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Review Article

Liver transplantation and combined hepatocellular-cholangiocarcinoma: Feasibility and outcomes

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ABSTRACT

Introduction: Combined hepatocellular-cholangiocarcinoma (CHC or cHCC-CC) is a rare primary liver tumor displaying histological features of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA). Most patients are not suitable for surgery because of the advanced stage of the disease at the moment of diagnosis. We decided to review the literature in order to identify the outcomes after liver transplantation for CHC and to clarify which is the most appropriate treatment.
Material and methods: A systematic literature search was performed. Studies reporting outcomes of liver transplantation (LT) for CHC and studies comparing oncologic outcomes after LT versus liver resection (LR) for CHC were included in this review.
Results: The mean 5-y Disease Free Survival (DFS) reported in literature is 45.4%, while the mean 5-y overall survival (OS) is 41.8%, analyzing a cohort of 418 cases. The mean DSF in our series after LT was 7.97 months, while the mean OS was 11.7 months.
Conclusions: LT should be avoided for the treatment of CHC, in order to allocate organs for more appropriate diseases. Moreover, surgical resections, and in particular major hepatectomies, seem to be associated with acceptable outcomes. An accurate preoperative management is needed, and the use of PET-CT when differential diagnosis is difficult should be considered.

1. Introduction

Liver cancer represents the second leading cause of cancer mortality and the fifth most commonly diagnosed cancer in the world [1]. Combined hepatocellular-cholangiocarcinoma (CHC or cHCC-CC) is a rare primary liver tumor that is considered as a mixed neoplasm composed of cells displaying histological features of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA) [2]. CHC accounts for less than 1% of all liver carcinomas, and shares with HCC similar geographical distribution differences and a similar age and sex distribution, but showing worse prognosis. In fact, some reports in the literature highlighted a higher frequency of lymph node metastasis compared to HCC [3]. The diagnosis of CHC requires the demonstration of bile canaliculi by polyclonal CEA (mixed biliary glycoproteins) combined with Hep Par immunoexpression (hepatocellular carcinomatous component), and that of neutral epithelial mucin by the PAS-diastase reaction (cholangiocarcinomatous component) [3]. Wells described these mixed tumors in 1903 for the first time, while the first classification was issued only in 1949 by Allen & Lisa. They identified three subtypes of CHC: in Type A the two components of the CHC are completely separated (distinct lesions); in Type B the two components are close and can merge together during their growth; finally, in Type C we find true mixed neoplasms that are believed to originate from the same nodule. In 1985 Goodman et al. presented a new histological classification of CHC defining three classes: Type I or "collision tumors", where a coincidental occurrence of both HCC and CCA in the same patient can be found; Type II or "transitional tumors," in which there are areas of intermediate differentiation and an identifiable transition between HCC and CCA; and finally Type III or 'fibrolamellar tumors' that are very similar to fibrolamellar HCC but they also include mucus secreting pseudo-glands [4]. In 2010 the WHO proposed a new classification that identifies two groups of CHC [5]: (1) "classic CHC", that includes Allen Type 1 and Goodman Type A (distinct nodules of HCC and CCA: the two components can range from low to high grade); (2) "stem cells-CHC", which

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Table 1
Main findings from literature review on outcomes after liver transplantation (n.a. = not applicable; n.r. = not reported; DSF = disease free survival; OS = overall survival; y = years).

Author	Year	Study interval	n. CHC of patients	Follow-up	DFS	OS
Chan et al. [9]	2007	1998–2003	3	n.r.	n.r.	n.r.
Maganty et al. [10]	2010	2001–2008	3	n.r.	n.r.	n.r.
Panjala et al. [11]	2010	1998–2008	12	335 days (median)	n.r.	79% 1-y 66% 3-y 16% 5-y
Groeschl et al. [12]	2013	1973–2008	19	n.r.	n.r.	89% 1-y 48% 3-y
Song et al. [13]	2013	1995–2012	8	40 months (mean)	37.5% 5-y	50% 5y
Park et al. [14]	2013	1999–2009	15	n.r.	60% 1-y 53.3% 3-y 53.3% 5-y	66.7% 1-y 60% 3-y 60% 5-y
Garancini et al. [2]	2014	1988–2009	61	n.r.	n.r.	41.1% 5-y

