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OUTCOME OF LIVING DONOR LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA

Thesis

Submitted for partial fulfillment of the MD degree in General Surgery

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List of Contents

List of Tables

List of Tables

List of Figures

List of Figures

List of Abbreviations

AFP	Alpha-fetoprotein
ALG	Anti lymphocyte globulin
BCLCG	Barcelona Clinic Liver Cancer Group
BCLC	Barcelona- Clinic-Liver-Cancer
CLIP	Cancer of the Liver Italian Program
CLD	Chronic liver disease
CBD	Common bile duct
CHD	Common hepatic duct
CT	Contrast-enhanced computed tomography
CEUS	Contrast-enhanced Ultra Sound
CsA	Cyclosporine
CMV	Cytomegalovirus
DDLT	Deceased donor liver transplantation
DCP	Des-gamma carboxy-prothrombin
DFP	Disease free period (DFP)
DFS	Disease-free survival
DD	Duct-to-duct
ELITA	European Liver and Intestine Transplant Association
GDA	Gastroduodenal artery
HR	Hazard ratios
HFL	Hepatic focal lesion
HR	Hepatic resection
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCC	Hepatocellular carcinoma
HIF-1α	Hypoxia-inducible factor 1, alpha
ICG	Indocyanine green
IVC	Inferior vena cava
ILTS	International Liver Transplant Society
INR	International normalized ratio
IM	Intrahepatic metastasis
KFTs	Kidney function tests
LCA	Lectinlens culinarisagglutin
LGA	Left gastric artery
LHA	Left hepatic artery
LHD	Left hepatic duct
LHL	Left hepatic lobe
LFTs	Liver function tests
LR	Liver resection
LT	Liver transplantation
LDLT	Living donor liver transplantation
LN	Lymph node
MRI	Magnetic resonance imaging

List of Abbreviations

MRT	Magnetic spin resonance tomography
mTOR	Mammalian target of rapamycin
MVI	Microvascular invasion
MC	Milan Criteria
MELD	Model of End-Stage Liver Disease
MO	Multicentricoccurrence
OPTN	Organ Procurement Transplant Network
OLT	Orthotopic liver transplantation
OS	Overall Survival
PAI	Percutaneous acetic acid
PEI	Percutaneous ethanol injection
PV	Portal vein
PLT group	Primary OLT
PIVKA-II	Protein induced by vitamin K absence or antagonist-II
RFA	Radiofrequency ablation
RHA	Right hepatic artery
RHD	Right hepatic duct
RHL	Right hepatic lobe
SLT	Salvage liver transplantation
SIR	Sirolimus
SLT group	SLT after prior partial hepatectomy
SMA	Superior mesenteric artery
SPR	Survival post-recurrence
ST	Survival time
PET scan	Total body positron emissiontomography scan
TACE	Transarterial chemo-embolization
TARE	Transarterialradioembolization
US	Ultrasound
UNOS	United Network for Organ Sharing
U.S.	United States
USA	United States of America
UCSF	University of California, San Francisco
VEGF	Vascular endothelial growth factor

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and most patients with HCC also suffer from coexisting cirrhosis. For the treatment of patients without cirrhosis, resection should be considered whenever possible. Hepatic reserve is the one of the major determinants of liver resection. When compared with resection, transplantation restores liver function and has the advantage of removing tissue with an oncogenic potential ***(Kassahun et al., 2006)***.

Liver resection (LR) and liver transplantation (LT) are considered the only two potentially curative treatments for this tumor. LT offers the best chance for cure in patients with HCC localized to the liver because both the tumor and the underlying cirrhosis are treated. In the 1980s and early 1990s, LT was often performed in patients with large or advanced, unresectable HCC. This resulted in high recurrence rates and unfavorable long-term survival ***(Lee et al., 2010)***.

The field of liver transplantation has undergone remarkable advances in the last two decades. An essentially experimental procedure in the early 1980s, a liver transplant is now the treatment of choice for patients with acute and chronic liver failure. Patient survival at 1 year post transplant has increased from 30% in the early 1980s to more than 85% at present. The major reasons for this dramatic increase include refined surgical and preservation techniques, better immunosuppressive protocols, more effective treatment of infections, and improved care during the critical perioperative period. However, a liver transplant remains a major undertaking, with the potential for complications affecting every major organ system ***(Busuttil et al., 2005)***.

LT is the best therapeutic option for early, unresectable HCC, although it is limited by graft shortage and the need for appropriate patient selection. In the late 1980s, the results after LT for HCC were

disappointing, with high early recurrence and 5-year survival rates ranging between 18 and 40%. This discouraging experience and shortage of deceased donor grafts compelled the transplant community to establish stringent selection criteria to predict post transplant survival of HCC patients ***(Mazzaferro et al., 2008)***.

