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MINIREVIEWS

Liver transplantation for cholangiocarcinoma: Current status and new insights

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Abstract

Cholangiocarcinoma is a malignant tumor of the biliary system that can be classified into intrahepatic (iCCA), perihiliar (phCCA) and distal. Initial experiences with orthotopic liver transplantation (OLT) for patients with iCCA and phCCA had very poor results and this treatment strategy was abandoned. In the last decade, thanks to a strict selection process and a neoadjuvant chemoradiation protocol, the results of OLT for patients with non-resectable phCCA have been shown to be excellent and this strategy has been extended worldwide in selected transplant centers. Intrahepatic cholangiocarcinoma is a growing disease in most countries and can be diagnosed both in cirrhotic and in non-cirrhotic livers. Even though OLT is contraindicated in most centers, recent investigations analyzing patients that were transplanted with a misdiagnosis of HCC and were found to have an iCCA have shown encouraging results. There is some information suggesting that patients with early stages of the disease could benefit from OLT. In this review we analyze the current state-of-the-art of OLT for cholangiocarcinoma as well as the new insights and future perspectives.

Key words: Orthotopic liver transplantation; Perihiliar cholangiocarcinoma; Intrahepatic cholangiocarcinoma

Core tip: Cholangiocarcinoma is a malignant tumor of the biliary system. Perihilar cholangiocarcinoma is an accepted indication for orthotopic liver transplantation (OLT) in some centers under a strict selection process and after neoadjuvant chemoradiation. Intrahepatic cholangiocarcinoma is a formal contraindication for LT in most centers worldwide due to the poor reported results. Nevertheless, there is some novel research showing that the results of OLT in early stages of this disease may not be as bad and could potentially be accepted as an indication for transplant. In this review we will analyze the current state-of-the-art of liver transplantation for cholangiocarcinoma.

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INTRODUCTION

Cholangiocarcinoma (CCA) is a malignant tumor of the biliary system that represents approximately 10% of all hepatobiliary malignancies, standing as the second most common primary hepatic tumor of the liver after hepatocellular carcinoma (HCC)[1-3]. Depending on the anatomic location, it is classified into three subtypes: Intrahepatic CCA (iCCA), perihiliar CCA (phCCA) and distal CCA[4].

Surgical treatment is the only curative option for all subtypes[4]. Radical resection offers 5-year survival ranging between 25%-45%[2]. Unfortunately, most tumors are diagnosed at an advanced stage and the resectability rate is low. Many patients are not candidates for surgical excision due to the extent and location of the tumor or due to the underlying liver disease. In these patients, orthotopic liver transplantation (OLT) would appear a possible alternative of treatment[5].

Liver grafts are a scarce source. In these regards, it is important to take into account the maximum benefit of OLT offered to recipients who are included in the waiting list[6]. There are many authors who consider that long-term survival of recipients after OLT for a specific condition must reach the results of all other accepted indications[5,7,8]. Nevertheless, a 5-year survival after OLT over 50% has been considered acceptable[6] and it is currently the accepted survival for patients undergoing OLT for malignancies (mostly HCC) in most centers worldwide.

The aim of this paper is to review the role of OLT in the management of CCA and to describe the most recent advances in knowledge and the ongoing research in the field.

PHCCA

phCCA is an uncommon and aggressive malignancy of the biliary tract whose incidence is increasing[9,10]. It represents about two-thirds of all cases of CCA[5] and can be defined as a tumor that involves or is in close vicinity to the bile duct confluence[11]. Although no specific etiologic factor can be found in most patients, an association between long-standing biliary inflammation and development of CCA has been observed[9]. The risk factors for the development of CCA include primary sclerosing cholangitis (PSC), with a prevalence of phCCA ranging between 5% to 15%, choledocal cyst disease, hepatolithiasis and infection with certain parasites[9,10,12-15].

The existence of different nomenclatures and the lack of a reliable staging system have created problems to compare the management and outcomes of phCCA. The term phCCA was initially introduced by the John Hopkins group, and most recently adopted by the American Joint Committee on Cancer[16]. Fortunately, nowadays, this term is widely employed by the surgical community worldwide, making it easier to study outcomes of patients diagnosed with these tumors[11,16,17].