is further divided into three subgroups: typical, intermediate and cholangiocellular. The origin of CHC is still debated; a bipotential precursor may explain the origin of this tumor [6]. Patients are often asymptomatic until the disease is advanced. Common symptoms are non-specific, such as weight loss, malaise, abdominal discomfort, jaundice, hepatomegaly or a palpable abdominal mass [7]. Therefore, many patients are not suitable for a surgical approach because of the advanced stage of the disease [8]. Moreover, the majority of CHC diagnoses is post-operative, due to misdiagnoses. We decided to review the literature in order to identify the outcomes after liver transplantation for CHC and to clarify which is the most appropriate treatment. In addition, we herein reported the experience of our center with CHC.

2. Material and methods

2.1. Literature search

PRISMA statement guidelines for conducting and reporting systematic reviews were followed as previously reported.

A systematic literature search was performed independently by two of the manuscript's authors (PM and GT) using PubMed, EMBASE, Scopus and the Cochrane Library CENTRAL. The search was limited to studies in humans and to those reported in the English language, without any filter set for year of publication or type of publication.

The following MESH search headings were used: "combined hepatocellular cholangiocarcinoma" AND "liver transplantation" OR "liver transplant". Extensive crosschecking of the reference lists of all retrieved articles that fulfilled the inclusion criteria further broadened the search. For all of the databases, the last search was run on June 12th, 2016.

2.2. Study selection

The same two authors independently screened the titles and abstracts of the primary studies that were identified in the electronic search. Duplicate studies were excluded. The following criteria were set for inclusion in this review: (1) Studies reporting outcomes of liver transplantation (LT); (2) Studies comparing oncologic outcomes after LT versus liver resection (LR); and (3) If more than one study was reported by the same institute, only the most recent or the highest quality study was included.

The following exclusion criteria were set: (1) Review articles, letters, comments and case reports; and (2) Studies in which it was impossible to retrieve or calculate data of interest.

The literature search yielded 69 articles; after duplicates were removed, 58 titles and abstracts were reviewed. Most relevant data and papers are reported in the results section and later discussed.

2.3. Data extraction

All relevant texts, tables and figures were reviewed for data extraction.

Discrepancies between the two reviewers were resolved by consensus discussion or with the opinion of the Senior Author (FDB).

3. Results

3.1. Literature review

Seven papers were finally included in this review, results are summarized in Table 1.

In 2007 Chan et al. reported three cases of LT for CHC [9]. The first patient underwent LT for a suspected HCC; he remained disease-free until 4 months later, then a metastatic right lung lesion was identified on CT scan. Serum α-fetoprotein was elevated from10 ng/mL to 76 ng/mL at that time. He underwent video-assisted thoracoscopic resection of the right lung lesion but at 5 months increasing number and size of pulmonary metastases was revealed on CT scan, in addition to bony metastases to the left humerus, and finally died 16.5 months after LT. In the second case a patient underwent LT for HCC as well, and a CHC was revealed on final histology. His postoperative course was uneventful and he was discharged on p.o.d. 12; he remained disease-free until 35 months after LT. The third patient underwent LT due to poor liver function complicated by refractory ascites and hydrothorax, and a small CHC was incidentally found on final histology. She was discharged on p.o.d. 23 and had no evidence of tumor recurrence for 25 months after LT.

Maganty et al. in 2010 reported their experience with three cases of CHC who had undergone LT, 2 for suspected HCC and 1 with an incidental finding of the nodule in the explanted liver [10]. The post-operative course of the first patient was complicated by hepatic artery thrombosis (HAT) requiring re-transplantation at 32 days; she eventually developed visual loss, stroke, malnutrition, and hypercalcemia. Moreover, a metastatic carcinoma infiltrating the bone marrow with immunohistochemical features of combined HCC-cholangiocarcinoma with a mixture of tumor cells expressing hepatocellular antigen and cytokeratin-7 was demonstrated and she died of pneumonia and renal-respiratory failure 144 days after the initial transplant. The second patient was tumor free for 8.5 years from LT, although this patient needed a second transplant 7 years after the first one due to intractable biliary strictures. The third patient died 1 year after LT of sepsis and multi-organ failure and a suspected graft-versus-host grade 2. Histopathological examination of the patient's lung tissue revealed organizing pneumonia, foci of metastatic cholangiocarcinoma, and Kaposi's sarcoma (the patient was negative for HIV) in the peribronchial tissue with metastasis to the perihilar node.

