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Long-Term Recurrence-Free Survival after Liver Transplantation in the Presence of Intrahepatic Cholangiocellular Carcinoma

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Abstract

Intrahepatic cholangiocellular carcinoma (ICC) in the presence of liver cirrhosis is challenging to treat. Surgical resection is rarely feasible due to portal hypertension and limited functional reserve. Initial results after liver transplantation (LT) were poor due to a high rate of early tumor recurrence. We here present the case of a 48-year-old male patient who underwent LT due to Wilson's disease and suspected hepatocellular carcinoma (HCC) on radiologic imaging. As a bridge to LT, the patient had undergone transarterial chemoembolization (TACE). Explant pathology provided evidence of moderately differentiated ICC in two tumor lesions, measuring 18 mm and 15 mm. The perioperative course was uneventful and the patient was discharged on postoperative day 15. Initial immunosuppression consisted of tacrolimus, mycophenolate mofetil and prednisone and was adapted to prolonged-release tacrolimus and everolimus in the later course. The patient did not receive preemptive adjuvant treatment. For follow-up, CT scan of chest and abdomen was performed at six months, 1 year, and then every two years post LT. The patient is alive and well without signs of tumor recurrence 12 years post LT. As recent studies suggest, patients with ICC ≤2 cm may become candidates for LT.

Keywords: Intrahepatic cholangiocellular carcinoma; Liver transplantation; Recurrence-free survival; Transarterial chemoembolization

Abbreviations

AFP: Alpha-fetoprotein; CT: Computed Tomography; ICC: Intrahepatic Cholangiocellular Carcinoma; HCC: Hepatocellular Carcinoma; LT: Liver Transplantation; MRI: Magnetic Resonance Imaging; MELD: Model of End-stage Liver Disease; POD: Postoperative Day; PSC: Primary Sclerosing Cholangitis; TACE: Transarterial Chemoembolization

Introduction

Cholangiocelluar carcinomas are a heterogenous group of tumors classified based on their anatomic location as intrahepatic, perihilar or distal [1]. Intrahepatic cholangiocelluar carcinoma (ICC) accounts for 5-10% of all cholangiocellular carcinomas and is the second most common primary hepatic malignancy [2]. The average annual incidence of ICC in the United States is 1.6/100,000/year [2]. Typically, ICC lesions take up contrast agent progressively during the arterial and venous phases of computed tomography (CT) and magnetic resonance imaging (MRI) series. CA19-9 may identify patients with ICC, with 62% sensitivity and 63% specificity [3]. The level of elevated CA19-9 may even predict tumor stage and prognosis [4].

Treatment options for ICC are limited and associated with high rates of tumor recurrence and short survival times. Surgical resection offers the only potential chance of cure in ICC [5]. In patients with cirrhosis, severe portal hypertension represents a contraindication for resection of ICC. The 5-year survival rate for non-resectable cases is less than 5% in general [6].

Successful outcomes after liver transplantation (LT) have been reported for selected patients with hilar cholangiocellular carcinoma and primary sclerosing cholangitis (PSC). ICC has been considered a contraindication to LT in many transplant centers worldwide because of the initially high rate of post-transplant tumor recurrence [7,8]. Recently, studies have shown that selected patients with "very early" ICC, *i.e.* single tumors ≤2 cm, may become candidates for LT [9-11].

Here we report on a patient who underwent LT in the setting of suspected HCC but was found to have ICC during the explant pathological examination. Up to now, only approximately 100 cases of ICC treated with liver transplantation have been published. There are still limited data on the difficulties in pre-transplant imaging diagnostics, possible pre-transplant treatments as well as post-transplant tumor recurrence and survival. On the basis of the reported patient's course and the previously published data, we discuss the possible treatment strategies.

Case Presentation

A 48-year-old patient was evaluated and listed for LT in the setting of Wilson's disease and suspected hepatocellular carcinoma (HCC). The patient had been diagnosed with Wilson's disease 10 years prior to liver transplant evaluation and was under medical treatment with penicillamin 300 mg *bid* ever since. Liver cirrhosis was complicated by esophageal varices up to grade IV, ascites and recurrent episodes of hepatic encephalopathy. Model of end-stage liver disease (MELD) score was 16 at the time of placement on the LT waitlist. On account of the initial MELD score and the stable clinical course, there was no MELD update during the waiting time until LT.

