Surgical management, including the role of transplantation, for intrahepatic and peri-hilar cholangiocarcinoma

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Abstract

Intrahepatic and peri-hilar cholangiocarcinoma are life threatening disease with poor outcomes despite optimal treatment currently available (5-year overall survival following resection 20-35%, and <10% cured at 10-years post resection). The insidious onset makes diagnosis difficult, the majority do not have a resection option and the high recurrence rate post-resection suggests that occult metastatic disease is frequently present. Advances in perioperative management, such as ipsilateral portal vein (and hepatic vein) embolisation methods to increase the future liver remnant volume, genomic profiling, and (neo)adjuvant therapies demonstrate great potential in improving outcomes. However multiple areas of controversy exist. Surgical resection rate and outcomes vary between centres with no global consensus on how 'resectable' disease is defined – molecular profiling and genomic analysis could potentially identify patients unlikely to benefit from resection or likely to benefit from targeted therapies. FDG-PET scanning has also improved the ability to detect metastatic disease preoperatively and avoid futile resection. However tumours frequently invade major vasculo-biliary structures, with resection and reconstruction associated with significant morbidity and mortality even in specialist centres. Liver transplantation has been investigated for very selected patients for the last decade and yet the selection algorithm, surgical approach and both value of both neoadjuvant and adjuvant therapies remain to be clarified. In this review, we discuss the contemporary management of intrahepatic and peri-hilar cholangiocarcinoma.

Introduction

Cholangiocarcinoma arises from the biliary epithelial cells, and is associated with a poor prognosis due to late presentation. Anatomically, it is categorised as intrahepatic (iCCA), peri-hilar (pCCA) or distal cholangiocarcinoma (dCCA)[1]. ICC arises from within the intrahepatic bile ducts, pCCA arises in between the second order ducts and the insertion of the cystic duct into the common hepatic duct, and dCCA arises from the common bile duct, below the cystic duct insertion. The three anatomical subtypes demonstrate distinct clinico-pathological features, and require tailored approaches to optimise outcome[2]. A detailed discussion of dCCA is beyond the scope of this review, which will focus on iCCA and pCCA for which liver resection (with a tumour-free margin) is the only established curative-intent treatment.

However the majority of patients developing cholangiocarcinoma will present with locally advanced or metastatic disease and will be ineligible for liver resection or transplantation[3]. Of those who do undergo resection, 5-year and 10-year survival rates of 20-35%[4-10] and <10%[11-13] have been reported, respectively.

Current challenges relate to managing biliary obstruction (and/or sepsis) at the time of presentation and ensuring accurate staging prior to surgical intervention. These factors determine whether a patient will proceed safely to curative-intent surgery.
However no standard consensus exists regarding the best drainage strategy or staging protocol. Similarly, the definition of 'resectable' disease has not been established, with a wide variation between centres globally[14]. More extensive resections involving arterial reconstructions[7, 15-21] and/or extended lymphadenectomy[8, 22-25] were initially thought to provide better disease control. However such radical surgeries are controversial given the high morbidity and mortality associated with complex surgery and the resulting morbidity, impact on quality of life and the high recurrence rates. Liver transplantation has also been investigated as a curative-intent option, often in single centres outside of the oversight of a clinical trial, resulting in delay and uncertainty in establishing its role as a therapeutic option[10, 14, 26-28]. Expanding the indications for transplantation requires careful consideration and improved evaluation as increased demand for liver grafts for treating cancer will result in longer waiting times for those with end stage liver disease.

We discuss the diagnosis, staging, surgical management and (neo)adjuvant treatment of iCCA and pCCA, identify the limitations of the current approach and suggest strategies to improve long term outcome. We conclude by addressing areas where future research efforts should be focused and specifically discuss the role of liver transplantation.

Classification and pathology

pCCA and dCCA are considered 'extra-hepatic', and account for up to 80% cases, whereas iCCA accounts for the remainder[29]; pCCA can be usefully subcategorised by the Bismuth-Corlette system based on the precise location of the tumour (figure 1). All three subtypes of cholangiocarcinoma are associated with distinct risk factors, pathology, presentation, and management. Previous misclassification of pCCA into the intrahepatic group (as pCCA was not formally categorised in previous disease classifications[3]) may account for a proportion of the observed increase but does not explain the overall increase in the total number of cases.

Pathologically there are distinct macroscopic features differentiating iCCA from pCCA. The majority of intrahepatic lesions demonstrate a 'mass-forming' phenotype, with a large defined, firm polypoid mass which may be accompanied by multiple satellite lesions[30]. Macroscopically pCCA is characterised by a 'periductal infiltrating' lesion in approximately 80% of patients[31], spreading along the extrahepatic bile ducts and causing a stricture with proximal dilatation[32]. The remaining 20% pCCA patients demonstrate an intraductal growth, which typically presents early with a small polypoid tumour causing proximal obstruction[33], and is associated with a better prognosis compared to periductal infiltrating lesions. In iCCA, lesions can be 'mass-forming' (characterised by an intraparenchymal mass which may be accompanied by associated satellite nodules), periductal infiltrating or intraductal growths.

Mass forming lesions are observed in 65% patients, whereas a 'mixed-type' of mass-forming with periductal infiltrating tumours are observed in 25%; the remaining 10% of patients have either intraductal growths or periductal infiltrating tumours[31]. There are no histological or immunohistological features which would be a contra-indication to surgery in resectable disease however there are well-established features associated with a poor prognosis including a poorly differentiated tumour, the presence of satellite nodules (iCCA), vascular invasion and perineural invasion (particularly for pCCA)[31]. Furthermore, molecular subtyping of cholangiocarcinoma has great potential in identifying patients likely to respond to particular treatment strategies and aid prognostication[34]. The MOSCATO-01 trial was an

umbrella trial investigating the use of high throughput genomics to identify druggable targets in '*hard to treat*' solid organ cancers and match patients to a targeted therapy[35-37].

Diagnosis and staging

Early diagnosis of pCCA and iCCA continues to prove challenging. Early iCCA may be completely asymptomatic, whereas pCCA usually presents with obstructive jaundice. Elevated liver enzymes may be the only sign of a liver pathology in some patients. Symptoms of early-stage disease are non-specific (vague abdominal pain, anorexia, weight loss); in iCCA jaundice often occurs late in the disease process with the onset of large duct obstruction. In such circumstances, the disease is usually beyond curative resection due to invasion of local structures and/or development of metastases. Abdominal imaging may reveal a large mass (in iCCA) and/or biliary dilatation (particularly in pCCA) when symptoms are investigated. Correlation with tumour markers may aid in forming the diagnosis, with CA 19-9 particularly associated with pancreato-biliary malignancy. However approximately 10% patients lack Lewis blood group antigen and cannot synthesise CA 19-9[38], and multiple other conditions can result in an elevated serum level (biliary obstruction independent of cause, pancreatitis, cirrhosis, hepatocellular carcinoma, pancreatic ductal adenocarcinoma), limiting its specificity to cholangiocarcinoma.

When detected incidentally on imaging, the tumour may be at an early-stage when curative-intent resection may be feasible. An Italian survey of 41 different centres managing patients with cholangiocarcinoma reported that 28% patients with iCCA had an incidental asymptomatic presentation[39]. It is plausible that such patients could have a higher cure rate due to earlier stage disease potentially being resected prior to local invasion and/or the development of metastases. However the authors did not compare survival in this group with patients presenting symptomatically, and to our knowledge no studies have been published comparing these two groups of patients.

Diagnosis is usually suggested using a combination of computerised tomography (CT) scanning, MRI/MRCP, positron-emission tomography (PET) scanning, and/or histopathological (or cytological) assessment. CT chest, abdomen and pelvis is mandatory to ensure accurate staging prior to commencing any treatment. Diagnostic imaging studies should be performed prior to any biliary intervention[40] as the subsequent inflammatory

changes may mask the underlying pathology and disease stage, making both the diagnosis and optimal treatment plan uncertain.

Following identification of a liver mass suggestive of cholangiocarcinoma (and before any biliary intervention[40]), a high-quality quadruple phase contrast-enhanced CT[41] scan is the imaging modality of choice and can demonstrate features indicative of cholangiocarcinoma, and exclude other benign or malignant liver lesions[42]. This also provides key information for determining resectability through delineating anatomical relationships to local vascular structures. Diagnostic features observed on CT are early arterial-phase enhancement with progressive central filling[43]. Delayed phase images will also show enhancement of iCCA compared with surrounding liver parenchyma. Contrast-enhanced CT can accurately delineate portal vein and hepatic arterial involvement, however MRI has a higher sensitivity for detecting smaller lesions[44], provides sharper soft tissue contrast and enables more accurate assessment of tumour spread along the bile ducts[45-47], aiding decisions surrounding resectability.

While CT and MRI can provide detailed information on tumour morphology[48, 49] and its relationship to critical structures, they are inadequate for assessing lymph node involvement[47]. A retrospective study of 146 patients with 'biliary cancer' (iCCA, pCCA, dCCA and gallbladder carcinoma) who underwent curative-intent resection with lymphadenectomy found that there was no correlation between CT findings and histological confirmed lymph node involvement[50]. Despite this, radiological findings have been found to correlate with histopathology in patients with iCCA[48]. King et al reported that radiological findings could predict tumour grade and stage with fair accuracy.

PET scanning is recommended primarily for assessment of lymph node involvement and the presence of distant metastases rather than diagnosis of the primary tumour by the British Society of Gastroenterology, the European Association for Study of the Liver, and the Japanese Society of Hepato-Biliary-Pancreatic Surgery[42, 51, 52]. In a recent meta-analysis investigating the role of PET-scanning, the authors found that at least 15% patients with biliary tract cancers had their management modified by the PET-scan[53] (mostly through upward stage migration). The reported specificity for lymph node metastasis was very high at 97%, with a 95% specificity for distant metastasis. The presence of either lymph node or distant metastasis is likely to indicate systemic treatment, therefore accurate assessment is

essential for optimising management. A false negative for lymph node or distant metastasis could lead to a patient undergoing 'futile' surgery due to the presence of metastatic disease, whereas a false positive could preclude patients with resectable disease from undergoing surgery.

The role of biopsy in the management of a resectable iCCA is controversial[54]. Biopsy introduces a risk of cancer seeding outside the liver, potentially converting a potentially curative surgery into disease palliation.. Furthermore, given the resection specimen will undergo full histopathological assessment, the value of a preoperative biopsy is questionable. Biopsy is considered essential if patients with iCCA or pCCA are being enrolled in transplant trials or evaluations or if the cancer is borderline for a curative resection (anticipated R1 resection) and neoadjuvant chemotherapy is being proposed.

