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HCC Recurrence after Liver Transplantation

Essay

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By

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LIST OF ABBREVIATIONS

HCC	Hepatocellular Carcinoma
ALF	acute liver failure
LT	Liver transplantation
OS	Overall survival
DFS	Disease free survival
UNOS	United Network of Organ Sharing
UCSF	University of San Francisco
MELD	The *Mayo end-stage liver disease*
INR	international normalized ratio
ACLF	acute-on-chronic liver failure
DDLT	Deceased Donor Liver Transplantation
LDLT	Living Donor Liver Transplantation
AFP	Alpha Feto Protein
PIVKA	Protein Induced Vitamin K Antagonist
CT	computed tomography
PET	positron emission tomography
IVC	Inferior vena cava
PV	Portal Vein
ECD	Extended Criteria Donor
OPTN	Organ Procurement and Transplantation Network
MHV	middle hepatic vein
A2ALL	Adult-to-Adult LDLT
MC	Milan criteria
CMC	Conventional Milan Criteria
BCLC	Barcelona Clinic Liver Cancer
CLIP	Cancer of the Liver Italian Program
LR	Liver Resection
PLT	Primary Liver Transplantation
ITT	intention-to-treat
TACE	transarterial chemo-embolization
RFA	radiofrequency ablation
EI	alcohol injection
TACI	Transarterial Chemo-Infusion

HVPG	Hepatic Vein Pressure Gradient
PLT	Platelet
OLT	Orthotopic Liver Transplantation
IM	Intrahepatic Metastasis
SLT	Salvage Liver Transplantation
MRI	Magnetic Resonance Imaging
IMRT	intensity modulated radiation therapy
SBRT	stereotactic body radiation therapy
IAT	intra-arterial therapy
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus

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Fig 10	Survival after HCC recurrence following liver transplantation: Comparison of resectable (solid) vs. unresectable (dotted line) patients (57% vs. 14% at 4-years, p=0.02); Used with permission: *Regalia E, et al.: Pattern and management of recurrent hepatocellular*

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common and the third most deadly cancer worldwide. More than half a million cases are identified and about a similar number die of the disease each year. HCC is closely associated with chronic liver disease and as many as 80% of cases occur in cirrhotic livers. Although liver resection and local ablation are regarded as potentially curative treatments, the limited functional reserve of the liver restricts their application and there is a high chance of recurrence in the liver remnant. Liver transplantation is the only treatment that offers a chance of cure for the tumor and the underlying cirrhosis by complete extirpation of both. The outcome of liver transplantation for early HCC in Western countries is encouraging, but the limitation of organ supply remains the main issue. Tumor frequently develops in a background of cirrhosis; the leading cause of liver cancer is viral infection with hepatitis B virus or hepatitis C virus. The cancer usually forms secondary to cirrhosis caused by these viruses. For this reason, the highest rates of liver cancer occur where these viruses are endemic, including East-Asia and sub-Saharan Africa. (Llovet , et al.2005)

Liver transplantation may be the best curative treatment for HCC. First, it removes the tumor with the widest margin together with any intrahepatic metastasis. Second, it cures the underlying cirrhosis that is responsible for both hepatic decompensation and metachronous tumor after partial hepatectomy. Finally, it allows the histological examination of the entire liver explant for the most accurate pathologic staging. The early results that focused primarily

on patients with advanced HCC were, however, poor because of frequent tumor recurrence. Over the last decade, there has been considerable improvement in the outcome of liver transplantation for HCC, which is attributed almost entirely to better patient selection rather than better surgery or adjuvant therapy. (Iwatsuki, et al.1991m)

The objective of the selection criteria for HCC is to set a transplantable limit in order to achieve survival duration comparable with that of other patients with benign liver disease receiving transplants, so as to justify or prioritize the allocation of a liver graft. For >10 years since the landmark study by Mazzaferro et al. in 1996, the Milan criteria have remained the gold standard. By restricting transplantation to patients with a solitary tumor up to 5 cm in diameter or with two to three tumor nodules each up to 3 cm in the absence of extrahepatic disease, 4-year overall and disease-free survival rates of 75% and 83%, respectively, can be achieved. Extended criteria, such as the University of California at San Francisco (UCSF) criteria, have been proposed to expand the tumor number–size limits to solitary tumor up to 6.5 cm or a maximum of 3 tumor nodules each up to 4.5 cm, and a total tumor diameter not exceeding 8 cm, without compromising patient survival. The traditional pathologic tumor–node–metastasis staging system has poor predictive value for outcome after liver transplantation, and the University of Pittsburgh group has therefore modified the criteria by including specific tumor characteristics, such as lobar distribution (unilobar or bilobar) and type of vascular invasion (microscopic or macroscopic), into a staging classification with better prognostic value. The main drawback of the Pittsburgh criteria that limited its clinical application in practice was the need for information on vascular invasion, which is difficult to ascertain preoperatively without examining the liver explant. The

