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Original Research

Resection in Patients with Combined Hepatocellular-Cholangiocarcinoma

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Abstract

Objectives: Combined hepatocellular-cholangiocarcinoma (cHCC-CC) is a rare tumor that accounts for 2-3% of primary liver cancers. cHCC-CC mostly have a poor prognosis. There are publications reporting highly contradictory results regarding long-term survival after resection. The aim of this study is to examine the post-resection results of patients with cHCC-CC.

Methods: The data of 7 patients with histopathologically proven cHCC-CC collected prospectively at Inonu University Liver Transplantation Institute, between 2013-2023, were retrospectively analyzed. The preoperative variables examined were age, gender, underlying liver disease, alpha-fetoprotein (AFP) and carbonhydrate antigen (CA 19-9) levels. No patient was diagnosed with cHCC-CC in the preoperative tru-cut biopsies.

Results: Patients were predominantly male (M/F: 6/1) and median age 57 years. All patients had chronic hepatitis or cirrhosis. AFP levels were above 10 ng/dL in 5 cases (7-813 ng/dL) and CA 19-9 levels were normal in all cases. Perihilar lymph nodes resected during hepatectomy were involved with tumor in three patients. The maximum tumor diameter was 11 cm and the mean tumor diameter was 4.5 cm. Bisegmental resection was performed in four patients with cHCC-CC. Major hepatectomy was performed in two cases. Histopathologically, surgical margins were not tumor-free in two patients. The seventh case first underwent segment II-III resection for hepatocellular carcinoma (HCC), but left hemihepatectomy was performed 1.5 months later due to the presence of histopathological tumor in the surgical margins. Histopathological diagnosis confirmed HCC. After 27 months, the patient underwent salvage transplantation due to tumor recurrence within Milan criteria. Histopathological diagnosis was cHCC-CC. The patient who underwent right hemihepatectomy died on the 3rd postoperative day due to reasons other than hepatic failure (cardiac instability). One-year survival of the remaining 6 cases was 71.4%, 3-year survival was 14.3%, and 5-year survival was 14.3%.

Conclusion: cHCC-CC is an aggressive primary liver tumor associated with poor long-term oncological outcomes. Surgical resection is the only curative or palliative treatment option to improve the poor prognosis. In this study, we discussed the diagnosis, treatment and survival of 7 patients with advanced stage cHCC-CC. Studies that require a multidisciplinary approach for the treatment of these tumors are necessary to improve the survival of the patients.

Keywords: Combined hepatocellular cholangiocarcinoma, hepatocellular carcinoma, intrahepatic cholangiocarcinoma

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Combined hepatocellular-cholangiocarcinoma (cHCC-CC) is a rare tumor that accounts for 2-3% of primary liver cancers.[1] This tumor is characterized by histological heterogeneity of both hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCC) elements. Preoperative demographic, clinical, and radiological features are not pathognomonic and may indicate either of the two tumors. Biopsy results are often inconsistent with post-resection pathological results. There are publications reporting highly contradictory results regarding long-term survival after resection.[2-4] The aim of this study is to examine the post-resection results of patients with cHCC-CC.

Methods

In this study, the data of 7 patients with cHCC-CC collected prospectively at Inonu University Liver Transplantation Institute, between 2013-2023, were retrospectively analyzed. The preoperative variables examined were age, gender, underlying liver disease, alpha-fetoprotein (AFP) and carbonhydrate antigen (CA 19-9) levels. Histopathological examination of the postoperative resection materials were reviewed in detail. All patients assessed with dynamic enhanced computed tomography (CT) and five patients revealed with upper abdominal magnetic resonance imaging (MRI) with hepatospecific contrast medium preoperatively. No patient was diagnosed with cHCC-CC in the preoperative tru-cut biopsies. In all 7 patients who underwent surgical resection, serum bilirubin was below 2 mg/dL, platelet levels were above 150.000 /mm^3, and nobody had splenomegaly, ascites, or esophageal varices. The patients were followed up postoperatively with imaging tools (CT and MRI) and serial tumor marker examinations.

Biostatistical Analysis

Quantitative variables were summarized as median (95 % Confidence Intervals), and qualitative variables were given as number (percentage). The Kaplan-Meier estimate was used to calculate overall survival. Analyzes were performed using IBM SPSS Statistics 25.