While iCCA is often accessible for percutaneous biopsy, peri-hilar lesions are more difficult to access given their deep location and proximity to important vasculobiliary structures. For peri-hilar lesions endoscopic ultrasound-guided biopsy or fine-needle aspiration for cytology can be used for obtaining a tissue diagnosis. However preoperative biopsy for peri-hilar lesions is associated with a low sensitivity (high false-negative rate). Endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) offer direct visualisation of the bile ducts, and allow for brushings to be taken easily at the time of the procedure. Brushings are associated with a specificity approaching 100%, however sensitivity is relatively poor ranging from 20-60%[55-58].

Recently cholangioscopy-guided biopsy has been possible at the time of ERCP and may improve diagnosis and local staging of pCCA[59-61]. Cholangioscopy allows for assessment and biopsy of intraductal lesions, and may detect radiologically occult disease that could affect management (presence of 'skip' lesions or bilateral disease). Two meta-analyses reported that digital single-operator cholangioscopy has a very high diagnostic performance in detecting malignant biliary strictures[62, 63]. However, both reports were based on data from non-randomised trials (Kulpatcharapoing et al included one randomised control trial[64]) and demonstrated significant heterogeneity between included studies, limiting the validity of the conclusions. However in the randomised study by Gerges et al[64], the sensitivity of visualisation (95.5% vs 66.7%) and overall accuracy (87.1% vs. 65.5%) for accurately

diagnosing indeterminate biliary strictures were significantly higher in patients undergoing cholangioscopy-guided biopsy compared to standard ERCP alone.

The use of staging laparoscopy in the workup of patients for liver resection varies considerably across centres[65, 66]. However exploratory laparotomy without resection should be avoided where possible due to the morbidity and significant risk of delaying (or preventing) palliative chemotherapy[67]. Routine staging laparoscopy is not universal[42, 51], given the increased sensitivity of modern CT (especially when combined with PET-CT) in detecting peritoneal disease. Currently, UK and European guidelines support a selective approach for staging laparoscopy in patients with risk factors for peritoneal disease (high CA 19-9, major vascular invasion, lymphadenopathy, large tumour, multifocal disease)[42, 51]. Detection rates for peritoneal disease in all comers vary from 10-17% [65, 66, 68-72].

Management of biliary obstruction

The role of biliary drainage, and the optimum method of drainage, is anothere contentious issue. Most patients with pCCA will present with obstructive jaundice and have a high risk of developing cholangitis secondary to the biliary obstruction. Drainage of patients with acute cholangitis is essential due to the high risk of mortality. Endoscopic biliary drainage (EBD), endonasobiliary drainage (ENBD), and PTC can each be used to relieve biliary obstruction. Morbidity associated with drainage procedures (such as bleeding, pancreatitis, and cholangitis) may decondition patients and delay curative-intent surgery due to a prolonged recovery phase. The approach to preoperative biliary drainage can significantly impact resectability, and should not be performed until a clear treatment plan has been proposed and ratified.

It has long been debated whether preoperative EBD or PTC is the optimum method of draining the FLR[73]. The evidence was previously conflicting and limited to retrospective series[73-80] with a significant risk of selection bias. The only recent randomised control trial performed comparing the two techniques enrolled 54 patients from 4 Dutch centres, but was prematurely closed due to a higher all-cause mortality rate in the PTC group (41% vs 11%)[81]. Observed morbidity rates were similar in both groups, however the small sample size significantly confounds this observation. ENBD has been practiced in East Asian centres (particularly Japan), and has been specifically associated with a lower risk of cholangitis and longer patency (defined as absence of jaundice)[79, 82, 83]. However ENBD may be poorly

tolerated by patients and the loss of bile may lead to electrolyte and fluid imbalances (unless oral recycling is practiced) requiring further intervention. Therefore while consensus exists regarding the need for preoperative biliary drainage in obstructed patients, the method remains uncertain.

In the absence of cholangitis some centres will resect patients with biliary obstruction, however the Japanese Society of Hepato-Biliary-Pancreatic Surgery guidelines recommend biliary drainage in all patients with pCCA (regardless of whether they are obstructed)[52] due to the morbidity associated with surgery in jaundiced patients[76]. In operable pCCA, preoperative biliary drainage is unilateral and performed only in the future liver remnant (FLR). Bilateral drainage is usually confined to those with sepsis or failed resolution of jaundice with unilateral drainage but should raise the possibility of significant parenchymal liver injury. Unilateral drainage has been shown to lead to compensatory liver hypertrophy of the FLR with atrophy of the obstructed segment[84-86], reducing the risk of post-hepatectomy liver failure (PHLF).

Future liver remnant

The risk of mortality after liver resection for CCA is dependent on the volume and quality of the remnant liver. Inadequate future liver remnant volume (FLRV) risks the development of post-hepatectomy liver failure (PHLF) which is associated with a high mortality risk (52-68%[87-89]).

Methods to increase the FLRV have allowed more extensive resection for pCCA, where an extended hepatectomy is usually required. The minimum recommended FLRV as a percentage of total liver volume for liver resection to reduce the risk of PHLF is 20% with normal liver parenchyma , 30% for patients post -chemotherapy and 40% for patients who have Childs-Pugh A cirrhosis, respectively[90]. Given the presence of biliary obstruction +/- sepsis at presentation most surgeons would consider augmentation for FLRV of <30% and some < 40%. The change in FLR following augmentation techniques is also an important metric, and can predict PHLF as it indicates the regenerative capacity of the patient's liver[91]. Multiple retrospective studies have demonstrated the utility of PVE prior to extended hepatectomy[92-97], where portal blood flow to the tumour-bearing lobe is interrupted to induce hypertrophy of the FLR. Other methods to increase the FLR include PVE with hepatic vein embolisation (PVE-HVE)[98] and associating liver partition and portal vein ligation for staged

hepatectomy (ALPPS)[99]. The advantage of PVE (and PVE-HVE) is that it is associated with a relatively low morbidity risk and can induce the required hypertrophy within 4 to 6 weeks post-embolisation. ALPPS requires a two-stage hepatectomy (with liver transection and portal vein ligation being performed in the first stage followed by resection in the second stage), with liver hypertrophy occurring during the intervening period (usually 7-10 days). Although rapid hypertrophy is achieved, ALPPS in cholangiocarcinoma is associated with a very high morbidity and mortality risk, with one multicentre series observing 48% mortality in pCCA within 90-days in high volume centres[100]. The role of ALPPS in pCCA is yet to be established, but could be a rescue intervention for patients who at time of surgery are considered to have inadequate volume or quality of liver parenchyma to complete an extended resection.

PVE-HVE simultaneously occludes both the inflow and outflow of the liver tissue to be resected; the embolisation of the hepatic veins results in complete venous deprivation of the liver to induce greater hypertrophy than with PVE alone[98]. In the context of pCCA, this would most commonly be embolisation of the right portal vein and the right and middle hepatic veins to facilitate an extended right hepatectomy. A multicentre retrospective study compared patients undergoing liver resection who had PVE-HVE with patients who had PVE alone[101], and found that PVE-HVE resulted in increased liver hypertrophy with lower morbidity (26% vs 34%) and 90-day mortality (3% vs. 16%) however neither reached statistical significance. In this series, 30 patients (15%) had pCCA and 28 patients (14%) had iCCA demonstrating feasibility in these groups. Further prospective investigation of PVE-HVE in cholangiocarcinoma is warranted to expand the evidence base and identify relevant predictors of outcome for both pCCA and iCCA. The DRAGON-1 trial is an ongoing prospective single-arm trial assessing the safety and feasibility of PVE-HVE in patients with borderline resectable colorectal liver metastases[102]. Although not specific to cholangiocarcinoma, the results will be very relevant and may characterise the risk profile of PVE-HVE prior to liver resection.

Liver resection

The aim of liver resection (for both pCCA and iCCA) is to cure the patient of cancer with minimal perioperative and recurrence risk, achieved through a complete R0 resection with an adequate FLRV for postoperative recovery and survival[42]. The approach to resection has evolved over time, with centres performing more radical resections facilitated through

perioperative techniques to increase the FLR[3, 77, 90, 97, 101, 103]. For cholangiocarcinoma a surgery approach is considered if:

1) complete macroscopic removal of tumour tissue can be achieved,
2) enough FLR is retained to prevent PHLF, and
3) vascular and/or biliary continuity to the liver remnant is maintained or can be reconstructed.

Tumours invading major vascular structures[15-20, 95, 104, 105], such as the inferior vena cava and portal vein, are more frequently considered for resection in specialist centres, whilst previously considered a contra-indication.

The associated morbidity and mortality risk highlights the need for careful preoperative assessment and multi-disciplinary management aimed at prehabilitation to avoid futile surgery in patients who may otherwise benefit from palliative chemotherapy or immunotherapy. The reported 5-year survival rate following resection for pCCA and iCCA is 15-40%, with the majority of patients developing disease recurrence even after an R0 resection[106]. Currently adjuvant chemotherapy with capecitabine is recommended for all patients with cholangiocarcinoma following resection to reduce recurrence risk, based on the results of the BILCAP study[107]. So far, no neoadjuvant treatments for patients with resectable disease have demonstrated efficacy in phase 3 trials[42]. However patients who demonstrate sufficient reduction in disease burden following palliative intent may warrant re-considering for curative-intent liver resection.

Currently there is no way to prospectively identify subsets of patients likely to undergo successful disease downstaging, however advances in molecular profiling and analysis of circulating tumour cells may aid understanding of tumour biology and genotypes associated with particular clinico-pathological features[108]. Genomic biomarkers may help identification of patients likely to respond to systemic therapy. For example, a phase 2 single-arm trial evaluated the efficacy and safety of Pemigainib (a fibroblast growth factor receptor [FGFR] inhibitor) in cholangicarcinoma patients with or without FGFR fusions or rearrangements reported a 35% objective response rate in patients with FGFR alterations, whereas patients without FGFR fusions/rearrangements did not respond.[109]. A combined approach of biomarker analysis (serum, bile, tissue[110]) and radiological assessment could improve prognostication and treatment-related decisions in patients with cholangiocarcinoma.

Analysis of biobanked samples of patients who are enrolled in prospective trials could identify predictors of treatment response.