In their paper published in 2010 Panjala et al. reported the outcomes of 12 patients that had received LT with a misdiagnosis of HCC, CC or a nonmalignant etiology, and at final histology were diagnosed with CHC [11]. The authors also reported a retrospective analysis of all images of patients included in the study by an expert hepatobiliary radiologist. Overall, the majority of CHC tumors had the following features: equal distribution in the central and the peripheral portions of the liver; well-circumscribed margins; MRI

Table 2
Patient's characteristics from our database.

	Patient 1	Patient 2	Patient 3
Sex	M	M	M
Age	47	61	58
MELD	9	11	17
Indication to LT	HCC in HCV related liver cirrhosis	HCC in HCV related liver cirrhosis	HCC in HCV related liver cirrhosis
Inside Milan criteria	No	No	Yes
Tumor size (max, cm)	2.5	3.2	2.7
Histological diagnosis	HCC/CHC (type II)	iCCA/CHC (type II)	HCC/CHC (type I)
Recurrence site	Liver and Lungs	Liver and bone (spine)	Liver and bone (spine)
Recurrence treatment	Liver Thermoablations	Doxorubicin	No
Immunosuppression	Tacrolimus	Tacrolimus	Tacrolimus
DSF (months)	14.38	1.55	8.03
OS (months)	17.27	3.91	13.91

imaging 100% sensitive for lesion detection. In their cohort 58% of patients developed metastases at an average of 539 days from LT, while at a median follow-up of 335 days (range: 48–3493) from LT, 58% of the LT recipients expired, 86% from metastases (1 patient died from LT-related complications at 48 days after LT). OS rates at 1, 3 and 5 years were 79%, 66% and 16%, respectively.

In 2013 Groeschl et al. reported a retrospective analysis of the SEER database comparing the outcomes after liver transplantation for HCC (1147 patients) orCHC (19 patients) [12]. The outcomes after LT showed that OS at 1 year was 90% and 89%, respectively for HCC and CHC, while at 3 years it was 78% and 48%, respectively ($p = 0.01$). Conversely, after liver resection 1 year survival rates were 77% and 71%, respectively, while at 3 years they were 55% and 46%, respectively ($p = 0.4$).

In the same year Song et al. reported their experience with patients diagnosed with CHC after either liver resection (LR) for primary liver cancer (68 patients) or after LT for primary liver cancer (8 patients) between 1995 and 2012 [13]. In their study, only 1 of 8 patients had undergone deceased donor LT while the others had undergone living donor LT. The authors reported that patients after LT showed slightly better Disease Free Survival (DFS) and overall survival (OS), although without any statistical significance. In detail, 5 year DFS rates were 26.2% vs 37.5%, respectively ($p = 0.333$), while 5 year OS rates were 42.1% vs 50%, respectively ($p = 0.591$).

Data regarding 15 patients who had undergone LT between January 1999 and December 2009 for HCC, with a final histology of CHC, were reported by Park et al. in 2013 [14]. In their cohort nine patients underwent 1–6 pretransplant transarterial chemoembolization (TACE) treatments for suspected HCC lesions; fourteen patients had undergone living donor LT and one a deceased donor LT. There was no perioperative mortality. Seven patients had tumor recurrences and, of these, 6 had recurrence during the first 12 months. All patients with tumor recurrences died between 2 and 57 months after diagnosis (median 4 months). OS rates were 66.7% at 1 year, and 60.0% at 3 and 5 years. DSF rates were 60.0% at 1 year and 53.3% at 3 and 5 years.