Milan and UCSF criteria are currently the most popular reference criteria in deciding the candidacy of patients with HCC for liver transplantation.(Jonas, et al,2001)

The limited availability of liver grafts not only restricts candidacy but also mandates a system of organ allocation according to priority. The prolonged waiting period frequently results in tumor progression to an extent beyond the transplantable criteria, leading to a patient's removal or dropout from the waiting list. Hence, intention-to-treat analysis is more appropriate. In a study from Spain, where the organ donation rate is the highest in the world and the average waiting time is <6 months, 23% of patients who met the Milan criteria dropped out and the 2-year intention-to-treat survival rate was only 54%. In another study from the U.S., the cumulative probabilities of dropout at 6, 12, and 24 months were 7.3%, 25.3%, and 43.6%, respectively. As a result of the high dropout rate for patients with HCC, the Organ Procurement and Transplantation Network (OPTN) of the U.S. has reconsidered the priority of liver graft allocation. While waiting list priority was determined primarily by liver disease severity based on the Model for End-Stage Liver Disease (MELD) score, patients with HCC that fulfilled the Milan criteria were registered with an adjusted score and were subsequently assigned additional scores at regular intervals to reflect their risk for dropout as a result of tumor progression. With such priority listing, the access to timely liver transplant for patients with HCC has improved in the U.S. (Yao, et al.2004)

Chronic inflammation in the cirrhotic liver promotes a dysplastic field. While transplantation offers the theoretic advantage of complete tumor excision with removal of the diseased liver, recurrence of HCC following OLT is the rate-limiting factor for long-term survival. Unfortunately,

HCC recurrence is reportedly as high as 40% after transplantation in the early days, nowadays Recurrence of HCC after transplantation remains a formidable problem in approximately 20% of patients despite refined selection criteria and exhaustive preoperative staging. Mechanisms of cancer recurrence include the presence of microscopic extrahepatic foci at the time of transplantation. Thus, HCC may resurface in the form of metastatic foci in distant organs, such as the lungs, brain, bone, and in the transplanted allograft. It is clear that several tumor-associated factors are prognostically important. Tumor size and the presence of vascular invasion have emerged as the most clinically significant characteristics for predicting recurrence.(Marsh, et al.1997) .

Cancer recurrence following surgical intervention is the major limitation to long-term survival. Several authors suggest that the incidence of HCC recurrence is significantly higher following liver resection than after transplantation. Recurrent tumor after liver resection is predominantly intrahepatic. Conversely, recurrent HCC after OLT may present at distant sites, including lung, bone, and brain, as well as the transplanted allograft. Recurrent tumor generally presents within a short interval from the time of transplantation. This suggests that preoperative or intraoperative microscopic metastasis is responsible for recurrent disease. (Llovet, et al.2005)

Few treatment options are currently available for patients with recurrent cancer after OLT. Unfortunately, most present with disseminated disease and are not candidates for local ablative therapy. However, aggressive surgical intervention has recently been advocated for a

subgroup of patients with localized recurrence.(Schwartz , et al.2005)

Aim of the Work

To review the incidence, pattern &risk factors of HCC recurrence after liver transplantation with stress on the early detection & early management for recurrence.

LIVER TRANSPLANTATION FOR H.C.C

CHAPTER (1)

Today, liver transplantation is a lifesaving procedure for patients with chronic end-stage liver disease and acute liver failure (ALF) when there are no available medical and surgical treatment options. ***(Murray, et al., 2005)***

History and Evolution of Liver Transplantation for HCC

Liver transplantation for HCC is almost as old as LT itself. The early series of Thomas Starzl from Denver at the University of Colorado in 1963, had four HCC patients including two children. The longest survival achieved was 16 months and only two patients survived more than 1 year.***(Starzl, et al., 1969)***

Early series of LT from various centers in the 70s and 80s yielded poor results and prompted the US Department of Health to declare HCC as a contraindication to LT in 1980. The unflattering outcomes of LT for HCC (high early recurrence and 18–40% 5-year OS) could be largely attributed to inclusion of patients with large tumors, evolutionary phase of modern imaging, and evolving surgical techniques (Fig. 1).***(Penni, 1991)***