Lymphadenectomy

Lymphadenectomy is performed to remove the regional lymphatic drainage of the cancer in the hope of increasing the chance of cure. It is currently recommended for intrahepatic and peri-hilar disease to facilitate cure but also improve disease staging and guide adjuvant strategies[24]. While lymph node metastasis is a poor prognostic factor[3, 51, 108, 111, 112], there is currently no proof that the lymphadenectomy improves oncological outcome[24, 25, 113, 114].

A regional lymphadenectomy involves excision of hepatoduodenal ligament nodes (station 12); right-sided lesions also require excision of nodes behind the pancreatic head (station 14) whereas left-sided lesions require excision of common hepatic artery lymph nodes (station 8) and nodes around the left gastric artery (station 7). An 'extended' lymphadenectomy does not have a standardised anatomical definition, but may involve a regional lymphadenectomy plus excision of para-aortic nodes (station 16) and/or nodes around the coeliac axis (station 9). As a minimum, it is recommended that at least 6 regional lymph nodes are sampled for histopathological analysis to ensure adequate staging post-resection[115].

Delineating the impact of lymphadenectomy on oncological outcome is not straightforward. A meta-analysis of 1377 patients from 13 studies reported that there was no difference in survival, but greater morbidity, in patients undergoing lymphadenectomy compared to non-lymphadenectomy patients[116]. However, the studies included in the meta-analysis were all retrospective and demonstrated significant heterogeneity, significantly confounding the analysis.

A recent retrospective study of 706 patients undergoing curative-intent resection for clinically node-negative iCCA investigated whether adequate lymphadenectomy (defined as excision of ≥6 regional lymph nodes) impacted survival. The study concluded that adequate lymphadenectomy was associated with improved survival compared to an 'inadequate' lymphadenectomy (median overall survival 28 vs 23 months)[25]. Patients with microscopic nodal disease on histology had a better outcome with a radical lymphadenectomy rather than a limited lymphadenectomy. The presence of microscopic disease will only be apparent on histopathological examination of the resection specimen (although biomarkers may suggest

that lymph node disease is present[117]). This finding supports a radical rather than limited lymphadenectomy but in the absence of randomised trials the effect of lymphadenectomy on survival remains unproven.

Patients who were node-positive following an inadequate lymphadenectomy may have had more advanced disease beyond the regional lymph nodes, particularly when considering that only 18% patients who had an inadequate lymphadenectomy were node-positive compared to 40% in the adequate lymphadenectomy group. Furthermore an inadequate lymphadenectomy will likely lead to a false-negative nodal staging which could impact on the approach to adjuvant therapy. Therefore an adequate regional lymphadenectomy of at least 6 lymph nodes should be attempted to improve staging.

The overall evidence to support an extended lymphadenectomy is controversial.
Several series have claimed a survival benefit[118-121], particularly when patients have node-negative disease in the extended field lymph nodes. However in these studies[118, 121], patients with node-negative disease undergoing an extended lymphadenectomy are compared with patients with node positive disease, therefore the 'improved' survival could be due to the disease status of the lymph nodes rather than the extent of lymphadenectomy. Where an extended lymphadenectomy has been compared with a standard lymphadenectomy and improved survival reported, patients in the standard group may have had inadequately staged disease extending beyond the standard nodal group. In the absence of a high-quality randomised control trial, no definitive conclusions can be made regarding the extent of lymphadenectomy.

A lymphadenectomy is a procedure with well recognised complications and morbidity[122], including devascularisation of the bile ducts, major vascular injury, and chylous ascites, especially in patients with cirrhosis[123]. Although 5-year survival rates in patients undergoing extended lymphadenectomy are reported in selected series to range from 26%-49%[119-121], a propensity-score matched analysis failed to demonstrate superiority of extended lymphadenectomy[23] suggesting that previous series are likely to be confounded by significant selection bias. No randomised evidence is currently available for iCCA or pCCA. However the Regional lymphadenectomy vs. extended lymphadenectomy for hilar cholangiocarcinoma (RELAY-HC) trial[124] is ongoing and should provide high quality evidence on whether extended lymphadenectomy improves survival for patients with pCCA.

Liver resection for peri-hilar cholangiocarcinoma

The proximity of tumours to critical vasculo-biliary structures presents a challenge in the management of pCCA . Critical structures require reconstruction following resection. The resection of pCCA requires careful evaluation of either an extended right or extended left liver resection. Optimal resection is based on the likely achievement of a clear resection margin whilst optimising residual liver volume. The left hepatic duct has a longer extrahepatic course compared to the right, and is typically easier to reconstruct into a Roux-en-Y hepaticojejunostomy.

However biliary reconstruction following right hemihepatectomy is technically easier due to the wider diameter and longer course of the left hepatic duct. The precise type of resection in pCCA depends on the location of the tumour, however generally an extended right hemi-hepatectomy is performed for Bismuth-Corlette IIIa and IV tumours, and an extended left hemi-hepatectomy is performed for Bismuth-Corlette IIIb tumours. Previously bile duct excisions were performed for type I and II lesions, however pCCA often has longitudinal spread along the hepatic ducts resulting in a high incidence of positive surgical resection margin, therefore an extended right hemi-hepatectomy is typically performed for such tumours[29, 31, 32, 94]. However in patients with limited FLR in the left lateral section, an extended left hemihepatectomy with resection and reconstruction of the right hepatic artery may be preferable [125], and can be performed with similar morbidity rates to an extended right hemihepatectomy.

Caudate lobe resection

The caudate lobe lymphatics drain into the hilar nodes of both the left and right hepatic ducts, which may explain a pCCA involving the caudate lobe. En bloc caudate lobe resection in pCCA has never been explored in a randomised study, possibly due to concern regarding the morbidity and impact on FLR. Negative resection margins are known to improve surgical outcomes[4, 29, 95, 126], therefore the risk of trying to achieve an R0 margin has to be balanced against the increased risk of morbidity and mortality. Multiple retrospective series have reported outcomes of patients undergoing en bloc caudate lobectomy[4, 95, 103, 127-130], with a recent meta-analysis[131] finding that en bloc caudate lobectomy was associated with significantly better survival (hazard ratio 0.45, 95% confidence interval 0.38 to 0.55) and likelihood of negative margins (hazard ratio 3.88, 96% confidence interval 2.18 to 6.90), without increasing morbidity and mortality compared to patients who did not undergo

caudate lobectomy. Despite significant heterogeneity between studies and the risk selection bias in published series, en bloc caudate lobectomy is recommended to improve outcomes following resection for pCCA through achieving a negative resection margin.

Vascular resection

Major vascular involvement is commonly observed in pCCA, with such patients requiring en bloc vascular resection and reconstruction to achieve a curative-intent resection with negative margins. However, such procedures are technically demanding and can be associated with a significant risk of morbidity and mortality necessitating careful preoperative assessment and patient selection. Whether routine en bloc portal vein resection is necessary is controversial (termed 'hilar en bloc resection[132]). The initial series published in 1999 reported that portal vein resection improved long-term survival in patients who underwent R0 resection. The rationale behind this approach was to perform a 'no touch' resection where the peritumoural planes are not violated to prevent microscopic residual disease at the resection margin. However this analysis was restricted to 14 patients who had R0 resections, and excluded postoperative deaths. Subsequent series have demonstrated significant morbidity and 90-day mortality (12-25%) with routine portal vein resection[133-135], therefore currently the evidence favours portal vein resection only in cases where the tumour involves and cannot be mobilised from the portal vein[136].

Whether contralateral arterial involvement necessitating resection and reconstruction is a contraindication to curative-intent resection is currently contested. Multiple series have been published with varying results[15, 17-21, 125, 137-141]. All series report outcomes in highly selected patients and are inadequately powered to offer evidence in favour of or against arterial resection. However the outcome of CCA resection with involvement of the hepatic artery is influenced by the performance status prior to surgery and the experience of the surgical centre[17, 21, 125, 138], This patient group would have a median survival of 3-6 months with palliative therapy[108]. Hepatic artery resection should be considered on a case-by-case basis in fit patients with arterial contact or invasion, and performed only in centres with significant experience.

Systemic chemotherapy

Patients with resected pCCA and iCCA have a high risk of cancer recurrence necessitating investigation of adjuvant therapies[108]. Systemic and locoregional therapies in the

neoadjuvant[142-144] and adjuvant setting[107, 145] have been explored, with increasing evidence in favour of adjuvant chemotherapy. However associated improvements in survival are modest, possibly related to the strong desmoplastic phenotype of CCA promoting chemotherapeutic resistance[146]. Molecular profiling may help stratify patients into treatment pathways[42, 51], however clinical trials are currently lacking and associated with specific challenges in their design and execution. The majority of randomised trials have investigated therapies for 'biliary tract cancers' with no grouping by anatomical location and have included patients with gallbladder cancers, iCCA, pCCA and dCCA in the same trial) significantly confounding the interpretation of results.

Neoadjuvant therapy

An objective radiological response to neoadjuvant therapy has been postulated to be a useful surrogate for tumour biology with a favourable response indicating less aggressive disease. However there have been no randomised studies comparing neoadjuvant therapy with upfront resection in patients with resectable CCA. Similarly there are no RCTs of downstaging with locally advanced and borderline resectable disease. Neoadjuvant therapy in patients with locally advanced disease may lead to successful downstaging, and facilitate liver resection with clear margins to improve outcome for patients with advanced disease. A meta-analysis of 1880 patients with CCA found that patients who underwent downstaging therapy followed by resection had superior survival compared to patients who did not[147]. However the study included retrospective cohort studies and case-control series, with significant selection bias and was therefore low-quality evidence of the benefit of downstaging.

Currently routine neoadjuvant therapy in patients with upfront resectable disease is not recommended[42]. A propensity-score matched analysis compared 299 patients who received neoadjuvant chemotherapy with 700 patients who received adjuvant chemotherapy for ICCA, and reported superior survival in the neoadjuvant group (40.3 months versus 32.8 months)[148]. However a multi-centre study reported no difference in survival when comparing neoadjuvant chemotherapy with upfront resection[149]. Patients in the neoadjuvant group who experience disease progression may have benefitted from upfront resection, posing an ethical challenge in not resecting such patients immediately. Therefore well-constructed prospective multi-centre randomised trials are required to determine the role of neoadjuvant therapy in resectable disease.