According to Garancini et al., after reviewing the SEER database, 465 patients had been diagnosed with CHC between 1988 and 2009 [2]. Among these, 65.2% had not received any invasive treatment, 4.0% had undergone tumor ablation, 7.6% had undergone a minor hepatectomy (MNH), 10.0% had undergone a major hepatectomy (MJH), and 13.1% had undergone LT. The mean reported tumor size was 5.8 ± 3.6 cm. At the definitive histology 24.1% of the 54 patients that had undergone regional lymph node removal had lymph node metastases. In this study, OS rates at 5 years for CHC, HCC, and CC patients were 10.5%, 11.7%, and 5.7%, respectively ($p < 0.001$); the 5-year disease specific survival (DSS) rates were 17.8%, 21.0%, and 11.9%, respectively ($p < 0.001$). The results from the multivariate analysis on patients affected by CHC showed that black race, distant SEER stage, and a tumor size of 5.1–10.0 cm are independently associated with compromised 5-year DSS. Interestingly, patients diagnosed after 1995 and patients who were treated with surgery (including MNH, MJH, or LT) had better outcomes. OS survival rates after LT, MJH, MNH, and ABL were 41.1%, 28.1%, 27.1% and 0%, respectively ($p < 0.001$), while DSS rates were 52.8%, 46.5%, 31.9% and 0%, respectively ($p < 0.001$).

3.2. Our experience

From January 2000 to May 2015, 655 LT were performed at the Liver Transplant Center in Modena, Italy. We retrospectively reviewed the pathological data of the explanted livers, finding 3 cases of incidental CHC: two cases of CHC associated with nodules of HCC and one case of CHC associated with intra-hepatic CCA (iCCA). Patients' characteristics are reported in Table 2. All patients received Tacrolimus as immunosuppressive regimen. The patient with histological findings of CHC associated with iCCA had postoperative elevation of the biohumoral marker Ca19.9 (4929 UI/mL) suggesting CCA recurrence. In this case a chemotherapy regimen based on doxorubicin was administered. The mean DSF in our series was 7.97 months, while the mean OS was 11.7 months.

4. Discussion

As reported in the literature, most CHC are treated with LT due to a misdiagnosis of HCC. Is it possible to get a precise diagnosis during preoperative assessment? According to Shetty et al. dynamic contrast-enhanced magnetic resonance imaging (MRI) and computed tomography (CT) are the imaging modalities of choice in the evaluation of CHC. In particular, MRI was reported to be 100% sensitive compared with 78% for CT in a small series [15]. The authors suggest that the possible presence of CHC should be considered when both HCC and CC features are evident in the same tumor [15]. de Campos et al. reported that a high signal on T2 sequences, portions of tumor showing progressive enhancement/contrast retention and lack of capsule are the clues to the diagnosis of CHC [16]. In 2013 Ijichi et al. reported their experience with 3 patients affected by CHC and studied with ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET-CT) [17]. In this case series all the CHCs were detected at PET, and the SUVmax values were 9.9, 12.0 and 13.0. Moreover, any correlation between SUVmax levels and tumor size or blood markers was found. An evaluation of the role of tumor markers was retrospectively conducted by Li et al. in their cohort of patients. They found a wide variety of behaviors among CHC in terms of AFP and CA19-9 expression. They concluded that combining simultaneous tumor marker elevation, or the evidence of discordance between the values of tumor markers with the imaging pattern of the lesions (i.e. AFP elevation and absence of classical imaging feature pointing to HCC), may lead significantly more patients to be diagnosed with CHC [18].

This is consistent with the findings of the study by Fowler et al., in which the authors evaluated the ability of experienced radiologists in retrospectively identify CHCs in a cohort of primary liver tumors including HCCs and CCs. They concluded that it is extremely difficult to correctly identify CHC only on the basis of imaging findings [19]. Lastly, some authors including Panjala et al., suggest a possible role of lesion biopsy to obtain a more precise diagnosis [11]. Garancini et al. reported that survival of CHC patients is related to the type of treatment received: according to their data, patients not undergoing surgical approaches or treated with ablative therapies had poorer prognoses [2]. Although the surgical group represents the minority in their study, they concluded that more aggressive treatments (MJH and LT) are related to better outcomes. Although retrospective, this is currently the largest series reported on this topic. Song et al. did not find any difference in DSF and OS comparing LR and LT. Given the limitation due to the retrospective nature of the study, they correctly reported that the role of LT is not clear and that in cases with tumors smaller than 5 cm and with preserved liver function, liver resection should be considered when complete resection with enough safety margin is possible [13]. In fact, Groeschl et al. [12] reported in their analysis of the SEER database a comparable 1- and 3-year survival between HCC and CHC patients after liver resection.