Elevated alpha-fetoprotein (AFP) was noticed (43.9 IU/mL) during routine screening but returned to normal (5.8 IU/mL) within 2 months without further treatment. Further tumor markers were negative (CEA 2,8 ng/mL, CA19-9 1,0 IU/mL) as well. On CT scan, a lesion measuring 44 mm with irregular contrast-uptake, suspicious of HCC, was detected (Figure 1). Angiography of the liver confirmed a hypervascularized tumor lesion in liver segment VIII, and transarterial

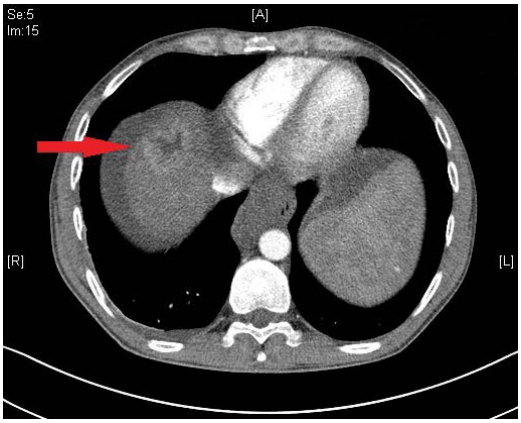

Figure 1: CT scan (arterial phase) with suspicious mass in liver segment VIII (the day before TACE).

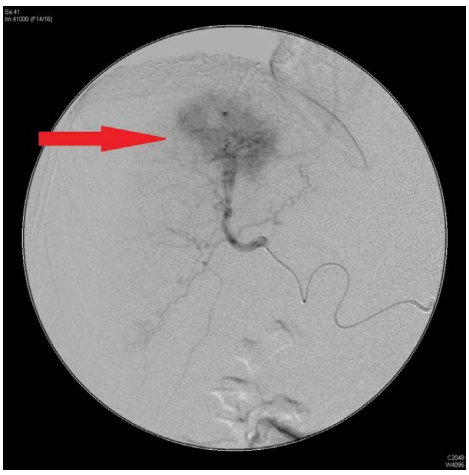

Figure 2: Angiography of the liver with hypervascularized tumor lesion in liver segment VIII.

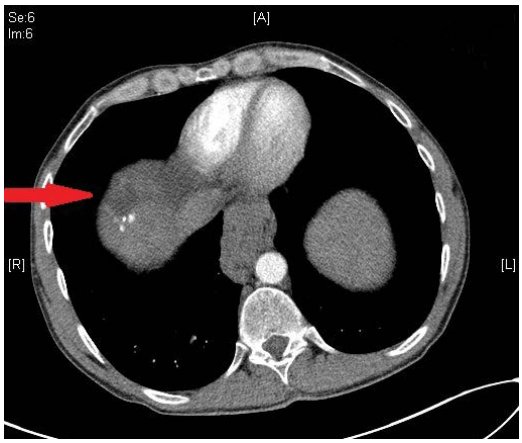

Figure 3: CT scan (arterial phase) three months after TACE.

chemoembolization (TACE) containing mitomycin C 5 mg and lipiodol 2,5 mL was performed (Figure 2). A CT scan 3 months after TACE demonstrated a hypodense tumor lesion measuring 25 mm with residual hypervascularization peripherally (Figure 3), *i.e.* radiologic signs of tumor necrosis. Hence, no further TACE was scheduled.

Approximately 10 months after TACE, the patient underwent LT. The operative as well as the postoperative course was uneventful. The patient was extubated on postoperative day (POD) 1 and transferred to the regular ward on POD 2. On POD 15, the patient was discharged. Initial immunosuppression consisted of tacrolimus, mycophenolate mofetil, and prednisone. Only subsequently, the immunosuppression regimen was adapted to prolonged-release tacrolimus and everolimus in respect of the history of malignancy.

On explant specimen, two lesions measuring 18 and 15 mm were detected with evidence of adenocarcinoma instead of suspected hepatocellular carcinoma. Both ICC were moderately differentiated and without presence of lymphangiosis or microvascular invasion; lymph node involvement was not assessed as no lymph nodes were sampled (pT2b Nx G2 L0 V0 R0, UICC seventh edition). The tumor lesions showed partial tumor necrosis.

The patient did not receive preemptive adjuvant treatment. For follow-up, the patient underwent CT scan of chest and abdomen at six months, 1 year, 2 years, 4 years, 6 years and 8 years post LT. As CA 19-9 was negative prior to treatment, routine assessment was not performed for follow-up. Over a follow-up period of 12 years now, there were no signs of recurrence. Liver function is adequate as well, but there are signs of ischemic-type biliary lesions without the necessity for regular endoscopic treatment.

Discussion

Here we present the case of a patient who was suspected to have HCC but was found to have ICC on explant pathology. Over a time period of 12 years, we performed 231 LT in patients with HCC; this was the only patient with evidence of ICC at explant pathologic examination. Furthermore, there were no patients with incidental ICC in our transplant center cohort.

