence).
CA19-9 and CT scan at 4 months, then every 6 months for 2 years, then every year.

6.5. Expected additional number of transplant

In the literature, 5% of patients with PHCC are eligible to NCR-LT[19], and the dropout rate is 30%. Approximately, **3.5% of patients with PHCC** could be listed for LT for PHCC.
Based on an annual incidence of PHCC in NZ of 40 patients per annum, the number of LT for PHCC could be in the order of **1 to 2 per year.**

7. Assessment of the protocol

The following data will be collected prospectively for the purposes of audit and protocol revision:

- Drop-out rate
- Overall survival rate
- Disease-free survival rate
- Recurrence rate
- Tolerance of NCR
- Post-transplant complications

8. References

[1] Moura D, de Moura E, Matuguma S, dos Santos M, Moura E, Baracat F, et al. EUS-FNA versus ERCP for tissue diagnosis of suspect malignant biliary strictures: a prospective comparative study. Endosc Int Open 2018;06:E769–77. https://doi.org/10.1055/s-0043-123186.

[2] Khan SA, Davidson BR, Goldin RD, Heaton N, Karani J, Pereira SP, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: An update. Gut 2012;61:1657–69. https://doi.org/10.1136/gutjnl-2011-301748.

[3] Murad SD, Kim WR, Harnois DM, David D, Burton J, Kulik LM, et al. Efficacy of Neoadjuvant Chemoradiation, Followed by Liver Transplantation, for Perihilar Cholangiocarcinoma at 12 US Centers. Gastroenterology 2012;143:e14. https://doi.org/10.1053/j.gastro.2012.05.029.

[4] Murad SD, Kim WR, Therneau T, Gores GJ, Rosen CB, Martenson JA, et al. Predictors of pretransplant dropout and posttransplant recurrence in patients with perihilar cholangiocarcinoma. Hepatology 2012;56:972–81. https://doi.org/10.1002/hep.25629.

[5] Heimbach JK, Sanchez W, Rosen CB, Gores GJ. Trans-peritoneal fine needle aspiration biopsy of hilar cholangiocarcinoma is associated with disease dissemination. Hpb 2011;13:356–60. https://doi.org/10.1111/j.1477-2574.2011.00298.x.

[6] Fritscher-Ravens A, Broering DC, Knoefel WT, Rogiers X, Swain P, Thonke F, et al. EUS-guided fine-needle aspiration of suspected hilar cholangiocarcinoma in potentially operable patients with negative brush cytology. Am J Gastroenterol 2004;99:45–51. https://doi.org/10.1046/j.1572-0241.2003.04006.x.

[7] Weilert F, Bhat YM, Binmoeller KF, Kane S, Jaffee IM, Shaw RE, et al. EUS-FNA is superior to ERCP-based tissue sampling in suspected malignant biliary obstruction: Results of a prospective, single-blind, comparative study. Gastrointest Endosc 2014;80:97–104. https://doi.org/10.1016/j.gie.2013.12.031.

[8] Gleeson FC, Rajan E, Levy MJ, Clain JE, Topazian MD, Harewood GC, et al. EUS-guided FNA of regional lymph nodes in patients with unresectable hilar cholangiocarcinoma. Gastrointest Endosc 2008;67:438–43. https://doi.org/10.1016/j.gie.2007.07.018.

[9] Nagino M, Ebata T, Yokoyama Y, Igami T, Sugawara G, Takahashi Y, et al. Evolution of surgical treatment for perihilar cholangiocarcinoma: A single-center 34-year review of 574 consecutive resections. Ann Surg 2013;258:129–40.

https://doi.org/10.1097/SLA.0b013e3182708b57.

[10] Nuzzo G. Improvement in Perioperative and Long-term Outcome After Surgical Treatment of Hilar Cholangiocarcinoma. Arch Surg 2012;147:26. https://doi.org/10.1001/archsurg.2011.771.

[11] Murad SD, Kim WR, Therneau T, Gores GJ, Rosen CB, Martenson JA, et al. Predictors of pretransplant dropout and posttransplant recurrence in patients with perihilar cholangiocarcinoma. Hepatology 2012;56:972–81. https://doi.org/10.1002/hep.25629.

[12] Tan EK, Taner T, Heimbach JK, Gores GJ, Rosen CB. Liver Transplantation for Peri-hilar Cholangiocarcinoma. J Gastrointest Surg 2020;24:2679–85. https://doi.org/10.1007/s11605-020-04721-4.

[13] Cambridge WA, Fairfield C, Powell JJ, Harrison EM, Søreide K, Wigmore SJ, et al. Meta-analysis and Meta-regression of Survival After Liver Transplantation for Unresectable Perihilar Cholangiocarcinoma. Ann Surg 2021;273:240–50. https://doi.org/10.1097/SLA.0000000000003801.

