The Challenge of Perihilar Cholangiocarcinoma

Subjects: Surgery

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Perihilar cholangiocarcinomas (pCCA) are rare yet aggressive tumors originating from the bile ducts. While surgery remains the mainstay of treatment, only a minority of patients are amenable to curative resection, and the prognosis of unresectable patients is dismal. The introduction of liver transplantation (LT) after neoadjuvant chemoradiation for unresectable pCCA in 1993 represented a major breakthrough, and it has been associated with 5-year survival rates consistently >50%. Despite these encouraging results, pCCA has remained a niche indication for LT, which is most likely due to the need for stringent candidate selection and the challenges in preoperative and surgical management.

Keywords: hilar cholangiocarcinoma ; donor pool expansion ; hypothermic oxygenated machine perfusion

1. Introduction

Perihilar cholangiocarcinomas (pCCA) are epithelial tumors originating from the biliary tree below second-order bile ducts and proximally to the confluence of the cystic duct, and they represent 50–70% of the tumors arising from the biliary tree [1]. They are relatively rare [2] but aggressive tumors, and surgical resection is generally considered the only potentially curative treatment [3][4]. However, most patients with pCCA are diagnosed at an advanced stage, and only 15–35% are amenable to curative resection [3][5][6], which is associated with a 15–40% 5-year survival [7][8][9]. The 5-year survival of patients suffering from unresectable pCCA is 2% [10].

The dismal prognosis of unresectable pCCA led to exploring liver transplantation (LT) following neoadjuvant treatment with external beam irradiation, brachytherapy, and 5-fluorouracil (5-FU) and/or oral capecitabine as a potential treatment. The first series from the Mayo Clinic reported an impressive intention-to-treat 54% 5-year survival and a 82% 5-year survival after transplantation [11]. However, although the survival benefit of this approach has been confirmed in subsequent series [12], LT for pCCA has not gained widespread acceptance due to the difficulties in applying the neoadjuvant protocol, patient selection and the lack of clear allocation rules in this setting.

The term “transplant oncology” refers to the application of oncology along with transplant medicine and surgery to improve the survival and quality of life of cancer patients [13]. This includes considering LT for patients affected by malignancies that classically represented contraindications for LT, such as liver metastases from colorectal cancer [14], hepatocellular carcinoma beyond the most widely adopted selection criteria, pCCA and intrahepatic cholangiocarcinoma [15]. The prerequisite to successfully implement LT as a treatment for these diseases is the availability of suitable liver grafts. Although the introduction of direct acting antivirals against hepatitis C virus has profoundly changed the landscape of indications for LT [16], increasing the number of available grafts for alternative indications, the supply–demand gap for liver grafts remains an unresolved issue. The two main strategies to expand the donor pool are currently represented by the utilization of extended criteria donors (ECD) and by living donation. In most cases, ECD are represented by donors whose death has been determined by circulatory criteria (DCD), elderly donors, or liver grafts with significant macrovesicular steatosis [17][18]. While utilizations of these grafts may allow expanding the donor pool, their use has been associated with inferior outcomes as compared to those of LT using standard donors.

In the last decade, machine perfusion (MP) has been re-introduced in clinical practice, which is prompted by the need to cope with the increased risks associated with the use of ECD grafts [19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53][54]. Several MP techniques exist, which are characterized by different principles and mechanisms of graft protection [55]. Apart from improving graft preservation and allowing for longer preservation times, MP has a very interesting feature: it allows testing the viability of a liver graft prior to implantation (so-called “viability assessment”) [18][56]. Although normothermic MP (NMP) has been most frequently used as a tool for viability assessment, information about liver viability can be obtained also during hypothermic perfusion [33][57]. Assessing the viability of a graft should ideally allow for an increase in the number of transplanted grafts while minimizing recipient

risk and avoiding discarding potentially usable grafts solely based on donor characteristics. In addition, other aspects of machine perfusion technology make its application in the setting of LT for pCCA appealing.