Adjuvant therapy for cholangiocarcinoma

Adjuvant therapy may improve outcomes for patients with resected pCCA and/or iCCA. The BCAT trial[41] randomised 225 patients with resected extrahepatic bile duct cancer (pCCA and dCCA) to adjuvant gemcitabine or observation, and reported no significant difference in survival. Similar negative findings were also reported in the PRODIGE 12-ACCORD 18-UNICANCER GI trial[150] comparing adjuvant gemcitabine and oxaliplatin with surveillance. However the BILCAP trial[107] compared adjuvant capecitabine therapy with observation in patients with resected biliary tract cancers (including dCCA and gallbladder cancer), and reported significantly better median overall survival in the capecitabine group on per protocol analysis (51.1 months versus 36.4 months). The authors concluded that adjuvant capecitabine should be considered standard of care, and adjuvant capecitabine is recommended in the UK following resection[42]. However there are multiple limitations to this trial, particularly with heterogeneity as it included patients with undergoing hemihepatectomy and pancreatoduodenectomy together. Future prospective studies should stratify by anatomical site and include placebo controls.

Immunotherapy

Immune-checkpoint inhibitors have recently demonstrated efficacy in improving oncological outcomes in patients with hepatocellular carcinoma in the adjuvant[151] and advanced settings[152]. Recently a South Korean phase 2 randomised control trial of 128 patients with advanced biliary tract cancer reported an objective response rate of 72% in patients treated with durvalumab (a PD-1 inhibitor) with gemcitabine and cisplatin chemotherapy[153]. At present, there are no published trials reporting on (neo)adjuvant immunotherapy in patients with resectable iCCA or pCCA. However the results of two phase 2 studies of neoadjuvant immunotherapy (NCT04308174 and NCT04506281) eagerly anticipated to assess whether immunotherapy improves outcomes in patients with resectable disease when delivered in the neoadjuvant setting.

Liver transplantation

Peri-hilar cholangiocarcinoma

Liver transplantation is a potential treatment for patients with unresectable CCA, either due to disease burden or associated cirrhosis, that is confined to the liver. Initial experience with pCCA was disappointing due to the high recurrence rate and low post-transplant survival[132, 154-156],in comparison to transplantation for other disease processes. However the general

outcome was still superior to the survival following palliative chemotherapy. The reported 5-year survival rates of 20-40% were significantly worse than those for hepatocellular carcinoma within Milan criteria[157], suggesting that refinement in patient selection may lead to improved outcomes. Seehofer reported 6 out 16 patients with CCA alive and recurrence free at 10 years post-transplantation[154], with 5 out of the 6 having negative lymph nodes on histopathology, suggesting that long-term survival may be achievable in selected patients.

The Mayo Clinic combined neoadjuvant chemoradiotherapy and liver transplantation, and reported 5-year survival of 82%, exceeding patients who underwent resection at the same institution (5-year survival 21%)[158]. The protocol involved external beam radiotherapy with 5-fluorouracil for chemosensitisation, followed by brachytherapy. Patients were listed if they had unresectable pCCA or pCCA with background primary sclerosing cholangitis and a solitary tumour less than 3cm in diameter. However the authors did not provide a definition for nonresectable disease, and patients enrolled in the transplant protocol may not be equivalent to the historical resection cohort introducing significant bias in the study. A subsequent multicentre series involving 12 US centres reported 5-year recurrence-free survival rate of 65% based on the Mayo Clinic protocol with 49% (60 patients) dying pre-transplant, highlighting the high waiting list mortality for such patients. Living organ donation may provide an alternative source of suitable liver grafts for selected patients. Because live donor transplant can proceed rapidly the risk of CCA progression and death during the waiting period for transplant is reduced.

It remains unclear what proportion of patients who underwent transplantation had *truly* unresectable disease with a solitary 3cm tumour[159], particularly in the context of excellent reported outcomes following extended hepatectomy[85, 92-94, 103, 134, 160] (with vascular resection if required). A retrospective series of 17 patients who underwent resection for a solitary 3cm peri-hilar tumour (similar to the transplant cohort) reported a 5-year overall survival rate of 82%, compared with 23% in resected patients with later stage tumours. This data questions the relevance of transplantation for pCCA[161]. The French TRANSPHIL trial (NCT02232932) is an ongoing randomised control trial comparing neoadjuvant chemoradiotherapy and liver transplantation with liver resection for pCCA, and may potentially indicate which treatment strategy is superior.

The importance of neoadjuvant therapy in patients with pCCA undergoing transplantation is unclear. An analysis of the European Liver Transplant Registry examined 28 patients who underwent liver transplantation and were within the Mayo Clinic protocol listing criteria but did not receive neoadjuvant therapy. The authors reported a 5-year overall survival rate of 59%, suggesting that patient selection may be more important than neoadjuvant therapy. However in the Mayo series, 16 out of 38 patients who were transplanted demonstrated a complete pathological response on explant histopathology[158], which is likely an indicator of effective neoadjuvant therapy but tissue confirmation was not obtained in all cases. A recent meta-analysis of 428 patients with pCCA undergoing liver transplantation identified better pooled survival in patients who completed neoadjuvant therapy[28]. Interpretation of this data is limited by significant heterogeneity between studies and imbalanced comparator groups. The International Liver Transplant Society Consensus[162] and the British Society of Gastroenterology guidelines[42] currently recommend neoadjuvant therapy in patients with unresectable early-stage pCCA undergoing liver transplantation.

Intrahepatic cholangiocarcinoma

Initial experiences with transplantation for iCCA were with patients misdiagnosed as having hepatocellular carcinoma pre-transplant, and subsequent explant pathology demonstrating iCCA. Patients with very early iCCA (≤2cm) and cirrhosis who underwent transplantation had good outcomes, with 65% 5-year survival in one retrospective multicentre series based on explant pathology in 29 patients initially thought to have hepatocellular carcinoma and cirrhosis[163]. A further series of 48 patients with iCCA diagnosed on explant also reported a 5-year survival rate of 65% in patients with very early iCCA. This sharply contrasts with the 5-year survival rate of less than 25% in an earlier series reporting outcomes following transplantation for unresectable iCCA[164]. Unfortunately the proportion of patients with very early iCCA and cirrhosis is very small, and prospective identification of patients likely to benefit from transplantation is challenging.

Liver transplantation for non-cirrhotic patients with unresectable iCCA has been reported in a prospective series[165]. Patients were treated with neoadjuvant chemotherapy, with 12 out of 21 patients demonstrating a sustained response to chemotherapy which was the criteria to list for transplantation. Six of the twelve patients received a liver graft, with 3 patients developing recurrence and 3-year survival reported at 80%. Neoadjuvant therapy and observation may aid selection of patients with favourable tumour biology, however non-cirrhotic patients who

are successfully converted to resectable pose a unique challenge. Such patients could feasibly undergo resection[166] which could be explored in a randomised study. Liver transplantation may offer better chance of cure given the greater likelihood of achieving a negative margin. Alternatively, a non-cirrhotic patient with resectable iCCA is likely to have a longer waiting time, risking disease progression and waiting list dropout. Such patients may also benefit from living donation if available.

Current guidelines recommend that patients with iCCA ≤2cm diameter with cirrhosis may benefit from upfront transplantation, whereas iCCA in a non-cirrhotic liver may be considered for transplantation if the disease remains stable following neoadjuvant therapy. Both indications are currently experimental, and prospective data is eagerly awaited to validate these approaches.

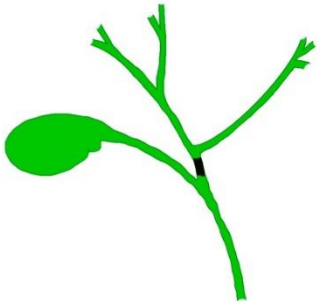
Future challenges

iCCA and pCCA remain devastating diseases with poor outcomes for the majority of patients. Multiple advances in recent years have improved our understanding of disease biology and perioperative management of patients to facilitate curative-intent liver resection. Close collaboration between hepatobiliary surgeons, radiologists, oncologists, and endoscopists is essential to optimise the outcomes. The modest impact of chemotherapy on improving long-term outcome demonstrates that surgical excision (and possibly transplantation in selected patients) remains the cornerstone of curative treatment, and future advances should focus on developing effective adjuvant and neoadjuvant therapies. Well-designed prospective randomised trials need to replace guidance and dogma based on poor quality retrospective cohorts.

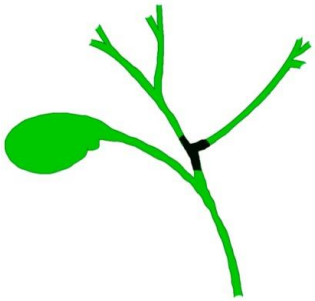
Figure legend

Figure 1 - Bismuth-Corlette system for classifying peri-hilar cholangiocarcinoma. Type I – distal to the confluence of the hepatic ducts; type II – at the confluence of the hepatic ducts; type IIIa – at the confluence of the hepatic ducts extending into the right hepatic duct; type IIIb – at the confluence of the hepatic ducts extending into the left hepatic duct; type IV – involving both the right and left ductal systems.

Figures



Type I



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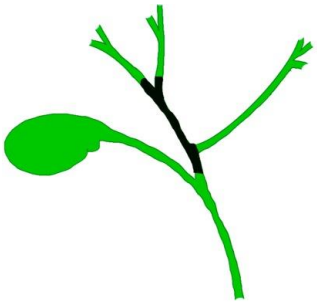
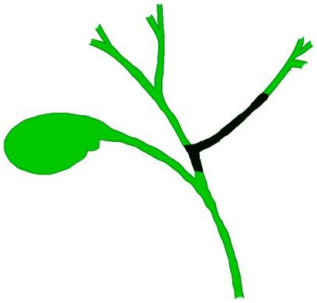
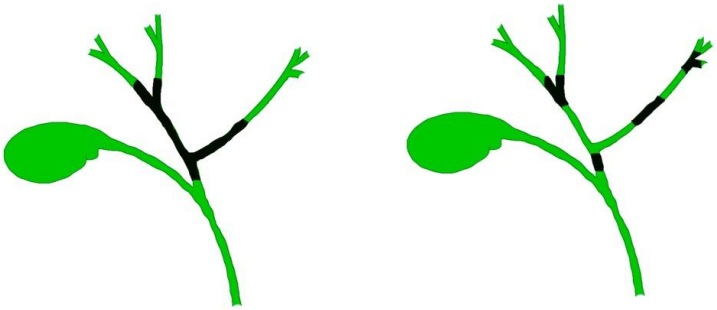


Type IIIa



Type IIIb



Type IV

Figure 1 – Bismuth-Corlette system for classifying peri-hilar cholangiocarcinoma. Type I – distal to the confluence of the hepatic ducts; type II – at the confluence of the hepatic ducts; type IIIa – at the confluence of the hepatic ducts extending into the right hepatic duct; type IIIb – at the confluence of the hepatic ducts extending into the left hepatic duct; type IV – involving both the right and left ductal systems.

