Clinical Imaging 40 (2016) 1131–1134

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: http://www.clinicalimaging.org

Hepatocellular carcinoma recurrence pattern following liver transplantation and a suggested surveillance algorithm

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ARTICLE INFO

Article history:
Received 26 February 2016
Received in revised form 16 June 2016
Accepted 5 July 2016
Available online xxxx

Keywords:
Hepatocellular carcinoma
HCC
Liver transplantation
Surveillance
Metastasis

ABSTRACT

Purpose: This study aims to evaluate the recurrence pattern of hepatocellular carcinoma (HCC) following liver transplantation.
Materials and methods: A total of 54 patients underwent liver transplantation for HCC; 9 patients developed biopsy-proven recurrent HCC (16.6%). The site of HCC recurrence along with other factors was analyzed.
Results: Seven patients were diagnosed with HCC prior to liver transplantation and 2 patients had incidental HCC in the explanted liver. Two patients had locoregional recurrence, 4 patients had distant metastasis, and 3 patients had synchronous locoregional recurrence and distant metastasis.
Conclusion: A significant proportion of HCC recurrence following liver transplantation is extrahepatic.

1. Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cancer affecting humans and is the most common primary liver cancer [1]. The worldwide incidence of HCC is on the rise with 75,000 cases occurring annually [2]. Incidence is likely to rise with hepatitis C virus (HCV) epidemic, increasing obesity and nonalcoholic steatohepatitis. Analysis of the liver allocation process by the United Network for Organ Sharing showed that HCC has become a major indication for orthotopic liver transplantation (OLT) [3–5].

There are two major imaging-based systems for selecting HCC patients for OLT. The "Milan Criteria" and the University of California San Francisco Criteria, also called "UCSF Criteria" (Table 1). OLT patients who fit one of these criteria experience better disease outcomes [3]. Post-OLT, the explants are routinely assessed for the accuracy of preoperative staging; the evaluation of explants, with reference to the selecting criteria, is a better indicator of prognosis compared with the preoperative imaging.

The recurrence rate following OLT for HCC has been reported to be around 20% [4]. Due to the increase in OLT for HCC, the number of patients requiring surveillance for HCC is expected to be a growing problem. Additionally, there is no consensus on the imaging protocol for transplant recipients for HCC. Guidelines from the National Comprehensive Cancer Network (NCCN) suggest imaging of the liver every 3–6 months for 2 years then annually, in addition to assay of serum alpha-fetoprotein (AFP), if initially elevated, every 3 months for 2 years, then every 6 months. Guidelines for posttransplant management from a 2010 international consensus conference include contrast-enhanced CT scan or MRI and AFP measurements every 6–12 months [5].

We report the recurrence pattern of HCC following the OLT at our institution, in addition to similar published series, and propose a comprehensive imaging protocol for posttransplant surveillance.

2. Materials and methods

This Health Insurance Portability and Accountability Act-compliant retrospective study received approval from our institutional review board and informed consent was waived due to its retrospective nature.

Between January 2008 and November 2013, 251 liver transplantations were performed at our institution; 54 patients (21%) had HCC based on both preoperative diagnosis and/or histological evaluation of the explanted liver. Preoperative diagnosis of HCC was based on imaging and/or histology i.e. percutaneous biopsy. Out of the 54 patients, 9 (16.6%) were subsequently diagnosed with biopsy-proven HCC recurrence following liver transplantation. The electronic medical records

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http://dx.doi.org/10.1016/j.clinimag.2016.07.002
0899-7071/

Table 1
Milan and "UCSF" Criteria: most commonly used systems to evaluate eligibility of patients with HCC for liver transplantation

Milan Criteria	One tumor ≤5 cm; or up to 3 tumors with the largest ≤3 cm
"UCSF" Criteria	One tumor ≤6.5 cm; or up to 3 tumors with the largest ≤4.5 cm and the total tumor diameter ≤8 cm

were reviewed by two abdominal imaging radiologists (ES and ARK) with 7 and 11 years of experience, respectively. The following parameters were tabulated: indication for liver transplantation, predisposing underlying liver disease, preoperative diagnosis, staging based on imaging and/or biopsy, and postoperative staging based on explant evaluation, posttransplant rise in AFP levels, and the time elapsed between the transplantation and HCC recurrence's location.

HCC disease recurrence was categorized as locoregional (intrahepatic, perihepatic peritoneal space, metastatic porta hepatis lymphadenopathy) or distant metastases. Synchronous recurrence was defined as detected within 90 days (Table 2). Our data were compared with the published series on this topic. Our institutional data were compared to published HCC recurrence series in the English literature, recovered after conducting a systematic PubMed search. One additional series was presented by one of the coauthors (CB) at the American Association for the Study of Liver Disease meeting in 2010.

