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REVIEW

Moving forward in the treatment of cholangiocarcinoma

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Abstract

Despite being the second most frequent primary liver tumor in humans, early diagnosis and treatment of cholangiocarcinoma (CCA) are still unsatisfactory. In fact, survival after 5 years is expected in less than one fourth of patients diagnosed with this disease. Rare incidence, late appearance of symptoms and heterogeneous biology are all factors contributing to our limited knowledge of this cancer and determining its poor prognosis in the clinical setting. Several efforts have been made in the last decades in order to achieve an improved classification/understanding with regard to the diverse CCA forms. Location within the biliary tree has helped to distinguish between intrahepatic, perihilar and distal CCA types. Sequence analysis contributed to identifying several characteristic genetic aberrations in CCA that may also serve as possible targets for therapy. Novel findings are expected to significantly improve the management of this malignancy in the near future. In this changing scenario our review focuses on the current and future strategies for CCA treatment. Both systemic and surgical treatments are discussed in detail. The results of the main studies in this field are reported, together with the ongoing trials. The current findings suggest that an integrated multidisciplinary approach to this malignancy would be helpful to improve its outcome.

Key Words: Cholangiocarcinoma; Treatment; Genetic aberration; Immunotherapy; Liver resection; Liver transplantation

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Core Tip: Cholangiocarcinoma is a lethal malignancy characterized by a poor survival. In this review we discuss in detail the actual treatment and the future therapeutic perspectives for this cancer. Systemic and surgical strategies are reported with the corresponding results. Improved knowledge of this malignancy and a multidisciplinary therapeutic approach are likely to improve the cholangiocarcinoma outcome in the future.

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INTRODUCTION

Cholangiocarcinoma (CCA) is a primary malignancy of the biliary system and represents the second most common primary hepatic malignancy after hepatocellular carcinoma (HCC), constituting around 15% of primary liver tumors and 3% of gastrointestinal malignancies[1,2]. It is a rare tumor with a global incidence of 0.3-6 per 100000 inhabitants per year, displaying an increasing trend in the last decades[1]. However, in some Asian countries, such as Thailand, Cambodia and Laos, rates can be as high as 85 per 100000 due to infection with liver flukes[2].

Distinction into subgroups of CCA is anatomical: intrahepatic CCA (iCCA) arises in the liver above the second order bile ducts; perihilar CCA (pCCA), also known as Klatskin tumor, arises in the first order or main bile duct above the junction with the cystic duct; and distal CCA (dCCA) originates distally to the cystic duct (Figure 1). This classification is crucial as each subtype has distinct clinical characteristics and therapeutic strategies. pCCA accounts for the majority of diagnoses (50%-60%), with dCCA (20%-30%) and iCCA (10-20%) being less frequent[3]. iCCA can be further classified on the basis of the cells of origin as large and small duct types, with chronic biliary inflammation and chronic hepatis as risk factors, respectively[4]. On top of this, a recent interesting study involved the epigenomic and transcriptomic analysis of CCAs from 10 different countries in order to further understand and classify the genetic basis of CCA. The authors performed the analysis on CCA samples associated with liver flukes (mainly *Opisthorchis viverrine* and *Clonorchis sinensis*) and non-fluke cases. Four CCA clusters were likely driven by distinct etiologies, with separate genetic, epigenetic and clinical features found, highlighting how distinct cancer subtypes in the same organ may arise through different carcinogenic pathways[5].

Unfortunately, symptoms often appear when the disease is already advanced, resulting in a poor prognosis. In fact, this malignancy has an overall survival rate at 5 years of 5%-20%[1,3]. Nonetheless, many promising new approaches are currently under investigation.

Several issues have been encountered in the pursuit of a curative treatment for CCA in humans. Despite the evidence of different biological and epidemiological risk factors and genetic aberrations between diverse types of CCAs, these tumors are still frequently pooled together (also with gallbladder cancer) or misclassified in studies focusing on natural history or treatment[6,7]. On the other hand, histological classification (in particular for iCCA forms) remains suboptimal and also relies on heterogeneous genetic aberrations identified in this cancer[2]. The difficulties in CCA classification and in the comprehension of its biology therefore affect both clinical and basic research in this field. For instance, despite next generation models now attempting the construction of complex 3D CCA systems in culture (such as organoids or spheroids), an adequate reproduction of this tumor remains difficult in the preclinical experimental setting[8].

