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LIVER RESECTION FOR HCC IN HIV-INFECTED PATIENTS: A SINGLE CENTER EXPERIENCE

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ABSTRACT: *HIV-infected patients now live longer and often have complications of liver disease, especially with hepatitis B or C virus co-infection. Hepatocellular carcinoma (HCC) is an increasing cause of mortality in HIV positive and negative individuals. There is a lack of consensus regarding the clinical presentation, treatment options, and outcome in HIV-infected patients with HCC. Unfortunately, HCC is frequently diagnosed at an advanced stage, and mortality continues to be very high. Earlier diagnosis, which may allow potentially curative therapy, is necessary.*

Liver resection is considered the most potentially curative treatment for HCC patients when liver transplantation is not an option or is not immediately accessible.

The aim of this article was to describe our liver resection strategy, describing our experience, for HCC in HIV infected patients.

KEY WORDS: *HIV infected patients, Hepatocellular carcinoma, Liver resection.*

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver, and according to the World Health Organization Report, the fourth most common cause of death[1].

In HIV-positive patients, co-infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) is common, and a significantly higher risk for developing HCC as a result of chronic viral hepatitis is well documented. The risk for HCC in these patients is sevenfold higher than in HIV uninfected patients[2,3]. Since the introduction of highly active antiretroviral treatment (HAART), no decrease in the incidence of HCC has been observed, unlike for other HIV-associated cancers[1,2,4].

However, it is unclear whether HIV infection directly increases the likelihood of HCC in patients with viral hepatitis[5-7]. A role could be played by HIV-1 Tat protein[8].

The clinical course of HCC in HIV infected patients is not well defined yet. Most previous studies had small sample size and many patients were not undergoing HAART[9,10]. The most important studies on this field have been published by Brau et al[11], Puoti et al[12] and Berretta et al[13] with different results.

Treatments for HCC are usually classified as curative or palliative[14]. Curative treatments are

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surgical resection, liver transplantation and local ablative therapies. The choice of the appropriate treatment is related to tumor staging, performance status, liver function (presence and stage of chronic liver disease) and viral-immunological status. A key step, especially in HIV infected patients who are already frail, is the correct assessment of functional reserve of the liver, which is important as much as the staging of the tumor.

Liver resection remains a mainstay of HCC treatment. Thanks to the considerable improvements in surgical technique, peri-operative care and post-operative care, the rates of death and complications after liver resection have remarkably decreased over time, giving added value to this procedure[15,16].

The purpose of this article was to illustrate our liver resection strategy, describing our experience, for HCC in HIV infected patients.

UNIVERSITY OF MODENA EXPERIENCE

HCC Surveillance

The achievement of a curative treatment for HCC depends on the detection of the tumor at an early stage. HIV infected patients are considered a population at risk to develop HCC. Screening of HCC was based on ultrasonography according to the American Association for the Study of Liver Disease guidelines (AASLD) every three months[17].

Analysis of recent studies shows that alpha-fetoprotein (AFP) detection does not show adequate sensitivity and specificity for effective surveillance, and thus diagnosis[17-18].

Once the presence of HCC is confirmed, the s-AFP level can be correlated with tumor stage, particularly with the size and multifocality of the tumor and the presence of microvascular invasion. Overall, a screening strategy that combines abdominal ultrasonography and measurement of s-AFP every three months can reduce HCC mortality by approximately 40%[17,19].

HCC Diagnosis

Patients with high index of suspicion for HCC on screening then undergo additional non-invasive testing with either contrast enhanced computed tomography (CT) or gadolinium enhanced magnetic resonance imaging (MR). These imaging modalities can reliably establish the diagnosis of HCC in most patients without the need for biopsy and also provide information on the size and number of lesions, relationship with vascular structures and evidence of extra-hepatic spread. Recent reports have demonstrated that MR has a higher sensitivity compared with CT[20]; however, if the data from the first imaging procedure are not conclusive, confirmation using a different technique is recommended. In cases in which the diagnosis is uncertain, a s-AFP level >400 ng/mL has a high positive predictive value[21]. Histological confirmation through percutaneous liver biopsy should be restricted to those nodules with features on MR or CT that are not typical enough to allow a diagnosis[22]. Additionally, chest CTs and bone scans are routinely used to assess for metastatic disease.

Hepatic resection

Given the complexity of the clinical scenario, the decision on the most appropriate treatment for a patient HIV-positive with HCC should be made by a multidisciplinary team that includes a hepatologist, hepatobiliary/transplant surgeon, oncologist, radiologist, infectious disease specialist and pathologist. No single treatment strategy can be applied to all patients, and treatment should be individualized.