3. Results

In 9 patients, there were 8 males and 1 female, ranging between 42 and 67 years of age (mean 57.1). Seven patients were diagnosed with HCC prior to the liver transplantation and 2 patients had incidental HCC found in the explanted liver. In 6 (67%), the disease extent was within Milan Criteria on the preoperative imaging but outside, more severe than Milan Criteria, on explant analysis. In 1 case (11%), neither the preoperative imaging nor explant pathology records available in our records. Two (22%) patients had locoregional recurrence, 4 (45%) patients had distant metastasis, and 3 (33%) had synchronous locoregional recurrence and distant metastasis (Table 2). The mean time interval between OLT and disease recurrence [interval between transplant and recurrence (IBTR)] based on AFP elevation was 10.1 months (7 patients) and based on imaging was 13.5 months (9 patients). Seven patients had elevated AFP prior to OLT and 7 patients developed AFP elevation at time of recurrence. However, there was disconnect between pre-OLT and post-OLT AFP elevation pattern. Post-OLT AFP elevation occurred in two patients who did not have pre-OLT AFP elevation and two patients who had pre-OLT AFP elevation did not have AFP elevation at the time of recurrence. Both patients who did not have post-OLT AFP elevation had intrahepatic only recurrence. Thus, all recurrences in our series were detected by either abdominal cross-sectional imaging or elevated AFP that prompted restaging imaging studies.

4. Discussion

Several risk factors have been associated with higher incidence of HCC recurrence following OLT. The most common risk factor is the discrepancy in the preoperative assignment of the Milan or UCSF Criteria describing the extent of the disease versus the explant analysis. Discrepancy is frequently due to a failure to identify subcentimeter HCCs not detected on pretransplant imaging. Another independent risk factor is a preoperatively elevated AFP and posttransplant factors such as immunosuppression. Retrospective studies suggest that mammalian target of rapamycin (mTOR) inhibitors as immunosuppression may reduce the risk of HCC recurrence when compared to mTOR inhibitor-free immunosuppression [4].

Based on the current literature, analysis of the preoperative and explant staging discrepancy reveals an error rate of up to 53%, with 30% falsely considered being inside and 23% falsely determined outside the Milan Criteria [6]. In our patients, 6 out of 9 patients (67%) were under staged on preoperative imaging, turning out to be outside the Milan Criteria on pathological evaluation of the liver explants. In 5 of the above 6 cases, imaging under staging was secondary to the undetectable subcentimeter lesions on preoperative imaging due to the limited sensitivity of the current imaging modalities. One case had an ill-defined infiltrative tumor, which was later seen retrospectively upon careful analysis of the pretransplant imaging. In our 9 patients, 4 cases had distant metastasis while 2 patients had only locoregional recurrence, and the remaining 3 patients had synchronous locoregional

Table 2
Patients with recurrent HCC following liver transplantation (IBTR: interval between transplant and recurrence in months)

Age at OLT	Gender	Indication	AFP elevated pre-OLT	Milan Criteria (imaging)	Milan Criteria (Explant/pathology)	Location of recurrence	Locoregional (LR) or distant (DM)	IBTR AFP (months)	IBTR imaging (months)
65	Male	NASH related cirrhosis	No	Clinically occult tumor (noncontrast CT scan)	No (incidental 8.5 cm tumor involving the portal vein)	Portal vein thrombus/liver (anastomosis) and bone (left shoulder)	LR/DM	10	11
47	Male	HCV related cirrhosis, HCC	Yes	Yes	No (four tumors: 3 cm; 1.2 cm; 0.5 cm; 0.3 cm)	Bone (right scapula)	DM	12	21
65	Male	ETOH related cirrhosis, HCC	Yes	Yes	No (four tumors: 2 cm; 1.3 cm; 0.7 cm; 0.4 cm)	Peritoneal implants	LR	AFP not elevated	16
42	Male	HCV/ETOH related cirrhosis	Yes	Clinically occult tumor	No (two incidental tumors 4 cm; 0.3 cm)	Liver (multifocal)	LR	AFP not elevated	8
67	Male	ETOH related cirrhosis, HCC	No	Yes	No (two tumors: 4.5 cm; 3 cm). HCC with; porta hepatis and celiac lymph node metastasis.	Liver, spleen, and bone (thoracic spine)	LR/DM	3	5
48	Male	HCV related cirrhosis, HCC	Yes	Yes	Yes (one tumor: 3.5 cm)	Porta hepatic lymph nodes and lung metastasis	LR/DM	8	14
59	Male	HCV related cirrhosis, HCC	Yes	Yes	Yes (one tumor: 2.5 cm)	Bone (T8)	DM	28	28
58	Female	ETOH related cirrhosis	Yes	Yes	No (six tumors: 2.3 cm; 2 cm; 1.5 cm; 0.8 cm; 0.5 cm; 0.5 cm)	Bone (skull) and epidural metastasis	DM	2	11
63	Male	HCV related cirrhosis, HCC	Yes	Yes	Unknown	Right adrenal metastasis	DM	8	8