In the setting of well-compensated cirrhosis, patients diagnosed with ICC may be offered surgical resection as first treatment option [1]. Our patient would not have been eligible for any curative treatment or in fact many palliative treatment options. In the setting of decompensated cirrhosis, surgical resection as well as (repeated) locoregional treatments and systemic chemotherapy have limited applicability and efficacy [9].

LT in patients with ICC has been associated with a poor prognosis and a high rate of tumor recurrence, mainly due to an unrefined selection process [12]. Recently, a large international multicenter cohort study on patients who had been diagnosed with ICC on explant pathology demonstrated that patients with a single ICC ≤2 cm at pathologic examination after LT achieve good 5-year survival and a low recurrence rate [9].

As in most published reports, our patient was found to have ICC only after explant pathology examination. Even with distinct radiologic patterns, ICC continues to be misdiagnosed and unintentionally transplanted among roughly 1% of all LT [9,13,14]. In general, ICC is difficult to diagnose owing to its silent clinical character, the low specificity of most diagnostic modalities and the lack of absolute diagnostic criteria [3]. Especially in cirrhosis, the radiological diagnosis of ICC poses a challenge. Small ICC <2 cm may mimic HCC because of the absence of a progressive enhancement pattern [15]. In patients awaiting liver transplantation, some authors recommend a tumor biopsy of nodules without typical radiological HCC patterns [16].

The published evidence with LT for cirrhotic patients diagnosed with ICC on pathology examination, *i.e.* incidental tumors or tumors misdiagnosed as HCC, is scarce and the study cohorts are diverse (Table 1). [9,11-14,17-20] Therefore, it remains difficult to assemble coherent data for comparison. Many reported studies treat patients with ICC and patients with combined ICC-HCC lesions as one entity as they judge the differences in tumor features and outcome to be minimal

Table 1: Patients transplanted with isolated ICC detected on explant pathology examination and rate of tumor recurrence.

Author	Patients (n)	Tumor recurrence (%)
Sotiropoulos, GC (2008) [19]	10	20.0
Sapisochin, G (2011) [12]	4	57.1 *
Vallin, M (2013) [14]	4	25.0
Sapisochin, G (2014) [10]	18	21.4 #
Sapisochin, G (2014) [11]	29	24.1
Facciuto, ME (2015) [17]	7	28.6
Sapisochin, G (2016) [9]	48	13.3 / 51.5 †
Takahashi, K (2016) [13]	9	53.8 ‡
Lee, DD (2018) [18]	9	29.4 §
Hara, T (2021) [20]	19	53

* overall recurrence rate for patients with isolated ICC (n=4), mixed ICC/HCC (n=8) and ICC+HCC (n=2)

overall recurrence rate for patients with isolated ICC (n=18), mixed ICC/HCC (n=15) and ICC+HCC (n=9)

† recurrence rate for patients with "very early" ICC and for patients with advanced ICC

‡ overall recurrence rate for patients with isolated ICC (n=9) and mixed ICC/HCC (n=4)

§ overall recurrence rate for patients with isolated ICC (n=9) and mixed ICC/HCC (n=8)

[10,13,18]. As all reported sample sizes are small, it seems slightly bold to make this assumption. Tumor recurrence ranges from 20% to over 50% [9,11-14,17-20]. For patients with single ICC lesions ≤2 cm at pathologic examination, excellent results are achieved with a tumor recurrence rate of 0-13% [9,11].

So far, there is no sufficient data supporting pre-transplant treatment of ICC. In many centers, patients with an expected waiting list time >6 months typically undergo locoregional treatment of suspicious lesions [9.11]. Due to the small number of patients and tumors and the great heterogeneity in preoperative tumor treatments, no conclusions can be drawn as to the effectiveness of these treatments in patients with ICC [11]. Data on tumor necrosis post-treatment is inconclusive as well; some percentage of necrosis seems to be achieved in less than 50% [9,11]. In our patient, the tumor lesion showed partial necrosis after TACE.

Advanced ICC, *i.e.* >2cm, multiple tumors, should still remain a contraindication for LT as Sapisochin *et al.* detected a tumor recurrence rate of 51.5% with an associated mortality of 88.2% [9]. In an exploratory analysis of possible risk factors for tumor recurrence, the presence of microvascular invasion and poor differentiation are associated with an increased risk of tumor recurrence as well [9,11]. Whether patients with ICC >2cm could become LT candidates after undergoing locoregional treatment, *e.g.* TACE, remains to be investigated.

Further research on inclusion criteria and pre-transplant treatment is of interest. Another open question is whether the outcome of patients preoperatively diagnosed of an ICC will be the same as that of patients diagnosed on pathology examination.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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