From the clinical side, CCA symptoms are generally not specific and share similarities with inflammatory diseases of the biliary tract. Moreover, general biomarkers used in medical practice, such as carbohydrate antigen 19-9 exhibit a sensitivity and specificity lower than 70%, underscoring the importance of the identification of possible novel genomic or proteomic biomarkers[9]. Also the appropriate surveillance of CCA-predisposing conditions, such as primary sclerosing cholangitis,

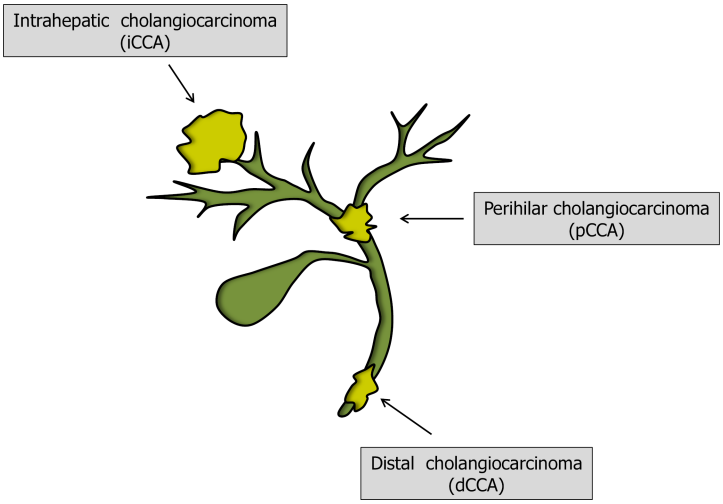

Figure 1 The anatomical location of intrahepatic, perihilar and distal cholangiocarcinoma is depicted.

remains undefined, leading to disappointing late-stage tumor identification in the majority of patients[10].

Furthermore, CCA remains an infrequent cancer in the majority of countries, several cases arise in the absence of recognized risk factors, and when some intraductal papillary or tubular forms are excluded[11], there is usually a short-term poor prognosis. Due to all of the above, clinical investigations and trials remain complicated and of partial impact. Framed in this perspective, this paper summarizes and critically reviews existing therapeutic strategies (both drug-based and surgical) for CCA and provides an overview of future perspectives in the treatment of this malignancy.

CCA PHARMACOLOGICAL TREATMENT: THE PRESENT

As described in detail in the dedicated paragraphs, the opportunity for a complete CCA cure should be offered in rare cases just employing surgical techniques. On the other hand, despite the fact that current drug therapy for this cancer is unsatisfactory, the pharmacological approach may present a larger margin of improvement in the future in comparison with operative methods.

Palliative treatments

At present, in subjects with unresectable, advanced disease, the best option is represented by cisplatin/gemcitabine first-line treatment. Confirmation of the utility of this treatment was obtained by a large study comparing this association with gemcitabine alone[12]. Two-hundred and four patients affected by biliary tumor (nearly one third with gallbladder cancer) treated with the gemcitabine/cisplatin regimen had an increased tumor response (81.4% *vs* 71.8%, $P = 0.049$) and median survival (11.7 *vs* 8.1 mo, $P < 0.001$) in comparison with a similar group treated with gemcitabine alone. In the absence of an adequate second-line treatment, a recent Phase 3, open-label, randomized trial (ABC 06) was published on patients with CCA progression under gemcitabine/cisplatin comparing folinic acid/fluorouracil/oxaliplatin therapy to active symptom control[13]. Overall survival was longer in the folinic acid/fluorouracil/oxaliplatin group (6.2 *vs* 5.3 mo, $P = 0.03$), thus demonstrating the possible feasibility of second level therapy and possibly changing our clinical approach to these patients in the near future.

Adjuvant treatments

With regard to adjuvant therapy in subjects amenable to surgical resection, the major indication came from the BILCAP trial[14]. In this study, patients undergoing surgical treatment of biliary cancer ($n = 447$) were allocated to receive capecitabine or just observation after a macroscopically complete tumor resection. Capecitabine increased survival by almost one third. This difference was statistically significant in the per-protocol (53 mo *vs* 36 mo, $P = 0.02$) but not in the intention-to-treat analysis. Serious adverse events occurred in the two groups at a similar rate. A randomized Phase 3 clinical trial conducted with adjuvant gemcitabine chemotherapy did not show

significant improvement in overall survival or relapse-free survival in comparison with untreated control[15]. An attempt was also conducted with adjuvant gemcitabine/oxaliplatin in the PRODIGE 12 study[16], and again no improvements were observed in comparison with supportive care.