The results of nonsurgical therapies for phCCA have been disappointing and most of the patients survive less than 1 year after diagnosis[9,18]. The most important prognostic factor is to achieve a complete resection at the time of surgery, but this is only achieved in 25%-40% of the cases[5,19-21]. The current 5-year survival rate after surgery, even in select cases, rarely exceeds 40%[20,22-24]. Moreover, currently, no effective neoadjuvant or adjuvant therapy is available for ameliorating the outcomes of liver resection[25].

For tumors that are locally unresectable due to the invasion of major vessels, bilobar tumor involvement or insufficient hepatic reserve, a total hepatectomy with regional lymphadenectomy followed by an OLT could be a good alternative. This approach achieves a wide resection margin and the treatment of the underlying disease[26].

The early experience before 2005 with OLT in phCCA was disappointing. The first series reported 5-year survivals ranging from 18% to 25%[9,27-31]. However, these figures were refuted when two American groups developed a new concept that improved the outcomes of OLT for these tumors. The University of Nebraska introduced the routine use of neoadjuvant therapy prior to OLT[32] and this new approach was posteriorly adopted and redefined by the Mayo Clinic group[33]. Before this year, some authors had already suggested that the use of neoadjuvant therapy enhanced the outcomes of OLT in phCCA[3,10,34-36]. The Mayo Clinic group reported the inclusion of 71 patients in the transplant treatment protocol and 38 underwent OLT. One-, 3- and 5-year survival rates were 92%, 82% and 82% after OLT. Once recurrence and survival rates were analyzed, they found better outcomes in transplanted patients compared to patients undergoing resection[33]. The Mayo Clinic protocol involves careful selection of patients with unresectable *de novo* phCCA or phCCA in the setting of PSC without intrahepatic or extrahepatic metastases. Positive lymph nodes are an absolute contraindication. Criteria for anatomical unresectability include bilateral segmental ductal extension, encasement of the main portal vein, unilateral segmental ductal extension with contralateral vascular encasement and unilateral atrophy with contralateral segmental ductal or vascular involvement. There are no longitudinal limits for bile duct involvement[37]. A pancreaticoduodenectomy combined with OLT is justified to reach a R0 resection. The upper limit of tumor size is 3 cm when a mass is visible on cross sectional imaging studies. Patients initially receive external-beam radiation (45 Gy in 30 fractions, 1.5 Gy twice daily) and continuous infusion of 5-flurouracil administered over 3 wk. Brachytherapy (20 Gy at 1 cm in approximately 20-25 h) is administered 2 wk following completion of external beam radiation therapy.

After that, patients are treated with oral capecitabine, administered until the time of transplantation. An exploratory laparotomy is performed to exclude metastatic disease in all patients. Staging laparotomies are performed as patients come close to being on the top of the waiting list for deceased donor liver transplantation or the day before in the setting of live donor liver transplantation[10,33,37].

The Mayo Clinic group also published an update to their series with the aim of identifying prognostic factors. They found that older recipient age, prior cholecystectomy, CA-19.9 more than 100 at the time of OLT, visible mass on cross-sectional imaging and prolonged waiting times were related with worse prognosis[34]. This group attributes their success to both patient selection and neoadjuvant treatment. Currently, 10-20 patients are enrolled in the neoadjuvant therapy and OLT transplantation per year in this center[37].

The survival for transplanted patients with phCCA arising in the setting of PSC is better than for patients with *de novo* phCCA. It could be explained due to close follow-up in PSC patients, making an earlier diagnosis compared to patients with *de novo* CCA[38,39]. The same authors observed that pretreatment pathological confirmation was not associated with a statistically significantly higher risk for recurrence after OLT and they concluded that pathological confirmation before therapy is desirable, but it should not be a requirement for enrolling into their protocol[39].

Encouraged by the Mayo Clinic outcomes, in 2009, the United Network of Organ Sharing/Organ Procurement and Transplantation Network approved the allocation of a standard Model of End-stage Liver Disease (MELD) exception score for patients with phCCA who completed a standardized neoadjuvant therapy protocol[40,41]. Due to the lack of data, the MELD score was set to equal the current standard assigned score for HCC[40].