The elements that must be taken into account when considering resection of a patient HIV-infected with chronic liver disease are the Child-Pugh and MELD scores of the underlying liver disease, the viral-immunological status, the degree of portal hypertension and the extension of the parenchymal excision required to obtain a free resection margin.

The aim of the surgical approach is to obtain radical resection with limited surgical morbidity; to achieve this goal, patient selection is really crucial. For the last several decades, the selection of candidates for resection has been based on only Child-Pugh classification. However, Child-Pugh classification is far from accurate for predicting postoperative liver failure; in fact, some Child-Pugh A patients already have liver functional impairment (HIV seems to accelerate the progression of the liver damage) with an increased bilirubin concentration, clinically significant portal hypertension or even minor fluid retention necessitating diuretic treatment[23].

The further investigation of hepatic functional reserve tests, such as the clearance of indocyanine green (ICG) and the measurement of the portal-systemic pressure gradient are very useful tools[17,24]. Recently, a preoperative MELD score ≥10 was associated with a higher incidence (40%) of postoperative liver failure[24].

Markers of portal hypertension including a porto-caval gradient >10 mmHg, the presence of esophageal varices, splenomegaly and a platelet count lower than 1×10^{11}/L are predictors of post-operative morbidity and mortality[2].

In patients without relevant portal hypertension and normal concentrations of bilirubin, the 5-year survival is 70%, whereas this value is 50% for individuals with portal hypertension and is even lower when both these risk factors are present[27,28].

By integrating all of these factors, hepatic resection can be safely performed on patients with Child-Pugh class A chronic liver disease, a MELD score ≤10, a platelet count >100.000/mm^3 and a porto-caval gradient ≤10 mmHg.

However, these factors dramatically limit the potential number of candidates, and overall, less than 30% of patients are candidates for liver resection[26]. Considering these data, we believe that the percentage of patients HIV infected suitable of hepatic resection could be the same or even more if an active surveillance is performed.

After liver resection in general population, the 5-year survival for cirrhotic patients with HCC ranges from 30% to 50%, whereas the operative mortality ranges from 3% to 8%[26]. The severity of cirrhosis, size of the tumor, number of tumors, presence of vascular tumor invasion and presence of satellite nodules are well-established prognostic factors for recurrence and survival[24,28]. Late recurrence is mainly due to the carcinogenic effect of underlying chronic liver disease[29].

Absolute contraindications to hepatic resection are the presence of extrahepatic metastases or neoplastic invasion of the main portal trunk. Neoplastic portal vein thrombosis is a poor prognostic factor; however, in highly selected cases, hemihepatectomy can be feasible, particularly when thrombosis of a main branch of the portal vein has led to hypertrophy of the contralateral hemiliver.

When compared with open surgery, laparoscopy in cirrhotic patients could have the advantage of avoiding the interruption of collateral abdominal veins that are present as a result of portal hypertension. Several studies have indeed demonstrated the benefits of the laparoscopic approach in terms reduced bleeding and lower post-operative morbidity and mortality[30,31].

Our Data

Our Transplant Center is one of the datum point for HIV-infected patients in Italy[13,32-39]. Forty-two HIV-infected patients with chronic liver disease were transplanted over 11 years period from January 1, 2003 to December 31, 2014.

According to the staging and grade of chronic liver disease and the staging of the HCC, six patients underwent hepatic resection. We analyzed these 6 patients retrospectively.

Pre-operative patient's characteristics are show in Table 1. The mean age was 47±3.9 years and all 6 patients were male. All patients were HIV-positive. Two patients were HCV and HBV co-infected and 4 HCV co-infected. The mean pre-operative CD4$^+$ cell count was 178±11.2/ml and the HIV viremia was undetectable. Moreover, all 6 patients were on HAART. The pre-operative Child-Pugh score was stage A in all 6 patients and the mean MELD was 6±0.75.

The tumor characteristics are summarized in Table 2. The HCC presentation was a single node and the mean size was 4.45±2.8 cm. All patients had early stage HCC according to Barcelona Clinic Liver Cancer (BCLC) classification[17]. No neoplastic portal vein thrombosis was detected and mean porto-caval gradient was 6.33±1.75 mmHg. The mean pre-operative s-AFP was 117 (0-684) ng/ml.

Three patients underwent segmentectomy and 3 patients underwent major hepatectomy (2 right hepatectomy and 1 left hepatectomy). No medical or surgical post-operative complications were observed.