Results

There were 7 patients with cHCC-CC who were diagnosed histopathologically following resection. Patients were predominantly male (M/F: 6/1) and median age 57 years (95% CI=38-77 years). All patients had chronic hepatitis or cirrhosis. Four patients were positive for hepatitis B virus and two were positive for hepatitis B plus D viruses. Despite another patient being negative for viral serology, she had histopathological findings of chronic hepatitis. AFP levels were above 10 ng/dL in 5 cases (7-813 ng/dL) and CA 19-9 levels were normal in all cases. Perihilar lymph nodes resected during hepatectomy were involved with tumor in three patients. Tumors had a single nodule in four patients and multiple nodules in three patients. The maximum tumor diameter was 11 cm and the mean tumor diameter was 4.5 cm (3.2-11 cm).

The tumors were not significantly different from 'conventional' HCCs on macroscopic examination. Most of the cases were unifocal, three of them were multifocal. On postoperative histopathological examination, the tumors showed a combination of the two components, either close to each other or deeply intermingled. The cholangiocarcinomatous component revealed an adenocarcinoma morphology with variable desmoplastic reaction. The hepatocellular carcinoma component demonstrated hepatocytic differentiation with the appropriate immunohistochemical features. Confirmation of a hepatocellular carcinoma component was shown by immunohistochemical cytoplasmic staining with HepPar-1, Arginase1, canalicular staining with polyclonal CEA or CD10 and sinusoidal capillarization pattern by CD34. The cholangiocarcinomatous component was stained positive for CK7 and CK19 immunohistochemically. In most of the cases, hepatocellular carcinoma was poorly differentiated and cholangiocarcinoma component was poorly or moderately differentiated in all cases.

The imaging features that favor ICC over HCC were present for most of the lesion at CT and MRI. The prominent features of the cases were the early rim enhancement and delayed central enhancement in the portal venous and delayed phase of contrast injection. The less common imaging features that favor the diagnosis of ICC were liver surface retraction, hypointensity on T2W images and target appearance of DWI. One lesion had imaging findings of HCC including arterial non-rim enhancement and portal venous washout. The only one lesion with the largest diameter that occupying right lobe of the liver had findings of right portal venous invasion.

Bisegmental resection was performed in 4 patients with cHCC-CC, which consisted of segments VI-VII in two cases, segments VI and VIII in one case, and segment II- III in one case. Major hepatectomy was performed in two cases consisting of right hemihepatectomy and central hepatectomy. In the patient who underwent right hemihepatectomy, there was tumor thrombus in the right portal vein branch extending to the left portal vein confluence (vP3). Histopathologically, surgical margins were not tumor-free in two patients who underwent bisegmental resection localized to the right lobe and in the patient who underwent central hepatectomy. In the seventh case, there was a different scenario. The 24-year-old male patient first underwent segment II- III resection for HCC, but left hemihepatectomy

was performed 1.5 months later due to the presence of histopathological tumor in the surgical margins. Histopathological diagnosis confirmed HCC. After 27 months, the patient underwent salvage transplantation due to tumor recurrence within Milan criteria. Histopathological diagnosis was cHCC-CC. This patient is alive for 10 years after the transplant. The patient who underwent right hemihepatectomy died on the 3rd postoperative day due to reasons other than hepatic failure (cardiac instability). The median follow up time of the remaining 6 cases was 380 days (95% CI: 112-3422). One-year survival was 71.4%, 3-year survival was 14.3%, and 5-year survival was 14.3% (Fig. 1). Six cases are currently not alive. The cause of death in all cases was tumor recurrence. The patients with tumor recurrence were treated with systemic chemotherapy.

Discussion

Although radical surgical interventions are the most emphasized treatments for patients with cHCC-CC, 5-year survival rates are about 30% due to the aggressiveness of the tumor. Major or segmental hepatic resections together with lymphadenectomy is the recommended treatment.[5-8] Age, male gender, elevated GGT, macrovascular invasion and hilar lymph node metastases are associated with poor prognosis after resection.[9] No effect of adjuvant treatments on recurrence or survival has been demonstrated.[10] The inability to draw a conclusion from the publications containing a small number of patients is a disadvantageous issue regarding the treatment of this tumor. In our study, seven cases were also reviewed. Despite surgical interventions that we consider radical, our survival rate was 71.4% at 1 year, but it was only 14.3% at 5 years, even with salvage liver transplantation. This result is a summary of how aggressive this tumor is.