[14] Sudan D, DeRoover A, Chinnakotla S, Fox I, Shaw B, McCashland T, et al. Radiochemotherapy and transplantation allow long-term survival for nonresectable hilar cholangiocarcinoma. Am J Transplant 2002;2:774–9. https://doi.org/10.1034/j.1600-6143.2002.20812.x.

[15] De Vreede I, Steers JL, Burch PA, Rosen CB, Gunderson LL, Haddock MG, et al. Prolonged disease-free survival after orthotopic liver transplantation plus adjuvant chemoirradiation for cholangiocarcinoma. Liver Transplant 2000;6:309–16. https://doi.org/10.1053/lv.2000.6143.

[16] Heimbach JK, Haddock MG, Alberts SR, Nyberg SL, Ishitani MB, Rosen CB, et al. Transplantation for hilar cholangiocarcinoma. Liver Transplant 2004;10:65–8. https://doi.org/10.1002/lt.20266.

[17] Croome KP, Rosen CB, Heimbach JK, Nagorney DM. Is Liver Transplantation Appropriate for Patients with Potentially Resectable De Novo Hilar Cholangiocarcinoma? J Am Coll Surg 2015;221:130–9. https://doi.org/10.1016/j.jamcollsurg.2015.01.064.

[18] Lehrke HD, Heimbach JK, Wu TT, Jenkins SM, Gores GJ, Rosen CB, et al. Prognostic significance of the histologic response of perihilar cholangiocarcinoma to preoperative neoadjuvant chemoradiation in liver explants. Am J Surg Pathol 2016;40:510–8. https://doi.org/10.1097/PAS.0000000000000588.

[19] Vugts JJA, Gaspersz MP, Roos E, Franken LF, Olthof PB, Coelen RJS, et al. Eligibility for Liver Transplantation in Patients with Perihilar Cholangiocarcinoma. Ann Surg Oncol 2021;28:1483–92. https://doi.org/10.1245/s10434-020-09001-8.

Appendix: External Beam Radiation Protocol

Radiation Treatment Equipment

-Treatment will be delivered with 6 to 10MV photons, with selection of appropriate energies to optimize the radiotherapy dose distribution within the target volume and minimize the dose to non-target tissues.

-The treatment unit will have image guidance capabilities, preferably with kV cone beam CT.

Simulation and Immobilization

-Patients will be positioned in an immobilization bodyfix couch in the supine position.

- Imaging for simulation and motion assessment will include a contrast CT in end exhale breath hold position

-IV CT contrast will not be used if there is a contraindication.

-A 4D CT will follow the contrast CT to measure liver motion.

Prescription and Voluming

-Treatment will consist of two phases of external beam RT. Phase I includes the primary target and regional nodes, to receive 45 Gy in 1.5 Gy twice daily, with 6 hour inter fraction interval, and a subsequent phase II includes a further dose escalation to the primary target and gross nodes (LN), to a total dose of 54 – 75 Gy in 1.5 Gy bd, dependent on normal tissue constraints.

-Areas at risk include unresected tumour as well as areas of potential microscopic ductal and nodal involvement.

-The porta hepatis LN are to be included along with the primary lesion. Pancreaticoduodenal nodes (defined by fat plane between pancreatic head and duodenum with the inferior extent at minimum where the biliary duct enters the duodenum, and at maximum to bottom of duodenum) and celiac axis (1 cm expansion around the celiac trunk, excluding organs at risk) should also be encompassed. Although the SMA nodes are not primary targets, they can be included if dose limiting organs do not preclude their treatment (1 cm around the SMA).

-The dose-limiting organs include small intestine, stomach, liver, kidneys, and spinal cord. While high precision radiation techniques can allow appropriate sparing of the left kidney and spinal cord, portions of the liver, duodenum, and stomach remain within the moderate or high-dose volumes.

-The gross tumour volume (GTV) will be defined using the IV contrast CT and contrast MRI (if available) and information obtained from THC and/or ERCP. Radiologically suspicious regional lymph nodes will be defined as separate GTVs (i.e. GTVLN1, GTVLN2 …)

-The clinical target volume (CTV) is the GTV + 20mm along the biliary ducts and 10 mm radially. Lymph node CTVs will include the GTVLN + 5mm expansion.

-A separate CTV will also be generated for regional lymph nodes at risk as outlined above and will be targeted to receive 45Gy in 1.50Gy twice daily fractions.

-Another clinical target volume (CTV) to receive more dose is the primary GTV + 5 - 10mm along the biliary ducts (depending on certainty of GTV definition) and 5mm radially, and the GTVLN (larger than 10 mm) + a 5mm expansion. All these CTVs are intended to receive an extra 10 – 30 Gy (depending on normal tissue constraints for a total dose of 55 – 75 Gy).