The mean follow-up was 8.46±4.62 years, the median survival was 35,51 months, the survival

TABLE 1. PRE-OPERATIVE CHARACTERISTICS OF THE PATIENTS

Patient	Age (year)	Co-infection	Pre-operative CD4+ /ml	MELD score	Child-Pugh score	Porto-caval gradient pressure (mmHg)
#1	48	HCV+/HBV+	177	7	A	5
#2	47	HCV+/HBV+	173	5	A	7
#3	44	HCV+	197	7	A	9
#4	52	HCV+	186	6	A	4
#5	49	HCV+	170	6	A	6
#6	41	HCV+	167	6	A	7

TABLE 2. TUMOR CHARACTERISTICS

Patient	Number of tumors	Tumor size (cm)	Portal vein thrombus	Presence of distant metastases	BCLC staging
#1	1	5	No	No	A
#2	1	2.5	No	No	A
#3	1	1.3	No	No	A
#4	1	3.4	No	No	A
#5	1	9.5	No	No	A
#6	1	5	No	No	A

(BCLC); Barcelona Clinic Liver Cancer classification

rate was 100%, 50%, 50% and 33.3% at 1, 2, 3 and 5 years, respectively. Two patient died for HCV recurrence and two patients died for HCC recurrence. One out of 6 patients underwent liver transplantation for the decline of the liver function after one year.

DISCUSSION

The management of HCC in HIV infected patients is complex and requires an inter-disciplinary approach. Despite improving results of non-surgical approach, liver resection represents a cornerstone for potential curative treatment of HCC in selected patients, able to offer long term survival rate[14,40,41].

Few article analyzed in depth the presentation and outcome of HCC in HIV-positive patients with conflicting results.

Puoti et al[10] in 2004 investigated the main clinical and epidemiological characteristics of HCC in HIV infected patients. Forty-one HIV infected patients were compared with two different cohort of patients HIV-uninfected.

They found that in patients with HIV infection, liver disease stage was significantly more advanced, and liver tumor had a significantly higher prevalence of multifocal and infiltrating lesions.

The overall survival in HIV infected patients was 28% at 1 year and 11% at 2 years compared to 57% and 41% in one cohort of HIV uninfected patients and 60% and 40% in the other cohort of HIV-negative patients. But he also showed that the treatment for HCC was an independent predictor of survival. The proportional of survival of HIV infected patients who received treatment was 51% at 1 year and 41% at 2 years.

Brau et al[11] presented their analysis in 2007. This was a USA-Canadian multicenter study. They compared 63 HIV infected patients with HCC to 226 HIV-negative patients with HCC. HIV-positive patients were diagnosed with advanced stage of HCC (BCLC stage C and D) in 50% of the cases. The patients with solitary tumor were 44.4% but potential curative therapy was performed in just 28.6% of the patients and the hepatic resection in only one patient.

Median survival was no different between HIV infected and uninfected patients (5.5 vs 4.4 months, p=0.98). The survival was higher when they considered just patients who received potentially curative in both group (17 vs 22 months, p=0.14). We can also notice in this study that only 49% of HIV-positive patients initially presented with an elevated AFP level or mass lesion on imaging studies and probably had active surveillance.

In 2011 Berretta et al[13] presented a multicenter observational retrospective study. They compared 104 HIV-infected patients to 484 uninfected patients with HCC. This is the largest analysis of HIV-positive patients who all had an HCC diagnosis made in the HAART era. The HCC was diagnosed in patients with well-controlled HIV disease and good performance status and in an early stage (66% at BCLC stage A or B). In 55.7% of the patients the diagnosis of HCC was made under a screening program. The percent of patients underwent hepatic resection was (14.7%).

The median survival was shorter in HIV-infected patients than in HIV-uninfected patients (35 vs 59 months, p=0.04) but when they considered the median survival in patients treated with potentially curative treatment, it was not different in both group (52 vs 62 months, p=0.9).

These data was confirmed in an other study conducted by Yopp et al[42] in 2012. The survival rate was similar in HIV-positive and HIV-negative patients undergoing curative treatment (90 vs 86% at 1 year, p=0.3). The liver resection was performed in 27% of the patients.

From these two last articles we could speculate that increasing the rate of patients underwent surgi-

cal resection, we could have a significant improvement in the survival rate in HIV infected patients.

Early diagnosis in HIV infected patients, therefore, become key to controlling the healthcare burden of the disease. A more active HCC screening could led to earlier detection, more frequent curative therapy (liver resection) and ultimately better survival.

In conclusion, we strongly believe that hepatic resection is the treatment of choice for HCC in selected HIV-infected patients. The patients need to have a well-preserved liver function (Child-Pugh A), with early stage of HCC (single lesion) and with a stable viral-immunological status. Has been showed that the median survival in HIV-infected patients with HCC was longer in those with undetectable plasma HIV RNA than in those with uncontrolled viremia[11].

Moreover, efficacy of surgery is dependent on ability to achieve negative margins while maintaining an adequately functioning liver remnant.

However, the optimal screening and the impact of liver resection for HCC in this setting of patients has to be better defined, ideally through randomized controlled studies.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

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