2. The Challenge of Perihilar Cholangiocarcinoma

As the international classification of cholangiocarcinoma does not distinguish between perihepatic and distal cholangiocarcinoma [4], estimating the true incidence of pCCA is difficult. In the West, age standardized incidence rates range between 0.5 and 2 per 100,000 individuals, whereas in eastern Asia, incidence is higher due to endemic liver flukes (*Opisthorchis viverrini* and *Clonorchis sinensis*) infection as well as a higher incidence of hepatolithiasis. Worldwide, the incidence of pCCA has increased in recent years, which has been linked to the increased incidence of metabolic syndrome, especially in countries with historically low incidence rates [2].

Perihilar CCA is an aggressive disease. A large study from the Netherlands on 2031 patients showed an overall median survival of 5.2 months [58]. Patients undergoing palliative systemic treatment, loco-regional treatment or best supportive care had a median survival of 12.2, 14.5 and 2.9 months, respectively. Notably, only 15% of patients underwent curative resection, which was associated with a median survival of 29.6 months [58].

2.1. Surgery for Perihilar Cholangiocarcinoma

The outcome of patients suffering from pCCA is primarily determined by the possibility to undergo curative resection. However, only a minority of patients are eligible for surgical resection due to several factors. Early diagnosis is infrequent in pCCA because most patients with early disease are asymptomatic or symptoms are poorly specific (dyspepsia, abdominal discomfort, fatigue, weight loss) [3]. Furthermore, pCCA are desmoplastic and paucicellular tumors, which complicates obtaining histological confirmation once the clinical diagnosis becomes more evident [59]. At this stage, most patients will present with jaundice and/or cholangitis and will frequently require preoperative biliary drainage (PBD). In patients undergoing surgery for pCCA, preoperative cholangitis is associated with increased mortality, overall morbidity, incidence of liver failure, and sepsis, and it is an absolute indication for PBD [60]. In patients with jaundice but not cholangitis, PBD is still frequently indicated due to the concerns for impaired liver regeneration capability, as pCCA patients are frequently candidate for major liver resections. However, PBD has been associated with higher overall morbidity, perioperative transfusion, cholangitis, infection and bile leakage [61][62], suggesting that it could be reasonably avoided in patients with sufficient future liver remnant (≥50%). It is significant that regardless of the technique used for PBD (endoscopic versus percutaneous transhepatic biliary drainage), about 15% of patients will fail to proceed to surgery because of PBD complications and progressive deterioration [63]. Another factor complicating the surgical approach is the necessity to perform an oncologically adequate (R0) surgery, which frequently involves an extended hepatectomy associated with the resection of the biliary confluence and the reconstruction by an hepaticojejunostomy while preserving a sufficient portion of liver parenchyma. Portal vein embolization has traditionally been used to induce future liver remnant hypertrophy. Associating liver partition and portal vein ligation for stage hepatectomy (ALPPS) represents an alternative approach [64]. However, ALPPS is still debated in the setting of pCCA [65][66]. In patients who do not develop sufficient liver hypertrophy after portal vein embolization alone, associating hepatic vein embolization (so-called liver venous deprivation) could contribute to enhancing the growth of future liver remnants and improve access to curative resection [67].

Patients who can access resection with curative intent are exposed to an overall major morbidity rate of 43–65%, whereas postoperative mortality rates as high as 17% have been reported [68][69]. In a study evaluating outcomes of pCCA resection in 708 low-risk patients at 24 high-volume centers, the benchmark values (i.e., the 75% or 25% percentiles of the medians of each center) for Clavien–Dindo ≥ 3 complications rate and in-hospital mortality were ≤70% and ≤8%, respectively [70].

About 80% of patients will experience recurrence after resection, in most cases within 2 years from surgery [71][72]. Overall 5-year survival is 11–44% and appears to be strongly influenced by the radicality of surgical resection, being ~60% in patients undergoing R0 resection versus <10% after R1 resection [69]. Interestingly, benchmark value for R1 resection has been set at ≤43% [70].