In conclusion, excluding the modest, above-described, therapeutic options, physicians and patients are lacking any further pharmacological strategy. Also, radiation therapy gave inconclusive results in this setting[17], meaning that current national guidelines are not able to give an unequivocal indication on this approach[18]. In conclusion, the scarce results of systemic therapy have prompted extensive research in recent decades in order to find a more satisfactory pharmacological approach for this cancer. Current preclinical models and results together with ongoing trials are reported in the following paragraph.

CCA PHARMACOLOGICAL TREATMENT: THE FUTURE

The possible evolution of systemic therapy for CCA is largely dependent on the resolution of some issues with regard to this cancer[19]. First, scientists are still searching for an appropriate preclinical model of CCA[20]. CCA cell culture and tumor xenotransplantation in nude mice are the most commonly used strategies, but they do not adequately reproduce the neoplastic microenvironment[21]. From the clinical experimental side, the rarity of this neoplasm and competition between new molecules do not facilitate the performance of trials with an adequate number and homogeneous type of CCAs. While exploring this undefined horizon, research efforts are oriented in some main fronts, as reported in the following subparagraphs.

Trying to overcome chemoresistance

One of the main issues greatly limiting chemotherapy effectiveness in CCA is represented by chemoresistance[22]. Chemoresistance describes the capacity of cancer cells to escape or attenuate therapeutic drug effects[23]. Several mechanisms have been identified as the basis of chemoresistance, some opposing drug uptake or increasing its extracellular export and others reducing cellular necrosis/apoptosis or stimulating tumoral phenotypic changes. For instance, the reduced expression of organic cation transporter 1, as observed in both CCA and HCC, has been related to a poor response to tyrosine kinase inhibitors such as sorafenib[24]. On the other hand, the phenotypic CCA evolution from an epithelial to a mesenchymal trait (so-called epithelial-mesenchymal-transition) not only counteracts chemotherapy effects but also seems to favor metastatic progression[25]. Several strategies have been attempted in preclinical experimental studies to improve therapeutic response to chemotherapy, such as drug transporter induction or export pump inhibition in CCA cells or targeting cells with specific organic molecules such as bile acids or vesicles. With regard to human trials, a gemcitabine analogue (NUC-1031)[26] not requiring nucleoside cellular transport or intracellular kinase activation is currently being tested in a Phase 3 trial (NCT 04163900).

Targeting genetic aberrations

Several genetic aberrations have been identified in CCA, with a different distribution among intrahepatic, perihilar or distal CCA[27]. Kirsten rat sarcoma gene mutations are frequently encountered, ranging from 9%-40% of cases according to CCA location within the biliary tract[28]. A specific molecule (AMG 510) targeting the Kirsten rat sarcoma/G12C mutation is currently being tested in a Phase1/2 trial (NCT03600883); however, downstream pathway suppression, obtained by kinase inhibition (such as those of the Raf or MEK family) also may be attempted. In this perspective, the dual suppression of BRAF and MEK, obtained with dabrafenib and trametinib, gave excellent results in anecdotal cases[29], thus stimulating the Phase 2 ROAR study in patients with the BRAFV600E solid tumor mutation (NCT02034110). In an interim analysis of this trial of 43 patients with biliary tract cancer, the overall response rate (after external data review) accounted for 20% of cases[30].

The fibroblast growth factor (FGF) family comprises a group of proteins that react with their specific receptors (FGFRs) to stimulate several developmental and proliferative processes, also involving stem cell differentiation[31]. FGFR (subtype 2) genetic alterations, characterized by fusion with other genes, have been observed in nearly 15% of iCCAs, so FGF/FGFR signaling has emerged as a possible target to cure this cancer[32]. Among the FGFR inhibitors, infigratinib and pemigatinib have been evaluated in Phase 2 trials (NCT02150967 and NCT02924376, respectively) on advanced

iCCA harboring FGFR aberrations[33,34]. Progression-free survival was slightly better with pemigatinib, accounting for 62% at 6 mo for patients with an FGFR2 mutation. On the basis of these results, this drug was approved by the FDA in April 2020 for the treatment of advanced iCCA harboring this genetic aberration. Other molecules, such as derazantinib, futibatinib and Debio 1347, have been registered for evaluation in clinical trials (NCT03230318, NCT04093362 and NCT03834220), but the results are not yet available.