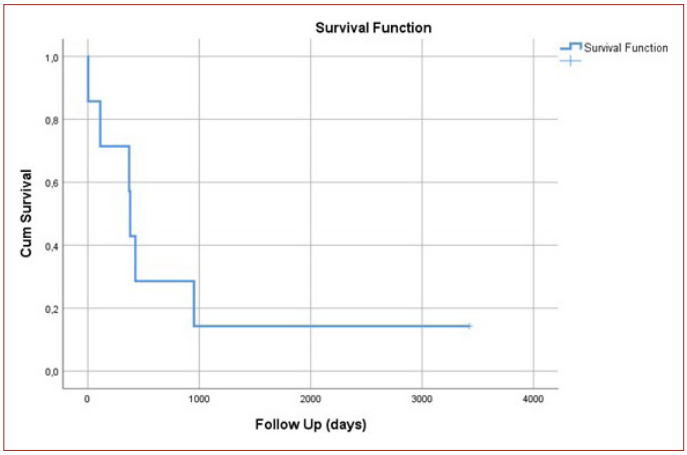

Figure 1. Survival curve of 7 patients with cHCC-CC treated with resection.

Radiologically findings suggestive of malignancy but atypical for HCC or CC should suggest cHCC-CC. In resectable tumors, the diagnosis of this tumor can be established by detailed histopathologic examination of the explant, but failure to diagnose it in unresectable cases cHCC-CC may be suggested by unresponsiveness to locoregional and systemic chemotherapy.[11] No radiological or histopathological preoperative diagnosis of cHCC-CC could be made in any of our cases, and even in the case that underwent to salvage LT, the histopathologic diagnosis was HCC even in the previous two hepatic resections. This raises the question of whether cHCC-CC diagnosed after LT develops as a separate tumor or after differentiation of the primary tumor.

Metastatic lymph nodes in the porta hepatis are predictors of long survival. The contribution of lymphadenectomy to survival in these cases is controversial.[12] Could it be a useful multidisciplinary treatment modality to consider surgical intervention after possible downstaging with systemic or local chemotherapy in these cases? Answering this question may contribute to survival in patients with cHCC-CC. Perineural invasion in liver tumors is a factor that adversely affects overall survival.[13] However, there is insufficient data on whether this is a prognostic factor in cHCC-CC. Metastatic porta hepatis lymph nodes in 3, lymphovascular invasion in 4, and perineural invasion in 2 of our cases were present. More importantly, all cases had signs of cirrhosis or chronic hepatitis, and all tumors were histopathologically undifferentiated. It is likely that these parameters, which negatively affect survival, explain the low survival rate in our cases.

It has been shown that anatomical resections in liver cancers are associated with better survival than non-anatomical resections.[14] However, cirrhosis or chronic hepatitis findings in our cases seem to lead us to parenchyma-preserving anatomic resections. Despite this strategy, we performed major hepatectomy in 2 cases with tumors larger than 10 cm. We believe that survival of more than 1 year despite positive surgical margins in the case who underwent central hepatectomy is an acceptable palliation in such an advanced stage tumor.

Extrahepatic portal vein invasion is rare in patients with cHCC-CC, but hepatic vein invasion is more common. One of our cases had portal vein invasion at vP3 level and we performed a right hemihepatectomy. It is known that these cases probably released tumor cells into the systemic circulation and their survival was not good.[15] The role of liver transplantation in cHCC-CC is controversial. It has been reported that cHCC-CC cases within the Milan criteria have similar survivals to HCC within the same criteria.[16] The survival over 10 years in our case, within the Milan criteria,

who underwent salvage LT seems to be a confirmation of this. This subject is out of the scope of the present article and will be presented in another study of our institute.

In summary, cHCC-CC is an aggressive primary liver tumor associated with poor long-term oncological outcomes. Surgical resection is the only curative or palliative treatment option to improve the poor prognosis. In this study, we discussed the diagnosis, treatment and survival of 7 patients with advanced stage cHCC-CC. Studies that require a multidisciplinary approach for the treatment of these tumors are necessary to improve the survival of the patients.

Disclosures

Ethics Committee Approval: Since this study was prepared as a retrospective archive data review, ethics committee approval was not obtained.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – S.Y., S.K., B.I.C; Design – V.I., S.A., S.Y.; Supervision – S.Y., B.I.C.; Materials – V.I., A.S.K., B.I., A.N.A.; Data collection &/or processing – V.I., S.K., S.Y.; Analysis and/or interpretation – T.T.S., S.A; Literature search – T.T.S., S.Y., S.A; Writing – Z.K., S.A; Critical review – S.A., S.Y., B.I., B.I.C.

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