-The planning target volume (PTV) will be determined by the immobilization device used and/or the individual patient breathing motion (minimum PTV 5 mm). With daily imaging, repositioning and breath hold, a 5 mm margin should be sufficient for setup variability for most patients. If free breathing is used, an additional margin (e.g. 90% of the amplitude of motion based on 4DCT) is required. The margins may be variable in three directions (e.g. if the planning CT is done in exhale, then larger margins will be required inferiorly to account for free breathing). PTVs will be created for all CTVs and GTVs. The maximal PTV margin in any direction is 25 mm.

<u>Dose Limitation to Critical Structures</u> (for the cumulative combined dose distribution)

-Normal Liver: The normal liver is defined as the liver volume minus all GTVs.

This volume must be at least 700cc of normal liver. The maximum mean liver dose (minus GTV) allowed will be 31 Gy based on previous work from the University of Michigan. The estimated NTCP for liver injury must be < 2%.

-Kidney: 50% of the combined kidney volume should receive less than 18Gy (and mean dose of combined kidneys is recommended to be < 18Gy). If one kidney is non-functional or has impaired function (or is required to be irradiated with a mean dose > 18Gy), then the other kidney should receive a mean dose of <8Gy.

-Spinal Cord: The maximum allowable dose to a 7mm Cord PRV is 48Gy.

-Large bowel: The maximum allowable bowel dose to 0.5cc is 56Gy.

-Duodenum: The maximum allowable duodenum dose to 0.5cc volume is 55Gy.

-Stomach: The maximum allowable stomach dose to 0.5cc volume is 54Gy.

Radiation Treatment Planning

-CT based 3D treatment planning or IMRT/VMAT will be used for all patients.

-Dose volume histograms (DHVs) shall be calculated for the target lesions (GTV, CTV and PTVs), liver, liver minus GTV, both kidneys, spinal cord, duodenum, esophagus, small bowel, large bowel and stomach.

-A renal function scan should be performed at or before the start of treatment.

-Verification imaging to localize the liver is required prior to every radiation fraction. A minimum of one pair of angled verification images must be acquired to confirm the position of at least one isocentre. Cone beam CT is preferred with kV fluoroscopy for image guidance at the time of treatment, using the stent as a surrogate for the primary CTV. Oral contrast may also be useful for localizing the duodenum, that may be a dose limiting normal tissue.

-Repositioning will be recommended if the liver position is more than 3 mm from its planned position.

-Up to 250 cc of oral contrast with or without water may be taken by patients prior to each treatment to improve soft tissue delineation (i.e. liver from stomach/duodenum) on the cone beam CT if determined to be useful for image guidance. Efforts should be made to maintain a similar luminal GI structure filling status as at baseline CT. Stomach should not be maximally full.

-Efforts should be made to reduce the volume irradiated when possible. Efforts should be made in all patients to exclude unnecessary stomach, small intestine, liver and kidney from radiation.

-Prophylactic anti-emetics or H2 antagonists will not be routinely used but should be strongly considered if the stomach or duodenum receives more than 50 Gy.

Dose-time factors.

-Radiation will be delivered in 1.5Gy given twice daily over 4 – 5 weeks with a ≥ 6-hour interfraction interval.

-The PTV surrounding all CTVs including the electively treated lymph node regions will receive a dose of 45Gy. A lower dose of 40.5Gy given over 27 Fx can be used if required based on the normal tissue constraints.

-The PTV2 (PTV around the primary GTV plus 5-10 mm and any nodal GTVs plus 5mm) will receive a boost dose of 10Gy – 30Gy in 10-20 fractions of 1.5 Gy, 2 Fx /day (≥ 6 hours separation between Fx). The upper cumulative dose will vary from 54 to 75Gy given over 36

to 50 fractions depending on normal tissue constraints listed above.

Radiation Checklist

-Patients will be seen in a review clinic at least weekly during radiation with notation of toxicity, weight, blood counts and liver function tests.

-FBC will be done weekly. Irradiation will be temporarily interrupted during periods when the WBC < 2 or platelets < 50 and can be resumed once they are again above these levels

-If hemoglobin <100mg/dL, the patient will be transfused as indicated, but chemotherapy and/ or radiation therapy will not be interrupted.

-Appropriate precautions against infection should be taken in the event of severe leukopenia and platelet transfusions should be utilised for thrombocytopenia associated with bleeding

-If bilirubin or transaminases rise by a factor of 2 or more CTC3.0 toxicity grades then radiotherapy will be held. It will only be re-continued if the levels return to their baseline.