Since isocitrate dehydrogenase 1 mutations have been identified in approximately 13% of iCCA and 0.8% of other CCAs and the impairment of this enzyme may lead to the accumulation of the pro-oncogenic metabolite D-2-hydroxyglutarate, isocitrate dehydrogenase 1 inhibitors have been suggested for treatment of this cancer. The ClarIDHy phase 3 trial tested the isocitrate dehydrogenase 1 inhibitor ivosidenib in CCAs with a mutation of this enzyme and refractory to previous systemic therapy[35]. Six-month progression-free survival was 32% in the ivosidenib group in comparison with 0% in the placebo group. Other inhibitors are currently being examined in different trials, as summarized in a recent review on this issue[36]. Other genetic aberrations, such as those involving the ERRB family and proto-oncogene tyrosine-protein kinase 1, represent possible targets for CCA therapy; some drugs are under evaluation[37].

Immune checkpoint targeting

The activation of immune checkpoint (IC) pathways seems to be involved, under normal conditions, in tolerance and the prevention of autoimmune diseases[38]; however, tumor-mediated stimulation, hindering immune surveillance, may favor cancer proliferation and spread[39]. In this perspective, IC inhibitors have recently gained major importance with regard to cancer therapy, achieving a complete response in 20% of melanoma patients[40]. Among diverse IC pathways, the cytotoxic T-lymphocyte antigen 4 and programmed cell death protein 1/programmed cell death protein ligand 1 are those that are mainly recognized and targeted in oncology. In another study, 22 patients harboring CCA characterized by microsatellite instability and mismatch repair reduced protein (findings related to IC upregulation) were treated with the programmed cell death protein ligand 1 inhibitor pembrolizumab, obtaining a median progression free survival of 4.2 mo and a median overall survival of 24.3 mo[41]. However, these results might be improved with careful patient selection since an increased response has been observed as a function of programmed cell death protein ligand 1 expression[42]. Several trials with IC inhibitors alone or in combination and including CCA patients are ongoing.

Newly identified pathways as possible targets for therapy

The neuroendocrine regulation of CCA expansion (as shown by preclinical experimental studies) might be an important factor to consider while searching for a therapy for this cancer[43]. Secretin, somatostatin and melatonin have all been demonstrated to decrease CCA growth, as observed in cancer cell lines or in animal models such as tumor xenotransplantation in nude mice[44-46]. At present, however, no clinical data are available with either secretin or melatonin for CCA treatment, while a trial with somatostatin gave negative results[47]. Also, angiogenic factors such as vascular endothelial growth factor are considered possible targets for CCA therapy. Vascular endothelial growth factor in fact seems to be increased in half of human biliary tract cancers[48]. A trial using the anti- vascular endothelial growth factor antibody bevacizumab, in association with standard chemotherapy (gemcitabine, oxaliplatin), however, gave modest results[49].

SURGICAL TREATMENT: THE PRESENT

Surgery remains the best treatment option for long-term patient survival in CCA, and it is recommended to undertake surgical treatments in highly specialized centers to minimize morbidity and mortality[50].

Preoperative considerations

Preoperative workup and biliary drainage have been widely discussed in recent decades. The current consensus is that preoperative biliary drainage is required in cases of concomitant cholangitis, need for neoadjuvant therapy, malnutrition, hepatic or renal failure and need for portal vein embolization (PVE)[1]. When jaundice is the only indication, need for decompression is still a matter of debate. Asian guidelines

recommend preoperative drainage because of the higher risk of patients with cholangitis[51,52]. Furthermore, drainage may help restore liver function, decreasing the chance of postoperative liver failure[52]. On the other hand some studies have shown that, while biliary drainage is beneficial by reducing morbidity and mortality in patients with small future liver remnant (FLR), it is equally detrimental when FLR is large enough[53,54]. In Western countries, many centers prefer to use selective biliary drainage when FLR is less than 30%-40%[55]. When stenting is required, both endoscopic and percutaneous methods are used. Percutaneous transhepatic biliary drainage has some advantages, such as reducing the need for re-intervention, reducing the time to achieving a therapeutic effect and fewer procedural risks. However, a recent randomized trial of percutaneous *vs* endoscopic stenting was terminated early due to excess mortality in the percutaneous group (41% *vs* 11%), mandating further prospective studies and a reconsideration of drainage strategies[55]. Alternatively, nasobiliary drainage may be a valid option, showing good success rates and low morbidity despite greater patient discomfort[56,57]. The optimal timing of surgery in drained patients is currently unknown. A recent study identified a preoperative bilirubin level of < 75 μmol/L (2.9 mg/dL) to be correlated with fewer complications, less mortality and longer 5-year overall survival[58].