In 1996, Mazzaferro et al. reported favorable long-term survival after LT in a series of patients with solitary tumor less than 5 cm in diameter or 2–3 tumor nodules with the largest nodule diameter below 3 cm. The investigators found that the long-term survival in these patients was comparable to that of non-HCC patients after transplantation. Since that time, these criteria, known as the Milan criteria, have become widely accepted as the selection criteria for LT in patients with HCC ***(Lee et al., 2010)***.

The growing experience and success of LT for HCC have fueled controversies related to expansion of the Milan criteria for LT, since many studies have suggested that tumor stage beyond the Milan criteria does not necessarily predict worse survival after LT. Supported by studies showing that many patients with tumor stage beyond the Milan criteria can be cured by LT, a number of expanded criteria have been proposed. While expanding the criteria for LT allows more patients to be eligible for transplantation, arguments against expanding the criteria include the increased risk of vascular invasion and tumor recurrence at higher stages of HCC ***(Mazzaferro et al., 2008)***.

In 2001, Yao et al. from the University of California, San Francisco (UCSF), reported a 5-year survival of 75% in patients with a single tumor as large as 6.5 cm or a maximum of 3 tumors up to 4.5 cm and a cumulative tumor burden 8 cm. With mostly retrospective data, some groups have independently tested these criteria. These results have, however, been challenged because of the use of explant pathology, rather than preoperative imaging, as a determinant for the definition of the tumor stage ***(Silva et al., 2008)***.

Various other groups have published expanded criteria with results not dissimilar to the original "Milan criteria". The same group in Milan has recently published retrospective data regarding outcome in 1112 patients exceeding the original Milan criteria. In this study, a 71.2% 5-year overall survival could be achieved using the "up-to-7" criteria (the "rule of 7," whereby the sum of the size of the largest nodule plus the total number of nodules cannot exceed 7). It is clear that the larger the tumor size and number, the worse the outcome ***(Tanwar et al., 2009)***.

In the current era of increasing demand and unrelenting organ shortage, the foundation of the debate regarding expansion of the Milan criteria for HCC may ultimately rest on what the transplant community would consider an acceptable survival after Orthotopic liver transplantation (OLT) for HCC. Some groups have proposed a 50% 5-year patient survival to be the minimum acceptable cutoff. This mark may have been surpassed by the UCSF group, who has applied expanded criteria to benefit an additional 10% of patients with HCC with respect to post transplant survival and tumor recurrence ***(Mazzaferro et al., 2008)***.

For strictly selective criteria, such as the Milan and UCSF criteria, the 5-year survival rate of patients who undergo transplantation for HCC is comparable to recipients who undergo transplantation for benign liver diseases. Nonetheless, LT is greatly limited by the shortage of liver grafts. The long waiting period leads to tumor progression and dropout of patients from the waiting list. Living donor liver transplantation (LDLT) is perceived as an alternative to deceased donor liver transplantation (DDLT) due to the limited availability of cardiac death donors. It may expand the donor pool, shorten the waiting time and prevent dropout of patients from the waiting list due to tumor progression. However, some investigators have suggested that the long-term and recurrence-free survival rates of LDLT are not satisfactory ***(Li et al., 2010)***.

Aim of the Work

This study aims at assessment of the outcome of living donor liver transplantation for patients with HCC within Milan's criteria and beyond Milan's criteria and the impact of presence of micro vascular invasion on long-term and recurrence-free survival rates.

Chapter (1)

Liver Anatomy

Liver Segments

One of the greatest advances in hepatic surgery is the understanding of the segmental anatomy of the liver. The Couinaud system for liver segmental nomenclature is widely accepted in practice ***(Couinaud, 1999)***.

The liver is divided into longitudinal planes drawn through each hepatic vein to the vena cava, and a transverse plane at the level of the main portal bifurcation. The plane of the middle hepatic vein and the primary bifurcation of the portal vein (PV) divide the liver into a right and left lobe. This runs from the inferior vena cava (IVC) to the tip of the gallbladder fossa (also known as Cantlie's line or the portal fissure) ***(Couinaud, 1999) (Strasberg, 2005)***.

Each secondary portal bifurcation (right and left) gives rise to four sectors (or sections) each after branching (Figure 1). On the right side this produces the anterior and posterior sectors, which are split by the plane of the right hepatic vein. The tertiary branches on the right supply four segments, two in each sector. On the left, the secondary bifurcation is less symmetrical. The ascending branch of the left gives off recurrent branches to the medial sector of the left lobe. However, the left lateral sector is supplied by separate branches that supply the two segments (segments II and III). Segment I, the caudate lobe, receives blood supply from both the left and right portal pedicles; bile ducts from segment I also drain into the right and left hepatic ducts ***(Couinaud, 1999) (Strasberg, 2005)***.