Overall, surgery with curative intent appears to be an option only in a minority of patients suffering from pCCA, and it is burdened by a complicated preoperative management, high postoperative morbidity and mortality, and high recurrence rates, which highlights the urgent need for alternative strategies to improve the outcome in these patients.

2.2. Liver Transplantation as a Treatment for Perihilar Cholangiocarcinoma

In theory, LT is an interesting option for patients with pCCA because it allows for the radical excision of the tumor while avoiding the issue of residual hepatic functional reserve. Unfortunately, early results of LT performed in patients with pCCA were burdened by high recurrence rates, leading to pCCA being considered a contraindication for LT. [73][74]. However, observations that long-term survival could be achieved in patients with limited tumor burden, negative resection margins and no lymph node involvement opened to reconsider pCCA as a possible indication for LT in selected patients [75]. As aforementioned, the early experiences from the Mayo Clinic (Rochester, MN, USA) team showed that by stringent patient selection and by applying a neoadjuvant protocol of external beam radiotherapy, brachytherapy and 5-FU, excellent results could be achieved [11][76][77]. **Table 1** summarizes the results of LT for pCCA [11][12][76][78][79][80][81][82][83][84][85][86][87][88][89][90].

Table 1. Results of LT for pCCA.

Author	Country	Study Design	n	Dropout (%)	Neoadjuvant Treatment	Survival Outcomes
Figueras et al. [83]	Spain	Single center, retrospective	LT, n = 8 LR, n = 20	n.a.	None	5-year survival: - LT = 36% - Resection = 21%
Sudan et al. [91]	NE, USA	Single center, retrospective	LT, n = 11	35%	Brachytherapy 6000 cGy + 5-FU	Median survival after LT = 25 months; 45% disease-free with median 7.5 years follow-up
Heimbach et al. [11]	MN, USA	Single center, prospective	LT, n = 28	39%	EBRT 4500 cGy + Brachytherapy 2000-3000 cGy + 5-FU	5-year survival: - Whole cohort = 54% - LT = 82%
Robles et al. [88]	Spain	Multicenter, retrospective	LT, n = 36	n.a.	None	Overall survival at 1, 3, 5, and 10 years was 82%, 53%, 30%, and 18%. Disease-free survival at 1, 3, 5, and 10 years was 77%, 53%, 30%, and 18%.
Axelrod et al. [79]	IL, USA	Single center, retrospective	LT, n = 5	n.a.	EBRT 45 Gy + 5-FU	100% recurrence-free survival in 4 patients treated with neoadjuvant protocol (median follow-up = 18 months)
Jonas et al. [85]	Germany	Single center, retrospective	LT, n = 5	n.a.	None	Overall survival was 80% at a median follow-up of 20 months
Hidalgo et al. [84]	UK	Single center, retrospective	LT, n = 12 LR, n = 44	n.a.	None	5-year survival: - LT = 20% - Resection = 28%
Kaiser et al. [86]	Germany	Multicenter, retrospective	LT, n = 47	n.a.	None	Median survival = 35.5 months. Overall survival at 1, 3 and 5 years was 61%, 31% and 22%
Rosen et al. [92]	MN, USA	Single center, retrospective	LT, n = 136	36%	EBRT 4500 cGy + Brachytherapy 2000-3000 cGy + 5-FU + capecitabile	Overall survival at 1, 3 and 5 years was 92%, 81%, and 74%.
Darwish Murad et al. [12]	USA	Multicenter, retrospective	LT, n = 214	25%	EBRT 4500 cGy + Brachytherapy 2000-3000 cGy + 5-FU + capecitabile	Recurrence-free survival at 2, 5 and 10 years was 78%, 65% and 59%.
Schule et al. [89]	Germany	Single center, retrospective	LT, n = 16	n.a.	None	Overall survival (postoperative deaths excluded) at 3 and 5 years was 63% and 50% in N0 patients and 15% and 0% in N+ patients
Welling et al. [93]	USA	Single center, retrospective	LT, n = 6	42%	SBRT 50-60 Gy + capecitabine	Overall survival in transplanted patients at 1 year was 81%