Surgical considerations for iCCA

Patients are considered eligible for surgery whenever complete resection of the tumor with negative margins (R0) can be achieved, providing sufficient FLR. Bilateral multifocal or multicentric disease is associated in many studies to a significantly shorter overall survival (OS)[59,60]. In practice, only 32% of iCCAs satisfy resectability criteria at presentation. On top of this, around 30% of iCCAs will be deemed inoperable on the operating table. Staging laparoscopy can detect unresectable disease in around 36% of patients with minimal costs[61] and is advocated by current guidelines[62].

Principles: The established principles of surgery for iCCA are to achieve R0 resections and to provide adequate staging with hilar lymphadenectomy, sparing at the same time as much parenchyma as possible to avoid post-hepatectomy liver failure. Margin status is the primary objective in iCCA surgery. Evidence mainly derives from large single center and multicenter studies, which have demonstrated a significant survival impact of R0 resection. Overall survival at 5 years for R0, R1 and R2 resections are reported to be 28.7%, 13.9% and 0%, respectively[63], with an increased survival benefit for > 5 mm margins[64].

Lymphadenectomy and nodal disease: Nodal disease is recognized as the most important prognostic factor in most studies[59,63-66]. In fact, some authors have reported that margin status may have limited impact in the presence of nodal metastases[64]. Most guidelines suggest routine consideration of regional lymphadenectomy and a minimum of six lymph nodes are needed for accurate staging[2,62,67]. Nonetheless, the role of lymphadenectomy remains controversial in Western countries, where the practice is not widespread, and almost 50% of patients have no lymph nodes examined[68]. Regional lymph nodes include cystic, bile duct, hepatic artery and portal vein. Right and left hemi-livers have distinct lymphatic drainage: for right liver iCCA, the retropancreatic nodes along the common bile duct are considered regional nodes and should be removed, while for left liver iCCAs, the same considerations are true for the lesser curvature and inferior phrenic nodes. Lymph nodes may be positive in as many as 30% of cases, but with current adjuvant therapy, survival is acceptable, and this should not refrain the surgeon from resection[68]. On the contrary, distant nodes such as celiac, superior mesenteric, paraaortic or caval should be considered as distant metastatic disease and contraindicate extensive surgery as patients are unlikely to gain any benefit[2,62,67].

Extended procedures: Given the poor prognosis (0% 5-year OS) of unresectable disease or R2 resection[63,65], in recent years, some groups have explored the benefits of major vascular resections to obtain R0 resection, resulting in up to 84% of patients [66] with morbidity and mortality rates comparable to standard resection[69]. Overall survival of these patients is also comparable to patients who did not undergo vascular resection[66,69,70]. In general, all patients with localized iCCA should be considered for resection even if this implies major hepatectomy or vascular resection[62]. In recent decades, based on the principles of liver regeneration, some authors have pushed the boundaries for resectability in liver surgery by introducing the concept of two-stage hepatectomies, namely portal vein ligation and PVE. The latter can enhance the resectability rates of liver tumors, allowing extensive resection with adequate FLR and are

usually well-tolerated by the patient. However, a major drawback is the long waiting time for the second stage procedure, which can take up to several weeks, carrying the risk of tumor progression. To solve these problems, a German group of authors developed a new technique, known as associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), which was found to allow rapid growth of the FLR, with a median period of 9 d[71]. Another study investigated benchmark outcomes in ALPPS, demonstrating that it has a comparable standard outcome as other types of major liver surgery[72]. ALPPS for iCCA has been evaluated in an international multicenter study in which 102 patients underwent first-stage ALPPS; 99 completed the second procedure, and R0 resection was obtained in 85% of cases with 29% major morbidity and 7% mortality[60]. When disease is considered unresectable, neoadjuvant chemotherapy can convert as many as 53% of cases to secondary resectable disease[73].

Recurrent disease: Recurrence of iCCA is frequent. Most recurrences are intrahepatic and therefore potentially amenable to re-resection[74], with satisfactory outcomes when repeated resections are undertaken. These results lead to the recommendation that the same principles for resectability should be applied in consideration of primary and secondary resection[75].

Surgical considerations for pCCA

pCCA represents a surgical challenge due to its intrinsic anatomical location. Nonetheless, its higher prevalence (50% of CCAs) has translated into more extensive literature and pioneering advances in surgical treatment.

In pCCA, the main criteria that define surgical unresectability are inadequate FLR, absence of a suitable field for biliary reconstruction (*i.e.* bilateral segmental ductal extension) and major vascular infiltration[51]. Growth of FLR may be induced with two-stage hepatectomy techniques, broadening indications for resection. Nonetheless, 20%-50% of patients are deemed to be unresectable upon surgical exploration, making explorative laparoscopy a useful tool to avoid unnecessary laparotomies.