References

1. Blechacz B, Komuta M, Roskams T, Gores GJ. Clinical diagnosis and staging of cholangiocarcinoma. Nat Rev Gastroenterol Hepatol. 2011;8(9):512-22.
2. Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma - evolving concepts and therapeutic strategies. Nat Rev Clin Oncol. 2018;15(2):95-111.
3. Brindley PJ, Bachini M, Ilyas SI, Khan SA, Loukas A, Sirica AE, et al. Cholangiocarcinoma. Nat Rev Dis Primers. 2021;7(1):65.
4. Li B, Li Z, Qiu Z, Qin Y, Gao Q, Ao J, et al. Surgical treatment of hilar cholangiocarcinoma: retrospective analysis. BJS Open. 2023;7(3).
5. Soares KC, Jarnagin WR. The Landmark Series: Hilar Cholangiocarcinoma. Ann Surg Oncol. 2021;28(8):4158-70.
6. Hobeika C, Cauchy F, Fuks D, Barbier L, Fabre JM, Boleslawski E, et al. Laparoscopic versus open resection of intrahepatic cholangiocarcinoma: nationwide analysis. Br J Surg. 2021;108(4):419-26.
7. Wang Y, Li J, Xia Y, Gong R, Wang K, Yan Z, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. J Clin Oncol. 2013;31(9):1188-95.
8. Ribero D, Pinna AD, Guglielmi A, Ponti A, Nuzzo G, Giulini SM, et al. Surgical Approach for Long-term Survival of Patients With Intrahepatic Cholangiocarcinoma: A Multi-institutional Analysis of 434 Patients. Arch Surg. 2012;147(12):1107-13.
9. Farges O, Fuks D, Boleslawski E, Le Treut YP, Castaing D, Laurent A, et al. Influence of surgical margins on outcome in patients with intrahepatic cholangiocarcinoma: a multicenter study by the AFC-IHCC-2009 study group. Ann Surg. 2011;254(5):824-29; discussion 30.
10. Izquierdo-Sanchez L, Lamarca A, La Casta A, Buettner S, Utpatel K, Klumpen HJ, et al. Cholangiocarcinoma landscape in Europe: Diagnostic, prognostic and therapeutic insights from the ENSCCA Registry. J Hepatol. 2022;76(5):1109-21.
11. van Keulen AM, Olthof PB, Cescon M, Guglielmi A, Jarnagin WR, Nadalin S, et al. Actual 10-Year Survival after Resection of Perihilar Cholangiocarcinoma: What Factors Preclude a Chance for Cure? Cancers (Basel). 2021;13(24).
12. Buettner S, Van Keulen AM, Erdmann J, Groot Koerkamp B, Olthof P. Actual 10-year Survival after Resection of Perihilar Cholangiocarcinoma: What Factors Preclude Cure? HPB (Oxford). 2021;23.
13. Si A, Li J, Xiang H, Zhang S, Bai S, Yang P, et al. Actual over 10-year survival after liver resection for patients with intrahepatic cholangiocarcinoma. Oncotarget. 2017;8(27):44521-32.
14. Mazzaferro V, Gorgen A, Roayaie S, Droz Dit Busset M, Sapisochin G. Liver resection and transplantation for intrahepatic cholangiocarcinoma. J Hepatol. 2020;72(2):364-77.
15. Li YM, Bie ZX, Guo RQ, Li B, Wang CE, Yan F. Effect of hepatic artery resection and reconstruction on the prognosis of patients with advanced hilar cholangiocarcinoma. World J Gastrointest Oncol. 2022;14(4):887-96.
16. Song Y, Zhang Y, Zhen Z, Huang Z. Effects of portal vein resection and hepatic artery resection on long-term survival in Klatskin tumor: a meta-analysis. World J Surg Oncol. 2022;20(1):230.
17. Sugiura T, Uesaka K, Okamura Y, Ito T, Yamamoto Y, Ashida R, et al. Major hepatectomy with combined vascular resection for perihilar cholangiocarcinoma. BJS Open. 2021;5(4).
18. Matsuyama R, Mori R, Ota Y, Homma Y, Kumamoto T, Takeda K, et al. Significance of Vascular Resection and Reconstruction in Surgery for Hilar Cholangiocarcinoma: With Special

Reference to Hepatic Arterial Resection and Reconstruction. Ann Surg Oncol. 2016;23(Suppl 4):475-84.
19. Miyazaki M, Kato A, Ito H, Kimura F, Shimizu H, Ohtsuka M, et al. Combined vascular resection in operative resection for hilar cholangiocarcinoma: does it work or not? Surgery. 2007;141(5):581-8.
20. Higuchi R, Yazawa T, Uemura S, Izumo W, Ota T, Kiyohara K, et al. Surgical Outcomes for Perihilar Cholangiocarcinoma with Vascular Invasion. J Gastrointest Surg. 2019;23(7):1443-53.
21. Nagino M, Nimura Y, Nishio H, Ebata T, Igami T, Matsushita M, et al. Hepatectomy with simultaneous resection of the portal vein and hepatic artery for advanced perihilar cholangiocarcinoma: an audit of 50 consecutive cases. Ann Surg. 2010;252(1):115-23.
22. Li J, Zhou MH, Ma WJ, Li FY, Deng YL. Extended lymphadenectomy in hilar cholangiocarcinoma: What it will bring? World J Gastroenterol. 2020;26(24):3318-25.
23. Ma WJ, Wu ZR, Hu HJ, Wang JK, Yin CH, Shi YJ, et al. Extended Lymphadenectomy Versus Regional Lymphadenectomy in Resectable Hilar Cholangiocarcinoma. J Gastrointest Surg. 2020;24(7):1619-29.
24. Sposito C, Droz Dit Busset M, Virdis M, Citterio D, Flores M, Bongini M, et al. The role of lymphadenectomy in the surgical treatment of intrahepatic cholangiocarcinoma: A review. Eur J Surg Oncol. 2022;48(1):150-9.
25. Sposito C, Ratti F, Cucchetti A, Ardito F, Ruzzenente A, Di Sandro S, et al. Survival benefit of adequate lymphadenectomy in patients undergoing liver resection for clinically node-negative intrahepatic cholangiocarcinoma. J Hepatol. 2023;78(2):356-63.
26. Breuer E, Mueller M, Doyle MB, Yang L, Darwish Murad S, Anwar IJ, et al. Liver Transplantation as a New Standard of Care in Patients With Perihilar Cholangiocarcinoma? Results From an International Benchmark Study. Ann Surg. 2022;276(5):846-53.
27. Acher AW, Weber SM, Pawlik TM. Liver transplantation for perihilar cholangiocarcinoma: patient selection and outcomes. Expert Rev Gastroenterol Hepatol. 2021;15(5):555-66.
28. Cambridge WA, Fairfield C, Powell JJ, Harrison EM, Soreide K, Wigmore SJ, et al. Meta-analysis and Meta-regression of Survival After Liver Transplantation for Unresectable Perihilar Cholangiocarcinoma. Ann Surg. 2021;273(2):240-50.
29. DeOliveira ML, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. Ann Surg. 2007;245(5):755-62.
30. Kudo M, Kitano M, Sakurai T, Nishida N. General Rules for the Clinical and Pathological Study of Primary Liver Cancer, Nationwide Follow-Up Survey and Clinical Practice Guidelines: The Outstanding Achievements of the Liver Cancer Study Group of Japan. Dig Dis. 2015;33(6):765-70.
31. Guedj N. Pathology of Cholangiocarcinomas. Curr Oncol. 2022;30(1):370-80.
32. Sakamoto E, Nimura Y, Hayakawa N, Kamiya J, Kondo S, Nagino M, et al. The pattern of infiltration at the proximal border of hilar bile duct carcinoma: a histologic analysis of 62 resected cases. Ann Surg. 1998;227(3):405-11.
33. Nakanuma Y, Kakuda Y. Pathologic classification of cholangiocarcinoma: New concepts. Best Pract Res Clin Gastroenterol. 2015;29(2):277-93.
34. Czauderna C, Kirstein MM, Tews HC, Vogel A, Marquardt JU. Molecular Subtypes and Precision Oncology in Intrahepatic Cholangiocarcinoma. J Clin Med. 2021;10(13).