5. Conclusions

According to the data reported in the literature to date, LT should be avoided for the treatment of CHC, in order to allocate organs for more appropriate diseases. Moreover, surgical resection, and in particular major hepatectomy, seems to be associated with acceptable outcomes. Therefore, an accurate preoperative management is needed, and the use of PET-CT should be considered when differential diagnosis is difficult.

Conflict of interest

None declared.

References

[1] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International Journal of Cancer 2015;136:E359–86.
[2] Garancini M, Goffredo P, Pagni F, et al. Combined hepatocellular-cholangiocarcinoma: a population-level analysis of an uncommon primary liver tumor. Liver Transplantation 2014;20:952–9.
[3] Wittekind C, Fischer HP, Ponchon T. Pathology and genetics of tumours of the digestive system; 2000.
[4] Goodman ZD, Ishak KG, Langloss JM, et al. Combined hepatocellular-cholangiocarcinoma. A histologic and immunohistochemical study. Cancer 1985;55:124–35.
[5] Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Digestive System. 4th ed. Lyon: IARC Press; 2010.
[6] Spagnoli FM, Amicone L, Tripodi M, et al. Identification of a bipotential precursor cell in hepatic cell lines derived from transgenic mice expressing cyto-Met in the liver. The Journal of Cell Biology 1998;143:1101–12.
[7] Zhang H, Yang T, Wu M, et al. Intrahepatic cholangiocarcinoma: epidemiology, risk factors, diagnosis and surgical management. Cancer Letters 2015;379:198–205.
[8] Lindner P, Norrby J, Olausson M, et al. Survival after liver transplantation for cholangiocarcinoma has increased during the last decade. Transplantation Proceedings 2003;35:811–2.
[9] Chan AC, Lo CM, Ng IO, et al. Liver transplantation for combined hepatocellular cholangiocarcinoma. Asian Journal of Surgery 2007;30:143–6.
[10] Maganty K, Levi D, Moon J, et al. Combined hepatocellular carcinoma and intrahepatic cholangiocarcinoma: outcome after liver transplantation. Digestive Diseases and Sciences 2010;55:3597–601.
[11] Panjala C, Senecal DL, Bridges MD, et al. The diagnostic conundrum and liver transplantation outcome for combined hepatocellular-cholangiocarcinoma. American Journal of Transplantation 2010;10:1263–7.
[12] Groeschl RT, Turaga KK, Gamblin TC. Transplantation versus resection for patients with combined hepatocellular carcinoma-cholangiocarcinoma. Journal of Surgical Oncology 2013;107:608–12.
[13] Song S, Moon HH, Lee S, et al. Comparison between resection and transplantation in combined hepatocellular and cholangiocarcinoma. Transplantation Proceedings 2013;45:3041–6.
[14] Park YH, Hwang S, Ahn CS, et al. Long-term outcome of liver transplantation for combined hepatocellular carcinoma and cholangiocarcinoma. Transplantation Proceedings 2013;45:3038–40.
[15] Shetty AS, Fowler KJ, Brunt EM, et al. Combined hepatocellular-cholangiocarcinoma: what the radiologist needs to know about biphenotypic liver carcinoma. Abdom Imaging 2014;39:310–22.
[16] de Campos ROP, Semelka RC, Azevedo RM, et al. Combined hepatocellular carcinoma-cholangiocarcinoma: report of MR appearance in eleven patients. Journal of Magnetic Resonance Imaging 2012;36:1139–47.
[17] Ijichi H, Shirabe K, Taketomi A, et al. Clinical usefulness of (18) F-fluorodeoxyglucose positron emission tomography/computed tomography for patients with primary liver cancer with special reference to rare histological types, hepatocellular carcinoma with sarcomatous change and combined hepatocellular and cholangiocarcinoma. Hepatology Research 2013;43:481–7.
[18] Li R, Yang D, Tang C-L, et al. Combined hepatocellular carcinoma and cholangiocarcinoma (biphenotypic) tumors: clinical characteristics, imaging features of contrast-enhanced ultrasound and computed tomography. BMC Cancer 2016;16:158.
[19] Fowler KJ, Sheybani A, Parker RA, et al. Combined hepatocellular and cholangiocarcinoma (biphenotypic) tumors: imaging features and diagnostic accuracy of contrast-enhanced CT and MRI. American Journal of Roentgenology 2013;201:332–9.