Author	Country	Study Design	n	Dropout (%)	Neoadjuvant Treatment	Survival Outcomes
Duignan et al. [81]	Ireland	Single center, retrospective	LT, n = 20	26%	EBRT 45-55 Gy + Brachytherapy 7.5 Gy + 5-FU + capecitabile	Overall survival at 1, 3 and 4 years was 75%, 60% and 51%
Marchan et al. [87]	GA, USA	Single center, retrospective	LT, n = 8	20%	EBRT 4500 cGy + Brachytherapy 2000-3000 cGy + 5-FU + capecitabile	Median survival = 30.2 months. Overall survival at 6, 12 and 24 months was 100%, 87.5%, and 87.5%
Dondorf et al. [80]	Germany	Single center, retrospective	LT, n = 22	31%	None	Median survival = 29 months. Overall survival at 1, 3 and 5 years was 89,2%, 36% and 28.8%.
Ethun et al. [82]	USA	Multicenter, retrospective	LT, n = 41 LR, n = 191	34%	EBRT 4500 cGy + Brachytherapy 2000-3000 cGy + 5-FU	Median survival: - LT = 77.4 months - Resection = 27 months
Zaborowski et al. [90]	Ireland	Multicenter, retrospective	LT, n = 26	30%	EBRT 45-55 Gy + Brachytherapy 7.5 Gy + 5-FU + capecitabile	Median survival = 53 months. Overall survival at 1, 3 and 5 years was 81%, 69% and 55%.
Ahmed et al. [78]	MO, USA	Single center, retrospective	LT, n = 38	34%	EBRT 4500 cGy + Brachytherapy 2000-3000 cGy + 5-FU	Overall survival at 1, 3 and 5 years was 91%, 58% and 52%

Abbreviations: LT, liver transplantation; LR, liver resection; EBRT, external beam radiotherapy; SBRT, stereotactic beam radiotherapy; 5-FU, 5-fluoruracil.

In the absence of a neoadjuvant protocol, LT has been associated with 5-year overall survival rates ranging from 20% to 36%, whereas using a pre-transplant chemoradiation protocol has resulted in 5-year survival rates ranging from 52% to 82%. These positive outcomes have come at the expense of strict patient selection and the morbidity of the neoadjuvant treatment itself. Indeed, 25–42% of patients initially candidate to LT after chemoradiation will not be transplanted due to inability to tolerate the treatment, complications, or tumor progression. Furthermore, LT can be technically complicated due to the effects of radiotherapy on the hepatic hilum. Since the early reports [11], an increased incidence of hepatic artery and portal vein thrombosis has been reported, leading to the frequent choice of utilizing an interposition graft anastomosed to infrarenal aorta for arterial vascularization. Early postoperative outcomes have been marked by a higher rate of complications, sometimes directly related to preoperative radiation therapy. Another element of difficulty may be represented by the presence of adhesions. Indeed, a staging laparotomy is indicated to rule out peritoneal disease or extrahepatic lymphnodes involvement before the patient can be considered eligible for LT. In the setting of deceased donor LT, considerable time can separate the staging laparotomy from LT operation, further complicating an already difficult dissection. An alternative option, which has been adopted by some centers, is performing the staging laparotomy simultaneously with LT, to avoid a repeat operation and peritoneal adhesions. While this is a viable option in living donor liver transplantation, in deceased donor LT, it necessitates the availability of a back-up recipient and has the disadvantage of significantly prolonging preservation time, which may have a negative impact on postoperative graft function.

In summary, although excellent outcomes have been reported, LT for pCCA has not gained widespread adoption. This is likely explained by the limited number of eligible patients, the difficulties in preoperative management and the technical and logistical difficulties linked to the neoadjuvant chemoradiation protocol.

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