Principles: Surgery for pCCA routinely involves en bloc hemi-hepatectomy and bile duct resection to achieve negative biliary and parenchymal margins, with additional resection of the caudate lobe, regional lymphadenectomy[51,76] and biliary reconstruction. Negative margins are paramount. The caudate lobe usually drains directly into the biliary confluence, hence the necessity of its resection for curative intent is advised by current guidelines as it improves OS[51,77]. A number of studies have demonstrated that intraoperative additional resection to achieve R0 confers a significant survival advantage with few complications and a prognosis comparable to primary R0[78,79]. In particular, aggressive approaches such as pancreaticoduodenectomy seem to offer improved results[78]. Lately, a new concept of isolated circumferential margin has been introduced for pCCA. Stremitzer *et al*[80] identified a group of patients who, despite being classified as R1, did not have distal or proximal margin positivity but only focal circumferential positivity. These patients had better survival than those with surgical resection margin positivity, although inferior when compared to their R0 counterparts. Finally, a recent study has challenged these surgical dogmas, arguing that with current adjuvant therapies R1 patients may have similar survival to R0[77].

Lymphadenectomy and nodal disease: European guidelines affirm that lymphadenectomy should be considered the standard of care, but there is no consensus on the extent of lymphadenectomy for pCCA[81]. A recent systematic review identified a minimum of seven lymph nodes to convey sufficient information avoiding understaging, with no benefit coming from higher lymph node counts (≥ 15) which could only be achieved with extended lymphadenectomy[82]. The regional nodes for pCCA are cystic, biliary, hepatic artery, portal vein and retropancreatic. The impact of extended lymphadenectomy of N2 nodes (dissection of celiac, superior mesenteric and paraaortic nodes) on survival has not been established, but trials are ongoing[83,84]. For known N2 positive disease, current expert consensus suggests no benefit of resection[2].

Extended procedures: Extended resections have been explored for pCCA, including two-stage hepatectomies such as portal vein ligation/PVE and ALPPS with acceptable outcomes. The first reports of 29 ALPPS procedures for this indication featured a strikingly high mortality rate, although statistically comparable to results of 29 matched patients who underwent non-ALPPS resection[85]. These poor initial results

have dramatically improved for most ALPPS indications with better patient selection and inter-stage management and will hopefully improve for hCCA as well[86]. As of 2020, ALPPS should only be considered in highly experienced institutions. Hepatopancreaticoduodenectomy entails resection of the entire extrahepatic biliary tree, thus necessitating resection of the pancreatic head and duodenum. It is used for tumors with concomitant distal bile duct spread. This procedure is associated with high major morbidity rates of up to 37%. Nonetheless, the latest reports from highly specialized centers have been encouraging and suggest that hepatopancreaticoduodenectomy could be considered in young, fit patients when it represents the only chance of a cure [87]. Vascular resection can be adopted to increase R0 rates. Long-term oncological results are in the range of 25%-45%[88,89].

Surgical considerations for dCCA

dCCA affects the third portion of the extrahepatic biliary duct, which lies in a retro/intra pancreatic position. This particular anatomical configuration translates into a completely different surgical approach compared to iCCA and pCCA. In particular, resection involves pancreaticoduodenectomy, as for cancer of the pancreatic head. Negative margin status is imperative, as positive margins increase anastomotic recurrence rates and herald poor survival. An aggressive approach is justified in cases with vascular infiltration. Resection of the superior mesenteric or portal vein and reconstruction to obtain R0 obtains survival comparable to patients without vascular resection with no additional morbidity and mortality[90]. Data on arterial resection is more limited[91]. Specific for dCCA is the need to resect the bile duct high in the liver hilum as well as a lymphadenectomy of the porta hepatis and gastroduodenal ligament[76]. Unfortunately, dCCA diagnosis is not always defined preoperatively, and these steps may be omitted, increasing the chance of R1 if the tumor has prominent intraductal spread.

SURGICAL TREATMENT: FUTURE PERSPECTIVES

Progress in the field of surgery for CCA has been limited for many years, yet the coming decade harbors great promise, with numerous innovations on the horizon. The main ongoing surgical trials are reported in Table 1.

Preoperative care

Resectability for CCA is limited mainly by inadequate FLR, especially when extensive resections are required. Portal vein ligation, PVE and ALPPS are compelling procedures for enhancing resectability with adequate FLR. On top of this, recently Guiu *et al*[92] described an interesting new technique, named liver venous deprivation, which involves PVE with simultaneous embolization of one or two hepatic veins. In a subsequent study, the same group demonstrated that liver venous deprivation permits a significantly greater increase in both FLR volume and function compared to PVE [93]. A randomized trial is ongoing with the aim of establishing the superiority of this technique (NCT03841305). Liver venous deprivation could represent an important advancement in liver surgery, combining the low morbidity of PVE with the greater efficacy and rapidity of ALPPS.