Other studies have confirmed the good outcomes of OLT for phCCA following this protocol. Darwish Murad *et al*[40] presented a multicenter study including 12 large-volume centers in the United States. Centers with three or more cases performed between 1993 and 2010 were included. They found that patients with phCCA who were treated with neoadjuvant therapy followed by OLT had a 65% 5-year disease-free survival and the intention-to-treat 5-year survival was 53%. The drop-out rate after 3.5 mo of treatment was 11.5%. Forty-three patients (20%) developed recurrence after OLT. This figure is very low compared with recurrence in patients who were transplanted without the use of any neoadjuvant protocol, which ranged from 53% to 84%. They concluded that this therapy was highly effective and that the MELD exception was appropriate[40].

The use of a multimodality oncologic approach including neoadjuvant chemo radiotherapy with subsequent OLT achieves excellent results for patients with localized, regional lymph node-negative phCCA. Patient survival after OLT is comparable to the results of OLT for other causes. OLT for phCCA should be considered an option in patients diagnosed of an un-resectable phCCA, in centers where the pre-transplant treatment of these patients is optimal. One of the main challenges of this protocol is to determine what patients are unresectable as this can differ between centers.

ICCA

The incidence of iCCA or peripheral CCA is increasing globally[5,17], and this tumor is responsible for 0%-20% of deaths related to an hepatobiliary malignancies[2,41]. In United States, 5000 new cases of iCCA are diagnosed each year[2].

Recent publications have suggested a strong association between the development of iCCA, hepatitis B and C and metabolic syndrome[5,42,43]. Hepatitis C virus (HCV), whose incidence is still increasing, is an etiological factor for hepatitis and cirrhosis and it has been clearly identified as one of the main risk factors for the development of HCC[42]. Different studies have found an increased prevalence of HCV in patients diagnosed of iCCA. Other publications also suggest that hepatic cirrhosis is one of the main risk factors for the development of iCCA as it is for HCC[42-46]. Hepatocytes and cholangiocytes share progenitor cells, therefore some authors have postulated that HCV could induce carcinogenesis in both cell types by the same mechanism[42].

HCC represents the most common primary tumor encountered in the liver and its incidence is also growing in Western countries[47]. The increased incidence of iCCA and its association with the presence of cirrhosis makes necessary to accurately differentiate between both tumors, as their treatment options and prognosis differ significantly[44]. However, diagnosis is particularly complex in cirrhotic patients; the distinction between high-grade dysplastic nodules, iCCA and HCC can pose a challenge[48]. When dynamic imaging studies (contrast enhanced computed tomography or magnetic resonance imaging) show an intrahepatic lesion in a cirrhotic liver, with atypical features of HCC, a tumor biopsy should be the next diagnostic step. The problem is that a biopsy is not always feasible due to coagulopathy or refractory ascites and does not always provide a reliable diagnosis[49,50].

Surgical treatment with hepatic resection and R0 margins is the only potential curative option[2,51], but this goal is achieved in less than 30% of patients as many of them are not candidates for resection at the time of presentation[4,20]. Following surgical resection, the median disease-free survival is around 26 mo and the reported rates of recurrence range around 60%-65%[52-54]. There are some cases where resection is not feasible due to the presence of decompensated cirrhosis or significant portal hypertension. Also, the proximity or involvement of main vascular structures of the liver may preclude surgical treatment. It is in such cases where OLT may become an alternative to surgical resection[7].

Table 1 Patient survival and tumor-free survival in patients with intrahepatic cholangiocarcinoma and mixed hepatocellular-cholangiocarcinoma

Ref.	*n*	No. of iCCA/HCC-CC	Patient survival (%)			Tumor-free survival (%)		
			1-yr	3-yr	5-yr	1-yr	3-yr	5-yr
O'Grady *et al*[76]	13	13 iCCA	38	10	10	-	-	-
Yokoyama *et al*[77]	2	2 iCCA	50	0	-	-	-	-
Pichlmayr *et al*[78]	18	18 iCCA	13.9	0	-	-	-	-
Pichlmayr *et al*[78]	22	22 iCCA	20.8	0	-	-	-	-
Casavilla *et al*[55]	20	20 iCCA	70	29	18	67	31	31
Shimoda *et al*[63]	16	8 iCCA 8 HCC-CC	62	39	-	70	35	-
Robles *et al*[27]	23	23 iCCa	77	65	42	68	45	27
Ghali *et al*[56]	10	9 iCCA 1 HCC-CC	-	30	-	-	-	-
Fu *et al*[66]	11	11 iCCA	50.5	50.5	-	51.9	51.9	-
Sapisochin *et al*[64]	14	6 iCCA 8 HCC-CC	79	66	47	60	50	30
Vallin *et al*[65]	10	10 iCCA	80	60	24	40	50	50
Sapisochin *et al*[68]	29	29 iCCA	79	61	45	89	71	71
	⩽ 2 cm	8 iCCA	100	73	73	0	0	0
	Multiple or single > 2 cm	21 iCCA	71	43	43	74	58	58
Facciuto *et al*[71]	32	16 iCCA 16 HCC-CC	71	-	57	62	-	44

iCCA: Intrahepatic cholangiocarcinoma; HCC-CC: Hepatocellular-cholangiocarcinoma.