35. Massard C, Michiels S, Ferte C, Le Deley MC, Lacroix L, Hollebecque A, et al. High-Throughput Genomics and Clinical Outcome in Hard-to-Treat Advanced Cancers: Results of the MOSCATO 01 Trial. Cancer Discov. 2017;7(6):586-95.
36. Verlingue L, Malka D, Allorant A, Massard C, Ferte C, Lacroix L, et al. Precision medicine for patients with advanced biliary tract cancers: An effective strategy within the prospective MOSCATO-01 trial. Eur J Cancer. 2017;87:122-30.
37. Tomczak A, Springfeld C, Dill MT, Chang DH, Kazdal D, Wagner U, et al. Precision oncology for intrahepatic cholangiocarcinoma in clinical practice. Br J Cancer. 2022;127(9):1701-8.
38. Locker GY, Hamilton S, Harris J, Jessup JM, Kemeny N, Macdonald JS, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol. 2006;24(33):5313-27.
39. Alvaro D, Bragazzi MC, Benedetti A, Fabris L, Fava G, Invernizzi P, et al. Cholangiocarcinoma in Italy: A national survey on clinical characteristics, diagnostic modalities and treatment. Results from the "Cholangiocarcinoma" committee of the Italian Association for the Study of Liver disease. Dig Liver Dis. 2011;43(1):60-5.
40. Ni Q, Wang H, Zhang Y, Qian L, Chi J, Liang X, et al. MDCT assessment of resectability in hilar cholangiocarcinoma. Abdom Radiol (NY). 2017;42(3):851-60.
41. Ebata T, Hirano S, Konishi M, Uesaka K, Tsuchiya Y, Ohtsuka M, et al. Randomized clinical trial of adjuvant gemcitabine chemotherapy versus observation in resected bile duct cancer. Br J Surg. 2018;105(3):192-202.
42. Rushbrook SM, Kendall TJ, Zen Y, Albazaz R, Manoharan P, Pereira SP, et al. British Society of Gastroenterology guidelines for the diagnosis and management of cholangiocarcinoma. Gut. 2023.
43. Rimola J, Forner A, Reig M, Vilana R, de Lope CR, Ayuso C, et al. Cholangiocarcinoma in cirrhosis: absence of contrast washout in delayed phases by magnetic resonance imaging avoids misdiagnosis of hepatocellular carcinoma. Hepatology. 2009;50(3):791-8.
44. Kim YY, Yeom SK, Shin H, Choi SH, Rhee H, Park JH, et al. Clinical Staging of Mass-Forming Intrahepatic Cholangiocarcinoma: Computed Tomography Versus Magnetic Resonance Imaging. Hepatol Commun. 2021;5(12):2009-18.
45. Jhaveri KS, Hosseini-Nik H. MRI of cholangiocarcinoma. J Magn Reson Imaging. 2015;42(5):1165-79.
46. Fabrega-Foster K, Ghasabeh MA, Pawlik TM, Kamel IR. Multimodality imaging of intrahepatic cholangiocarcinoma. Hepatobiliary Surg Nutr. 2017;6(2):67-78.
47. Ruys AT, van Beem BE, Engelbrecht MR, Bipat S, Stoker J, Van Gulik TM. Radiological staging in patients with hilar cholangiocarcinoma: a systematic review and meta-analysis. Br J Radiol. 2012;85(1017):1255-62.
48. King MJ, Hectors S, Lee KM, Omidele O, Babb JS, Schwartz M, et al. Outcomes assessment in intrahepatic cholangiocarcinoma using qualitative and quantitative imaging features. Cancer Imaging. 2020;20(1):43.
49. Chryssou E, Guthrie JA, Ward J, Robinson PJ. Hilar cholangiocarcinoma: MR correlation with surgical and histological findings. Clin Radiol. 2010;65(10):781-8.
50. Noji T, Kondo S, Hirano S, Tanaka E, Suzuki O, Shichinohe T. Computed tomography evaluation of regional lymph node metastases in patients with biliary cancer. Br J Surg. 2008;95(1):92-6.

51. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL-ILCA Clinical Practice Guidelines on the management of intrahepatic cholangiocarcinoma. J Hepatol. 2023;79(1):181-208.
52. Nagino M, Hirano S, Yoshitomi H, Aoki T, Uesaka K, Unno M, et al. Clinical practice guidelines for the management of biliary tract cancers 2019: The 3rd English edition. J Hepatobiliary Pancreat Sci. 2021;28(1):26-54.
53. Lamarca A, Barriuso J, Chander A, McNamara MG, Hubner RA, D OR, et al. (18)F-fluorodeoxyglucose positron emission tomography ((18)FDG-PET) for patients with biliary tract cancer: Systematic review and meta-analysis. J Hepatol. 2019;71(1):115-29.
54. Fong ZV, Brownlee SA, Qadan M, Tanabe KK. The Clinical Management of Cholangiocarcinoma in the United States and Europe: A Comprehensive and Evidence-Based Comparison of Guidelines. Ann Surg Oncol. 2021;28(5):2660-74.
55. Sethi R, Singh K, Warner B, Mahadeva U, Wilkinson M. The impact of brush cytology from endoscopic retrograde cholangiopancreatography (ERCP) on patient management at a UK teaching hospital. Frontline Gastroenterol. 2016;7(2):97-101.
56. Glasbrenner B, Ardan M, Boeck W, Preclik G, Moller P, Adler G. Prospective evaluation of brush cytology of biliary strictures during endoscopic retrograde cholangiopancreatography. Endoscopy. 1999;31(9):712-7.
57. Foutch PG, Kerr DM, Harlan JR, Kummet TD. A prospective, controlled analysis of endoscopic cytotechniques for diagnosis of malignant biliary strictures. Am J Gastroenterol. 1991;86(5):577-80.
58. Trikudanathan G, Navaneethan U, Njei B, Vargo JJ, Parsi MA. Diagnostic yield of bile duct brushings for cholangiocarcinoma in primary sclerosing cholangitis: a systematic review and meta-analysis. Gastrointest Endosc. 2014;79(5):783-9.
59. Chiang CH, Chen KC, Devereaux B, Chung CS, Kuo KC, Lin CC, et al. Precise mapping of hilar cholangiocarcinoma with a skip lesion by SpyGlass cholangioscopy: A case report. World J Gastrointest Surg. 2023;15(5):965-71.
60. Chen YK, Pleskow DK. SpyGlass single-operator peroral cholangiopancreatoscopy system for the diagnosis and therapy of bile-duct disorders: a clinical feasibility study (with video). Gastrointest Endosc. 2007;65(6):832-41.
61. Angsuwatcharakon P, Kulpatcharapong S, Moon JH, Ramchandani M, Lau J, Isayama H, et al. Consensus guidelines on the role of cholangioscopy to diagnose indeterminate biliary stricture. HPB (Oxford). 2022;24(1):17-29.
62. Kulpatcharapong S, Pittayanon R, Kerr SJ, Rerknimitr R. Diagnostic performance of digital and video cholangioscopes in patients with suspected malignant biliary strictures: a systematic review and meta-analysis. Surg Endosc. 2022;36(5):2827-41.
63. de Oliveira P, de Moura DTH, Ribeiro IB, Bazarbashi AN, Franzini TAP, Dos Santos MEL, et al. Efficacy of digital single-operator cholangioscopy in the visual interpretation of indeterminate biliary strictures: a systematic review and meta-analysis. Surg Endosc. 2020;34(8):3321-9.
64. Gerges C, Beyna T, Tang RSY, Bahin F, Lau JYW, van Geenen E, et al. Digital single-operator peroral cholangioscopy-guided biopsy sampling versus ERCP-guided brushing for indeterminate biliary strictures: a prospective, randomized, multicenter trial (with video). Gastrointest Endosc. 2020;91(5):1105-13.
65. Coelen RJ, Ruys AT, Besselink MG, Busch OR, van Gulik TM. Diagnostic accuracy of staging laparoscopy for detecting metastasized or locally advanced perihilar

cholangiocarcinoma: a systematic review and meta-analysis. Surg Endosc. 2016;30(10):4163-73.
66. Tian Y, Liu L, Yeolkar NV, Shen F, Li J, He Z. Diagnostic role of staging laparoscopy in a subset of biliary cancers: a meta-analysis. ANZ J Surg. 2017;87(1-2):22-7.
67. Weber SM, Ribero D, O'Reilly EM, Kokudo N, Miyazaki M, Pawlik TM. Intrahepatic cholangiocarcinoma: expert consensus statement. HPB (Oxford). 2015;17(8):669-80.
68. Corvera CU, Weber SM, Jarnagin WR. Role of laparoscopy in the evaluation of biliary tract cancer. Surg Oncol Clin N Am. 2002;11(4):877-91.
69. D'Angelica M, Fong Y, Weber S, Gonen M, DeMatteo RP, Conlon K, et al. The role of staging laparoscopy in hepatobiliary malignancy: prospective analysis of 401 cases. Ann Surg Oncol. 2003;10(2):183-9.
70. Bird N, Elmasry M, Jones R, Elniel M, Kelly M, Palmer D, et al. Role of staging laparoscopy in the stratification of patients with perihilar cholangiocarcinoma. Br J Surg. 2017;104(4):418-25.
71. Davidson JTt, Jin LX, Krasnick B, Ethun CG, Pawlik TM, Poultsides GA, et al. Staging laparoscopy among three subtypes of extra-hepatic biliary malignancy: a 15-year experience from 10 institutions. J Surg Oncol. 2019;119(3):288-94.
72. Ruys AT, Busch OR, Gouma DJ, van Gulik TM. Staging laparoscopy for hilar cholangiocarcinoma: is it still worthwhile? Ann Surg Oncol. 2011;18(9):2647-53.
73. Paik WH, Loganathan N, Hwang JH. Preoperative biliary drainage in hilar cholangiocarcinoma: When and how? World J Gastrointest Endosc. 2014;6(3):68-73.
74. Inamdar S, Slattery E, Bhalla R, Sejpal DV, Trindade AJ. Comparison of Adverse Events for Endoscopic vs Percutaneous Biliary Drainage in the Treatment of Malignant Biliary Tract Obstruction in an Inpatient National Cohort. JAMA Oncol. 2016;2(1):112-7.
75. Kloek JJ, van der Gaag NA, Aziz Y, Rauws EA, van Delden OM, Lameris JS, et al. Endoscopic and percutaneous preoperative biliary drainage in patients with suspected hilar cholangiocarcinoma. J Gastrointest Surg. 2010;14(1):119-25.
76. Cherqui D, Benoist S, Malassagne B, Humeres R, Rodriguez V, Fagniez PL. Major liver resection for carcinoma in jaundiced patients without preoperative biliary drainage. Arch Surg. 2000;135(3):302-8.
77. Rassam F, Roos E, van Lienden KP, van Hooft JE, Klumpen HJ, van Tienhoven G, et al. Modern work-up and extended resection in perihilar cholangiocarcinoma: the AMC experience. Langenbecks Arch Surg. 2018;403(3):289-307.
78. Celotti A, Solaini L, Montori G, Coccolini F, Tognali D, Baiocchi G. Preoperative biliary drainage in hilar cholangiocarcinoma: Systematic review and meta-analysis. Eur J Surg Oncol. 2017;43(9):1628-35.
79. Wiggers JK, Rauws EA, Gouma DJ, van Gulik TM. Preoperative Endoscopic Nasobiliary Drainage in Patients With Suspected Hilar Cholangiocarcinoma; Better Than Endoscopic or Percutaneous Biliary Drainage? Ann Surg. 2015;262(2):e55.
80. Lidsky ME, Jarnagin WR. Surgical management of hilar cholangiocarcinoma at Memorial Sloan Kettering Cancer Center. Ann Gastroenterol Surg. 2018;2(4):304-12.
81. Coelen RJS, Roos E, Wiggers JK, Besselink MG, Buis CI, Busch ORC, et al. Endoscopic versus percutaneous biliary drainage in patients with resectable perihilar cholangiocarcinoma: a multicentre, randomised controlled trial. Lancet Gastroenterol Hepatol. 2018;3(10):681-90.