Minimally invasive surgery and enhanced recovery protocols

Minimally invasive approaches have developed slowly in liver surgery. Few studies specifically address the use of minimally invasive surgery for CCA with comparable outcomes, although no benefit has been clearly demonstrated so far[94]. For pCCA, the literature is discordant, but nevertheless it is possible that it could develop further in the near future[94].

Liver transplantation for unresectable CCA

Liver transplantation (LT) for hCCA has been investigated for many years, but the practice was abandoned due to very poor results compared to other indications, in the setting of the ongoing organ shortage. Initial experiences featured 5-year OS survival rates of 23%-38%, mainly due to early recurrence[95].

In the early 2000s, the idea of LT for unresectable iCCA changed thanks to the work of Vreede *et al*[96] at the Mayo Clinic. They developed a very rigorous protocol to optimize the selection of patients who were most likely to benefit from LT. In particular, patients with a diagnosis of unresectable, non-metastatic hCCA were

Table 1 Surgical ongoing trials for cholangiocarcinoma

CCA Type	Domain	Trial name	Summary
iCCA/pCCA	Hepatic venous deprivation	NCT03841305	Randomized trial of portal vein embolization *vs* hepatic venous deprivation. Primary endpoint: future liver remnant at 3 wk
iCCA	Liver transplantation	NCT02878473	Liver transplantation for early (< 3 cm) iCCA. Single group assignment
iCCA	Liver transplantation	NCT04556214	Liver transplantation for stable (> 6 mo), advanced (unresectable) iCCA. Single group assignment
iCCA	Liver transplantation	NCT04195503	Liver transplantation for stable (> 6 mo), advanced (unresectable) iCCA. Single group assignment
pCCA	Lymphadenectomy	ChiCTR1800015688	Randomized trial of extended *vs* regional lymphadenectomy for resectable pCCA. Primary endpoint: overall survival
pCCA	Liver transplantation	NCT02232932	Randomized trial of liver transplantation *vs* resection for resectable pCCA (< 3 cm). Primary endpoint: overall survival at 5 yr

iCCA: Intrahepatic cholangiocarcinoma; pCCA: Perihilar cholangiocarcinoma.

treated with external beam radiotherapy (4500 cGy in 30 fractions) with concomitant intravenous 5 fluorouracil followed 3 wk later by transcatheter brachytherapy with an iridium-193 wire and finally maintenance oral capecitabine (as tolerated) until transplantation. Before LT, patients underwent staging laparotomy to exclude any intra-abdominal disease, including distant lymph node sampling. With this protocol, they reported a 5-year survival of 82% for patients undergoing LT[97]. Of note, almost half of the patients who enrolled in the protocol were not transplanted due to death or disease progression. Surgical exploration resulted in findings that precluded transplantation in 23% of cases.

Sahai *et al*[98] reported similar efficacy with a different neoadjuvant protocol consisting of higher brachytherapy doses and the omission of external beam radiotherapy. These successful experiences have been replicated in other studies[99-101]. Other studies investigated risk factors for drop-out or recurrence. Elevation of carbohydrate antigen 19-9 above 500 U/mL, a mass larger than 3 cm and Model End-stage Liver Disease score above 20 points predicted protocol drop-out before LT[102]. On the other hand, predictors for recurrence were elevated carbohydrate antigen 19-9, portal vein encasement and incomplete response to neoadjuvant therapy defined as residual tumor on the hepatectomy specimen as well as pathologic stage and perineural and perivascular invasion[99,100,102,103].

Notably, patients with hCCA developing in the setting of primary sclerosing cholangitis had a significantly better outlook than sporadic hCCA[104]. Given the technical and management complexity of this surgery, outcomes are influenced by center experience, with centers having performed at least six procedures providing the best results[104,105]. These experiences have led neoadjuvant therapy followed by LT to become the current standard of care for locally advanced non-metastatic unresectable hCCA, with both cadaveric and living donor programs active in highly specialized centers worldwide.