iCCA as an indication for OLT is still highly controversial. OLT seems a promising treatment as it provides both a wider surgical margin and a potential cure for the underlying liver disease[55]. Nevertheless, most of the publications regarding OLT and iCCA have shown high tumor recurrence rates and poor long-term survival[5,27,55-59]. The main cause of death following OLT for iCCA is tumor recurrence, occurring in a range between 60%-90% of the patients[54,58,60,61]. These poor outcomes have also been described in patients with subtypes of iCCA such as mixed hepatocellular-cholangiocarcinomas (HCC-CC)[5]. It is important to address though, that most of these studies are single-center experiences, with a small number of patients, without differentiation between iCCA and phCCA and including patients both with and without liver cirrhosis. As with HCC, the presence of an iCCA on a cirrhotic liver may have a different behaviour than its development on a healthy liver and the results after OLT may also be different[62].

The results published until late 2000, showed a 5-year actuarial survival that ranges between 10%-18% (Table 1).

Robles *et al*[27] published a multicentre retrospective study in 2004 in which 23 transplanted patients with iCCA were analyzed, finding a 5-year survival of 42%, and a recurrence rate of 35%. The mean time between transplantation and recurrence was 22 mo. Ghali *et al*[56], in a retrospective study that aimed to review the outcomes after OLT in recipients found to have an incidental iCCA in their explanted native liver, showed that the long-term survival rates were not better than those seen in patients with known iCCA. We reported, in collaboration with the University of California, San Francisco, a study comparing patients that were transplanted due to HCC, but were found to have a pathological diagnosis of iCCA or HCC-CC, with a group of patients with pathological diagnosis of HCC. The incidence of iCCA and HCC-CC previously undiagnosed was 3.3%. It was observed that these tumors were associated with bad prognosis and high recurrence rate after OLT, finding a significant difference with those patients with HCC[63,64]. In all of the previous studies, probably due to the number of patients included, no subgroups could be made according to different tumor sizes or numbers.

Due to the poor results of OLT for iCCA, many authors have proposed to determine the tumor factors responsible for recurrence. Different factors such as vascular or lymphatic invasion and size or number of lesions[1,27,55,58] may need to be considered for strict patient selection. Recent studies have shown encouraging results that could potentially change the management of patients with iCCA on cirrhotic livers. Along these lines, Vallin *et al*[65], knowing that small iCCA might be undiagnosed or misdiagnosed as HCC in the context of liver cirrhosis, tried to determine the prevalence and clinical impact of undetected iCCA in liver explants of adult cirrhotic patients undergoing OLT. They identified iCCA in 10 patients (1%), being 4 of them less than 2 cm. Post-transplant tumor recurrence of the whole cohort was observed in 5 patients (50%) and all of them died. The authors couldn't determine if tumor size was associated with recurrence[65]. Fu *et al*[66] reported a retrospective study, evaluating 11 patients who, in absence of lymph node, vascular or bile duct involvement, underwent OLT and whose 3-year disease-free survival rate was 52% and recurrence rate was 45%. They reported a 4-year survival for selected patients of 50%.

In 2014, we coordinated a Spanish multicenter effort with the participation of 16 Spanish groups and published some novel results. The first part of the study aimed to evaluate the outcome of cirrhotic patients with HCC-CC or iCCA on pathological examination after OLT for HCC. This group of patients was compared to a control group of patients with HCC. The total number of patients with both tumors was 42, being the largest series published to date. A subdivision was made, according to the size and number of tumors, following the Barcelona Clinic Liver Cancer staging classification. The tumors were classified in single tumors $\leqslant$ 2 cm and multinodular or uninodular > 2 cm. One of the most salient results of that study was that there were no significant differences in the actuarial survival between patients in both the study and the control groups. Contrary, those patients with multinodular or larger tumors had a worst survival when compared to similar HCCs[67-69].