82. Kawakubo K, Kawakami H, Kuwatani M, Haba S, Kudo T, Taya YA, et al. Lower incidence of complications in endoscopic nasobiliary drainage for hilar cholangiocarcinoma. World J Gastrointest Endosc. 2016;8(9):385-90.
83. Kawashima H, Itoh A, Ohno E, Itoh Y, Ebata T, Nagino M, et al. Preoperative endoscopic nasobiliary drainage in 164 consecutive patients with suspected perihilar cholangiocarcinoma: a retrospective study of efficacy and risk factors related to complications. Ann Surg. 2013;257(1):121-7.
84. Kaido T, Yoshikawa A, Seto S, Yamaoka S, Sato M, Ishii T, et al. Hepatocyte growth factor supply accelerates compensatory hypertrophy caused by portal branch ligation in normal and jaundiced rats. J Surg Res. 1999;85(1):115-9.
85. Miyagawa S, Makuuchi M, Kawasaki S. Outcome of extended right hepatectomy after biliary drainage in hilar bile duct cancer. Arch Surg. 1995;130(7):759-63.
86. Yokoyama Y, Nagino M, Nimura Y. Mechanism of impaired hepatic regeneration in cholestatic liver. J Hepatobiliary Pancreat Surg. 2007;14(2):159-66.
87. Olthof PB, Wiggers JK, Groot Koerkamp B, Coelen RJ, Allen PJ, Besselink MG, et al. Postoperative Liver Failure Risk Score: Identifying Patients with Resectable Perihilar Cholangiocarcinoma Who Can Benefit from Portal Vein Embolization. J Am Coll Surg. 2017;225(3):387-94.
88. Yokoyama Y, Ebata T, Igami T, Sugawara G, Mizuno T, Yamaguchi J, et al. The Predictive Value of Indocyanine Green Clearance in Future Liver Remnant for Posthepatectomy Liver Failure Following Hepatectomy with Extrahepatic Bile Duct Resection. World J Surg. 2016;40(6):1440-7.
89. Ribero D, Zimmitti G, Aloia TA, Shindoh J, Fabio F, Amisano M, et al. Preoperative Cholangitis and Future Liver Remnant Volume Determine the Risk of Liver Failure in Patients Undergoing Resection for Hilar Cholangiocarcinoma. J Am Coll Surg. 2016;223(1):87-97.
90. Dixon M, Cruz J, Sarwani N, Gusani N. The Future Liver Remnant : Definition, Evaluation, and Management. Am Surg. 2021;87(2):276-86.
91. Madoff DC, Abdalla EK, Vauthey JN. Portal vein embolization in preparation for major hepatic resection: evolution of a new standard of care. J Vasc Interv Radiol. 2005;16(6):779-90.
92. Seyama Y, Kubota K, Sano K, Noie T, Takayama T, Kosuge T, et al. Long-term outcome of extended hemihepatectomy for hilar bile duct cancer with no mortality and high survival rate. Ann Surg. 2003;238(1):73-83.
93. Kawasaki S, Imamura H, Kobayashi A, Noike T, Miwa S, Miyagawa S. Results of surgical resection for patients with hilar bile duct cancer: application of extended hepatectomy after biliary drainage and hemihepatic portal vein embolization. Ann Surg. 2003;238(1):84-92.
94. Sano T, Shimada K, Sakamoto Y, Yamamoto J, Yamasaki S, Kosuge T. One hundred two consecutive hepatobiliary resections for perihilar cholangiocarcinoma with zero mortality. Ann Surg. 2006;244(2):240-7.
95. 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(1):129-40.
96. Franken LC, Rassam F, van Lienden KP, Bennink RJ, Besselink MG, Busch OR, et al. Effect of structured use of preoperative portal vein embolization on outcomes after liver resection of perihilar cholangiocarcinoma. BJS Open. 2020;4(3):449-55.

97. Olthof PB, Aldrighetti L, Alikhanov R, Cescon M, Groot Koerkamp B, Jarnagin WR, et al. Portal Vein Embolization is Associated with Reduced Liver Failure and Mortality in High-Risk Resections for Perihilar Cholangiocarcinoma. Ann Surg Oncol. 2020;27(7):2311-8.
98. Guiu B, Quenet F, Escal L, Bibeau F, Piron L, Rouanet P, et al. Extended liver venous deprivation before major hepatectomy induces marked and very rapid increase in future liver remnant function. Eur Radiol. 2017;27(8):3343-52.
99. Schnitzbauer AA, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg. 2012;255(3):405-14.
100. Olthof PB, Coelen RJS, Wiggers JK, Groot Koerkamp B, Malago M, Hernandez-Alejandro R, et al. High mortality after ALPPS for perihilar cholangiocarcinoma: case-control analysis including the first series from the international ALPPS registry. HPB (Oxford). 2017;19(5):381-7.
101. Heil J, Korenblik R, Heid F, Bechstein WO, Bemelmans M, Binkert C, et al. Preoperative portal vein or portal and hepatic vein embolization: DRAGON collaborative group analysis. Br J Surg. 2021;108(7):834-42.
102. Korenblik R, Olij B, Aldrighetti LA, Hilal MA, Ahle M, Arslan B, et al. Dragon 1 Protocol Manuscript: Training, Accreditation, Implementation and Safety Evaluation of Portal and Hepatic Vein Embolization (PVE/HVE) to Accelerate Future Liver Remnant (FLR) Hypertrophy. Cardiovasc Intervent Radiol. 2022;45(9):1391-8.
103. Nagino M, Kamiya J, Nishio H, Ebata T, Arai T, Nimura Y. Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer: surgical outcome and long-term follow-up. Ann Surg. 2006;243(3):364-72.
104. Ebata T, Nagino M, Kamiya J, Uesaka K, Nagasaka T, Nimura Y. Hepatectomy with portal vein resection for hilar cholangiocarcinoma: audit of 52 consecutive cases. Ann Surg. 2003;238(5):720-7.
105. Alikhanov R, Dudareva A, Trigo MA, Serrablo A. Vascular Resection for Intrahepatic Cholangiocarcinoma: Current Considerations. J Clin Med. 2021;10(17).
106. Cillo U, Fondevila C, Donadon M, Gringeri E, Mocchegiani F, Schlitt HJ, et al. Surgery for cholangiocarcinoma. Liver Int. 2019;39 Suppl 1(Suppl Suppl 1):143-55.
107. Primrose JN, Fox RP, Palmer DH, Malik HZ, Prasad R, Mirza D, et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. Lancet Oncol. 2019;20(5):663-73.
108. Banales JM, Marin JJG, Lamarca A, Rodrigues PM, Khan SA, Roberts LR, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol. 2020;17(9):557-88.
109. Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol. 2020;21(5):671-84.
110. Brown ZJ, Patwardhan S, Bean J, Pawlik TM. Molecular diagnostics and biomarkers in cholangiocarcinoma. Surg Oncol. 2022;44:101851.
111. Lamarca A, Santos-Laso A, Utpatel K, La Casta A, Stock S, Forner A, et al. Liver Metastases of Intrahepatic Cholangiocarcinoma: Implications for an Updated Staging System. Hepatology. 2021;73(6):2311-25.

112. de Jong MC, Nathan H, Sotiropoulos GC, Paul A, Alexandrescu S, Marques H, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. J Clin Oncol. 2011;29(23):3140-5.
113. Hu H, Xu G, Du S, Luo Z, Zhao H, Cai J. The role of lymph node dissection in intrahepatic cholangiocarcinoma: a multicenter retrospective study. BMC Surg. 2021;21(1):359.
114. Koerkamp BG, Clavien PA, Polak WG. Surgical resection for intrahepatic cholangiocarcinoma - can we really improve survival by resecting more lymph nodes? J Hepatol. 2023;78(2):235-7.
115. AJCC Cancer Staging Manual. 8th ed: Springer; 2017.
116. Zhou R, Lu D, Li W, Tan W, Zhu S, Chen X, et al. Is lymph node dissection necessary for resectable intrahepatic cholangiocarcinoma? A systematic review and meta-analysis. HPB (Oxford). 2019;21(7):784-92.
117. Cheng Q, Feng F, Zhu L, Zheng Y, Luo X, Liu C, et al. Circulating miR-106a is a Novel Prognostic and Lymph Node Metastasis Indicator for Cholangiocarcinoma. Sci Rep. 2015;5:16103.
118. Kitagawa Y, Nagino M, Kamiya J, Uesaka K, Sano T, Yamamoto H, et al. Lymph node metastasis from hilar cholangiocarcinoma: audit of 110 patients who underwent regional and paraaortic node dissection. Ann Surg. 2001;233(3):385-92.
119. Hakeem AR, Marangoni G, Chapman SJ, Young RS, Nair A, Hidalgo EL, et al. Does the extent of lymphadenectomy, number of lymph nodes, positive lymph node ratio and neutrophil-lymphocyte ratio impact surgical outcome of perihilar cholangiocarcinoma? Eur J Gastroenterol Hepatol. 2014;26(9):1047-54.
120. Aoba T, Ebata T, Yokoyama Y, Igami T, Sugawara G, Takahashi Y, et al. Assessment of nodal status for perihilar cholangiocarcinoma: location, number, or ratio of involved nodes. Ann Surg. 2013;257(4):718-25.
121. Murakami Y, Uemura K, Sudo T, Hashimoto Y, Nakashima A, Kondo N, et al. Is para-aortic lymph node metastasis a contraindication for radical resection in biliary carcinoma? World J Surg. 2011;35(5):1085-93.
122. Kim DH, Choi DW, Choi SH, Heo JS, Kow AW. Is there a role for systematic hepatic pedicle lymphadenectomy in intrahepatic cholangiocarcinoma? A review of 17 years of experience in a tertiary institution. Surgery. 2015;157(4):666-75.
123. Bagante F, Spolverato G, Weiss M, Alexandrescu S, Marques HP, Aldrighetti L, et al. Surgical Management of Intrahepatic Cholangiocarcinoma in Patients with Cirrhosis: Impact of Lymphadenectomy on Peri-Operative Outcomes. World J Surg. 2018;42(8):2551-60.
124. He M, Xu X, Feng H, Chen W, Liu H, Zhang Y, et al. Regional lymphadenectomy vs. extended lymphadenectomy for hilar cholangiocarcinoma (Relay-HC trial): study protocol for a prospective, multicenter, randomized controlled trial. Trials. 2019;20(1):528.
125. Sugiura T, Okamura Y, Ito T, Yamamoto Y, Ashida R, Ohgi K, et al. Left Hepatectomy with Combined Resection and Reconstruction of Right Hepatic Artery for Bismuth Type I and II Perihilar Cholangiocarcinoma. World J Surg. 2019;43(3):894-901.
126. Cannon RM, Brock G, Buell JF. Surgical resection for hilar cholangiocarcinoma: experience improves resectability. HPB (Oxford). 2012;14(2):142-9.
127. Cho MS, Kim SH, Park SW, Lim JH, Choi GH, Park JS, et al. Surgical outcomes and predicting factors of curative resection in patients with hilar cholangiocarcinoma: 10-year single-institution experience. J Gastrointest Surg. 2012;16(9):1672-9.