To date, iCCA is generally considered a contraindication to LT due to poor results in initial experiences[106]. Vilchez analyzed 440 patients with iCCA from the UNOS database and reported a significantly reduced OS with respect to HCC patients undergoing LT[107]. Yet, it may not be correct to generalize these poor results as analysis of the National Cancer Data Base revealed that only 2.2% of patients with iCCA underwent LT[107]. Furthermore, none of the studies cited so far have investigated the benefits of preoperative neoadjuvant therapy. The success and implementation of LT programs for pCCA compels consideration of this strategy for iCCA. Lunsford *et al*[108] in 2018 first reported results of their single center LT program for iCCA involving neoadjuvant chemotherapy[108]. Twelve patients were enrolled in the program, and six were transplanted. OS and disease-free survival were 83% and 50% at 5 years, respectively. Two large randomized trials are currently evaluating this approach (NCT04556214 and NCT04195503).

Whether mixed HCC-iCCA should be considered for LT is also debated. The literature is conflicting, with some studies reporting outcomes similar to HCC and others to iCCA[107,109].

Table 2 The new systemic, surgical and combined approaches to cholangiocarcinoma

	Approaches
Systemic therapy	(1) Overcoming chemoresistance; (2) Genetic aberration targeted therapy; (3) Immune checkpoint inhibitors; and (4) Neuroendocrine modulation of cancer growth
Surgical therapy	(1) Liver venous deprivation; (2) Minimally invasive surgery; and (3) Liver transplantation
Combined therapy	Liver transplantation or surgical resection after radiotherapy and/or neoadjuvant treatment

Liver transplantation for resectable CCA

Successful results of LT after neoadjuvant therapy have induced investigators to compare them with conventional resection for resectable hCCA. Rea *et al*[97] reported a significantly improved OS at 5 years for patients undergoing LT compared to those undergoing resection. Ethun *et al*[110] showed similar results in an intention-to-treat analysis as well. They also went further and analyzed results for a subgroup of patients that were selected to be more comparable to patients in the resection group (*i.e.* hCCA not associated with primary sclerosing cholangitis, < 3 cm and lymph node negative). Even in this case, results were significantly better in the LT group. The authors suggest that the available data should prompt consideration of LT for hCCA patients with resectable disease. Indeed, this may be the new frontier in hCCA surgery. Nonetheless, some obstacles remain before the implementation of this strategy becomes widespread, the main one being the scarcity of allograft availability. In fact, critics of this approach argue that the benefit of LT (14% 5-year survival increase) is too little compared to the minimum benefit commonly applied to LT (50% at 5 years) and does not justify use of a deceased or living donor allograft. Better identification of patients who would benefit most from LT (*e.g.*, patients who are less likely to undergo an R0 resection) could maximize the benefit and justify an LT program. In any case, a randomized trial is currently ongoing (NCT02232932).

Regarding resectable iCCA, Facciuto *et al*[111] recently published a small series of patients transplanted for HCC or iCCA. Their analysis showed that when iCCA features were within the Milan Criteria survival was comparable to that achieved for HCC. Further insights have come in recent years. Sapisochin *et al*[109] reported that the subgroup of patients transplanted for small iCCA (< 2 cm) had similar survival to HCC. In two subsequent studies, these results were confirmed with OS being significantly different between small (< 2 cm) and large tumors (> 2 cm)[71,112], 65%-73% *vs* 40%-45% respectively. Trials of LT for small iCCA are currently ongoing (NCT02878473).

Neoadjuvant therapy for resectable CCA

Experience with neoadjuvant therapy followed by LT has shown that disease can be stabilized in more than 50% of patients and that 57% of patients who ultimately undergo LT benefit from a complete response[97,103]. While LT seems to offer superior survival compared to resection, it is unknown to what extent neoadjuvant therapy or strict selection criteria contribute to the effect[113]. Neoadjuvant therapy may therefore prove useful in cases of resectable disease as well to increase chances of R0 resection. Consideration should be given to the risk of disease progression and loss of chance of resection. To date, there is little data available on this possible approach [114].

CONCLUSION

Poor CCA prognosis requires important therapeutic improvements in the next few years. Table 2 summarizes the new approaches in CCA therapy. Several attempts are being made or hypothesized at present, as described above in this review, with regard to systemic and/or surgical treatment for this cancer. The heterogeneity and rare occurrence of this tumor, however, impede the design of large trials with homogeneous patients. An increased understanding of the genetic changes occurring in CCA and the institution of collaborative international studies may improve this picture. The results of these efforts would be the possible definition of a model integrating different resources (diagnostic, radiological, surgical and chemotherapeutic) in order to achieve an early diagnosis and the best outcome, according to patient and tumor hallmarks. This integrated model should be implemented over time,

maintaining a strict relationship with new findings on CCA in order to adopt best practice for this lethal cancer.

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