In a subsequent study, the risk factors for iCCA recurrence after OLT in cirrhotic patients were analyzed in 29 patients whose explanted liver showed an iCCA (both misdiagnosed as an HCC in preoperative imaging or incidental tumor). The main objective of this research was to analyze if there was a subgroup of patients with iCCA in which the results of OLT, in terms of survival, were acceptable. A subgroup of patients with single $\leqslant$ 2 cm (described as "very early" iCCA) was identified. Patients in this group did not present tumor recurrence and the 1-, 3- and 5-year survival was 100%, 73% and 73%, respectively, with a median survival of 52 mo[68]. This was the first study to report that patients with "very early" iCCA can have an acceptable survival after transplant and this may "open" a new indication for OLT for these patients. Nevertheless, the number of patients analyzed in that study was very limited and these outcome will need to be validated in new studies[4,68,70]. On-going research in the field is being conducted to validate the previous results of this experience but ultimately a prospective study will need to be performed to ensure these good results and to be able to include patients with "early or very early" iCCA in the waiting list for OLT. In our opinion, as occurred with OLT for HCC, the identification of a subgroup of patients with iCCa at initial phases will expand the indication for transplantation in these cases.

Subsequently, Facciuto *et al*[71] published a retrospective study where they identified 32 patients with cirrhosis and intrahepatic bile duct tumor on explant specimen. This series showed that patients with iCCA within Milan criteria[72] had a 5-year tumor recurrence rate of 10% and a 5-year survival rate of 78%, comparable with patients with HCC within Milan criteria. The conclusion of this paper suggests that patients with iCCA within Milan criteria may be able to achieve acceptable long-term post-OLT survival. Furthermore, in a review published by the Mayo Clinic group in 2013, they proposed that, despite the high rate of recurrence reported for these patients, OLT could be considered as an option of treatment in patients with very small iCCA ($\leqslant$ 2 cm) in the context of cirrhosis[52].

According to all these data, LT for "very early" or "early" iCCA may be an option for cirrhotic patients in the future, but further research must be conducted. If the results of these new investigations confirm the good expected outcome, this could potentially become a new indication for LT for a growing disease.

In the International Liver Cancer Association guidelines, the committee suggested that future studies should focus on standardized selection criteria for giving neoadjuvant chemotherapy for patients with iCCA who could be considered candidates for OLT[73]. In spite of the disappointing outcomes of the studies that analyze the role of neoadjuvant therapy in combination with OLT for these tumors[49,69], taking into account the benefits of neoadjuvant therapy for early phCCA, future clinical trials should evaluate the use of combining neoadjuvant therapy with OLT for iCCA[45,73]. The guidelines published in 2014 by Bridgewater *et al*[73] for the diagnosis and management of iCCA affirm that OLT for iCCA or HCC-CC should only be offered in centers with designed clinical research protocols employing adjuvant or neoadjuvant therapy and that futures studies should focus on standardized selection criteria plus adjuvant and/or neoadjuvant therapies with OLT as definitive therapy for iCCA.

The group from the University of California, Los Angeles, has been working on a neoadjuvant protocol for patients with iCCA. They administered chemotherapy alone or combined with radiation before and/or after surgical treatment. They reviewed a series of 40 patients who underwent OLT for locally advanced iCCA and phCCA (26 iCCA and 14 phCCA). The overall 5-year disease recurrence-free survival after OLT was 29% and the recurrence rate was 38%. The shortcoming of this score relies on the low number of cases, mixing different types of tumors and the lack of external validation[5,74]. Indeed this strategy for the management of iCCA looks very promising but future investigation needs to be conducted. With advances in stereotactic body radiation for the treatment of hepatic malignancies this therapy can play an important role in this strategy in the future[75]. Preoperative chemoradiation may be more applicable in patients with large iCCA developing in non-cirrhotic livers than in those patients with cirrhosis that present with a "very early" iCCA but this will need to be assessed in the future.

CONCLUSION

In conclusion, OLT for selected patients with non-resectable phCCA is an established strategy with good results when a strict protocol is applied. Transplantation for iCCA in cirrhotic patients is still very controversial but may be a good option in a highly selective group of patients with small unresectable tumors. Future investigations in the field may confirm previous results and change the management of patients diagnosed

with this growing disease.

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