128. Song SC, Choi DW, Kow AW, Choi SH, Heo JS, Kim WS, et al. Surgical outcomes of 230 resected hilar cholangiocarcinoma in a single centre. ANZ J Surg. 2013;83(4):268-74.
129. Kow AW, Wook CD, Song SC, Kim WS, Kim MJ, Park HJ, et al. Role of caudate lobectomy in type III A and III B hilar cholangiocarcinoma: a 15-year experience in a tertiary institution. World J Surg. 2012;36(5):1112-21.
130. Bhutiani N, Scoggins CR, McMasters KM, Ethun CG, Poultsides GA, Pawlik TM, et al. The impact of caudate lobe resection on margin status and outcomes in patients with hilar cholangiocarcinoma: a multi-institutional analysis from the US Extrahepatic Biliary Malignancy Consortium. Surgery. 2018;163(4):726-31.
131. Yang M, Li WW, Chen JH, Cui MH, Liu JL. The value of caudate lobectomy in hilar cholangiocarcinoma treatment: A meta-analysis. Medicine (Baltimore). 2021;100(7):e24727.
132. Neuhaus P, Jonas S, Bechstein WO, Lohmann R, Radke C, Kling N, et al. Extended resections for hilar cholangiocarcinoma. Ann Surg. 1999;230(6):808-18; discussion 19.
133. Benzing C, Krenzien F, Mieg A, Wolfsberger A, Andreou A, Nevermann N, et al. A tailored approach in lymph node-positive perihilar cholangiocarcinoma. Langenbecks Arch Surg. 2021;406(5):1499-509.
134. Molina V, Sampson J, Ferrer J, Diaz A, Ayuso JR, Sanchez-Cabus S, et al. Surgical treatment of perihilar cholangiocarcinoma: early results of en bloc portal vein resection. Langenbecks Arch Surg. 2017;402(1):95-104.
135. Neuhaus P, Thelen A, Jonas S, Puhl G, Denecke T, Veltzke-Schlieker W, et al. Oncological superiority of hilar en bloc resection for the treatment of hilar cholangiocarcinoma. Ann Surg Oncol. 2012;19(5):1602-8.
136. Nagino M, Clavien PA. Demise of "Hilar En Bloc Resection by No-touch Technique" as Surgery for Perihilar Cholangiocarcinoma: Dissociation Between Theory and Practice. Ann Surg. 2021;274(5):e385-e7.
137. Wang ST, Shen SL, Peng BG, Hua YP, Chen B, Kuang M, et al. Combined vascular resection and analysis of prognostic factors for hilar cholangiocarcinoma. Hepatobiliary Pancreat Dis Int. 2015;14(6):626-32.
138. Mizuno T, Ebata T, Yokoyama Y, Igami T, Yamaguchi J, Onoe S, et al. Combined Vascular Resection for Locally Advanced Perihilar Cholangiocarcinoma. Ann Surg. 2022;275(2):382-90.
139. Hu HJ, Jin YW, Zhou RX, Shrestha A, Ma WJ, Yang Q, et al. Hepatic Artery Resection for Bismuth Type III and IV Hilar Cholangiocarcinoma: Is Reconstruction Always Required? J Gastrointest Surg. 2018;22(7):1204-12.
140. Schimizzi GV, Jin LX, Davidson JTt, Krasnick BA, Ethun CG, Pawlik TM, et al. Outcomes after vascular resection during curative-intent resection for hilar cholangiocarcinoma: a multi-institution study from the US extrahepatic biliary malignancy consortium. HPB (Oxford). 2018;20(4):332-9.
141. Igami T, Nishio H, Ebata T, Yokoyama Y, Sugawara G, Nimura Y, et al. Surgical treatment of hilar cholangiocarcinoma in the "new era": the Nagoya University experience. J Hepatobiliary Pancreat Sci. 2010;17(4):449-54.
142. Le Roy B, Gelli M, Pittau G, Allard MA, Pereira B, Serji B, et al. Neoadjuvant chemotherapy for initially unresectable intrahepatic cholangiocarcinoma. Br J Surg. 2018;105(7):839-47.
143. Sutton TL, Billingsley KG, Walker BS, Enestvedt CK, Dewey EN, Orloff SL, et al. Neoadjuvant chemotherapy is associated with improved survival in patients undergoing hepatic resection for intrahepatic cholangiocarcinoma. Am J Surg. 2021;221(6):1182-7.

144. Riby D, Mazzotta AD, Bergeat D, Verdure L, Sulpice L, Bourien H, et al. Downstaging with Radioembolization or Chemotherapy for Initially Unresectable Intrahepatic Cholangiocarcinoma. Ann Surg Oncol. 2020;27(10):3729-37.
145. Shroff RT, Kennedy EB, Bachini M, Bekaii-Saab T, Crane C, Edeline J, et al. Adjuvant Therapy for Resected Biliary Tract Cancer: ASCO Clinical Practice Guideline. J Clin Oncol. 2019;37(12):1015-27.
146. Fabris L, Perugorria MJ, Mertens J, Bjorkstrom NK, Cramer T, Lleo A, et al. The tumour microenvironment and immune milieu of cholangiocarcinoma. Liver Int. 2019;39 Suppl 1:63-78.
147. Kamarajah S, Giovinazzo F, Roberts KJ, Punia P, Sutcliffe RP, Marudanayagam R, et al. The role of down staging treatment in the management of locally advanced intrahepatic cholangiocarcinoma: Review of literature and pooled analysis. Ann Hepatobiliary Pancreat Surg. 2020;24(1):6-16.
148. Yadav S, Xie H, Bin-Riaz I, Sharma P, Durani U, Goyal G, et al. Neoadjuvant vs. adjuvant chemotherapy for cholangiocarcinoma: A propensity score matched analysis. Eur J Surg Oncol. 2019;45(8):1432-8.
149. Buettner S, Koerkamp BG, Ejaz A, Buisman FE, Kim Y, Margonis GA, et al. The effect of preoperative chemotherapy treatment in surgically treated intrahepatic cholangiocarcinoma patients-A multi-institutional analysis. J Surg Oncol. 2017;115(3):312-8.
150. Edeline J, Benabdelghani M, Bertaut A, Watelet J, Hammel P, Joly JP, et al. Gemcitabine and Oxaliplatin Chemotherapy or Surveillance in Resected Biliary Tract Cancer (PRODIGE 12-ACCORD 18-UNICANCER GI): A Randomized Phase III Study. J Clin Oncol. 2019;37(8):658-67.
151. Qin S, Chen M, Cheng AL, Kaseb AO, Kudo M, Lee HC, et al. Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial. Lancet. 2023;402(10415):1835-47.
152. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020;382(20):1894-905.
153. Oh DY, Lee KH, Lee DW, Yoon J, Kim TY, Bang JH, et al. Gemcitabine and cisplatin plus durvalumab with or without tremelimumab in chemotherapy-naive patients with advanced biliary tract cancer: an open-label, single-centre, phase 2 study. Lancet Gastroenterol Hepatol. 2022;7(6):522-32.
154. Seehofer D, Thelen A, Neumann UP, Veltzke-Schlieker W, Denecke T, Kamphues C, et al. Extended bile duct resection and [corrected] liver and transplantation in patients with hilar cholangiocarcinoma: long-term results. Liver Transpl. 2009;15(11):1499-507.
155. Robles R, Figueras J, Turrion VS, Margarit C, Moya A, Varo E, et al. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. Ann Surg. 2004;239(2):265-71.
156. Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. Transplantation. 2000;69(8):1633-7.
157. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334(11):693-9.

158. Rea DJ, Heimbach JK, Rosen CB, Haddock MG, Alberts SR, Kremers WK, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. Ann Surg. 2005;242(3):451-8; discussion 8-61.
159. Nagino M. Surgical Treatment of Perihilar Cholangiocarcinoma: Resection or Transplant? Ann Surg. 2018;267(5):806-7.
160. Chebaro A, Buc E, Durin T, Chiche L, Brustia R, Didier A, et al. Liver Venous Deprivation or Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy?: A Retrospective Multicentric Study. Ann Surg. 2021;274(5):874-80.
161. Stremitzer S, Jones RP, Quinn LM, Fenwick SW, Diaz-Nieto R, Poston GJ, et al. Clinical outcome after resection of early-stage hilar cholangiocarcinoma. Eur J Surg Oncol. 2019;45(2):213-7.
162. Sapisochin G, Javle M, Lerut J, Ohtsuka M, Ghobrial M, Hibi T, et al. Liver Transplantation for Cholangiocarcinoma and Mixed Hepatocellular Cholangiocarcinoma: Working Group Report From the ILTS Transplant Oncology Consensus Conference. Transplantation. 2020;104(6):1125-30.
163. Sapisochin G, Rodriguez de Lope C, Gastaca M, Ortiz de Urbina J, Suarez MA, Santoyo J, et al. "Very early" intrahepatic cholangiocarcinoma in cirrhotic patients: should liver transplantation be reconsidered in these patients? Am J Transplant. 2014;14(3):660-7.
164. Pichlmayr R, Weimann A, Oldhafer KJ, Schlitt HJ, Klempnauer J, Bornscheuer A, et al. Role of liver transplantation in the treatment of unresectable liver cancer. World J Surg. 1995;19(6):807-13.
165. Lunsford KE, Javle M, Heyne K, Shroff RT, Abdel-Wahab R, Gupta N, et al. Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series. Lancet Gastroenterol Hepatol. 2018;3(5):337-48.
166. Rayar M, Sulpice L, Edeline J, Garin E, Levi Sandri GB, Meunier B, et al. Intra-arterial yttrium-90 radioembolization combined with systemic chemotherapy is a promising method for downstaging unresectable huge intrahepatic cholangiocarcinoma to surgical treatment. Ann Surg Oncol. 2015;22(9):3102-8.